16.1.9   Documentation of Statistical Methods

The final approved Statistical Analysis Plan and other statistical documents, as applicable, for this study are provided in the .

STATISTICAL ANALYSIS PLAN

Study Protocol Number: E5501-G000-310

Study Protocol Title: A Randomized, Global, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Once-daily Oral Avatrombopag for the Treatment of Adults with Thrombocytopenia Associated with Liver Disease Prior to an Elective Procedure

Date: Feb. 16, 2017

Version: Final 3.0

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1   TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ANOVA	analysis of variance
ATC	anatomical therapeutic class
BARC	Bleeding Academic Research Consortium
BCLC	Barcelona-Clinic Liver Cancer
BMI	body mass index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CTCAE	common terminology criteria for adverse events
CTP	Child-Turcotte-Pugh
DSMB	data safety monitoring board
ECG	electrocardiogram
FAS	full analysis set
HCC	hepatocellular carcinoma
LNH	low/normal/high
INR	international normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-stage Liver Disease
NI	non-inferiority
PD	pharmacodynamic
PK	pharmacokinetic
PP	per protocol analysis set
PT	preferred term
QTcB	corrected QT interval by Bazett's formula
QTcF	corrected QT interval by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	Système International
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TLG	tables, listings, and graphs
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary

Final 3.0, 16 Feb. 2017
Page 5 of 29
CONFIDENTIAL

Eisai
Confidential
Page 6 of 3365

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 E5501-G000-310 (Version 7.0), Amendment 4.

This document is prepared based on the study protocol (dated December 2, 2016). Reader is referred to the final study protocol, the case report form (CRF), general CRF completion guidelines for details of study design, conduct and data collection.

3.1 STUDY OBJECTIVES

3.1.1 Primary Objective(s)

The primary objective of the study is to confirm that avatrombopag (60 mg avatrombopag for subjects with platelet count $<40 \times 10^9$/L and 40 mg avatrombopag for subjects with platelet count from 40 to $<50 \times 10^9$/L) is superior to placebo in removing the need for platelet transfusions or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure in chronic liver disease patients who have thrombocytopenia.

3.1.2 Secondary Objective(s)

The secondary objectives of the study are:

- To confirm that avatrombopag is superior to placebo in achieving a platelet count of $\geq 50 \times 10^9$/L on Procedure Day in the proposed target population
- To confirm that avatrombopag is superior to placebo in elevating platelet counts from baseline on Procedure Day in the proposed target population
- To evaluate the safety of avatrombopag in the proposed target population

3.1.3 Exploratory Objective(s)

The exploratory objectives of the study are:

- To characterize the pharmacokinetics (PK) and the relationship between avatrombopag plasma concentrations and platelet count using the population approach
- To characterize platelet count changes from baseline, the extent of platelet transfusion use, evaluate the incidence of bleeding events, and assess the severity of any bleeding events
- To evaluate the health economic impact associated with minimizing the need for platelet transfusions and any rescue procedure for bleeding associated with an elective procedure

3.2 OVERALL STUDY DESIGN AND PLAN

E5501-G000-310 is a Phase 3, global, multicenter, randomized, double-blind, placebo-controlled, parallel group study using avatrombopag to treat adults with thrombocytopenia associated with liver disease prior to an elective procedure.

Subjects meeting all entry criteria will be enrolled into 2 cohorts according to mean baseline platelet count ($<40 \times 10^9$/L or from 40 to $<50 \times 10^9$/L). Within each cohort, subjects will be further stratified by the risk of bleeding associated with the elective procedure (low, moderate or high) and hepatocellular carcinoma (HCC) status (Yes or No). From previous studies, it is anticipated that the 2 baseline platelet count cohorts ($<40 \times 10^9$/L and from 40 to $<50 \times 10^9$/L) will be equally represented. However, neither baseline platelet count cohort will be permitted to comprise greater than 55% of the total number of subjects enrolled into the study.

Permitted procedures and the risk of bleeding associated with each procedure are listed in Table 1. It is planned that no fewer than 10% of subjects will be enrolled into the high risk group and no more than 60% of subjects in the low-risk group.

Table 1   Permitted Procedures and the Risk of Bleeding Associated with Each Procedure

Risk of Bleeding Associated with Procedure	Procedure
Low risk	Paracentesis
	Thoracentesis
	Gastrointestinal endoscopy with or without plans for biopsy, colonoscopy, polypectomy, or variceal banding
Moderate risk	Liver biopsy
	Bronchoscopy with or without plans for biopsy
	Ethanol ablation therapy or chemoembolization for HCC
High risk	Vascular catheterization (including right side procedures in subjects with pulmonary hypertension)
	Transjugular intrahepatic portosystemic shunt
	Dental procedures
	Renal biopsy
	Biliary interventions
	Nephrostomy tube placement
	Radiofrequency ablation
	Laparoscopic interventions

Level of risk based on key opinion leader (KOL) input and Malloy PC, Grassi CJ, Kundu S, Gervais DA, Miller DL, Osnis RB, et al. for the Standards of Practice Committee with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. J Vasc Interv Radiol 2009; 20:S240–9.

Within the **lower** baseline platelet count cohort ($<40 \times 10^9$/L) and each stratum, subjects will be randomized in a 2:1 ratio to receive avatrombopag or matching placebo as follows:

- 60 mg avatrombopag on Days 1 to 5 (Group A)

- Matching placebo on Days 1 to 5 (Group B)

Within the **higher** baseline platelet count cohort (from 40 to $<50 \times 10^9$/L) and each stratum, subjects will be randomized in a 2:1 ratio to receive avatrombopag or matching placebo as follows:

- 40 mg avatrombopag on Days 1 to 5 (Group C)

- Matching placebo on Days 1 to 5 (Group D)

Platelet counts must be measured on 2 separate occasions, during the Screening Period and at Baseline, and must be performed at least one day apart with neither platelet count $>60 \times 10^9$/L. The average of these 2 platelet counts will be used for entry criteria (the mean baseline platelet count of $<50 \times 10^9$/L). The elective surgical or diagnostic procedure is scheduled to be performed within 10 to 13 days of first dose of study drug.

