STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2814-G000-103
Study Protocol Title:	An Open-Label Phase 1b/2 Study to Assess Safety and Target Engagement of E2814 in Subjects with Mild to Moderate Cognitive Impairment due to Dominantly Inherited Alzheimer's Disease
Date:	23 July 2024
Version:	Final Version 1.0

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	anti-drug antibody
AE	adverse event
ALQ	above the limit of quantification
ATC	anatomical therapeutic class
$AUC_{(0\text{-inf})}$	area under the concentration-time curve from zero time (pre-dose) extrapolated to infinite time
$AUC_{(0\text{-t})}$	area under the concentration-time curve from zero time (pre-dose) to time of last quantifiable concentration
BLQ	below the limit of quantification
BMI	body mass index
C_{max}	maximum observed concentration
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DIAD	Dominantly Inherited Alzheimer's Disease
ECG	electrocardiogram
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MTBR	microtubule binding region
NAb	Neutralizing antibody
NCA-MNL	Eisai Non-compartmental Pharmacokinetic Analysis Manual
PT	preferred term
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
Q4W	every 4 weeks
SAP	statistical analysis plan
SD	standard deviation
SI	Système International
SOC	system organ class

Abbreviation	Term
TE	target engagement
t_{max}	time at which the highest drug concentration occurs
$t_{½}$	terminal elimination phase half-life
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TLG	tables, listings, and graphs
ULOQ	upper limit of quantification
WHO	World Health Organization

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E2814-G000-103 (Amendment 04).

3.1 Study Objectives

3.1.1 Primary Objectives

The primary objectives of the study were:

- To assess the safety and tolerability of intravenous (IV) infusions of E2814 in subjects with Dominantly Inherited Alzheimer's Disease (DIAD)
- To evaluate target engagement (TE) of E2814 on microtubule binding region (MTBR)-tau species in CSF in subjects with DIAD

3.1.2 Secondary Objectives

The secondary objectives of the study were:

- To assess the pharmacokinetics (PK) of E2814 in serum, plasma, and cerebrospinal fluid (CSF)
- To assess the immunogenicity (production of anti-E2814 antibody) of E2814
- To assess the effect of E2814 on CSF, blood, and imaging biomarkers

3.1.3 Exploratory Objectives

The exploratory objectives of the study were:

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3.2 Overall Study Design and Plan

E2814-G000-103 was an open-label Phase 1b/2 study to evaluate the safety and TE of E2814 on MTBR-tau species in CSF following IV infusions of E2814 in DIAD subjects. Subjects in this study were confirmed mutation positive for genes known to be associated with DIAD. The mutations in presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*) and amyloid precursor protein (*APP*) that are associated with DIAD have very high penetrance (near 100%).

The study consisted of 2 Cohorts (A and B).

Cohort A consisted of 2 phases: A Pretreatment Phase consisting of a Screening Period and a Treatment Phase consisting of 3 periods: 1b, 2, and Follow Up.

Cohort B was to consist of a Pretreatment Phase and a Treatment Phase consisting of 2 periods (52-week Treatment Period and 12-week Follow Up Period).

4 DETERMINATION OF SAMPLE SIZE

No formal sample size calculations were performed. For this Phase 1b/2 study, up to 8 subjects in Cohort A and up to 5 subjects in Cohort B were considered adequate to evaluate the initial safety and PK in symptomatic DIAD subjects and to establish evidence of TE.

5 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

5.1 Study Endpoints

All endpoints were measured in both Cohort A and Cohort B.

5.1.1 Efficacy Endpoints

- Change from baseline in cognitive and clinical assessments

5.1.2 Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), laboratory parameters, vital signs, and ECGs

5.1.3 Pharmacokinetic (PK) Endpoint(s)

- Serum and plasma PK parameters following dosing on Days 1 and 85
- CSF E2814 concentrations.

5.1.4 Pharmacodynamic (PD) Endpoint(s)

- Change from baseline in CSF free and bound MTBR-tau and total MTBR-tau post-treatment
- Change from baseline in CSF biomarkers [redacted]
- Change from baseline in tau PET signal

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The Safety Analysis Set is the group of all allocated subjects who received at least 1 dose of study treatment. At least 1 laboratory, vital sign, or ECG measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required. This is the analysis population used for all safety analyses which will be based on as-treated principle.

