
# STATISTICAL ANALYSIS PLAN

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|---|---|
| **Study Protocol Number:** | E7080-G000-207 |
| **Study Protocol Title:** | Phase 1/2 Study of Lenvatinib in Children and Adolescents With Refractory or Relapsed Solid Malignancies and Young Adults with Osteosarcoma |
| **Date:** | 26 Mar 2019 |
| **Version:** | Final 1.0 |

# 1 TABLE OF CONTENTS

# 2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term or Definition |
|---|---|
| AE | adverse event |
| AESI | adverse events of special interest |
| ATC | Anatomical Therapeutic Chemical classification |
| BLQ | below limit of quantification |
| BMI | body mass index |
| BOR | best overall response |
| BSA | body surface area |
| CBR | clinical benefit rate |
| CI | confidence interval |
| CR | complete response |
| CRF | case report form |
| CSAE | clinically significant adverse events |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | coefficient of variation |
| DBP | diastolic blood pressure |
| DCR | disease control rate |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| DTC | differentiated thyroid cancer |
| ECG | electrocardiogram |
| ECOG PS | Eastern Cooperative Oncology Group performance status |
| FDA | Food and Drug Administration |
| eCRF | electronic case report form |
| KM | Kaplan-Meier |
| KPS | Karnofsy performance status |
| LLN | lower limit of normal |
| LVEF | left ventricular ejection fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NA | not applicable |
| NE | not evaluable |
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |

| Abbreviation | Term or Definition |
|---|---|
| PFS-4 | progression-free survival at 4 months |
| PK | pharmacokinetic |
| PR | partial response |
| PSC | Protocol Steering Committee |
| PT | preferred term |
| q6w | every 6 weeks |
| q8w | every 8 weeks |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RD | recommended dose |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SBP | systolic blood pressure |
| SD | stable disease / standard deviation |
| SI | Système International |
| SOC | system organ class |
| TEAE | treatment-emergent adverse event |
| TiTE-CRM | time-to-event continual-reassessment method |
| TLG | Tables, Listings, and Graphs |
| TNM | tumor, node, metastasis staging system |
| TTP | time to progression |
| ULN | upper limit of normal |
| VEGF | vascular endothelial growth factor |
| VEGFR | vascular endothelial growth factor receptor |
| 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 the results for Phases 1 and 2 of Eisai Study E7080-G000-207. This SAP is based on Protocol V3.0 Amendment 03 (dated 1 Sep 2016) and final electronic Case Report Form (eCRF) (17 Oct 2018).

## 3.1 Study Objectives

### 3.1.1 Primary Objectives

The primary objectives of this study are to:

**Cohort 1 (Single-Agent Dose-Finding)**

- Identify the recommended dose (RD) of lenvatinib as a single agent in children and adolescents with relapsed or refractory solid malignant tumors

**Cohort 2 (Single-Agent Expansion)**

- Evaluate the activity of lenvatinib in 2 separate malignancy groups:
  - Cohort 2A: $^{131}$I- refractory differentiated thyroid cancer: by objective response rate (ORR) for subjects with measurable disease and best overall response (BOR) for all subjects
  - Cohort 2B: Relapsed or refractory osteosarcoma: by progression-free survival at 4 months (PFS-4)

Note: The tumors types under study in the Single-Agent Expansion portion of the study may be modified based on preliminary efficacy and safety signals observed in Cohort 1 of the study.

**Cohort 3 (Combination Dose-Finding and Expansion)**

- **Cohort 3A (Combination Dose-Finding)**
  - To identify the RD of lenvatinib in combination with ifosfamide and etoposide in osteosarcoma subjects
- **Cohort 3B (Combination Expansion)**
  - Evaluate the activity of lenvatinib in combination with ifosfamide and etoposide in osteosarcoma subjects by PFS-4

### 3.1.2 Secondary Objectives

The secondary objectives of this study are to:

**Cohort 1 (Single-Agent Dose-Finding)**

- Assess the safety and toxicity profile of lenvatinib in children and adolescents
- Evaluate the activity of lenvatinib as assessed by best overall response (BOR), ORR, duration of response (DOR), progression-free survival (PFS), time to progression (TTP), based on RECIST 1.1 [Eisenhauer, 2009], disease control rate (DCR), and clinical benefit rate (CBR)
- Examine blood and tumor biomarkers and correlate with clinical response to lenvatinib
- Determine population-based pharmacokinetic (PK) parameters of lenvatinib
- Assess the palatability and acceptability of the suspension formulation of lenvatinib

**Cohort 2 (Single-Agent Expansion)**

- Assess the safety and toxicity profile of lenvatinib in children and adolescents, and young adults with relapsed or refractory osteosarcoma
- Evaluate the efficacy of lenvatinib as assessed by BOR (osteosarcoma only), ORR (osteosarcoma only), DOR (measurable DTC and osteosarcoma only), PFS, TTP , DCR and CBR
- Examine blood and tumor biomarkers and correlate with clinical response to lenvatinib
- Determine population-based PK parameters of lenvatinib
- Assess the palatability and acceptability of the suspension formulation of lenvatinib

**Cohort 3 (Combination Dose-Finding and Expansion)**

- Assess the safety and toxicity of lenvatinib in combination with ifosfamide and etoposide in children and adolescents, and young adults with relapsed or refractory osteosarcoma
- Evaluate the efficacy of lenvatinib as assessed by BOR, ORR, DOR, PFS, TTP, DCR and CBR
- Examine blood and tumor biomarkers and correlate with clinical response to lenvatinib
- Determine population-based PK parameters of lenvatinib
- Assess the palatability and acceptability of the suspension formulation of lenvatinib

## 3.2 Exploratory Objectives

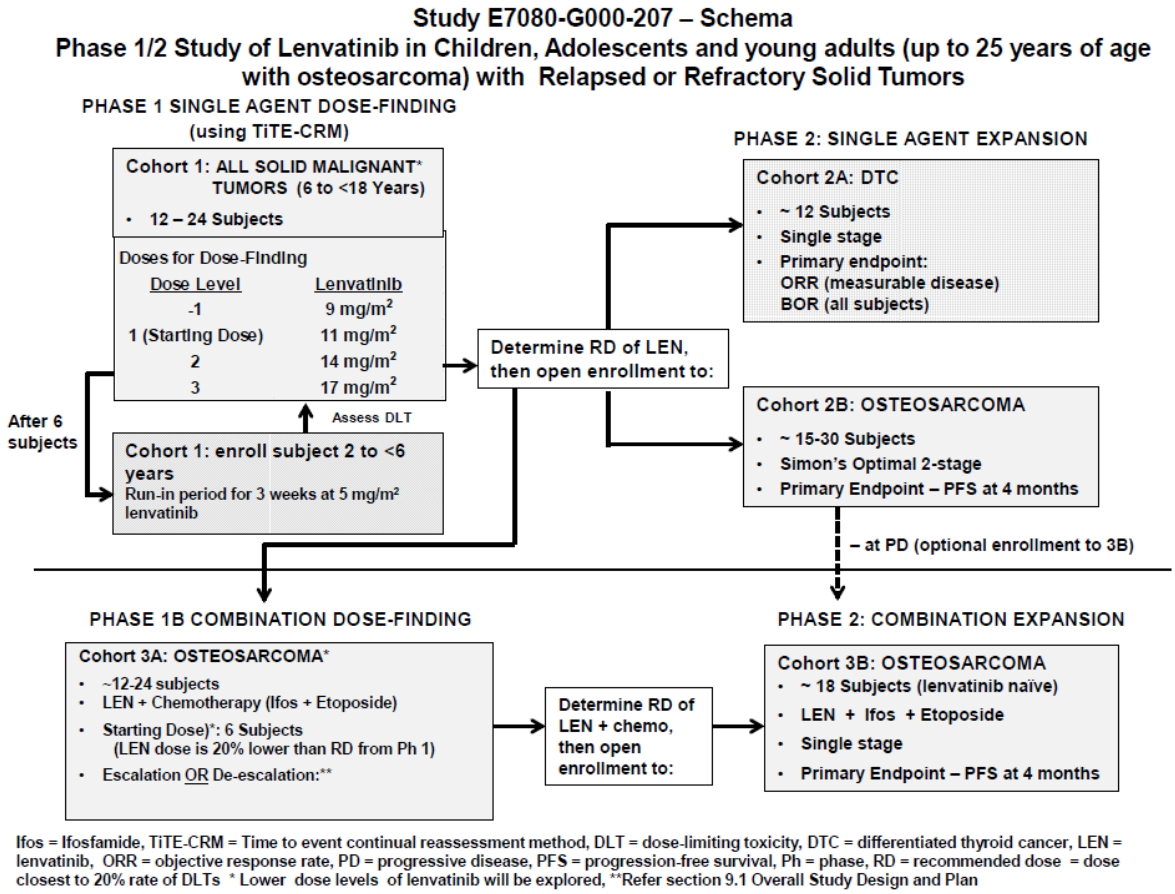
The exploratory objectives of this study are to:

- Explore the relationship of lenvatinib exposure to clinical response in children and adolescents (assessed during Cohort 1 [Single-Agent Dose-Finding] and Cohort 2 [Single-Agent Expansion])

- Evaluate the efficacy of lenvatinib as assessed by overall survival (OS)

## 3.3 Overall Study Design and Plan

This is a Phase 1/2, multicenter, open-label, study. The study will be conducted in 5 cohorts:




## Figure 1 Overall Study Design

**Cohort 1 (Single-Agent Dose-Finding)**: Dose-escalation to find the RD of lenvatinib using a time-to-event continual-reassessment method (TiTE-CRM) design in children and adolescents with relapsed or refractory solid malignant tumors (Doussau et al, 2012). When the RD is identified, Cohorts 2A, 2B, and Cohort 3A will start in parallel. After the RD is determined in Cohort 1, subsequent osteosarcoma subjects will be assigned to either Cohort 2B (Single-Agent Expansion) or Cohort 3A (Combination Dose-Finding), depending on whether the subject is deemed by the investigator to be a candidate for ifosfamide and etoposide. (If not, the subject would only be assigned to Cohort 2B).

**Cohorts 2 (Single-Agent Expansion):** To test the efficacy of lenvatinib in children and adolescents with $^{131}$I-refractory DTC (Cohort 2A), or subjects with relapsed or refractory osteosarcoma (Cohort 2B). Osteosarcoma subjects will be assigned to either Cohort 2B (Single-Agent Expansion) or Cohort 3A (Combination Dose-Finding), depending on whether the subject is deemed by the investigator to be a candidate for ifosfamide and etoposide, If not, the subject would only be assigned to Cohort 2B. Cohort 2A and Cohort 2B will be enrolled in parallel with Cohort 3A (Combination Dose-Finding).

**Cohort 3**

**Cohort 3A (Combination Dose-Finding):** To define the RD of lenvatinib in combination with ifosfamide and etoposide in subjects with relapsed or refractory osteosarcoma. This cohort will be open for enrollment in parallel with Cohort 2 (Single-Agent Expansion).

After defining the RD of lenvatinib in combination with chemotherapy in Cohort 3A, subsequent osteosarcoma subjects will be assigned to either Cohort 2B (Single-Agent Expansion) or Cohort 3B (Combination Expansion), depending on whether the subject is deemed by the investigator to be a candidate for ifosfamide and etoposide, If not, the subject would only be assigned to Cohort 2B.

**Cohort 3B (Combination Expansion):** To test the efficacy of lenvatinib in combination with ifosfamide and etoposide in subjects with relapsed or refractory osteosarcoma.

Subjects with osteosarcoma who have enrolled into Cohorts 1 or 2B and experienced progressive disease on lenvatinib (optional enrollment for subjects in Cohorts 1 and 2B) as well as lenvatinib-naïve subjects with relapsed or refractory osteosarcoma will be candidates for enrollment in Cohort 3B. The efficacy analyses will be based on lenvatinib-naïve subjects, while subjects from Cohorts 1 and 2B will only be summarized as appropriate.

The study will include 3 phases: Pretreatment (screening and baseline), Treatment (includes a Run-In Period for Cohort 1), and Post-treatment follow-up.

### 3.3.1 Pretreatment Phase (All Cohorts)

The pretreatment phase will last no longer than 28 days and will include a Screening Period and a Baseline Period.

### 3.3.2 Screening (All Cohorts)

Screening will occur between Day -28 and Day -2. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained prior to the conduct of any screening procedures or assessments.