This study will consist of 3 phases: Prerandomization, Randomization, and Follow-up Phases.

The Prerandomization Phase consists of a Screening Period (Visit 1) that will take place from Day -14 through Day -1. During this period, the type and schedule of the elective procedure will be confirmed.

The Randomization Phase includes the Baseline Period, Treatment Period, and Procedure Day. During the Baseline Period (Visit 2), subjects who have met all entry criteria, provided signed informed consent, and been randomized will be instructed to take study drug during the Treatment Period on Days 1 to 5. During the Treatment Period, subjects will come in for PK samplings on Day 4 (Visit 3). The elective procedure will be performed 5 to 8 days after last dose of study drug (Study Day 10 to 13) after all assessments on Visit 4 (Procedure Day) have been performed. The elective procedure for those subjects whose preprocedural platelet count is $>200 \times 10^9$/L on Visit 4 may be delayed at the discretion of the investigator until platelet counts are below 200×10^9/L. All subjects whose platelet count exceeds 200×10^9/L will be required to have a Doppler assessment at Visit 5.

The Follow-up Phase encompasses 2 visits: 7 days post Procedure Day (Visit 5) and 30 days after receiving the last dose of study drug (Visit 6).

An overview of the study design is presented in Figure 1
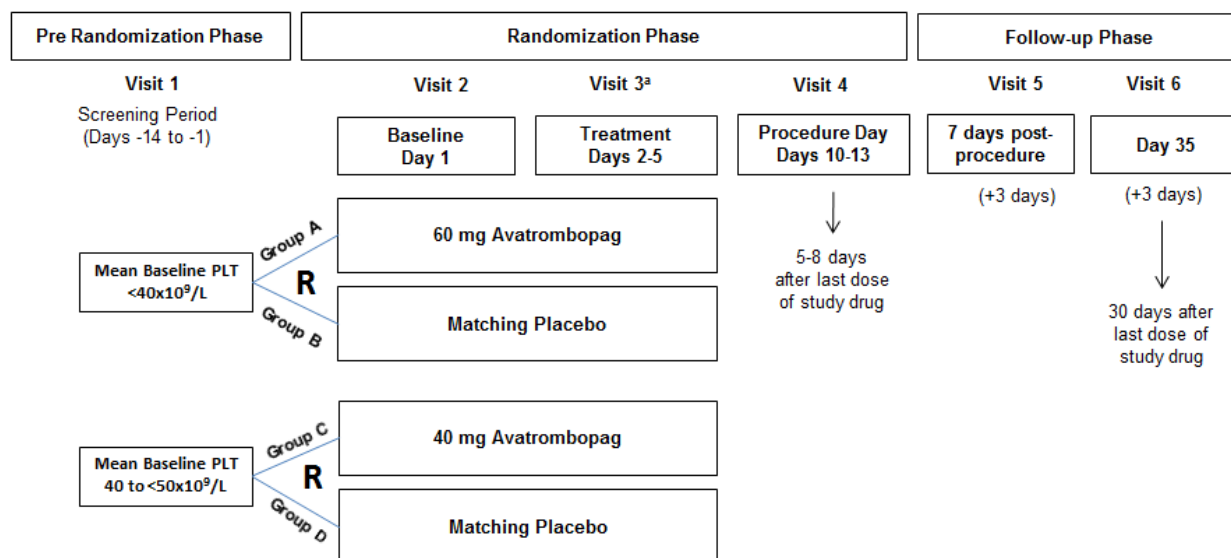
Figure 1   Study Design

PLT = platelet count; R = randomization

Platelet counts must be measured on 2 separate occasions, during the Screening Period and at Baseline, and must be performed at least one day apart with neither platelet count $>60 \times 10^9$/L. The mean of these 2 platelet counts (mean baseline platelet count $<50 \times 10^9$/L) will be used for entry criteria and determination of baseline platelet count.

a: Visit 3 occurs on Day 4 (±1 day) during the Treatment Period.

4   DETERMINATION OF SAMPLE SIZE

The proposed sample size was based on comparisons of the primary efficacy variable, with the response rate defined as the proportion of subjects who do not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. Based on clinical opinion and the published results of a similar compound in adults with thrombocytopenia associated with liver disease (ELtrombopag EValuated for its Ability to overcome Thrombocytopenia and Enable procedures [ELEVATE] study [*Afdahl, 2012*])[2], the response rate in the placebo group is assumed to be 18%. Within each baseline platelet count cohort, a sample size of 100 randomized subjects, 67 subjects for avatrombopag and 33 subjects for placebo, would have greater than 90% power to detect an absolute difference of 35% between the avatrombopag response rate and the placebo response rate assuming 18% response rate for placebo using Fisher's Exact tests with a 2-sided α=0.05. The hypothesized treatment group difference was based on platelet count changes found in the Phase 2 study (E5501-G000-202) and dose-response modeling using data from that study and others in the project development. Based on the baseline data in the Phase 2 study and assuming these were projected to be similar for this study, it was anticipated that this study would enroll roughly half of the total number of subjects in each of the 2 baseline platelet count cohorts to make the total sample size of 200 randomized subjects, 133 subjects for avatrombopag and 67 subjects for placebo.

5 STATISTICAL METHODS

Descriptive statistics will be reported for continuous variables using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized using frequency count as number (percentage) of subjects. Graphical displays of the data might be presented where appropriate to aid interpretation.