The Pharmacokinetic Analysis Set is the group of subjects who received at least 1 dose of test drug and had sufficient PK data to derive at least 1 PK parameter.

The Pharmacodynamic Analysis Set is the group of subjects who received at least 1 dose of study drug and had sufficient PD data to derive at least 1 PD parameter.

The definition of these analysis sets is the same for both the Phase 1b (Cohort A) and Phase 2 (Cohort A and Cohort B) Treatment Periods; actual determination of these analysis sets will be made separately for each study period. Data from Cohort A and B will be presented combined. In other words, there will one Safety Analysis Set, one Pharmacokinetic Analysis Set and one Pharmacodynamic Analysis Set.

5.2.2 Subject Disposition

Reasons for screening failure will be summarized.

The number and percentage of subjects who completed the study will be summarized and the number who discontinued prematurely will be summarized by reason for discontinuation.

5.2.3 Protocol Deviations

Important protocol deviations will be presented as a listing.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for all subjects using descriptive statistics. Continuous demographic and baseline variables include age, categorical variables include sex, age group and race.

MEDICAL HISTORY

A subject data listing of medical and surgical history will be provided.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded using the World Health Organization Drug Dictionary (WHO DD) (March 2024). Prior medications will be defined as medications that stopped before the 1st dose of study drug. Concomitant

medications will be defined as medications that (1) started before the 1st dose of study drug and were continuing at the time of the 1st dose of study drug, or (2) started on or after the date of the 1st dose of study drug up to 100 days after the subject's last dose. All medications will be presented in subject data listings.

5.2.6 Treatment Compliance

A listing of study drug administration showing dates, times and volumes of infusion will be presented by subject. Compliance will be determined by reviewing infusion volumes and assessing the number of missed or delayed doses presented in the extent of exposure tables described in Section 5.6.1 below.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Examination of Subgroups

No subgroup analyses are planned for this study.

5.3.3 Handling of Missing Data, Dropouts, and Outliers

See Section 8.1 of this SAP for guidance relating to PK and PD data handling. If no clear reason can be found to explain any anomalous values, then data summaries and graphs, both with and without, the anomalous values will be generated. Appendix 13.1 includes guidance for derivations to address missing responses for cognitive assessments.

5.3.4 Other Considerations

None

5.4 Efficacy Analyses

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5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The PK analysis will be performed on the PK Analysis Set. Serum and plasma concentrations of E2814 will be tabulated by nominal sampling time and summarized by dose using summary statistics in Cohort A. Individual serum, plasma and CSF concentration-time profiles will be displayed in linear and semi-log scale presenting actual sampling time on the x-axis.

Serum, plasma and CSF concentrations of E2814 will be listed for each subject by actual sampling time.

The Safety Analysis Set will be used for individual E2814 serum and plasma concentration listings. The PK Analysis Set will be used for the summaries of E2814 serum and plasma concentrations and for summaries and listings of PK parameters.

PK parameters will be derived by noncompartmental analysis using Phoenix WinNonlin software (version 7.0 or newer) according to Eisai's Non-compartmental Pharmacokinetic Analysis Manual (Version 0.1) (NCA-MNL, hereafter).

Serum and plasma E2814 PK parameters will include (but not be limited to) C_{max}, time to reach maximum drug concentration (t_{max}) and area under the concentration-time curve from zero time to the end of the dosing interval ($AUC_{(0\text{-}672h)}$) on Days 1 and 85 in Cohort A.

An integrated population analysis of E2814 PK will be performed by pooling data from Cohort A and Cohort B, and from all available studies. For population PK, the details will be described in a separately prepared analysis plan and its report, and the results will be provided in a separate report.

Summary statistics will be tabulated for the PK parameters of E2814 by dose. Summary statistics (n, mean, SD, geometric mean, %CV, median, minimum and maximum) will be presented for all parameters (apart from t_{max} where mean and SD are not required). In addition, geometric mean and %CV will also be presented for all parameters apart from t_{max}.

PK parameters of E2814 for each subject will be listed.