Subjects in Cohort 1 must have a histologically or cytologically confirmed diagnosis of solid malignant tumor. Subjects in Cohort 2 or Cohort 3 must have a histologically or cytologically confirmed diagnosis of either osteosarcoma or DTC meeting the criteria for being $^{131}$I-refractory (either papillary thyroid cancer [PTC] or follicular thyroid cancer [FTC]).

The Screening Disposition case report form (CRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

### 3.3.3 Baseline (All Cohorts)

The purpose of the Baseline Period is to confirm protocol eligibility as specified in the inclusion/exclusion criteria (as detailed in Protocol Section 9.3.1 and Section 9.3.2). Results of baseline assessments must be obtained prior to the first dose of study drug (Cycle 1 Day 1). Baseline assessments may be performed on Day 1 or on Cycle 1 Day 1 prior to dosing. Clinical laboratory tests, including a pregnancy test (where applicable), should be performed within 72 hours prior to the first dose of study drug.
Subjects who complete the Baseline Period and continue to meet the criteria for inclusion/exclusion will begin the Treatment Phase of this study.

### 3.3.4 Treatment Phase

In all the cohorts, lenvatinib is administered daily (QD) and 1 treatment cycle is defined as a 28-day period for Cohorts 1, 2A, and 2B and a 21-day period for Cohorts 3A and 3B. A new treatment cycle begins every 28 days for Single-Agent Cohorts 1, 2A, and 2B or 21-day period for Combination-Treatment Cohorts 3A and 3B, irrespective of dose interruptions. See Protocol Section 9.4.1 for rules regarding the calculation of lenvatinib dose based on body surface area (BSA).

#### 3.3.4.1 Cohort 1 (Single-Agent Dose-Finding)

This cohort will identify the RD of lenvatinib as a single agent in children and adolescents with relapsed or refractory solid malignant tumors. The RD in this study will be defined as the dose that has a DLT rate closest to the targeted 20% rate.

**DOSE-ESCALATION IN COHORT 1 CYCLE 1:**

Subjects 6 to <18 years, will enroll in Cohort 1 prior to subjects 2 to <6 years of age. Each subject will be assigned a dose in accordance with the rules of the TiTE-CRM design as detailed in SAP Section 5.4.1.1. The TiTE-CRM design is an accepted adaptive design used in Phase 1 trials and allows continuous accrual throughout the study while using the 4-week toxicity endpoint as the basis for dose-escalation. Four experimental doses of lenvatinib may be investigated in Cohort 1 as displayed in Table 1.

**Table 1 Lenvatinib Doses for Dose-Finding (Cohort 1)**

| Dose Level | Lenvatinib (QD) |
|---|---|
| -1 | 9 mg/m$^2$ |
| 1 (starting dose) | 11 mg/m$^2$ |
| 2 | 14 mg/m$^2$ |
| 3 | 17 mg/m$^2$ |

QD = once daily.

The starting dose (Dose Level 1) of lenvatinib for this cohort is 11 mg/m$^2$ QD (approximately 80% of the adult RD of 24 mg QD). The maximum daily dose should not

exceed 24 mg. If the 11 mg/m$^2$ dose is not safe and tolerable, the dose will be de-escalated to 9 mg/m$^2$ (Dose Level -1).

Determination as to whether a subject has experienced a DLT will be made by the principal investigator and the sponsor according to the DLT definition in Protocol Section 9.4.1.1, and as needed with the Protocol Steering Committee (PSC). At least 2 subjects should receive the full 4-week study treatment or report a DLT (at the starting dose) and complete the DLT evaluations before escalation to the next dose level. Intra-subject dose escalation will not be allowed. Subjects who discontinue the study during Cycle 1 (Cycle 1 Day 1 to Cycle 1 Day 28) for any reason other than DLT will be replaced.

Intra-subject dose-escalation prior to determining the RD will be allowed only for subjects 2 to <6 years who can escalate lenvatinib dose when they enter Cohort 1 Cycle 1 from the Run-In Period as described below.

Dose-escalation for Subjects 2 to <6 years old:

Run-In Period: All subjects 2 to <6 years of age should complete Screening and Baseline assessments. Eligible subjects will first enter a 21-day Run-In Period prior to entering Cohort 1. During the Run-In Period the subject will receive single-agent lenvatinib at 5 mg/m$^2$/day for 21 days and will be evaluated for DLTs, along with PSC as needed.

If a subject 2 to <6 years of age experiences a DLT during the Run-In Period, that subject will discontinue from the study without entering Cohort 1 Cycle 1, but the DLT data from that subject will be used for all subsequent TiTE-CRM calculations and the dose level for that subject in all subsequent calculations will be considered as Cohort 1 Dose Level -1 (9 mg/m$^2$), as 9 mg/m$^2$ is the lowest dose in the Cycle 1 single-agent lenvatinib dose-finding cohort.

Subjects 2 to <6 years of age can enter Cohort 1 Cycle 1 (following the completion of the Run-In Period without any DLT) only after: (1) at least 6 subjects 6 to <18 years of age have either completed 4 weeks of treatment in Cycle 1 or reported DLTs during Cycle 1, and (2) single-agent lenvatinib has been evaluated and considered by the PSC to be safe based on the DLT data from all the previous subjects including subjects 6 to <18 years of age. When a subject 2 to < 6 years of age enters Cohort 1 Cycle 1, the subject will receive a dose that is either (1) one level below what is calculated from TiTE-CRM if the calculated dose is greater than 9 mg/m$^2$, based on the DLT data from all previous subjects from 2 to <18 years of age, or (2) 9 mg/m$^2$ if the TiTE-CRM calculated dose is 9 mg/m$^2$. Consequently, that subject's DLT data in Cycle 1 will be included in all subsequent TiTE-CRM calculations.

Once the RD has been determined, subjects treated at a lower dose level should continue to be treated at that dose level.

#### 3.3.4.2 Cohort 2 (Single-Agent Expansion)

Cohort 2 will begin enrollment after the RD of lenvatinib is identified in Cohort 1. The efficacy of lenvatinib will be evaluated in 2 malignancy groups separately: DTC (Cohort 2A)

and osteosarcoma (Cohort 2B). Subjects will be treated at the RD identified in Cohort 1. The RD of Single-Agent lenvatinib determined in Cohort 1 is 14 mg/m$^2$ as recommended by TiTE-CRM and confirmed by PSC. Subjects in Cohorts 2A and 2B will receive 14 mg/m$^2$ lenvatinib (equivalent to 24 mg QD, adult daily dose). After adjustment for BSA, the daily dose should not exceed 24 mg QD.

#### 3.3.4.3 Cohort 3A: Combination Dose-Finding

Lenvatinib will be administered orally QD in combination with ifosfamide and etoposide from Day 1 to Day 3 of each cycle for a total of 5 cycles to subjects with relapsed or refractory osteosarcoma as described below and in Table 2 See Protocol Section 9.4.3 for additional details on cytotoxic chemotherapy.

**Table 2 Lenvatinib and Chemotherapy Doses for Combination Dose-Finding (Cohort 3A)**

| **Dose Modification of Lenvatinib** | | | | |
|---|---|---|---|---|
| | **Dose - Escalation** | **Starting Dose** | **De-escalation 1** | **De-escalation 2** |
| Lenvatinib | RD (from Cohort 1) | 20% lower than RD from Cohort 1 | 40% lower than RD from Cohort 1 | 60% lower than RD from Cohort 1 |

| **Dose Modification of Ifosfamide and Etoposide** | | | | |
|---|---|---|---|---|
| | **No Dose Escalation** | **Starting Dose** | **De-escalation 1*** | **De-escalation 2*** |
| Ifosfamide | | 3000 mg/m$^2$/day IV for 3 days | 2400 mg/m$^2$/day IV for 3 days | 1800 mg/m$^2$/day IV for 3 days |
| Etoposide | | 100 mg/m$^2$/day IV for 3 days | 80 mg/m$^2$/day IV for 3 days | 60 mg/m$^2$/day IV for 3 days |

RD = recommended dose, *each De-escalation dose level is 20% lower than the Starting Dose.

The chemotherapy cycles will be repeated every 21 days.

Lenvatinib is administered daily as a QD dose, and ifosfamide and etoposide will be administered on Days 1 to 3 of each cycle for a total of 5 cycles. Each Chemotherapy cycle is repeated every 21 days. Six subjects with osteosarcoma (who have not received prior lenvatinib) will be enrolled first to Cohort 3A at the Starting Dose of lenvatinib (20% below the Single-Agent RD in Cohort 1) in combination with ifosfamide 3000 mg/m$^2$/day for 3 days (ifosfamide total dose 9 g/m$^2$) and etoposide 100 mg/m$^2$/day for 3 days (etoposide total dose 300 mg/m$^2$). Subjects with lenvatinib dose capped after BSA adjustment (dose must not exceed 24 mg daily) actually take lower dose level than assigned. If a subject with capped dose experiences a DLT, the DLT data from that subject will be counted to determine the RD of the combination treatment. A subject with capped dose who does not experience a DLT will be replaced for the purpose of determining the RD.

DLTs occurring during Cycle 1 will be evaluated and the next 6 subjects will be assigned a dose based on the rules for Dose Escalation and Dose De-Escalation as follows:

a. If ≤1 out of 6 subjects experiences a DLT at the starting dose during Cycle 1 (Day 1 to Day 21), then assign 6 more subjects to the next higher dose level of lenvatinib (RD from Cohort 1) and keep the chemotherapy dose the same (starting dose).

b. If ≥2 out of 6 subjects experience a DLT at the starting dose during Cycle 1 (Day 1 to Day 21), then follow the instructions below;

   i. If ≥2 subjects experience hematologic DLT and ≤1 subject experiences non-hematologic DLT, then assign 6 more subjects to 20% lower doses (De-escalation 1) of ifosfamide and etoposide and keep the lenvatinib dose the same; or

   ii. If ≥2 subjects experience non-hematologic DLT and ≤1 subject experiences a hematologic DLT, then assign 6 more subjects to a 20% lower dose of lenvatinib (De-escalation 1) and keep the ifosfamide and etoposide doses the same; or

   iii. If ≥2 subjects experience hematologic DLTs and ≥2 subjects experiences non-hematologic DLTs, then assign 6 more subjects to 20% lower doses of lenvatinib, ifosfamide, and etoposide each (De-escalation 1); or

   iv. If only 1 subject experiences a hematologic DLT and only 1 subject experiences a non-hematologic DLT, then assign 6 more subjects to the same dose level of lenvatinib, ifosfamide and etoposide each.

c. Continue the above processes until the combination dose of lenvatinib, ifosfamide and etoposide results in ≤1 DLT per 6 subjects or only 1 subject experiences a hematologic DLT and only 1 subject experiences a nonhematologic DLT per 6 subjects upon repeating the same dose level. This dose will be considered as the RD of the combination treatment.

Once the RD has been determined, subjects treated at a lower dose level should continue to be treated at that dose level. Intrasubject dose-escalation is not permitted. Further dose de-escalation of lenvatinib or the chemotherapy dose may be considered (pending discussion with the Protocol Steering Committee [PSC]), if needed.

#### 3.3.4.4 Cohort 3B (Combination Expansion)

Subjects with either lenvatinib-naïve relapsed or refractory osteosarcoma or osteosarcoma subjects who progress on single-agent lenvatinib in Cohorts 1 or 2B (optional enrollment) will receive lenvatinib (at the RD identified from Cohort 3A) in combination with ifosfamide and etoposide, provided the combination of lenvatinib, ifosfamide, and etoposide in Cohort 3A (Combination Dose-Finding) is determined to be safe and tolerable.

Osteosarcoma subjects who experience progressive disease in Cohorts 1 or 2B and choose to receive the combination therapy of lenvatinib with ifosfamide and etoposide should meet only inclusion criteria numbers 6 through 17 and all the exclusion criteria except Criterion Number 6.

Subjects in Cohorts 3A and 3B will receive ifosfamide and etoposide for a maximum of 5 cycles. Subjects who discontinue ifosfamide and etoposide in Cohorts 3A and 3B (e.g., due to toxicity) prior to completing 5 cycles may continue on single-agent lenvatinib if they are benefiting from the treatment at the discretion of the investigator. Subjects who discontinue lenvatinib prior to completing 5 cycles may continue on ifosfamide and etoposide at the investigator's discretion for 5 cycles.