5.1 STUDY ENDPOINTS

5.1.1 Primary Endpoint(s)

The primary efficacy endpoint is the proportion of subjects who do not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure.

5.1.2 Secondary Endpoint(s)

The secondary efficacy endpoints are:

- Proportion of responders defined as subjects who achieve platelet counts of $\geq 50 \times 10^9$/L on Procedure Day (i.e., prior to receiving a platelet transfusion or undergoing the elective procedure)

- Change from baseline in platelet count on Procedure Day (i.e., prior to receiving a platelet transfusion or undergoing the elective procedure)

5.1.3 Exploratory Endpoint(s)

The exploratory endpoints are:

- Platelet count and change from baseline in platelet count at each visit

- Proportion of responders defined as subjects who achieve platelet counts of $\geq 50 \times 10^9$/L, $\geq 75 \times 10^9$/L, or $\geq 200 \times 10^9$/L at each visit

- Number of platelet units used per platelet transfusion episode

- Severity of bleeding event assessed by WHO bleeding score and Bleeding Academic Research Consortium (BARC) bleeding scale

- Proportion of subjects with a WHO bleeding score ≥ 2 after randomization and up to 7 days following an elective procedure

- Health economics assessed by resource use

Final 3.0, 16 Feb. 2017

Page 11 of 29
CONFIDENTIAL

Eisai

Confidential

Page 12 of 3365

5.2   STUDY SUBJECTS

5.2.1   Definitions of Analysis Sets

Full Analysis Set (FAS):   The FAS is the group of all subjects who are randomized into the study.

Per Protocol Analysis Set (PP):   The PP is the group of all randomized subjects who receive protocol-assigned study drug and do not meet any of the following criteria:

- Baseline platelet count of $>50 \times 10^9$/L
- Subjects who were enrolled in the study despite not being planned for transfusion even in the event of no significant increase of platelet count
- Taking prohibited prior medications or prior transfusion
- Presence of significant bleeding at baseline
- Did not have a protocol permitted procedure on Day 8 - 15
- Received dose different from the intended dose
- Received <80% of the total dose or received >40% of total dose without food
- No elective procedures or elective procedure outside day 8-15
- Subject received platelet transfusion before knowing V4 platelet count
- Subject refused platelet transfusion

Subjects who met any of the criteria listed above will be excluded from the PP due to possible introduction of bias.

Safety Analysis Set: The Safety Analysis Set is the group of subjects who receive at least one dose of study drug and have at least one post dose safety assessment.

The number (percentage) of subjects in each analysis set will be summarized by treatment groups using descriptive statistics.   The summaries for FAS and PP will be based on subjects "as randomized".   The summary for Safety Analysis Set will be based on subjects "as treated".

5.2.2   Subject Disposition

Subject disposition will be summarized by treatment group for FAS and the Safety Analysis Set. The number (percentage) of subjects who completed or discontinued prematurely from the study and their reason for discontinuation will be summarized by treatment group.   In addition, the number of subjects screened and the number and percentage of subjects who failed screening and the reasons for screen failure will be summarized, based on data recorded on the Screening Disposition CRF.

5.2.3 Protocol Deviations

Major protocol deviations will be identified, reviewed and documented by the clinical team prior to database lock/treatment unblinding. All protocol deviations will be categorized according to standard classifications including the following:

- Violations of inclusion/exclusion criteria

- Noncompliance with protocol procedures/assessments

- Noncompliance of drug dosage

- Use of prohibited treatments

All significant protocol deviations will be listed, and summarized by category and by treatment group.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and Safety Analysis set will be summarized for each treatment group and overall using descriptive statistics or frequency count. Continuous demographic variables include age, weight, height and body mass index (BMI); categorical variables include age group (<65, and ≥65 years old), sex, ethnicity, race, region and country. The following baseline disease characteristics will also be summarized:

- Baseline platelet count and its category ($<40 \times 10^9$/L and 40 to $<50 \times 10^9$/L)

- Bleeding risk associated with the elective procedure (low, moderate and high based on Amendment 02 categorization) and the type of elective procedure

- HCC status (yes and no) and Barcelona-Clinic Liver Cancer (BCLC) stage (0, A, B, C and D)

- Model for End-stage Liver Disease (MELD) score

- Child-Turcotte-Pugh (CTP) score and CTP grade (A, B and C)

- Baseline international normalized ratio (INR) and its category (≤1.6 and >1.6)

- Portal vein flow rate as per Doppler Sonography assessment

- Creatinine clearance and disease etiology.

MEDICAL HISTORY

All medical histories as documented by the Investigator will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The number (percentage) of subjects reporting a history of any medical condition will be summarized by System Organ Class (SOC), preferred term for each treatment group and overall based on FAS.

Final 3.0, 16 Feb. 2017

Page 13 of 29
CONFIDENTIAL

Eisai

Confidential

Page 14 of 3365

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded on the CRF will be coded using the WHO Drug Dictionary (WHO DD).

Prior medications are defined as medications that stop prior to the first dose of study drug. Concomitant medications are defined as medications that (1) start before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) start on or after the date of the first dose of study drug, up to 30 days after the last dose of study drug.

The number (percentage) of subjects who take prior and concomitant medications will be summarized using the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical (ATC) Classification, and WHO DD preferred term. In addition, the number (percentage) of subjects who take the concomitant medications associated with elective procedures will also be summarized using the Safety Analysis Set by treatment group, ATC Classification, and WHO DD preferred term.

If a subject takes the same medications for the same class level or drug name, the subject will be counted only once for that class level or drug name.