5.5.2 Pharmacodynamic Analyses

The PD Analysis Set will be used for both the listings and summaries of all biomarker CSF and plasma measurements [redacted] Biomarker measurements (fluid and imaging) and change from baseline will be summarized by time point and dose and presented graphically.

These analyses will be done for CSF, plasma and serum. Dose-response relationships will be evaluated.

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[redacted]

Derivations required for BLQ (below the limit of quantification) and ALQ (above the limit of quantification) values are described in Section 8.1.6 below.

Other exploratory biomarker analyses may be performed and reported separately, and the results will not be included in the clinical study report. Details of these analyses would be described in a separate analysis plan.

5.5.3 Pharmacokinetic/Pharmacodynamic Analyses

The relationship between PK and PD will be evaluated by visual inspection using plots. This will include the graphical exploration of the PK/PD relationship between E2814 concentrations and PD biomarker responses in CSF for different E2814 dose exposure levels.

5.5.4 Pharmacogenomic/Pharmacogenetic and Other Biomarker Analyses

PGx analyses may be performed and reported separately. Details of these analyses will be described in a separate analysis plan, and the results will not be included in the clinical study report.

5.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by dose, will be summarized using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include TEAEs, clinical laboratory parameters, vital signs, and 12-lead

ECG results. Study Day 1 for all safety analyses is defined as the date of the first dose of study drug.

5.6.1 Extent of Exposure

The total number of doses administered at each dose level will be summarized for each subject. This table will also present the number of missed or delayed doses. In addition, a table showing the duration of drug exposure at each dose will be generated for each subject.

5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 27) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerged during treatment, having been absent at pretreatment (Baseline) or

- Reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment state, when the AE is continuous.

During treatment is defined as the period between the administration of study drug and up to 113 days after the last study drug dose. Only those AEs that are treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by dose. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

Adverse events will be summarized on the Safety Analysis Set. The number of adverse events, number of subjects with adverse events, and incidence (%) will be calculated by dose and overall. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with adverse events by system organ class (SOC) and by preferred term (PT) in the Safety Analysis Set will be calculated.

Separate listings will be provided for subjects with deaths, SAEs, and AEs leading to discontinuation.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in protocol Section 9.5.1.4.4 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each postbaseline visit and to the end of treatment will be summarized by visit using descriptive statistics. Qualitative parameters listed in protocol Section 9.5.1.4.4 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be graded or assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Each laboratory parameter will be assessed based on shift tables that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment.

Appendix 13.2 presents the criteria (based upon Common Terminology Criteria for Adverse events (CTCAE) Version 5.0) that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. A listing of subjects with markedly abnormal laboratory values will be generated, which will be ordered by subject.

5.6.4 Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, body temperature, weight) and changes from baseline will be presented by visit.

Vital sign parameter values will also be presented in a listing, ordered by subject.

5.6.5 Electrocardiograms

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) by visit to end of treatment.

5.6.6 Other Safety Analyses

A listing presenting Columbia-Suicide Severity Rating Scale (C-SSRS) assessment results for all subjects will be generated which will be ordered by subject.

5.7 Other Analyses

The presence of anti-E2814 antibodies at various time points postdose will be presented in subject data listings. The number (percentage) of subjects with positive and negative anti-drug antibody (ADA) in serum and plasma will be summarized by visit and dose. A summary table showing ADA subject level status will be presented by dose, together with

summary statistics for the maximum postdose ADA titer value for TE ADA positive subjects. Corresponding tables for neutralizing antibodies (NAb) in serum will be generated as data permit.

5.8 Exploratory Analyses

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[redacted]

6 INTERIM ANALYSES

No interim analyses were planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

There were no changes to the planned analyses.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Pharmacokinetic Data Handling

8.1.1 Lower Limit of Quantification of E2814 Serum and Plasma concentration

The LLOQ of E2814 in serum and plasma is 1.00 ug/mL and in CSF is 1.00 ng/mL

8.1.2 BLQ Handling for Calculation of PK Parameters

While calculating PK parameters in WinNonlin, the following criteria should be used.