### 3.3.5 Post-treatment (All Cohorts)

The Post-treatment Follow-up begins when the subject discontinues treatment. After subject discontinues treatment, an Off-Treatment Visit and the procedures noted in the Schedule of Assessments Tables (see Protocol Table 7, Table 8, and Table 9) should be completed within 30 days after the last dose of drug. Subjects will be followed for survival every 3 months until death or for 1 year, whichever occurs first, unless the study is terminated or the subject discontinues due to withdrawal of consent or is lost to follow-up (see Protocol Section 9.3.3).

Subjects who discontinue treatment without disease progression will have tumor assessments performed every 6 or 8 weeks (per the appropriate tumor assessment schedule) for up to 1 year, or sooner if clinically indicated, for documented disease progression or until another anticancer therapy is initiated whichever occurs first. After data cutoff, tumor assessments may be performed as clinically indicated using the institutional guidelines, following the prevailing local standard of care.

As required by some regulatory agencies, the following estimates are provided:

- The study will begin in December 2014 and will end on or before December 2017 (revised estimate is April 202).
- The maximum estimated period for the study is anticipated to be approximately 36 months. However, subjects will continue to receive study treatment as long as they demonstrate clinical benefit. Subjects benefiting from study treatment in the opinion of the investigator will continue to receive treatment until disease progression, intolerable toxicity, subject noncompliance with safety or efficacy assessments, initiation of another anticancer therapy, voluntary discontinuation by the subject at any time, or study termination by the sponsor, whichever occurs first.

## 3.4 Doses for Cohorts 2A, 2B, 3A, and 3B

### 3.4.1 Doses for Cohorts 2A and 2B

The RD of single-agent lenvatinib determined in Cohort 1 is 14 mg/m$^2$ as recommended by the TiTE-CRM and confirmed by the PSC.

Cohorts 2A and 2B will receive 14 mg/m$^2$ lenvatinib (equivalent to 24 mg QD, the adult daily dose). After adjustment for BSA, the daily dose should not exceed 24 mg QD.

### 3.4.2 Doses for Cohorts 3A and 3B

The RD of the combination with ifosfamide and etoposide determined in Cohort 3A is lenvatinib 14 mg/m$^2$/day + ifosfamide 3000 mg/m$^2$/day and etoposide 100 mg/m$^2$/day as recommended by the above rules and confirmed by the PSC.

Cohort 3B will receive lenvatinib 14 mg/m$^2$/day + ifosfamide 3000 mg/m$^2$/day and etoposide 100 mg/m$^2$/day.

## 3.5 Toxicity Management

Toxicity will be managed by treatment interruption, dose reduction and/or treatment discontinuation. Dose reduction and interruption for subjects who experience lenvatinib-related toxicity and ifosfamide/etoposide-associated toxicity will be in accordance with the protocol-specified dose reduction and interruption instructions (Sections 9.4.1.2 and 9.4.1.11 of the Protocol).

# 4 DETERMINATION OF SAMPLE SIZE

**Cohort 1**: Approximately 12 to 24 subjects based on the TiTE-CRM algorithm in the single-agent dose-finding cohort.

**Cohort 3A**: Approximately 12 to 24 subjects with osteosarcoma will be enrolled in combination dose-finding cohort.

**Cohort 2A**: Approximately 12 subjects with evaluable or measurable disease are planned to be enrolled in the DTC cohort.

**Cohort 2B**: A minimum of 15 PFS-4 evaluable subjects will be assessed in the osteosarcoma single-agent expansion. The sample size estimates were based on Simon's Optimal Two-Stage Design (Simon, 1989). If < 5 subjects achieve PFS-4 among the 15 evaluable subjects in Stage I, accrual in the cohort will be suspended. Otherwise, if at any time during Stage I of the cohort, ≥5 subjects achieve PFS-4 among the 15 evaluable subjects, enrollment in the cohort will continue for a total of approximately 27 evaluable subjects. If, at the end of the second stage for the cohort, ≥10 subjects achieve PFS-4 among the 27 subjects in the cohort, lenvatinib will be considered active in the population. The above sample size estimates are based on the following assumptions: the null hypothesis PFS-4 ($H_0$) is ≤25%, and the alternative hypothesis PFS-4 ($H_1$) is ≥45%. One-sided Type I error ($\alpha$) = 0.1, and power = 80%. To account for nonevaluable subjects, a total of 15-30 osteosarcoma subjects will be enrolled in Cohort 2B.

**Cohort 3B**: With the following assumptions: $p_0$ = 25%, $p_1$ = 50%, 1-sided $\alpha$ = 10%, $\beta$ = 20%, where $p_0$ is an unacceptable rate of PFS, $p_1$ is the target rate of PFS, $\alpha$ is the probability of declaring lenvatinib effective when the true rate is $p_0$, and $\beta$ is the probability of declaring

lenvatinib not effective if the true rate is $p_1$, a sample size of 15 subjects will provide a statistical power of 80%. To account for nonevaluable subjects, a total of 18 lenvatinib-naïve subjects will be enrolled in the combination expansion, along with some subjects from Cohorts 1 and 2B.

# 5 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using n, mean, SD, median, 25$^{th}$ percentile (Q1), 75$^{th}$ percentile (Q3), minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects. The statistical analyses of the study data as described in this section will be performed as further outlined in this SAP, which will be finalized before database lock and be included in the CSR.

Efficacy will be evaluated based on the Full Analysis Set (see SAP Sections 5.2.1 and 7.2). Each cohort will have its own cutoff date for the final analysis for CSR reporting purposes. For Cohorts 1 and 3A, the data cutoff will occur when the RD is determined and the last enrolled subject completes 6 cycles of treatment or discontinues before the end of Cycle 6, whichever occurs first or pending discussion with the PSC. For DTC and osteosarcoma subjects in Cohorts 2A, 2B, and 3B, the cutoff will be after all subjects enrolled have either completed 6 cycles or have discontinued treatment before the end of Cycle 6, whichever occurs first.

## 5.1 Study Endpoints

### 5.1.1 Primary Endpoints

For Cohort 1, the primary endpoint is RD of lenvatinib based on the TiTE-CRM design. While for Cohort 3A, it is RD of the combination treatment (lenvatinib + etoposide + ifosfamide).

For the three Phase 2 cohorts, the primary endpoints are:

- Cohort 2A (DTC): ORR, ie, the proportion of subjects who have a BOR of complete response (CR) or partial response (PR) for subjects with measurable disease and BOR for all subjects based on RECIST 1.1
- Cohort 2B (Osteosarcoma): PFS-4, ie, the percentage of subjects evaluable for PFS-4 who are alive and without PD at 4 months from the first dose based on RECIST 1.1. Subjects evaluable for PFS-4 includes those treated at least 4 months or those who died or radiologically progressed within 4 months after first dose.
- Cohort 3B: PFS-4

### 5.1.2 Secondary Endpoints

- Efficacy endpoints:

- BOR over the treatment period (except for Cohort 2A): defined as the best response recorded from the start of study drug until 30 days after the last dose or until PD, whichever occurs earlier
- ORR (except for Cohort 2A): defined as the proportion of subjects who have BOR of CR or PR
- DOR: defined as the time from first documentation of tumor response (CR or PR) to PD
- Disease Control Rate (DCR): defined as the percentage of subjects with measurable disease who have a BOR of CR or PR or stable disease (SD) or subjects with evaluable disease who have a BOR of CR or Non-CR/Non-PD. To be assigned a BOR of SD or Non-CR/Non-PD, the time from the first administration of study drug until the date of documented SD or Non-CR/Non-PD should be ≥7 weeks
- Clinical Benefit Rate (CBR): defined as the percentage of subjects with measurable disease who have a BOR of CR or PR or durable SD lasting ≥23 weeks or subjects with evaluable disease who have a BOR of CR or durable Non-CR/Non-PD lasting ≥23 weeks
- TTP: defined as the time from the date of the first administration of study drug until the date of first documentation of PD.
- PFS: defined as the time from first dose to documented date of PD or death (whichever occurs first)

- Safety endpoints:
  - Adverse events (AEs), serious AEs (SAEs), clinical laboratory values, vital signs, 12-lead electrocardiograms (ECGs), urine dipstick, occult blood in stool, echocardiogram, Lansky play scores or Karnofsky performance status (KPS), physical examination findings, and height, and closure of proximal tibial growth plates during treatment and follow-up.
- Plasma lenvatinib exposure parameters
- Assessment of blood or tumor biomarkers that correlate with clinical response to lenvatinib treatment or AEs associated with lenvatinib treatment
- Palatability and acceptability of the suspension formulation of lenvatinib

### 5.1.3 Exploratory Endpoints

- Time to OS: defined as the time from first dose of study drug until the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cutoff will be censored at the date the subject was last known to be alive (or the data cutoff date).

- PFS-4 in Cohort 3A (see SAP Section 7.1).

## 5.2 Study Subjects

### 5.2.1 Definitions of Analysis Sets

The following analysis sets will be defined:

- **Full Analysis Set** includes all enrolled subjects who have not failed study screening. Demographic and baseline characteristics, previous anticancer medications, prior and concomitant medications, procedures and radiotherapy, medical history, and efficacy analyses will primarily be based on the Full Analysis Set.
- **Per Protocol Analysis Set** includes those subjects who (1) receive at least 1 dose of the assigned study drug; (2) have no major protocol deviations; (3) had both Baseline and at least 1 postbaseline tumor assessment. This will be the secondary analysis set for all tumor response-related efficacy endpoints.
- **Safety Analysis Set** includes all subjects who received study drug. This will be the analysis set for all safety evaluations.
- **Palatability Analysis Set** includes all subjects who received oral suspension of lenvatinib and answered at least 1 question in the Palatability Questionnaire CRF.
- **Pharmacokinetic (PK) Analysis Set** includes all subjects who have received at least 1 dose of any study drug and have evaluable lenvatinib concentration data.

This additional analysis set will be defined for Cohort 1:

- **DLT Analysis Set** includes all subjects who either a) experience DLT during Run-in Period or Cycle 1 or b) receive all scheduled doses of study drug on their scheduled days during Cycle 1 and complete Cycle 1 observation period without a DLT.

This additional analysis set will be defined for Cohort 3A:

- **DLT Analysis Set** includes all subjects who either a) experience DLT during Cycle 1 or b) receive all scheduled doses of study drug on their scheduled days during Cycle 1 and complete Cycle 1 observation period without a DLT.

See Section 7.2 explaining the analysis sets in addition to those listed in the protocol.

The number and percentage of subjects included in each analysis set will be presented by cohort and dose level in Phase 1 and by cohort in Phase 2. A listing will also be provided to identify subjects in each analysis set.

### 5.2.2 Subject Disposition

The number and percentage of enrolled and treated subjects who completed study drug and who discontinued study drug will be summarized according to the primary reason for discontinuation by cohort and dose level in Phase 1 and by cohort in Phase 2. Additionally,

the disposition of subjects who discontinued treatment or withdrew from the study will be summarized. For Cohorts 3A and 3B (combination therapy), reasons for prematurely discontinuing either lenvatinib or chemotherapy (etoposide + ifosfamide) will be summarized separately.

### 5.2.3 Protocol Deviations

All major protocol deviations will be determined and will be agreed upon after review of individual subject data prior to database lock. This review will be undertaken in collaboration between the Study Director, the Study Statistician, the Study Data Manager and the Study Clinical Operations Manager.

Major protocol deviations will be listed and summarized by cohort and dose level in Phase 1 and by cohort in Phase 2.

### 5.2.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics for the Full Analysis Set will be summarized by cohort using descriptive statistics. Continuous demographic and baseline variables including age (year), height (cm), weight (kg), BMI ($kg/m^2$) and BSA ($m^2$), results will be summarized and presented as n, mean, standard deviation, median, Q1, Q3, minimum and maximum values. For categorical variables, the number and percentage of subjects will be used. Demographics and Baseline categorical variables include age group (2 to <6 years, 6 to <18 years, 6 to <12 years, 12 to <16 years, 16 to <18 years, 18 to ≤25 years [Cohorts 2B, 3A and 3B only]), race (White, Black or African American, Asian [Japanese, Chinese, Other Asian], American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Other), ethnicity (Hispanic or Latino, not Hispanic or Latino), pregnancy test (present, absent), KPS or Lansky play scores.