5.2.6 Treatment Compliance

Treatment compliance is defined as follows:

$$\frac{\text{Total number of tablets dispensed} - \text{total number of tablets returned}}{\text{Total number of tablets subject should have taken}}$$

Treatment compliance will be summarized using descriptive statistics by treatment group based on FAS and Safety Analysis Set. Treatment compliance will also be summarized by treatment group using the categories <80%, ≥80% to ≤100%, >100% to ≤120%, and >120%.

5.3 DATA ANALYSIS GENERAL CONSIDERATIONS

The FAS will be used as the primary population for all efficacy analyses, while the PP will be used in supportive analyses of the primary efficacy endpoint and Safety analysis set will be used for all safety analyses. Unless stated otherwise, all efficacy analyses will be performed at α=0.05 significance level and only descriptive statistics or frequency count will be generated for safety analyses without any hypothesis testing.

5.3.1 Pooling of Centers

This study is a multicenter international study with an estimated 100 centers participating in the study. Due to small expected number of subjects in each center, all analyses will be performed with all centers pooled across the study unless stated otherwise. Consistency of results across geographic regions will be examined as specified in the respective sections in this document.

5.3.2 Adjustments for Covariates

The primary efficacy endpoint, the proportion of subjects without platelet transfusion or any rescue procedure for bleeding, and the first secondary efficacy endpoint, proportion of subjects with platelet count $\geq 50 \times 10^9$/L on Procedure Day, will be analysed separately within each

baseline platelet count cohort ($<40 \times 10^9$/L or from 40 to $<50 \times 10^9$/L) using the Cochran-Mantel-Haenszel (CMH) test adjusting for the risk of bleeding associated with the elective procedure (low, moderate, or high based on Amendment 02 categorization). Since the HCC status is included in the randomization stratification for safety purposes only, not for efficacy consideration, HCC will not be included in the CMH model for the primary efficacy analysis.

5.3.3 Multiple Comparisons/Multiplicity

The primary efficacy endpoint will be tested between the individual avatrombopag treatment group (40 or 60 mg) and matching placebo within each baseline platelet count cohort ($<40 \times 10^9$/L or from 40 to $<50 \times 10^9$/L), each at a significance level of $\alpha=0.05$. The primary efficacy endpoint is considered positive only if the tests are statistically significant for both baseline platelet count cohorts to control the family-wise Type I error rate at a significance level of $\alpha=0.05$.

A sequential gatekeeping testing procedure will be used for the secondary efficacy endpoints to control the family-wise Type I error rate at a significance level of $\alpha=0.05$. The secondary efficacy endpoints will be analyzed if the primary efficacy endpoint is statistically significant for both baseline platelet count cohorts. The first secondary efficacy endpoint is tested first within each baseline platelet count cohort, each at a significance level of $\alpha=0.05$. Only if the first secondary efficacy endpoint is statistically significant for both baseline platelet count cohorts, the analysis of second secondary efficacy endpoint will proceed within each baseline platelet count cohort, each at a significance level of $\alpha=0.05$. No alpha adjustment is planned for other efficacy endpoints.

5.3.4 Examination of Subgroups

Subgroup analysis of primary efficacy endpoint will be performed using age group (<65 and ≥65 years old), sex (male and female), race (white, black, Asian, and other), geographic region, bleeding risk associated with procedure (low, moderate, and high based on Amendment 02 categorization), MELD score (<10, 10-14, and >14), and CTP grade (A, B, and C). Additional subgroup analysis may also be explored, if deemed appropriate.

5.3.5 Handling of Missing Data, Drop-outs, and Outliers

Unless stated otherwise, missing values will be considered as non-responders in responder analyses for all efficacy analyses; observed data will be used in other type of efficacy analyses. Details can be found in Sections 5.4, Efficacy Analyses.

All safety analyses will be performed based on the observed data only.

5.3.6 Other Considerations

None

5.4   EFFICACY ANALYSES

The FAS will be used as the primary population for the efficacy analyses, while the PP will be used as a supportive analysis. All analyses of platelet counts will be based on local laboratory results.

5.4.1   Primary Efficacy Analyses

The primary efficacy variable is the proportion of subjects who do not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure.

The null hypothesis is that the proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure is the same between the avatrombopag and placebo treatment groups. The corresponding alternative hypothesis is that the proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure is not the same between avatrombopag and placebo. This hypothesis will be tested separately with each baseline platelet count cohort.

The proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding will be tested between the individual avatrombopag treatment group (40 or 60mg) and matching placebo within each baseline platelet count cohort ($<40 \times 10^9$/L or from 40 to $<50 \times 10^9$/L), each at a significance level of $\alpha=0.05$ using the generalized Cochran Mantel Haenszel (CMH) test adjusting for the risk of bleeding associated with the elective procedure (low, moderate, or high based on Amendment 02 categorization).

- For subjects with platelet count $<40 \times 10^9$/L at baseline, the treatment comparison will be carried out between the 60 mg avatrombopag treatment group (Group A) versus matching placebo (Group B).

- For subjects with platelet count from 40 to $<50 \times 10^9$/L at baseline, the treatment comparison will be carried out between the 40 mg avatrombopag treatment group (Group C) versus matching placebo (Group D).

This study will be considered as positive if statistical significance is achieved for primary efficacy endpoints for both baseline platelet count cohorts.

The 95% CI for the proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding will be calculated for each treatment group within each baseline platelet count cohort. In addition, the 95% CI for the difference between avatrombopag and matching placebo will also be provided within each baseline platelet count cohort using normal approximation method.

Since the HCC status is included in the randomization stratification for safety purposes only, not for efficacy consideration, HCC will not be included in the CMH model for the primary efficacy analysis.

Subjects with missing information about the primary efficacy outcome due to early withdrawal or other reasons will be considered as having received a transfusion for the primary analysis.