- Following single (or the first) dose, BLQ value(s) at pre-dose and up to the first quantifiable concentration, above lower limit of quantification (LLOQ), should be replaced with zero.
- Following the first quantifiable concentration, a single BLQ between 2 quantifiable concentrations should be set to “missing.”
- Following the first quantifiable concentration, if a quantifiable concentration is followed by 2 consecutive BLQs in terminal phase, all subsequent quantifiable concentrations should be assigned to “missing.”

8.1.3 BLQ Handling for Developing Concentration-Time Profiles

When developing individual concentration-time profiles, BLQ values are replaced with:

- Zero for time points prior to the first non-zero concentration following single (or first) dosing in a linear plot
- "Missing" for time points after the first non-zero concentration following single (or first) dosing in a linear plot
- "Missing" for all BLQ values in a semi-logarithmic plot

When calculating the mean (or median) value for the concentration at a given time point, all BLQ values are assigned as zero. If the proportion of values reported as BLQ is more than 50% or the calculated mean (or median) value is less than LLOQ at a time point, the value of mean (or median) is treated as:

- Zero for time points prior to the first non-zero mean (or median) concentration following single (or first) dosing in a linear plot
- "Missing" for time points after the first non-zero mean (or median) concentration following single (or first) dosing in a linear plot
- "Missing" for all BLQ values in a semi-logarithmic plot

8.1.4 Handling of Anomalous Concentration Values

Anomalous values are those that are inconsistent with known or expected PK behavior of the drug but are not defined on the basis of statistical tests for outliers. Individual concentrations deemed to be anomalous can be excluded from the PK analysis and median and mean profiles. Anomalous values will be identified in the CSR. Clear justification must be provided in the CSR for exclusion of any data.

8.1.5 General Rules for Presentation of Drug Concentrations and PK Parameters

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations and concentration-dependent pharmacokinetic parameters, all summary statistics (mean, median, geometric mean, SD, and CV) will have 3 significant digits. For t_{max} and t_{lag}, raw values and median have fixed 2 decimal places.

Typical variable	Standard Unit (depends on compound)	N	Digit rule	Raw Minimum Maximum	Mean Median	SD	Geometric Mean	CV (%)
E2814 concentration	Plasma/serum ug/mL CSF ng/mL	X	Significant digits	3	3	3	-	-
C_{max}, C_{min}	Plasma/serum ug/mL CSF ng/mL	X	Significant digits	3	3	3	3	3

Typical variable	Standard Unit (depends on compound)	N	Digit rule	Raw Minimum Maximum	Mean Median	SD	Geometric Mean	CV (%)
t_{max}, t_{lag}[a]	h	X	Fixed decimal places	2	2	-	-	-
λ_z	1/h	X	Significant digits	3	3	3	3	3
$t_{1/2}$	h	X	Significant digits	3	3	3	3	3
AUC	Plasma/serum ug·h/mL CSF ng.h/mL	X	Significant digits	3	3	3	3	3
$\%AUC_{ex}$	%	X	Significant digits	3	3	3	3	3
CL	L/h	X	Significant digits	3	3	3	3	3
V_d	L	X	Significant digits	3	3	3	3	3
MRT	h	X	Significant digits	3	3	3	3	3

a: Mean, SD, geometric mean and CV will not be calculated for t_{max} and t_{lag}.
CV(%) = sqrt(exp[SD^2 of log transformed data]-1)×100

8.1.6 General Rules for Presentation of PD Parameters

Summary statistics for the PD data will be presented to 3 significant digits.
For the PD biomarker assays, the LLOQ and ULLQ values will be provided together with the data.
When producing TLGs for the PD data, BLQ and ALQ values in tables and figures will be handled as follows:
For Free MTBR-Tau species (including, Free MTBR-Tau-299 and Free MTBR-Tau-354) and other PD biomarkers apart from Bound MTBR-tau species,

- BLQ values will be replaced with 0.5 x LLOQ and ALQ values replaced with 2 x ULOQ.

For Bound MTBR-tau species (including, Bound MTBR-Tau-299 and Bound MTBR-Tau-354):

- A concentration that is BLQ is assigned a value of zero if it is pre-dose or if it occurs in a profile after dosing at time zero and before the first measurable concentration.
- If a BLQ value occurs after a measurable concentration and is followed by a value above the lower limit of quantification, then the LLOQ/2 is used.
- If a BLQ value occurs after the last quantifiable concentration it is treated as LLOQ/2.