Previous anticancer therapy will be summarized by cohort and dose level in Phase 1 and by cohort in Phase 2 as follows:

- Number of previous therapy regimens
- Duration of last medication (months)
- Best response for last anticancer medication (CR, PR, SD, PD, not evaluable, not applicable, unknown)
- Time from end of last anticancer medication to first dose of study drug (months)
- Previous anticancer medication (administered as adjuvant, therapeutic, neoadjuvant, consolidation, maintenance, unknown)
- Previous anticancer procedures (yes, no)
- Time from prior anticancer procedures to first dose (months)
- Prior anticancer medication preferred term

Previous anti-VEGF/VEGFR (vascular endothelial growth factor/vascular endothelial growth factor receptor) therapy will be summarized by cohort and dose level in Phase 1 and by cohort in Phase 2 as follows:

- Number of subjects with any previous VEGF/VEGFR-targeted therapy
- Previous VEGF/VEGFR-targeted therapy (sunitinib, pazopanib, etc.)
- Duration of most recent VEGF/VEGFR-targeted therapy (months)
- Primary reason for discontinuation
- Time from end of most recent VEGF/VEGFR-targeted therapy to first dose of study drug

Prior radiotherapy and radioiodine therapies will be summarized by cohort and dose level in Phase 1 and by cohort in Phase 2 as follows:

- Subjects with any previous radiotherapy
- Tumor lesion at the site progressed since radiotherapy (yes, no, not evaluated)
- Time from last radiotherapy to first dose (months)
- Number of subjects with any previous radioiodine therapy
- Time from last radioiodine therapy to first dose (months)
- Type of previous radioiodine therapy (curative, palliative or other)

Disease history and characteristics at study entry will be summarized by cohort and dose level in Phase 1 and by cohort in Phase 2 as follows:

- Solid tumor diagnosis classification
- DTC subtype classification (papillary, follicular) and histologic subtypes (Cohort 2A only)
- Time since first diagnosis of solid tumor/DTC/osteosarcoma to date of first dose (months)
- Time since metastatic diagnosis to date of the first dose (months)
- Time Since Last Progression to First Dose of Study Drug (months)
- Age at diagnosis (in years)
- TNM staging and grade at diagnosis
- Target lesions (lymph node [yes/no], nonlymph node [yes/no]), and nontarget lesions [yes/no] based on the measurable disease criteria at study entry (nonlymph node: longest diameter ≥1.5 cm, lymph-node: short axis diameter ≥1.0 cm) based on RECIST version 1.1.

Previous anticancer therapies, anti-VEGF/VEGFR therapy, radiotherapy and radioiodine therapies, and disease history and characteristics at study entry will also be listed for each subject.

A subject data listing of medical history will be provided, including system organ class; current medical condition; date of diagnosis, surgical procedure, or onset of symptoms; and end date/ongoing. Coding will be done using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

Some items captured on the Previous Anti-Cancer Procedures CRF for Cohorts 1 and 2B are excluded from the summary table of Previous Anti-Cancer Procedures because they are diagnostic procedures considered as Medical History and Current Medical Conditions. These items will be flagged in the listing of Previous Anti-Cancer Procedures.

### 5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO) Drug Dictionary using the 2018 B2 version. The number (percentage) of subjects who have taken prior and concomitant medications will be summarized on the Full Analysis Set, by Anatomical Therapeutic Chemical (ATC) Classification, WHO drug preferred term, and by cohort. Prior medications will be defined as medications that started prior to the first dose of study drug and discontinued prior to the start of study drug. Concomitant medications will be defined as medications that (i) have started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (ii) have started on or after the date of the first dose of study drug up to 30 days following the last dose. Medications that cannot be determined to be prior/concomitant due to missing or incomplete dates will be regarded as concomitant (see Section 5.3.5.2).

The summary of prior and concomitant antihypertensive, antidiarrheal and other medications will be summarized by cohort and dose level in Phase 1 and by cohort in Phase 2. Data listings will be provided for all prior and concomitant medications.

All other concomitant therapies or diagnostic, therapeutic, or anticancer procedures relating to malignancy, and palliative radiotherapy will also be summarized and/or listed as applicable.

### 5.2.6 Treatment Compliance

Not collected on CRF.

## 5.3 Data Analysis General Considerations

For incomplete dates involving efficacy and other safety data, a conservative imputation will be used for calculation. See Section 8.2.1 for the outline of imputation rules, which will be specified in the study analysis dataset specifications with more details.

### 5.3.1 Pooling of Centers

Subject data from all centers will be pooled for all analyses. Center will not be considered as a factor in the analyses.

### 5.3.2 Adjustments for Covariates

No adjustment for covariates will be made for this study.

### 5.3.3 Multiple Comparisons/Multiplicity

No multiplicity adjustment will be made for this study.

### 5.3.4 Examination of Subgroups

Subgroup analyses may be conducted if appropriate.

### 5.3.5 Handling of Missing Data, Dropouts, and Outliers

#### 5.3.5.1 Adverse Events

Adverse events with incomplete start dates will be considered treatment emergent if:

- Day and month are missing and the year is equal to or after the year of the first study drug dose date
- Day is missing, and the year is after the year of the first study drug dose
- Day is missing and the year is equal to the year of the first study drug dose date and the month is equal to or after the month of the first dose date
- Year is missing; or complete date is missing

#### 5.3.5.2 Concomitant Medications

Medications will be considered concomitant if:

- Day and month are missing and the year is equal to or after the year of the first study drug dose date
- Day is missing, and the year is after the year of the first study drug dose
- Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first study drug dose date
- Year is missing; or complete date is missing

### 5.3.6 Other Considerations

Subjects in Cohort 1 will be assigned to the planned dose levels of 9 mg/m$^2$, 11 mg/m$^2$, 14 mg/m$^2$, and 17 mg/m$^2$, respectively. The actual dose level could be different from the planned dose level due to the adjustment of BSA and capped dose. The actual dose level resulting from capping the dose will be set as:

- 17 mg/m$^2$, if the rounded calculated dose level on Cycle 1 Day 1 ≥17 mg/m$^2$
- 14 mg/m$^2$, if 14 mg/m$^2$ ≤the rounded calculated dose level on Cycle 1 Day 1 <17 mg/m$^2$
- 11 mg/m$^2$, if 11 mg/m$^2$ ≤the rounded calculated dose level on Cycle 1 Day 1 <14 mg/m$^2$
- 9 mg/m$^2$, if 9 mg/m$^2$ ≤the rounded calculated dose level on Cycle 1 Day 1 <11 mg/m$^2$
- 7 mg/m$^2$, if 7 mg/m$^2$ ≤the rounded calculated dose level on Cycle 1 Day 1 < 9 mg/m$^2$
- 5 mg/m$^2$, if the rounded calculated dose level on Cycle 1 Day 1 < 7mg/m$^2$

Subjects in Cohort 3A (Combination Dose-Finding) will receive study drug as described in Table 2 of the Protocol. The actual dose level of lenvatinib could be different from the planned dose level due to the adjustment of BSA and capped dose. The actual dose level of lenvatinib resulted from capping the dose will be set as:

- 14 mg/m$^2$, if the rounded calculated dose level on Cycle 1 Day 1 ≥14 mg/m$^2$
- 11 mg/m$^2$, if 11 mg/m$^2$ ≤ the rounded calculated dose level on Cycle 1 Day 1 <14 mg/m$^2$
- 9 mg/m$^2$, if 9 mg/m$^2$ ≤ the rounded calculated dose level on Cycle 1 Day 1 <11 mg/m$^2$
- 7 mg/m$^2$, if 7 mg/m$^2$ ≤ the rounded calculated dose level on Cycle 1 Day 1 <9 mg/m$^2$
- 5 mg/m$^2$, if the rounded calculated dose level on Cycle 1 Day 1 <7 mg/m$^2$

The actual dose level of ifosfamide and etoposide that resulted from a BSA adjustment will be set as:

Ifosfamide:

- 3000 mg/m$^2$ if the calculated dose level on Cycle 1 Day 1 ≥2700 mg/m$^2$
- 2400 mg/m$^2$ if 2100 mg/m$^2$ ≤the calculated dose level on Cycle 1 Day 1<2700 mg/m$^2$
- 1800 mg/m$^2$ if 1500 mg/m$^2$ ≤the calculated dose level on Cycle 1 Day 1<2100 mg/m$^2$

Etoposide:

- 100 mg/m$^2$ if the calculated dose level on Cycle 1 Day 1 ≥90 mg/m$^2$
- 80 mg/m$^2$ if 70 mg/m$^2$ ≤ the calculated dose level on Cycle 1 Day 1< 90 mg/m$^2$
- 60 mg/m$^2$ if 50 mg/m$^2$ ≤ the calculated dose level on Cycle 1 Day 1< 70 mg/m$^2$

For subjects in expansion cohorts (2A, 2B and 3B), the actual dose level will be set to the planned dose level regardless of capped dose.

The planned dose level is used in the Full Analysis Set and Per Protocol Analysis Set, while the actual dose level (BSA-adjusted dose level) will be used for the Safety Analysis Set, PK Analysis Set, and DLT Analysis Set. Regarding summarization of mean and mean change from Baseline for laboratory, vital sign, and ECG data, if 2 or fewer subjects in each of the treatment groups have data for a given cycle, the applicable cycle(s) will not be summarized and the table will be curtailed. For example, if at Cycle 12 the 3 treatment groups have 4, 3 and 1 subjects, respectively, then Cycle 12 will be summarized for all treatment groups. If at Cycle 13, the 3 treatment groups have 2, 2 and 1 subject, respectively, and at subsequent cycles no treatment has 3 or more subjects, then the table will not be produced for Cycle 13 and all subsequent cycles. However, for shift tables and other analyses of worst postbaseline values, all data will be included.

## 5.4 Primary, Secondary and Exploratory Analyses

### 5.4.1 Primary Dose-Finding Analyses

#### 5.4.1.1 Cohort 1: (Single-Agent Dose-Finding)

Cohort 1, the lenvatinib single-agent dose-finding group, will enroll up to 24 subjects. A TiTE-CRM design will be used to determine the RD of lenvatinib and to increase the flexibility by allowing continuous accrual with no trial suspensions, which are typically needed when the toxicity assessment of subjects previously recruited is not completed (Smith, et al., 1998; Cheung, 2009). Using this TiTE-CRM design, an eligible subject can be included in the trial at any time, without waiting for the completion of prior subjects (Doussau, et al, 2012). The model will be re-estimated considering all the toxicity observations currently available. The subject will be treated at the best current estimate of the RD. Individual subjects on long-term treatment may be treated at a dose below the dose recommended by the model for safety reasons.

A 1-parameter empirical power model will be used to assess the relation between the dose level and the probability of DLT:

$$F(d,\alpha) = P_d{}^{\exp(\alpha)}$$

where $F(d,\alpha)$ is the estimated probability of DLT at dose-level d, $P_d$ is the prior probability of DLT at dose level d, and α is the unknown parameter to be estimated by the model.

The vector $\{p_{0d}\}$ represents the initial guesses of toxicity probabilities, reflecting the clinicians' prior impression. The skeleton of initial guesses of toxicity probabilities $\{p_{0d}\}$ is numerically calibrated using the approach of Lee et al. (2005) and Cheung (2009) and using the "getprior" function of R, ensuring good design operating characteristics. Based on consultation with the clinicians, the delta (half of the width of the CI) defining the indifference interval was set at 0.06 (indifference interval: 0.14 to 0.26) and the prior maximum tolerated dose ($MTD_0$) at Dose 2 (14 mg/m²) is likely to be the RD (same as in adults). This yields a vector of prior probabilities $\{p_{0k}\}$ equal to 0.03, 0.10, 0.20, and 0.33, for the doses 9 mg/m$^2$, 11 mg/m$^2$, 14 mg/m$^2$, and 17 mg/m$^2$, respectively, that was found reasonable by the clinicians. A noninformative prior distribution Normal (0, 1.34) has been assigned for α in the Bayesian computation.

The simulation study confirmed that the operating characteristics of the model defined with these parameters were reasonable, with more than 50% correct selection of the RD in 3 contrasted scenarios. Starting with Dose 1, the prior distribution of the parameter α will be updated by the accruing data on DLTs each time a subject completes evaluation for toxicity in Cycle 1.

#### 5.4.1.2 Cohort 3A: Osteosarcoma Combination Dose-Finding

The DLT will be assessed to determine the RD of lenvatinib in combination with ifosfamide and etoposide. DLTs occurring during Cycle 1 will be evaluated and the subjects will be assigned a dose based on the rules for dose escalation and de-escalation (see Section 3.3.4.3). The RD of lenvatinib in combination with ifosfamide and etoposide will be used to treat osteosarcoma subjects in Cohort 3B.