5.4.1.1   Sensitivity Analysis

The following analyses will be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described in Section 5.4.1 will be repeated based on the PP analysis set.

- Observed case: The same primary efficacy analyses described in Section 5.4.1 will be repeated based on observed data. Subjects with missing information about the primary efficacy outcome will be excluded from this analysis.

- Fisher's exact Test: The same primary efficacy analyses described in Section 5.4.1 will be carried out using Fisher's exact test.

- Modified primary efficacy endpoint: Proportion of subjects who do not require a platelet transfusion after randomization and up to 7 days following an elective procedure. This efficacy endpoint will be analyzed using the same approach as primary efficacy analysis using FAS

Additional sensitivity analyses may also be explored, if deemed appropriate.

5.4.1.2   Subgroup Analysis

The primary efficacy variable described in Section 5.4.1 will be summarized by each subgroup listed below.

- age group (<65 and ≥65 years old)
- sex (male and female)
- race (white, black, Asian and other)
- geographic region
- bleeding risk associated with the elective procedure (low, moderate and high based on Amendment 02 categorization)
- MELD score (<10, 10-14, and >14)
- CTP grade (A, B, and C)
- Disease etiology (alcoholic liver disease, chronic viral disease, nonalcoholic steatohepatitis, other)

Additional subgroups may also be explored, if deemed appropriate.

5.4.2   Secondary Efficacy Analyses

There are 2 secondary efficacy endpoints in this study:

- Proportion of responders, defined as subjects who achieve target platelet counts of $\geq 50 \times 10^9$/L on Procedure Day (prior to receiving a platelet transfusion or undergoing the elective procedure)

- Change from baseline in platelet count on Procedure Day (prior to receiving a platelet transfusion or undergoing the elective procedure)

The analysis of the secondary efficacy variables, as defined above, will proceed following a sequential gatekeeping testing procedure to control the family-wise Type I error rate at a significance level of α=0.05.

5.4.2.1   Proportion of subjects achieved platelet counts of $\geq 50 \times 10^9$/L on the Procedure Day

The proportion of subjects who achieve platelet counts of $\geq 50 \times 10^9$/L on the Procedure Day will be analyzed first.

The proportion of subjects with platelet counts of $\geq 50 \times 10^9$/L on the Procedure Day will be tested between the individual avatrombopag treatment group (40 or 60mg) and matching placebo separately within each baseline platelet count cohort ($<40 \times 10^9$/L or from 40 to $<50 \times 10^9$/L), each at a significance level of α=0.05 using the generalized CMH test adjusting for the risk of bleeding associated with the elective procedure (low, moderate, or high based on Amendment 02 categorization).

The 95% CI for the proportion of subjects with platelet counts of $\geq 50 \times 10^9$/L on the Procedure Day will be calculated for each treatment group within each baseline platelet count cohort. In addition, the 95% CI for the difference between avatrombopag and placebo will also be provided within each baseline platelet count cohort using normal approximation method.

Subjects with missing platelet count on Procedure Day will be considered as not achieving the platelet count of $\geq 50 \times 10^9$/L for this analysis.

5.4.2.2   Change from baseline in platelet count on the Procedure Day

The second secondary efficacy variable, change from baseline in platelet count on the Procedure Day, will be analyzed only if the first secondary efficacy variable is statistically significant for both baseline platelet count cohorts.

The change from baseline in platelet count on Procedure Day will be analyzed using the Wilcoxon rank sum test separately within each baseline platelet count cohort ($<40 \times 10^9$/L or from 40 to $<50 \times 10^9$/L), each at a significance level of α=0.05. The treatment difference

between avatrombopag and placebo will be provided within each baseline platelet count cohort using Hodges-Lehmann estimation along with associated asymptotic (Moses) 95% CIs.

Last observation carried forward will be used for subjects with missing platelet count on Procedure Day for this analysis.

5.4.3 Other Efficacy Analyses

The following efficacy analyses are for exploratory purpose only.

5.4.3.1 Platelet count and change from baseline in platelet count at each visit

Platelet count and change from baseline in platelet count will be compared between individual avatrombopag (40 or 60mg) and matching placebo separately within each baseline platelet count cohort at a significance level of α=0.05, using the Wilcoxon rank sum test based on observed data. Missing values will not be imputed.

5.4.3.2 Proportion of responders defined as subjects who achieve platelet counts of $\geq 50 \times 10^9$/L, $\geq 75 \times 10^9$/L, or $\geq 200 \times 10^9$/L at each visit

The number and percentage of responders will be summarized by treatment group within each baseline platelet count cohort at each visit. Missing values will not be imputed.

5.4.3.3 Number of platelet units used per platelet transfusion episode

The average number of platelet units used per platelet transfusion episode will be summarized by treatment group within each baseline platelet count cohort using descriptive statistics for subjects require platelet transfusion.

5.4.3.4 Severity of bleeding event assessed by WHO bleeding score and BARC bleeding scale

The number and percentages of subjects with bleeding events will be summarized by the highest bleeding score and by treatment group within each baseline platelet count cohort, separately for WHO bleeding score and BARC bleeding scale.

5.4.3.5 Proportion of subjects with a WHO bleeding score ≥2 after randomization and up to 7 days following an elective procedure

Proportion of subjects with a WHO bleeding score ≥2 after randomization and up to 7 days following an elective procedure, will be summarized by treatment group within each baseline cohort, and by overall treatment groups, regardless of the baseline platelet count cohorts.

A 2-sided 95% CI will be constructed by baseline cohort, and for the overall treatment difference (avatrombopag minus placebo) using normal approximation method for the proportion of subjects with the qualified WHO bleeding score.