For listings no derivations are required therefore values of BLQ and ALQ will be presented.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

Analysis will be performed using SAS (release 9.4 or newer), Phoenix WinNonlin (version 6.4 or newer) and Microsoft Excel (2010 or newer).

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

User Manual 302-104.01. Non-compartmental pharmacokinetic analysis. Version Date 28th June 2018.

13 APPENDICES

13.1 Derivations for Clinical and Cognitive Assessments.

Geriatric Depression Scale: Short Form

1. Are you basically satisfied with your life? YES / **NO**
2. Have you dropped many of your activities and interests? **YES** / NO
3. Do you feel that your life is empty? **YES** / NO
4. Do you often get bored? **YES** / NO
5. Are you in good spirits most of the time? YES / **NO**
6. Are you afraid that something bad is going to happen to you? **YES** / NO
7. Do you feel happy most of the time? YES / **NO**
8. Do you often feel helpless? **YES** / NO
9. Do you prefer to stay at home, rather than going out and doing new things? **YES** / NO
10. Do you feel you have more problems with memory than most? **YES** / NO
11. Do you think it is wonderful to be alive now? YES / **NO**
12. Do you feel pretty worthless the way you are now? **YES** / NO
13. Do you feel full of energy? YES / **NO**
14. Do you feel that your situation is hopeless? **YES** / NO
15. Do you think that most people are better off than you are? **YES** / NO

Answers in bold indicate depression. Score 1 point for each bolded answer.

A score > 5 points is suggestive of depression.
A score ≥ 10 points is almost always indicative of depression

For each of the following assessments, (Functional assessment scale [FAS], Neuropsychiatric Inventory–Questionnaire [NPI-Q], Memory Assessment Questionnaire [MAC-Q]), sum the individual component scores to generate a summary score for each. If a response is NA or unknown, treat as missing. If at any given visit, the number of missing items within a questionnaire is less than 30% of the total number of items, then the score for this component at this visit will be calculated as the sum of the non-missing items multiplied by the ratio of the total number of items to the number of the non-missing items. If the number of missing items is equal to or greater than 30%, then the score at this visit is considered missing.

Values captured within the FAS as ‘not applicable (e.g., never did)’ (NA) will be treated as missing.

13.2 Sponsor’s Grading for Determining Markedly Abnormal Laboratory Results

The following table of Sponsor’s Grading for Laboratory Values is copied from the protocol, Appendix 1.

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 2.5×ULN if baseline was normal; 2.0 – 2.5×baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
ALT	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
AST	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN if baseline was normal; 1.0 – 1.5×baseline if baseline was abnormal	>1.5 – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 10.0×ULN if baseline was normal; 3.0 – 10.0×baseline if baseline was abnormal	>10.0×ULN if baseline was normal; >10.0×baseline if baseline was abnormal
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium <LLN - 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	<6.0 mg/dL <1.5 mmol/L Ionized calcium <0.8 mmol/L; life-threatening consequences
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium >ULN - 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	>13.5 mg/dL >3.4 mmol/L Ionized calcium >1.8 mmol/L; life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 - 3.0×baseline; >1.5 – 3.0×ULN	>3.0×baseline; >3.0 – 6.0×ULN	>6.0×ULN
Fibrinogen plasma-low	>125 - 175 mg/dL	>80 – 125 mg/dL	50- 80 mg/dL	<50 mg/dL
Fibrinogen plasma-high	425 - 500 mg/dL	>500 - 600 mg/dL	>600 - 700 mg/dL	> 700 mg/dL
GGT (γ-glutamyl transpeptidase)	>ULN – 2.5×ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Glucose, serum-high (hyperglycemia)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	life-threatening consequences; urgent intervention indicated
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L; intervention initiated	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	125-129 mmol/L and asymptomatic	<125 – 129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Uric acid, serum-high (hyperuricemia)	>ULN without physiologic consequences	N/A	>ULN with physiologic consequences	life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 5.0. Published: 27 Nov 2017.

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