### 5.4.2 Efficacy Analyses

The tumor response data used in the primary analyses of the PFS-4 rate and ORR will be obtained from the investigator's assessment of the imaging scans. No independent tumor assessments will be performed as part of this study. Tumor response will be assessed by RECIST 1.1. All the efficacy analyses will be performed on the Full Analysis Set, and the Per Protocol Analysis Set for all tumor response-related efficacy endpoints. A tabular summary of key features of the efficacy analyses is described in SAP Appendix 13.2 (Summary of Efficacy Analyses).

#### 5.4.2.1 Primary Efficacy Analyses

**COHORT 2A: DTC**

The primary efficacy endpoint is ORR for subjects with measurable disease and BOR for all subjects. Tumor response will be based on RECIST 1.1 and assessed every 8 weeks. The analysis will be descriptively performed on the Full Analysis Set.

### COHORT 2B: SINGLE-AGENT EXPANSION

The primary efficacy endpoint is the PFS-4 rate based on RECIST 1.1. This is the proportion of subjects free of progression at 4 months. The PFS-4 rate will be estimated using the binomial proportion and the corresponding 80% and 95% exact binomial distribution CIs (Clopper and Pearson, 1934) will also be provided. The PFS-4 rate will also be tested using a null hypothesis that the PFS-4 rate is ≤25% tested against the alternative hypothesis of a PFS-4 rate ≥45%, using the 1-sample exact test of a single proportion, at the 1-sided 0.1 level. These analyses will be performed on the lenvatinib-naïve subjects in the Full Analysis Set and the Per Protocol Analysis Set.

The PFS-4 rate will be calculated using PFS-4 evaluable subjects. These are defined as follows.

PFS-4 evaluable subjects:

- includes subjects who were treated with study medication at least 16 weeks;
- includes subjects who died or radiologically progressed within 16 weeks after the first administration of study medication. These subjects are not considered free of progression at 4 months;
- includes subjects who received anticancer treatment within 16 weeks after the first administration of study medication. These subjects are not considered free of progression at 4 months;
- excludes those who discontinue the study due to AE or reasons other than disease progression, death, or receiving anticancer treatment within 16 weeks after the first administration of study medication;
- excludes subjects administered any study medication with no baseline or no postbaseline tumor assessments.

### COHORT 3B: OSTEOSARCOMA COMBINATION EXPANSION

The primary efficacy endpoint is the PFS-4 rate based on RECIST 1.1. This is the proportion of subjects free of progression free at 4 months. The PFS-4 rate will be estimated using the binomial proportion along with the corresponding exact binomial 80% and 95% CIs. The PFS-4 rate will be tested using a null hypothesis that PFS-4 rate is ≤25% tested against the alternative hypothesis of a PFS-4 rate ≥50%, using the 1-sample exact test of a single proportion, at the 1-sided 0.1 level. This analysis will be performed on the lenvatinib-naïve subjects in Full Analysis Set and Per Protocol Analysis Set, while subjects enrolled from Cohorts 1 and 2B will be summarized only as appropriate.

The PFS-4 rate will be analyzed using PFS-4 evaluable subjects. These are defined as follows.

PFS-4 evaluable subjects:

- includes subjects who were treated with study medication at least 18 weeks
- includes subjects who died or radiologically progressed within 18 weeks after the first administration of study medication. These subjects are not considered free of progression at 4 months.
- includes subjects who received anticancer treatment within 18 weeks after the first administration of study medication. These subjects are not considered free of progression at 4 months.
- excludes those who discontinue the study due to AE or other reasons than disease progression, death , or receiving anticancer treatment within 18 weeks after the first administration of study medication
- excludes subjects administered any study medication but had no baseline or no postbaseline tumor assessments.

**SURGICALLY REMOVED LESIONS**

For Cohorts 2B, 3A and 3B, removal of existing (not new) osteosarcoma metastatic lesion(s) is permitted after the completion of the first 4 months of the treatment period without PD. The time points for tumor response assessment after tumor removal will be considered 'Not Evaluable' unless the tumor response is considered PD for the following reasons:

- appearance of an unequivocal new lesion
- unequivocal progression of non-target lesions or target lesions

Lesions removed before the first 4 months are permitted only in the case of PD.

#### 5.4.2.2 Secondary Efficacy Analyses

The secondary efficacy endpoints include BOR over the treatment period (except for Cohort 2A), ORR (except for Cohort 2A), DCR, and CBR, as well as DOR (measurable disease only). PFS and TTP are defined in SAP Section 5.1 and will be performed for subjects in the Full Analysis and Per Protocol Analysis Sets.

Subjects who do not have a tumor response assessment for any reason will be considered nonresponders and will be included in the denominator when calculating the response rate. The count and percentage for ORR will be summarized by dose level for Cohorts 1 and 3A and by cohort for Cohorts 2B and 3B. ORR and corresponding 95% CI based on the exact binomial distribution will be estimated for all corresponding treatment cohorts.

The count and percentage for both the DCR and CBR will be summarized for each treatment cohort, along with the exact 95% CI for.

The median and quartiles of DOR will be estimated by the Kaplan-Meier (KM) method (Kaplan and Meier, 1958), and the 95% CI estimated with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley, 1982).

For PFS, if a subject has not experienced PD or death, then the subject's data will be censored on the date of the last adequate radiologic assessment.

TTP will be calculated using data from all subjects in the Full Analysis Set. The calculation for TTP does not classify deaths as events.

The PFS censoring rules in this SAP and definition of progression date follow the Food and Drug Administration (FDA), *Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)* (See SAP Table 3). The PFS censoring rules are referenced in SAP Table 3 and TTP censoring rules are referenced in SAP Table 4.

**Table 3 Censoring Rules for Analysis of Progression-Free Survival**

| No | Situation | Date of Progression or Censoring | Outcome |
|---|---|---|---|
| 1 | No baseline tumor assessments | Date of first dose | Censored |
| 2 | No postbaseline tumor assessments | Date of first dose | Censored |
| 3 | Progression documented between scheduled visits | Date of first radiologic PD assessment | Progressed |
| 4 | More than 1 NE tumor timepoint assessment | Date of last adequate radiologic assessment before NE tumor assessments | Censored |
| 5 | No progression at time of data cutoff | Date of last adequate radiologic assessment | Censored |
| 6 | New anticancer treatment started | Date of last adequate radiologic assessment prior to or on date of new anticancer treatment | Censored |
| 7 | Death before first tumor assessment | Date of death | Progressed |
| 8 | Death between adequate assessment visits* | Date of death | Progressed |
| 9 | Death or progression after more than one missed visit/tumor assessment** | Date of last adequate radiologic assessment before missed tumor assessments | Censored |
| 10 | Treatment discontinuation for reasons other than PD | Date of last radiologic assessment before treatment discontinuation | Censored |

CR = complete response, NE = not evaluable, PD = progressive disease, PR = partial response, q6w = every 6 weeks, q8w = every 8 weeks, SD =stable disease.

* Adequate tumor assessment is radiologic assessment at regular interval as defined in the protocol.

** More than 1 missed visit/adequate tumor assessment is defined as having either 1 of the following 2 durations being longer than 18 weeks – 1 day, which is 125 days ( = ((8+1) x 2 x 7) – 1) for subjects on the q8w tumor assessment schedule in Cohorts 1, 2A and 2B; while 14 weeks – 1 day, which is 97

days ( = ((6+1) x 2 x 7) – 1) for subjects on the q6w tumor assessment schedule in Cohorts 3A and 3B:

a. Duration between 2 consecutive tumor assessments

b. Duration between the last adequate tumor assessment and death or PD

The priority of the censoring rules is as follows:

1. If the subject had PD or death, the following sequence will be applied:
   - If a subject did not have a baseline or postbaseline tumor assessment (Nos. 1 and 2), the subject will be censored on the date of first dose. However, if the subject died within 125 days in Cohorts 1, 2A and 2B or 97 days in Cohorts 3A and 3B following the first dose and did not receive a new anticancer treatment, it will be counted as PFS event at the date of death. If a subject had new anticancer treatment before PD or death (No. 6), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment. If PD is reported after the drug discontinuation visit, the subject will be censored at the date of last radiologic assessment before drug discontinuation except when PD happened at the same visit as drug discontinuation (No. 10). If PD happened within 4 weeks of drug discontinuation (Week 16 for Cohort 2 and Week 18 for Cohorts 3A and 3B), it will be considered PD at drug discontinuation visit and counted as PFS event.
   - If a subject missed 2 or more tumor assessments before PD or death (No. 9), the subject will be censored on the date of the last adequate tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criterion, the earliest censoring date will be used.
   - Otherwise, if a subject had an event (No. 3, No. 7, or No. 8), the earliest event date will be used.

2. If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, No. 2, No. 4, No. 5, No. 6, No. 9).

## Table 4 Censoring Rules for Analysis of Time to Progression

| No | Situation | Date of Progression or Censoring | Outcome |
|---|---|---|---|
| 1 | No baseline tumor assessments | Date of first dose | Censored |
| 2 | No postbaseline tumor assessments | Date of first dose | Censored |
| 3 | Progression documented between scheduled visits | Date of first radiologic PD assessment | Progressed |
| 4 | More than 1 NE tumor timepoint assessment | Date of last adequate radiologic assessment before NE tumor assessments | Censored |
| 5 | No progression at time of data cutoff | Date of last adequate radiologic assessment | Censored |
| 6 | New anticancer treatment started | Date of last adequate radiologic assessment prior to or on date of new anticancer treatment | Censored |
| 7 | Death before first tumor assessment | Date of death | Censored |
| 8 | Death between adequate assessment visits* | Date of death | Censored |
| 9 | Death or progression after more than one missed visit/tumor assessment** | Date of last adequate radiologic assessment before missed tumor assessments | Censored |
| 10 | Treatment discontinuation for reasons other than PD | Date of last radiologic assessment before treatment discontinuation | Censored |

CR = complete response, NE = not evaluable, PD = progressive disease, PR = partial response, q6w = every 6 weeks, q8w = every 8 weeks, SD =stable disease.

* Adequate tumor assessment is radiologic assessment at regular interval as defined in the protocol.

** More than 1 missed visit/adequate tumor assessment is defined as having either 1 of the following 2 durations being longer than 18 weeks – 1 day, which is 125 days ( = ((8+1) × 2 × 7) – 1) for subjects on the q8w schedule for tumor assessment in Cohorts 1, 2A, and 2B; while 14 weeks – 1 day, which is 97 days ( = ((6+1) × 2 × 7) – 1) for subjects on the q6w schedule for tumor assessment in Cohorts 3A and 3B:

a. Duration between two consecutive tumor assessments

b. Duration between the last adequate tumor assessment and PD

The priority of the censoring rules is as follows:

1. If the subject had PD, the following sequence will be applied:
   - If a subject did not have a baseline or postbaseline tumor assessment (Nos. 1 and 2), the subject will be censored on the date of first dose. If a subject had new anticancer treatment before PD (No. 6), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment. If PD is reported after the drug discontinuation visit, the subject will be censored at the date of last radiologic assessment before drug discontinuation except when PD happened at the same visit as drug discontinuation (No. 8). If PD happened within 4 weeks of drug discontinuation (Week 16 for Cohort 2 and Week 18for Cohorts 3A and 3B), it will be censored at drug discontinuation visit.
   - If a subject died before first tumor assessment (No. 7) or died between adequate assessment visits (No. 8), the subject will be censored on the date of death.
   - If a subject missed 2 or more tumor assessments before PD or death (No. 9), the subject will be censored on the date of the last adequate tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criterion, the earliest censoring date will be used.
   - Otherwise, if a subject had an event (No. 3), the earliest event date will be used.
2. If a subject did not have PD, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, No. 2, No. 4, No. 5, No. 6, No 9).

The distribution of PFS and TTP will be estimated using the KM method. Median, Q1 and Q2 times to PFS, TTP, and the 95% CIs will be provided for each treatment cohort (estimated with the Brookmeyer and Crowley method). Four-month and 12-month PFS and TTP rates will be estimated using the KM method and corresponding 80 and 95% CIs will be provided (estimated with the Greenwood formula using the log-log transformation [Greenwood, 1926; Kalbfleisch and Prentice, 2002]) when an adequate number of at-risk subjects at those time points warrant the estimate. Follow-up time for PFS and follow-up time for progression-free duration will be presented for PFS and TTP, respectively (estimated using the KM method with median, Q1, and Q2 times). The 95% CIs will be estimated with the Brookmeyer and Crowley method. Estimates for both PFS and TTP follow-up times are calculated in the same way as the KM estimates of PFS and TTP, but with the meaning of 'censor' and 'event' status indicator reversed.