Subjects with missing WHO bleeding score will be considered as having a WHO bleeding score ≥2 in this analysis.

Final 3.0, 16 Feb. 2017

Page 19 of 29
CONFIDENTIAL

Eisai

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Page 20 of 3365

5.5 PHARMACOKINETIC , PHARMACODYNAMIC, AND PHARMACOGENOMIC/PHARMACOGENETIC ANALYSES

Population pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) analysis are specified in the protocol but will not be discussed in this SAP. Separate analysis plan(s) for these analyses will be developed and finalized before the database lock.

5.5.1 Pharmacokinetic Analyses

Not Applicable.

5.5.2 Pharmacodynamic Analyses

Not Applicable.

5.5.3 Pharmacogenomic/Pharmacogenetic Analyses

Not Applicable.

5.6 SAFETY ANALYSES

All safety analyses will be performed on the Safety Analysis Set. Unless specified, all safety assessments will be summarized both overall (regardless of baseline platelet count) and within each baseline platelet count cohort. Safety data, presented by treatment group, will be summarized on an "as treated" basis using descriptive statistics or frequency count.

Study Day 1 for all safety analyses is defined as the date of the first dose of study drug. Unless specified otherwise, the baseline value will be defined as the most recent value reported prior to the first dose of study drug.

5.6.1 Extent of Exposure

The extent of exposure to study drug will be characterized by duration of exposure (in days) for each treatment group.

Duration of exposure will be defined as the number of days between the date the subject received the first dose of study drug and the date the subject received the last dose of study drug, inclusive. Duration of exposure will be summarized using descriptive statistics by treatment group. In addition, the duration of exposure will be categorized, and will be summarized using frequency count by treatment group.

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 15.1 or higher) 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 AE (TEAE) is defined as an AE that

- Emerged during treatment (up to 30 days after the last dose of study drug), having been absent at pretreatment (Baseline) or

- Reemerged during treatment (up to 30 days after the last dose of study drug), having been present at pretreatment (Baseline) but stopped before the last dose of study drug plus 30 days, or

- Worsened in severity during treatment (up to 30 days after the last dose of study drug) relative to the pretreatment state, when the AE was continuous.

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.

An overview table of TEAE, including number of subjects with TEAEs, treatment-emergent serious adverse events (SAEs), deaths, severe TEAEs, study drug related TEAEs, TEAEs leading to study drug withdrawal will be provided. In addition, the following summaries will be produced:

- Incidence of TEAEs by SOC and PT

- Incidence of treatment-related TEAEs by SOC and PT

- Incidence of procedure-related TEAEs by SOC and PT

- Incidence of TEAEs after procedure (with an onset date on or after Procedure Day) by SOC and PT

- Incidence of TEAEs related to platelet transfusion complications by SOC and PT

- Incidence of TEAEs by SOC, PT, and common terminology criteria for adverse events (CTCAE) grade

- Incidence of treatment-related TEAEs by SOC, PT, and CTCAE grade

- Incidence of TEAEs by SOC, PT, and relationship to treatment

If a subject experiences more than one TEAE within a preferred term, the subject will be counted only once in the calculation of incidence of TEAE within that preferred term. Similarly, if a subject experiences more than one TEAE within a SOC, the subject will be counted only once in the calculation of incidence of TEAE within that SOC. If a subject experiences more than one TEAE within a preferred term (or SOC), the occurrence with the highest CTCAE grade will be used in the calculation of the incidence of TEAE within that preferred term (SOC) by CTCAE grade. If a subject experiences more than one TEAE within a preferred term (or SOC), the occurrence considered most closely related to study drug will be used in the calculation of the incidence of TEAE with that preferred term (SOC) by relationship (given by investigator).

The following summaries will also be presented for the treatment-emergent SAEs:

- Incidence of treatment-emergent SAEs by SOC and PT

- Incidence of treatment-related treatment-emergent SAEs by SOC and PT

- Incidence of treatment-emergent SAEs by SOC, PT, and relationship to treatment.

In addition, number (percentage) of subjects with TEAEs and treatment-related TEAEs leading to discontinuation from study treatment will also be summarized by MedDRA SOC, PT for each treatment group.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. With the exception of urinalysis, platelet function tests and platelet count (which is considered as an efficacy parameter),for all quantitative parameters listed in protocol Section 9.5.1.5 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline will be summarized by visit and treatment group using descriptive statistics. Analysis of changes from baseline will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value is below (L), within (N), or above (H) the laboratory parameter's reference range. Shifts from baseline (LNH) to Procedure Day and to the end of the Follow-up Phase will be presented for each laboratory parameter. Similar shift tables from baseline (LNH) to the highest/lowest postbaseline LNH classification will also be provided. A subject will be counted once in highest LNH classification and once in the lowest LNH classification.

The Sponsor's Grading for Laboratory Values (see Appendix 1) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). 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 was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject will be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

5.6.4 Vital Signs

For each vital signs parameters (diastolic and systolic blood pressure, pulse, respiration rate, temperature and weight), the actual value and changes from baseline will be summarized by visit and treatment group using descriptive statistics. Analysis of changes from baseline will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

5.6.5 Electrocardiograms

For each electrocardiogram (ECG) parameter (including PR interval, RR interval, QRS interval, QT interval, QTcB interval, QTcF interval and heart rate), the actual value and change from baseline will be summarized by visit and treatment group using descriptive statistics. ECG interpretation (categorized as normal and abnormal) will be summarized using frequency count at each visit by treatment group.

Maximum postbaseline QTcB and QTcF will also be tabulated by treatment group as follows:

- Number and percentage of subjects in the borderline (430-450 msec), abnormal category (> 450 msec), and highly abnormal (>500 msec) during the treatment, and

- Number and percentage of subjects with an increment of 30-60 msec and > 60 msec from the baseline visit.

QT will be corrected primarily using Fridericia's formula (QTcF) and also using Bazett's formula (QTcB) defined as:

- QTcF is the heart rate corrected QT interval by Fridericia's formula: $QTcF = QT/(RR)^{0.33}$

- QTcB is the heart rate corrected QT interval by Bazett's formula: $QTcB = QT/(RR)^{0.5}$.

5.6.6 Other Safety Analyses

5.6.6.1 Adverse Events of Special Interest

The incidence of treatment-emergent adverse events and treatment-related, treatment-emergent adverse events of special interest will be summarized by treatment group.
Adverse events of special interest include:

- Recurrence of thrombocytopenia (platelet count of $<10 \times 10^9$/L and 10×10^9/L less than baseline count within 30 days of discontinuation)
- Thromboembolic events
- Bleeding events (WHO Grade 2 to 4)

Recurrence of thrombocytopenia events include the adverse events with MedDRA preferred term belonging to 2nd level Standardized MedDRA Query (SMQ) 'Haematopoietic thrombocytopenia' and with 'Event of Special Interest per Protocol Definition' checked as 'Yes' on the AE CRF page.

Thromboembolic events include the adverse events with MedDRA preferred term belonging to SMQ 'Embolic and thrombotic events'.

Bleeding events (WHO Grade 2 to 4) include the adverse events with MedDRA preferred term belonging to 2nd level SMQ 'Haemorrhage terms (excl laboratory terms)' and with WHO Bleeding Scale score 2 to 4.

Additionally the incidence of treatment-emergent adverse events and treatment-related, treatment-emergent adverse events for thromboembolic events will be summarized by treatment group and by HCC status.

5.6.6.2 Doppler Sonography

The results from Doppler Sonography will be presented in the listings only.

5.6.6.3 Platelet Function Test

For each parameter of platelet function assessed via flow cytometric markers, the actual value and changes from baseline will be summarized by visit and treatment group using descriptive

statistics. Analysis of changes from baseline will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Only listings will be provided for platelet function assessed using platelet aggregometry.

5.7 OTHER ANALYSES

5.7.1 Health Outcome Economics Analyses

Health outcome economics data will be listed in the subject data listings only.

5.8 EXPLORATORY ANALYSES

Exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriately titled/labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

5.9 EXTENSION PHASE ANALYSES

Not applicable.

6 INTERIM ANALYSES

No interim efficacy analysis is planned for this study, and therefore no adjustment of the *P*-value for the final efficacy analysis is needed. However, to protect subjects' safety, an independent DSMB will be established to monitor the ongoing safety data in unblinded manner. To maintain the blinding of DSMB members on the efficacy data, no platelet transfusion data, by-subject listing on platelet count, and by-visit summary on platelet count and change from baseline in platelet count will be sent to DSMB. The only information DSMB will receive on platelet count is the percentage of subjects with extreme values (eg, exceeds 200 x 10^9/L) for safety reason. The DSMB safety interim analysis will be performed by an independent statistician and governed by an external DSMB. To maintain the blinding and integrity of the study, procedures will be implemented to ensure the DSMB and independent statistician have sole access to unblinded interim safety data.

Full details of the DSMB procedures including primary responsibilities of the DSMB, its relationship with other study components, its membership, and the purpose and timings of its meetings will be documented in a DSMB charter. These details will also include procedures to ensure confidentiality and proper communication, the guidelines to be implemented by the DSMB, and an outline of the content of the closed reports (unblinded) and open reports (blinded) that will be provided to the DSMB.

7 CHANGES IN THE PLANNED ANALYSES

SAP version (Final 3.0) is updated based on Protocol Amendment 04 with the following changes:

- Sections 3.1.2, 3.1.3, 5.1.2, 5.1.3, 5.3.3.1, 5.4.2, 5.4.2.3, 5.4.3 and 5.4.3.5: Efficacy endpoint "Proportion of subjects with a WHO bleeding score ≥2 after randomization and

up to 7 days following an elective procedure" is moved from secondary to exploratory endpoint to match the protocol amendment 4. These sections have been updated to reflect this change.

- Section 4: Sample size is reduced from 300 to 200. This section has been updated to match the protocol amendment 4.

- Section 5.4.2.2: Calculation of 95% CI for change from baseline in platelet count on Procedure Day for each treatment group within each baseline platelet count cohort has been removed to ensure consistency with the study objectives.

- Section 5.7.1: This section is updated to reflect that only listings will be provided for the Health Economics Assessment.

- Section 5.2.1: Per-Protocol exclusion criteria are finalized.

SAP version (Final 2.0) was updated based on Protocol Amendment 02 with the following changes:

- Section 3.2 table 1, and sections 5.2.4, 5.3.2, 5.3.4, 5.4.1, 5.4.1.2 and 5.4.2.1: Categorization of risk of bleeding is updated to match protocol amendment 02

- Section 5.6.6.3: Listing of platelet function test assessed using platelet aggregometry has been added.

- Section 13.1: "Fasting Glucose value" has been added to the criteria for determining grade 3 and 4 in the lab grading table.

SAP version (Final 2.0) was also updated from version Final 1.0 to ensure consistency with the eCRF/protocol as follows:

- Section 5.6.5: ECG interpretation category is updated.