The secondary efficacy analyses for Cohort 3B will be based on the lenvatinib-naïve subjects in the Full Analysis Set, while subjects enrolled from Cohorts 1 and 2B will be summarized as appropriate.

### 5.4.3 Other Efficacy Analyses

#### 5.4.3.1 Exploratory Efficacy Analyses

**OS**

OS is measured from the start date of the treatment period until date of death from any cause. All events of death will be included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject has no record of death, then the data will be censored at the date the subject was last known to be alive, or the data cutoff date, whichever is earlier (censoring rules see SAP Table 5). The distribution of OS will be estimated using the KM method. Median, Q1 and Q2 survival times will be estimated by KM method, and the 95% confidence interval estimated with the Brookmeyer and Crowley method. Survival rates at 4 and 12 months will be estimated using the KM method (and corresponding 95% CIs estimated with the Greenwood formula using the log-log transformation) for each treatment cohort when an adequate number of at-risk subjects at those time points warrant the estimate. Follow-up time for OS will be presented KM method. Median, Q1, and Q2 follow-up times, and the 95% CIs (using the Brookmeyer and Crowley method) will be estimated. Estimates for OS follow-up time are calculated in the same way as the KM estimate of OS, but with the meaning of 'censor' and 'event' status indicator reversed.

**Table 5 Censoring Rules for Overall Survival Endpoint**

| Situation | End Date | Outcome |
|---|---|---|
| Death during study | Date of death | Death |
| Death after data cut-off | Date of data cut-off | Censored event |
| Subject still alive at data cut-off | Date of data cut-off | Censored event |
| Subject lost to follow-up before data cut-off | Date last known to be alive | Censored event |

**PFS-4 RATE FOR COHORT 3A**

This analysis will be performed for Cohort 3A. See Section 5.4.2.1 cohort 3B: osteosarcoma combination expansion for details.

## 5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

### 5.5.1 Pharmacokinetic Analyses

Plasma concentration of lenvatinib versus time data will be listed. Pharmacokinetic data will be summarized using n, mean, SD, median, Q1, Q2, minimum, and maximum.

Plasma concentration of lenvatinib versus time data from all cohorts will be pooled and analyzed using a population PK approach to estimate population PK parameters. The analysis will be detailed in a separate analysis plan.

### 5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Correlation between clinical response to lenvatinib treatment or AEs associated with lenvatinib treatment and blood or tumor biomarkers may be examined using descriptive statistics and graphic displays as appropriate. A separate analysis plan will be developed for the analyses of PK/pharmacodynamics, pharmacogenomic and other biomarker analyses. Results from these analyses will not be included in the clinical study report but reported separately.

## 5.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, including treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, and left ventricular ejection fraction (LVEF) will be presented by study cohort and summarized on an "as treated" basis using descriptive statistics (e.g., n, mean, SD, median, Q1, Q3, minimum, and maximum values for continuous variables; n (%) for categorical variables). Study Day 1 for all safety analyses is defined as the date of the first dose of study drug.

In addition, results of urine dipstick (proteinuria), occult blood in stool, KPS or Lansky play scores, and proximal tibial growth plates at scheduled time points, as well as their changes from Baseline, will be summarized by study cohort using descriptive statistics, as appropriate.

### 5.6.1 Extent of Exposure

#### 5.6.1.1 Extent of Exposure of Study Drug

All parameters that represent the extent of exposure will be presented for Cohorts 1 and 3A of Phase 1, and Cohorts 2A, 2B and 3B of Phase 2. Number of cycles received will be summarized by descriptive statistics and by categories. Duration of treatment (days) for oral drug lenvatinib will be summarized by descriptive statistics. It is calculated as: Date of last dose – Date of first dose + 1. While the duration of treatment for the IV drugs, ifosfamide and etoposide (Cohorts 3A and 3B), will be counted in days as it is actually administrated.

#### 5.6.1.2 Study Drug Administration

Total cumulative dose per subject (mg) will be summarized separately for lenvatinib, ifosfamide and etoposide by descriptive statistics. It is calculated as the sum of daily doses.

Dose intensity (mg/$m^2$/day) will be summarized separately for lenvatinib, ifosfamide, and etoposide by descriptive statistics. It is calculated as: Total cumulative dose per subject (mg) /BSA ($m^2$)/ Duration of treatment (day).

The percentage of received dose relative to planned dose will be summarized separately for lenvatinib, ifosfamide and etoposide by descriptive statistics. It is calculated as: dose

intensity / planned dose level × 100. Interpretation: 100 means received dose was the same as the planned, 90 means that the actual dose was 90% of the planned.

#### 5.6.1.3 Study Drug Dose Modifications

Study drug dose modifications will be summarized separately for lenvatinib, ifosfamide, and etoposide, respectively.

Number of subjects with dose reductions, treatment interruptions, and treatment discontinuation due to AEs will be summarized by counts and percentage according to dosing data. Cycle of first dose interruption/reduction, and treatment discontinuation will be summarized by descriptive statistics. Frequency of dose interruptions will also be summarized by appropriate categories (e.g., 1, 2, 3, ≥4). Frequency of dose reductions will be summarized by categories (1, 2, 3).

The first dose reduction is defined as the first time the subject's daily dose level was reduced to a non-zero value from its maximum designated BSA-adjusted dose level and did not go back to the maximum designated BSA-adjusted dose level due to a reason other than BSA adjustment or dosing error. For example, 17 $mg/m^2$ followed by 0 $mg/m^2$ followed by 14 $mg/m^2$. If there is only dose interruption with no reduction in dose, such an event will not be considered as a dose reduction. The second and subsequent dose reductions will be defined accordingly. In addition, time to first dose reduction among subjects with dose reduction will also be summarized.

Dose interruptions will only be determined for lenvatinib. Definition of dose interruption:

1. Only includes the scenario that before and after dose 0 $mg/m^2$ (interruption period), the dose levels are the same. For example: 17 $mg/m^2$ followed by 0 $mg/m^2$ and followed by 17 $mg/m^2$; 14 $mg/m^2$ followed by 0 $mg/m^2$ followed by 14 $mg/m^2$.
2. If dose level reduces from previous dose level after dose interruption period (dose 0 $mg/m^2$), it should count as dose reduction and not dose interruption. For example: 17 $mg/m^2$ followed by 0 $mg/m^2$ followed by 14 $mg/m^2$, the period with 0 $mg/m^2$ should not count as dose interruption instead it should count as dose reduction.
3. If after dose level 0 $mg/m^2$, the subject discontinued from treatment permanently, it should count as treatment discontinuation instead of dose interruption.

Subject data listings will be provided for all dose administration records and for the variables calculated as above.

#### 5.6.1.4 Dose Limiting Toxicity

DLTs were recorded during Cycle 1 (Day 1 to Day 28) for Cohort 1 and during Cycle 1 (Day 1 to Day 21) for Cohort 3A. The DLT (Yes/No) and reason(s) (see Section 13.1) for each subject will be listed, as well as the date, and dosage of drug when the DLT occurred.

### 5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA version 21.1. Adverse events will be coded to primary System Organ Class (SOC), preferred term (PT) and lower level term (LLT) using MedDRA.

A TEAE is defined as an AE that had an onset date on or after the first dose of study drug up to 30 days following the last dose of study drug, or a worsening in severity from Baseline (pretreatment). In addition, if an AE reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, it is also counted as TEAE. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be used to assess the severity of AEs.

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. TEAEs will be summarized by cohort and dose level in Phase 1 and by cohort in Phase 2.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs within an SOC and PT. Subjects will be counted only once within an SOC and PT, even if the subject experiences more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by highest CTCAE grade. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be possibly or probably related to study drug or missing causality.

In summary, the following TEAE tables will be provided:

- Overview of TEAEs
- TEAEs by SOC and PT
- TEAEs in decreasing frequency of PT
- TEAEs by SOC, PT, and CTCAE grade
- TEAEs with CTCAE Grades ≥3 by decreasing frequency of PT
- Treatment-related TEAEs by SOC and PT
- Treatment-related TEAEs by SOC, PT, and CTCAE grade
- Treatment-related TEAEs by decreasing frequency of PT
- Treatment-related TEAEs by decreasing frequency of PT with CTCAE Grades ≥3
- Treatment-related TEAEs by decreasing frequency of PT with CTCAE Grades 3 or 4
- Treatment-related TEAEs with CTCAE Grades 3 or 4 by SOC and PT
- Grade 5 (fatal) treatment-related TEAEs by decreasing frequency of PT

- Grade 5 (fatal) treatment-related TEAEs by SOC and PT

The following TEAE tables will be provided by age group category (2 to <6 and 6 to <18).

- TEAEs in decreasing frequency of PT by age group
- Serious TEAEs in decreasing frequency of PT by age group

The number (percentage) of subjects with Grade 5 (fatal) TEAEs will be summarized by MedDRA SOC and PT and a subject data listing of all deaths (whether or not treatment emergent) will be provided. All deaths reported will also be summarized in a table.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation, dose modification (reduction or interruption) of study drug will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation, dose reduction, or dose interruption of study drug will also be summarized by MedDRA SOC and PT.

In summary, the following tables will be provided:

- All deaths in the safety analysis set
- Grade 5 (fatal) TEAEs by decreasing frequency of PT
- Grade 5 (fatal) TEAEs by SOC and PT
- Treatment-emergent SAEs by SOC and PT
- Treatment-related treatment-emergent SAEs by SOC and PT
- Treatment-emergent SAEs by decreasing frequency of PT
- Non-fatal treatment-emergent SAEs by SOC and PT
- TEAEs leading to study drug discontinuation by decreasing frequency of PT
- TEAEs leading to study drug discontinuation by SOC and PT
- TEAEs leading to study drug dose reduction and/or dose interruption by decreasing frequency of PT
- TEAEs leading to study drug dose reduction and/or dose interruption by SOC and PT
- TEAEs leading to study drug dose reduction by decreasing frequency of PT
- TEAEs leading to study drug dose reduction by SOC and PT

Clinically significant treatment-emergent AEs (CSAEs) for lenvatinib include arterial TE (thromboembolic) events, cardiac dysfunction, fistula formation, gastrointestinal (GI)

perforation, hemorrhage, hepatotoxicity, hypertension, hypocalcemia, palmar plantar erythrodysaesthesia syndrome (PPE), posterior reversible encephalopathy syndrome (PRES), proteinuria, QT prolongation, renal events, impaired wound healing, weight loss, and pneumothorax. The number and percentage of each category of treatment-emergent CSAEs will be summarized by overall, CTCAE grade and by dose level for Phase 1 and by cohort for Phase 2. Time to first onset of CSAEs for lenvatinib will also be summarized.

The following tables will be provided only for CSAEs.

- Summary of CSAEs by category and PT
- Summary of serious CSAEs by category and PT
- Overview of CSAEs by category
- Incidence and Time to First Onset of CSAEs
- Time to first onset of each CSAE for Lenvatinib
- CSAEs by SOC, PT, and CTCAE grade

The following tables will be provided only for Cohort 1.

- TEAEs in run-in period in decreasing frequency of PT
- TEAEs in run-in period by SOC and PT
- TEAEs in run-in period with CTCAE Grades ≥3 by decreasing frequency of PT

The following tables will be provided only for Cohorts 1 and 3A.

- TEAEs in Cycle 1 in decreasing frequency of PT
- TEAEs in Cycle 1 by SOC and PT
- TEAEs in Cycle 1 with CTCAE Grades ≥3 by decreasing frequency of PT

The following subject AE listings (treatment-emergent or otherwise) will be provided:

- All AEs
- All deaths for all enrolled subjects
- All SAEs
- All AEs leading to study drug discontinuation
- All AEs leading to dose reduction and / or dose interruption
- All CSAEs

The following subject TEAE listing will be provided only for Cohort 1.

- TEAES in run-in period

The following subject listings will be provided only for Cohorts 1 and 3A.

- DLTs in Cycle 1
- TEAEs in Cycle 1

### 5.6.3 Laboratory Values

Laboratory values that are nonmissing and reported as ”below the detectable limit” of an assay will be replaced by half the detectable limit in the summary tables. Laboratory results will be summarized using *Système international* (SI) units. Laboratory test results will be 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. Abnormal laboratory values will be identified as those outside the normal range. The abnormal values will be indicated in data listings. The CTCAE grade will also be included in the listing.

Laboratory tests during treatment are defined as laboratory tests conducted from the start of treatment to no more than 30 days after the last dose of study drug. Only laboratory parameters specified in the protocol will be summarized. Other laboratory parameters collected for some individual subjects will be presented in listings only. Baseline is defined as the last nonmissing result prior to the first administration of study drug.

For quantitative parameters, the actual value and the change from Baseline to each postbaseline visit will be summarized by visit and cohort using descriptive statistics. Qualitative parameters will be summarized using frequencies (number and percentage of subjects), and changes from baseline to the worst postbaseline visit will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

#### 5.6.3.1 Hematology and Clinical Chemistry

Laboratory parameters will be reported using the following methods for hematology and clinical chemistry:

- Descriptive summary statistics for all major hematology and clinical parameters and their changes from baseline will be calculated (n, mean, SD, median, Q1, Q3, min, max)
- Shifts from Baseline to worst postbaseline visits relative to CTCAE grade (presenting each dose level and overall shift table for all clinical chemistry parameters and the following hematology parameters: hemoglobin, platelets, WBC (leukocytes), neutrophils (ANC), and lymphocytes)

All hematology and clinical chemistry laboratory parameters will be listed by subject and visit.

#### 5.6.3.2 Thyroid-Stimulating Hormone

Thyroid-stimulating hormone values will be summarized in 2 categories (≤ULN and >ULN) for non-DTC Cohorts 1, 2B, 3A and 3B, and in 3 categories (≤0.5, 0.5-5.5 and >5.5) for DTC Cohort 2A.

#### 5.6.3.3 Urinalysis

The shift of worst postbaseline proteinuria from baseline will be summarized. All urinalysis parameters (RBCs/high-power-field [HPF], blood, and protein [dipstick], 24-hour urine protein) and guaiac fecal occult blood (negative, positive) will be provided by subject listing at each visit.

### 5.6.4 Vital Signs

Vital signs will be summarized by assessment time and cohort/dose level for Phase 1 or cohort for Phase 2 for the actual value and change from Baseline. Baseline will be defined as the last nonmissing result prior to the first administration of study drug.

Vital sign values will be evaluated on an individual basis by subject. Descriptive statistics for vital sign parameters (systolic [SBP] and diastolic [DBP] blood pressure, pulse rate, respiratory rate, body temperature) and weight and height, as well as changes from Baseline, will be presented by cohort for each cycle and day.

Percentiles for BP values (only for subjects <18 years old [see Protocol Appendix 7]) will also be summarized using a shift table of worst postbaseline from Baseline measurement by categories (<90th percentile, 90th to 95th percentile, 95th to ≤99th percentile, SBP or DBP >99th percentile). The overall percentile is taken as the worse of SBP/DBP percentiles.

### 5.6.5 Other Safety Analyses

#### 5.6.5.1 Electrocardiograms

ECG assessments will be performed at Screening and at Day 1 of each cycle. Descriptive statistics for electrocardiogram parameters (HR, PR, QRS, QT, QTcB, QTcF and RR) and changes from Baseline will be presented by visit. ECG findings will be summarized. A shift table of worst postbaseline values from Baseline for ECG findings will be provided. A subject data listing will also be provided.

In addition, the number (percentage) of subjects with at least 1 postbaseline ECG result in QTc Bazett and QTc Fridericia during the treatment phase will be summarized. ECG results in QTc Bazett and QTc Fridericia will be categorized as follows:

- For subjects with Baseline and postbaseline data, maximum increase from Baseline (msec) of ≤ 30, > 30 to ≤ 60, and >60
- Maximum postbaseline value (msec) of ≤ 450, > 450 to ≤ 480, > 480 to ≤ 500, and > 500

#### 5.6.5.2 Left Ventricular Ejection Fraction

The LVEF will be summarized by descriptive statistics by visit (mean, standard deviation, median, Q1, Q3, minimum, and maximum values), and percentage change from Baseline, and by percentage of reduction from Baseline (> 0 to ≤10%, >10 to ≤15%, >15%) as well as the occurrence of subjects having a lowest postbaseline value of <50%. A subject data listing will be provided.

#### 5.6.5.3 Lansky Play Scores or Karnofsky Performance Status Scores

Lansky play scores or KPS scores will be summarized by shifts from Baseline to worst postbaseline visit. A subject listing of Lansky play scores or KPS scores, will be provided.

#### 5.6.5.4 Proximal Tibial Growth Plates

Radiographic findings of proximal tibial growth plates will be listed.

### 5.7 Other Analyses

Each question in the Palatability and Acceptability Questionnaire will be listed using the Palatability Analysis Set.

### 5.8 Exploratory Analyses

See Section 5.4.3.1 for Exploratory Efficacy Analyses.

## 6 INTERIM ANALYSES

After completion of treatment in Cohort 1 and Cohort 3A, data will be reviewed with the PSC to determine the RD. In addition, the sponsor will closely evaluate the risks and benefits of the study throughout its conduct, along with the PSC as needed.

## 7 CHANGES IN THE PLANNED ANALYSES

The following are changes in the analyses compared to Protocol Amendment 3 (01 Ssep2016).

### 7.1 PFS-4 in Cohort 3A

PFS-4 rate in Cohort 3A has been added as an exploratory efficacy endpoint to further explore the efficacy of lenvatinib in combination with ifosfamide and etoposide in pediatric osteosarcoma subjects.

## 7.2 Analysis Sets

The following analysis sets have been included to help with analyses.

- Full Analysis Set
- Per Protocol Analysis Set
- Palatability Analysis Set

**The DLT Analysis Set** will be defined for Cohort 1 and 3A.

## 7.3 Proximal Tibial Growth Plates and Palatability and Acceptability Questionnaire

Because of small numbers of subjects, results for these two variables will be presented in subject listings and not formally analyzed.

# 8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

## 8.1 Visit Windows

Visit windows will be defined to be upper and lower bounds of 1 day of the scheduled visit, following the protocol, which states that efforts should be made to conduct laboratory assessments and administer treatment on the day scheduled (±1 day).

Tumor assessments for efficacy analysis are to be performed every 8 weeks (within Week 8) for Cohorts 1, 2A and 2B and every 6 weeks (within Week 6) for Cohort 3A and 3B (or sooner if clinically indicated) until documentation of PD.

In the calculation of descriptive statistics for laboratory values and vital signs, if a visit has multiple observations, the observation closest in date and time to the target visit day will be used in the analysis. If 2 or more observations have the same distance to the target visit day, the one that has the highest CTCAE grade or is farthest outside the normal range will be used. The purpose of this windowing is to provide a single record per subject per visit for the calculation of descriptive statistics and change from Baseline per visit. Other safety analyses (e.g., worst grade for laboratory results) will include all observations. All by-visit analyses will be performed using assessments at corresponding scheduled visits recorded in the eCRF. Data from all postbaseline assessments including those at scheduled and unscheduled visits will be used in the shift tables.

## 8.2 Safety and Efficacy Data Handling

### 8.2.1 Partial dates

Partial dates for AE and prior/concomitant medication, laboratory values, vital signs, and ECGs will not be imputed.

#### 8.2.1.1 Diagnosis date

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day
- If both the day and the month are missing, "July 1" will be used to replace the missing information

#### 8.2.1.2 Date of Death

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day
- If both the day and the month are missing, "Jan 1" will be used to replace the missing information
- If the entire date is missing, the date of death will be imputed as the last known date the subject was known to be alive + 1 day

#### 8.2.1.3 Date of Progression

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day
- If the day and month are missing or a date is completely missing, it will be considered as missing and no date will be imputed

In case the date of death is present (complete date), the imputed progression date will be compared with the date of death. The earlier date of imputed progression date and date of death will be considered as the date of progression.

#### 8.2.1.4 Date of Last Tumor Assessment

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day
- If the day and month are missing or a date is completely missing, it will be considered as missing and no date will be imputed

In case the date of death is present (complete date), the imputed date for tumor assessment parameters will be compared with the date of death. The earlier date of the imputed date and date of death will be considered as the date of last tumor assessment.

#### 8.2.1.5 Date of Start of Subsequent Anticancer Therapy

- When the day is missing, it is assumed that the subsequent therapy started on the first day of the given month if this day is later than the last dosing date. Otherwise, it is assumed that the subsequent therapy started on the day following the last dosing date.
- When the day and the month are missing, it is assumed that the subsequent therapy started on the first day of the given year if this day is later than the last dosing date. Otherwise, it is assumed that the subsequent therapy started on the day following the last dosing date.

## 8.3 Definitions, Derived Variables, and Data Sets

### 8.3.1 Baseline

Baseline value is defined as the predose value on Cycle 1 Day 1 or the last observation before start of drug if the predose value on Cycle 1 Day 1 is missing.

### 8.3.2 Date/Time Definitions

The following factors will be used to convert days to months or years:

1 month = 30.4375 days

- Time from first diagnosis to first dose (months) is:
  (Date of first dose – Date of first diagnosis) / 30.4375
- Time from first metastatic diagnosis to first dose (months) is:
  (Date of first dose – Date of first metastatic diagnosis) / 30.4375
- Time from last medication to first dose (months) is:
  (Date of first dose – End date of last medication) / 30.4375
- Time from last procedure to first dose (months) is:
  (Date of first dose – Start date of the last anti-cancer procedure) /30.4375
- Time from last radiotherapy to first dose (months) is:
  (Date of first dose – End date of the last radiotherapy) / 30.4375
- Time from last radioiodine therapy to first dose (months) is:
  (Date of first dose – End date of the last radioiodine therapy) /30.4375

### 8.3.3 Radioiodine Therapy Conversions

The SI unit for radioiodine therapy is GBq (1 gigabecquerel = $10^9$ Bq). Data was also collected with the unit mCi (millicuries). The conversion is 1 mCi = 0.037 GBq.

### 8.3.4 Creatinine Clearance

The pediatric Schwartz equation for creatinine clearance is:

- GFR (mL/min/1.73 $m^2$) = (0.41 x Height) / Scr, where Scr is serum/plasma creatinine in mg/dL

### 8.3.5 Last Known Alive Date

The last date the subject was known to be alive should be derived from survival follow-up date or the latest date among last treatment date, last radiologic follow-up date, last laboratory assessment date, last AE date, last concomitant medication date, or last vital sign measurement date.

## 8.4 Pharmacokinetics/Pharmacodynamics Data Handling

### 8.4.1 Lower Limit of Quantification of Lenvatinib Plasma Concentration

The lower limit of quantification (LLOQ) of lenvatinib plasma concentration is 0.25 ng/mL.

### 8.4.2 BLQ Handling for Developing Concentration-Time Profiles

When calculating the mean or median value for the concentration at a given time point, the BLQ values will be assigned as zero. If the proportion of values reported as BLQ is more than 50%, no summary statistics should be represented at that time point, and the value will be treated as missing in mean or median concentration profiles.

# 9 PROGRAMMING SPECIFICATIONS

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

# 10 STATISTICAL SOFTWARE

Statistical programming and analyses will be performed using SAS® (SAS Institute, Inc., Cary, NC, USA), version 9 or higher, and/or other validated statistical software as required.

# 11 MOCK TABLES, LISTINGS, AND GRAPHS

The 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

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# 13 APPENDICES

## 13.1 Dose-Limiting Toxicities

Dose-limiting toxicity (DLT): A DLT in subjects treated with lenvatinib will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and is defined as any of the following toxicities related to lenvatinib or chemotherapy drugs (ifosfamide and/or etoposide) occurring during Cycle 1 (Day 1 to Day 28) for Cohort 1 and during Cycle 1 (Day 1 to Day 21) for Cohort 3A.