- Section 5.2.4: Baseline summaries of creatinine clearance and disease etiology, and subgroup analysis by disease etiology have been added.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 VISIT WINDOW

Study Day 1 is defined as the date of the first dose of study drug. The analysis visits defined below will be used in the by-visit summaries:

Visit	Target Visit Date	Visit Window	Analysis Visit
Visit 2 (Baseline)	Study Day 1	Less or equal to Study Day 1	Last visit on or before Study Day 1
Visit 3	Study Day 4	Study Day 2 to 7	Closest visit to Study Day 4
Visit 4	Study Day	Subjects with procedure:	Subjects with platelet

Final 3.0, 16 Feb. 2017

Page 25 of 29
CONFIDENTIAL

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Page 26 of 3365

Visit	Target Visit Date	Visit Window	Analysis Visit
(Procedure Day)	10 to 13	Study Day 8 to actual procedure day Subjects without procedure: Study Day 8 to 13	transfusion: last visit before transfusion Subjects with procedure but without transfusion: last visit before procedure Subjects without platelet transfusion or procedure: closest visit to Study Day 10
Visit 5	7 Days post procedure	Subjects with procedure: 1 to 10 days post actual procedure day Subjects without procedure: Study Day 14 to 20	Subjects with procedure: visit closest to 7 days post actual procedure day Subjects without procedure: closest visit to Study Day 17
Visit 6	Study Day 35	Subjects with procedure: Greater or equal to actual procedure day +11 days Subject without procedure: Greater or equal to Study Day 21	Closest visit to Study Day 35

8.2 MISSING DATA HANDLING

For the responder analysis of primary and secondary efficacy endpoints, subjects without the required platelet transfusion data or platelet count data will be considered as non-responders. For other efficacy analyses, unless specified otherwise, observed data will be used without missing data imputation. Details can be found in Sections 5.4, Efficacy Analyses.

Safety data will be analyzed using observed data with no imputation for missing values.

9 PROGRAMMING SPECIFICATIONS

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

10 STATISTICAL SOFTWARE

All data analyses will be performed by Eisai Inc. or designee. Statistical analyses and summaries will be performed using SAS® or other validated statistical software as required.

Final 3.0, 16 Feb. 2017

Page 26 of 29
CONFIDENTIAL

Eisai
Confidential
Page 27 of 3365

11   MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

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

1. Malloy PC, Grassi CJ, Kundu S, Gervais DA, Miller DL, Osnis RB, et al. for the Standards of Practice Committee with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement. Consensus Guidelines for Periprocedural Management of Coagulation Status and Hemostasis Risk in Percutaneous Image-guided Interventions. J Vasc Interv Radiol 2009; 20:S240–S249.
2. Afdhal NH, Giannini EG, Tayyab G, Mohsin A, Lee JW, Andriulli A, Jeffers L, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. N Engl J Med. 2012;367:716-724.

13 APPENDICES

13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

	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 x 10^9/L < LLN – 3000/mm^3	< 3.0 – 2.0 x 10^9/L < 3000 – 2000/mm^3	< 2.0 – 1.0 x 10^9/L < 2000 – 1000/mm^3	< 1.0 x 10^9/L < 1000/mm^3
Lymphocytes	< LLN – 800/mm^3 < LLN – 0.8 x 10^9/L	< 800 – 500/mm^3 < 0.8 – 0.5 x 10^9/L	< 500 – 200/mm^3 < 0.5 – 0.2 x 10^9/L	< 200/mm^3 < 0.2 x 10^9/L
Neutrophils	< LLN – 1.5 x 10^9/L < LLN – 1500/mm^3	< 1.5 – 1.0 x 10^9/L < 1500 – 1000/mm^3	< 1.0 – 0.5 x 10^9/L < 1000 – 500/mm^3	< 0.5 x 10^9/L < 500/mm^3
Platelets	< LLN – 75.0 x 10^9/L < LLN – 75,000/mm^3	< 75.0 – 50.0 x 10^9/L < 75,000 – 50,000/mm^3	< 50.0 – 25.0 x 10^9/L < 50,000 – 25,000/mm^3	< 25.0 x 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 – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
ALT	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
AST	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Bicarbonate, serum-low	< LLN – 16 mmol/L	< 16 – 11 mmol/L	<11 – 8 mmol/L	< 8 mmol/L
Bilirubin (hyperbilirubinemia)	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN
Calcium, serum-low (hypocalcemia)	< LLN – 8.0 mg/dL < LLN – 2.0 mmol/L	< 8.0 – 7.0 mg/dL < 2.0 – 1.75 mmol/L	< 7.0 – 6.0 mg/dL < 1.75 – 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Calcium, serum-high (hypercalcemia)	> ULN – 11.5 mg/dL > ULN – 2.9 mmol/L	> 11.5 – 12.5 mg/dL > 2.9 – 3.1 mmol/L	> 12.5 – 13.5 mg/dL > 3.1 – 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
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 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN
GGT (γ-Glutamyl transpeptidase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: > ULN – 160 mg/dL > ULN – 8.9 mmol/L	Fasting glucose value: > 160 – 250 mg/dL > 8.9 – 13.9 mmol/L	Fasting glucose value: > 250 – 500 mg/dL; > 13.9 – 27.8 mmol/L; hospitalization indicated	Fasting glucose value: > 500 mg/dL; > 27.8 mmol/L; life-threatening consequences
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)	< LLN – 2.5 mg/dL < LLN – 0.8 mmol/L	< 2.5 – 2.0 mg/dL < 0.8 – 0.6 mmol/L	< 2.0 – 1.0 mg/dL < 0.6 – 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L 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	> 155 – 160 mmol/L hospitalization indicated	> 160 mmol/L life-threatening consequences

	Grade 1	Grade 2	Grade 3	Grade 4
Sodium, serum-low (hyponatremia)	< LLN – 130 mmol/L	N/A	< 130 – 120 mmol/L	< 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
Uric acid, serum-high (hyperuricemia)	> ULN – 10 mg/dL ≤ 0.59 mmol/L without physiologic consequences	N/A	> ULN – 10 mg/dL ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dL > 0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, 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 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).