- Hematologic Toxicity
  - Grade 4 neutropenia for ≥7 days (≥10 days for Cohort 3A)
  - Grade ≥3 thrombocytopenia with bleeding, or lasting >7 days (≥10 days for Cohort 3A)
  - Grade ≥3 febrile neutropenia(lasting ≥7 days for Cohort 3A)
  - Next course of chemotherapy delayed for ≥7 days (Cohort 3A)
- Nonhematologic toxicity
  - Grade ≥3 nonhematological toxicity persisting more than 7 days despite optimal supportive care. Isolated laboratory abnormalities that resolve within a week, allergic reactions, and symptoms related to tumor progression will be excluded.
  - Grade 4 hypertension, confirmed systolic or diastolic blood pressure more than 25 mmHg above the 95th percentile for age, or an elevated diastolic blood pressure (ie, >95th percentile for age) not controlled by a single antihypertensive medication within 14 days of use. An antihypertensive tablet or capsule that contains up to two antihypertensive ingredient medications will count as one antihypertensive medication.
  - Grade 3 proteinuria
  - Any recurrent Grade 2 nonhematological toxicity requiring ≥2 interruption and dose reductions
- Any dose interruption or reduction due to toxicity which results in administration of less than 75% of the planned dosage of lenvatinib.
- Any other Grade ≥3 toxicity (hematologic and nonhematologic) assessed as related to lenvatinib treatment, and which in the opinion of the principal investigator and Eisai medical monitor constitutes a dose-limiting toxicity

All DLTs must be reported to the Eisai medical monitor within 24 hours of their occurrence. Determination of a DLT will be made by the investigator and Eisai Medical Monitor in consultation with the PSC, as needed. Subjects who discontinue study drug for any reason other than DLT during Cycle 1 (Day 1 to Day 28) for Cohort 1 and Cycle 1 (Day 1 to Day 21) for Cohort 3A will be replaced.

## 13.2 Summary of Efficacy Analyses

| Efficacy Variable | Analysis Set | Statistical Method | Tumor Assessments |
|---|---|---|---|
| PFS-4 | Full Analysis Set, Per Protocol Analysis Set | Number (percent) of subjects who are alive, free of disease progression, and did not receive anticancer medication 4 months after the first dose, and its exact 80 and 95% CIs using method of Clopper and Pearson.<br><br>Cohort 2B: PFS-4 rate will be tested using a Null hypothesis that PFS-4 is ≤25% tested against the alternative hypothesis of a PFS-4 ≥45%, using the 1-sample exact test of a single proportion, at the 1-sided 0.1 level.<br><br>Cohort 3B: PFS-4 rate will be tested using a Null hypothesis that PFS-4 is ≤25% tested against the alternative hypothesis of a PFS-4 ≥50%, using the 1-sample exact test of a single proportion, at the 1-sided 0.1 level. | Investigator |
| ORR | Full Analysis Set, Per Protocol Analysis Set | Number (percent) of subjects (with PR + CR) and its exact 95% CI using method of Clopper and Pearson. | Investigator |
| PFS | Full Analysis Set, Per Protocol Analysis Set | KM method: Median, Q1, and Q2 PFS will be presented, with 2-sided 95% CIs (Brookmeyer and Crowley). Cumulative probability of PFS at 4 and 12 months will be presented with 2-sided 80 and 95% CIs (Greenwood using the log-log). KM plot will also be provided. | Investigator |
| OS | Full Analysis Set | KM method: Median, Q1, and Q2 OS, and cumulative probability of OS at 4 and 12 months will be presented. 2-sided 95% CIs (Brookmeyer and Crowley for quartiles and Greenwood using log-log for probability of 4 and 12 Months). KM | Not Applicable |

| Efficacy Variable | Analysis Set | Statistical Method | Tumor Assessments |
|---|---|---|---|
| | | plot will also be provided. | |
| BOR | Full Analysis Set, Per Protocol Analysis Set | Number (percent) and 95% exact CIs will be provided for each BOR category | Investigator |
| DOR | Full Analysis Set, Per Protocol Analysis Set | KM method: Median, Q1, and Q2 PFS will be presented, with 2-sided 95% CIs (Brookmeyer and Crowley). | Investigator |
| TTP | Full Analysis Set, Per Protocol Analysis Set | Kaplan-Meier method: Median, Q1, and Q2 TTP will be presented with 2-sided 95% CIs (Brookmeyer and Crowley). Cumulative probability of TTP at 4 and 12 months will be presented with 2-sided 80 and 95% CIs (Greenwood using log-log). Kaplan-Meier plot will also be provided. | Investigator |

| Efficacy Variable | Analysis Set | Statistical Method | Tumor Assessments |
|---|---|---|---|
| DCR | Full Analysis Set | Number (percent) of subjects (measurable disease with CR + PR + stable disease [SD] ≥ 7 weeks, evaluable disease with CR + Non-CR/Non-PD ≥ 7 weeks) and its exact 95% CI using method of Clopper and Pearson. | Investigator |
| CBR | Full Analysis Set | Number (percent) of subjects (measurable disease with CR+ PR + SD≥ 23weeks, evaluable disease with CR + Non-CR/Non-PD ≥ 23 weeks) and its exact 95% CI using method of Clopper and Pearson. | Investigator |

## 13.3 Common Terminology Criteria For Adverse Events (CTCAE) For Hematology & Clinical Chemistry

| Laboratory Parameter | Common Terminology Criteria for Adverse Events (CTCAE) | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| **Hematology** | | | | |
| Hemoglobin | < LLN – 10 *g/d*L<br>< LLN – 6.2 *mmol*/L | < 10 – 8 *g/d*L<br>< 6.2 – 4.9 *mmol*/L | < 8 – 6.5 *g/d*L<br>< 4.9 – 4 *mmol*/L | – |
| Platelet Count | < LLN – 75,000/*mm3*<br>< LLN – 75 x 109/L | < 75,000 – 50,000/$mm^3$<br>< 75 – 50 x $10^9$/L | < 50,000 – 25,000/$mm^3$<br>< 50 – 25 x $10^9$/L | < 25,000/$mm^3$<br>< 25 x $10^9$/L |
| Leukocytes (Total WBC) | < LLN – 3,000/$mm^3$<br>< LLN – 3 x $10^9$/L | < 3,000 – 2,000/$mm^3$<br>< 3 – 2 x $10^9$/L | < 2,000 – 1000/$mm^3$<br>< 2 – 1 x $10^9$/L | < 1,000/$mm^3$<br>< 1 x $10^9$/L |
| Lymphocytes (*hypo*) | < LLN – 800/$mm^3$<br>< LLN – 0.8 x $10^9$/L | < 800 – 500/$mm^3$<br>< 0.8 – 0.5 x $10^9$/L | < 500 – 200/$mm^3$<br>< 0.5 – 0.2 x $10^9$/L | < 200/$mm^3$<br>< 0.2 x $10^9$/L |
| Lymphocytes (*hyper*) | - | > 4,000 – 20,000/$mm^3$<br>> 4 – 20 x $10^9$/L | > 20,000/$mm^3$<br>> 20 x $10^9$/L | – |
| Neutrophils | < LLN – 1,500/$mm^3$<br>< LLN – 1.5 x $10^9$/L | < 1,500 – 1,000/$mm^3$<br>< 1.5 – 1 x $10^9$/L | < 1,000 – 500/$mm^3$<br>< 1 – 0.5 x $10^9$/L | < 500/$mm^3$<br>< 0.5 x $10^9$/L |
| **Clinical Chemistry** | | | | |
| Albumin | < LLN – 3 *g/d*L<br>< LLN – 30 *g*/L | < 3 – 2 *g/d*L<br>< 30 – 20 *g*/L | < 2 *g/d*L<br>< 20 *g*/L | |
| Alkaline Phosphatase | > 1 – ≤ 2.5 x ULN | > 2.5 – ≤ 5 x ULN | > 5 – ≤ 20 x ULN | > 20 x ULN |
| ALT | > 1 – ≤ 3 x ULN | > 3 – ≤ 5 x ULN | > 5 – ≤ 20 x ULN | > 20 x ULN |
| Amylase | > 1 – ≤ 1.5 x ULN | > 1.5 – ≤ 2 x ULN | > 2 – ≤ 5 x ULN | > 5 x ULN |

| Laboratory Parameter | Common Terminology Criteria for Adverse Events (CTCAE) | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| AST | > 1 – ≤ 3 x ULN | > 3 – ≤ 5 x ULN | > 5 – ≤ 20 x ULN | > 20 x ULN |
| Bilirubin, Total | > 1 – ≤ 1.5 x ULN | > 1.5 – ≤ 3 x ULN | > 3 – ≤ 10 x ULN | > 10 x ULN |
| Calcium (*hyper*) | > ULN – ≤ 11.5 *mg/d*L<br>> ULN – ≤ 2.9 *mmol*/L | > 11.5 – ≤ 12.5 *mg/d*L<br>> 2.9 – ≤ 3.1 *mmol*/L | > 12.5 – ≤ 13.5 *mg/d*L<br>> 3.1 – ≤ 3.4 *mmol*/L | > 13.5 *mg/d*L<br>> 3.4 *mmol*/L |
| Calcium (*hypo*) | < LLN – 8 *mg/d*L<br>< LLN – 2 *mmol*/L | < 8 – 7 *mg/d*L<br>< 2 – 1.75 *mmol*/L | < 7 – 6 *mg/d*L<br>< 1.75 – 1.5 *mmol*/L | < 6 *mg/d*L<br>< 1.5 *mmol*/L |
| Cholesterol, Total | > ULN – 300 *mg/d*L<br>> ULN – 7.75 *mmol*/L | > 300 – 400 *mg/d*L<br>> 7.75 – 10.34 *mmol*/L | > 400 – 500 *mg/d*L<br>> 10.34 – 12.92 *mmol*/L | > 500 *mg/d*L<br>> 12.92 *mmol*/L |
| Creatinine | > 1 – ≤ 1.5 x ULN | > 1.5 – ≤ 3 x ULN | > 3 – ≤ 6 x ULN | > 6 x ULN |
| Glucose (*hyper*) | > ULN – ≤ 160 *mg/d*L<br>> ULN – ≤ 8.9 *mmol*/L | > 160 – ≤ 250 *mg/d*L<br>> 8.9 – ≤ 13.9 *mmol*/L | > 250 – ≤ 500 *mg/d*L<br>> 13.9 – ≤ 27.8 *mmol*/L | > 500 *mg/d*L<br>> 27.8 *mmol*/L |
| Glucose (*hypo*) | < LLN – 55 *mg/d*L<br>< LLN – 3 *mmol*/L | < 55 – 40 *mg*/dL<br>< 3 – 2.2 *mmol*/L | < 40 – 30 *mg/d*L<br>< 2.2 – 1.7 *mmol*/L | < 30 *mg/d*L<br>< 1.7 *mmol*/L |
| Lipase | > 1 – 1.5 x ULN | > 1.5 – ≤ 2 x ULN | > 2 – 5 x ULN | > 5 x ULN |
| Magnesium (*hyper*) | > ULN – ≤ 3 *mg/d*L<br>> ULN – ≤ 1.23 *mmol*/L | – | > 3 – ≤ 8 *mg/d*L<br>> 1.23 – ≤ 3.3 *mmol*/L | > 8 *mg/d*L<br>> 3.3 *mmol*/L |
| Magnesium (*hypo*) | < LLN – 1.2 *mg/d*L<br>< LLN – 0.5 *mmol*/L | < 1.2 – 0.9 *mg/d*L<br>< 0.5 – 0.4 *mmol*/L | < 0.9 – 0.7 *mg/d*L<br>< 0.4 – 0.3 *mmol*/L | < 0.7 *mg/d*L<br>< 0.3 *mmol*/L |
| Phosphate | < LLN – 2.5 *mg*/dL<br>< LLN – 0.8 *mmol*/L | < 2.5 – 2 *mg/d*L<br>< 0.8 – 0.6 *mmol*/L | < 2 – 1 *mg/d*L<br>< 0.6 – 0.3 *mmol*/L | < 1 *mg/d*L<br>< 0.3 *mmol*/L |
| Potassium (*hyper*) | > ULN – ≤ 5.5 *mmol*/L | > 5.5 – ≤ 6 *mmol*/L | > 6 – ≤ 7 *mmol*/L | > 7 *mmol*/L |

| Laboratory Parameter | Common Terminology Criteria for Adverse Events (CTCAE) | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Potassium (*hypo*) | < LLN – 3 *mmol*/L | – | < 3 – 2.5 *mmol*/L | < 2.5 *mmol*/L |
| Sodium (*hyper*) | > ULN – ≤ 150 *mmol*/I | > 150 – ≤ 155 *mmol*/L | > 155 – ≤ 160 *mmol*/L | > 160 *mmol*/L |
| Sodium (*hypo*) | < LLN – 130 *mmol*/L | – | < 130 – 120 *mmol*/L | < 120 *mmol*/L |

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