1 TITLE PAGE

Clinical Study Protocol

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
Sponsor:	Eisai Inc. 300 Tice Boulevard Woodcliff Lake New Jersey 07677 USA Eisai Ltd. Mosquito Way Hatfield, Hertfordshire, AL10 9SN United Kingdom
Investigational Product Name:	Lenvatinib
Indication:	Refractory or relapsed solid malignancies in children and adolescents
Phase:	1/2
Approval Date:	V1.0 08 May 2014 (original protocol) V2.0 12 Sep 2014 (Amendment 1) V3.0 12 Sep 2014 minor editorial corrections (Amendment 1) 14 Apr 2015 (Amendment 2) 01 Sep 2016 (Amendment 3) 22 Nov 2019 (Amendment 4)
IND Number:	113656
EudraCT Number:	2013-005534-38
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality	This document is confidential. It contains proprietary information of

Statement: Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

Revision History

Revisions per Amendment 04
Date: 22 Nov 2019

Change	Rationale	Affected Protocol Sections
Updated abbreviation for ICH as per current definition.	Administrative change	• Title page • Section 4 • Section 5.2 • Investigator Signature page
The objective "Evaluate the efficacy of lenvatinib as assessed by overall survival" was updated as a secondary objective (previously exploratory objective). Corresponding changes were also made in the endpoints and statistical analyses sections.	Update made to align with lenvatinib paediatric investigation plan.	• Synopsis: Objectives, Endpoints, Statistical Analyses • Section 8 • Section 9.7.1.1 • Section 9.7.1.5
Clarified that for subjects continuing study treatment at the time of the data cutoff date for the primary analysis, the study drugs will be ordered and dispensed manually, and IxRS dispensing will be closed out once the procedure for reconciliation of study drugs is complete for the purpose of the clinical study report.	Procedure for procurement of study drugs after data cutoff date for primary analysis was clarified.	• Section 9.4.10
Clarified that in subjects ongoing in the study at the time of data cut off date for the primary analysis, the biomarker samples will be collected at the Off-Treatment visit.	Schedule of biomarkers was updated to minimize sample collection after data cutoff date for primary analysis.	• Synopsis: Pharmacodynamic Assessments • Section 9.5.1.4 • Section 9.5.2.1 (Table 7, Table 8, Table 9
Procedure for preparation of lenvatinib suspension was updated to clarify that the suspension should be taken immediately after preparation rather than within 24 hours. Also added that for nasogastric administration, it is recommended where possible, that the syringe is held in the horizontal position while administering the suspension. Additional edits were made for further clarity of individual steps and general instructions were added.	Administrative change to clarify the preparation of lenvatinib suspension in-line with the lenvatinib SMPC. Also, the recommendation that the syringe is held in the horizontal position while administering the suspension was added to avoid the possibility of blocking the nasogastric tubing with undissolved granules.	• Appendix 12

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7080

Name of Active Ingredient: Lenvatinib

Study Protocol Title

Phase 1/2 Study of Lenvatinib in Children and Adolescents With Refractory or Relapsed Solid Malignancies and Young Adults with Osteosarcoma

Investigators

Principal Investigator: Nathalie Gaspar

Sites

Approximately 12 sites in Europe and US

Study Period and Phase of Development

Approximately 36 months

Phase 1/2

Objectives

Primary Objectives

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 by best overall response (BOR) for all subjects.
    - Cohort 2B: Relapsed or refractory osteosarcoma: by progression-free survival at 4 months (PFS-4)

Note: The tumor 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

Secondary Objectives

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), objective response rate (ORR), duration of response (DOR), progression free survival (PFS), time to progression (TTP), based on RECIST 1.1 (Appendix 1), disease control rate (DCR), and clinical benefit rate (CBR)
- Evaluate the efficacy of lenvatinib as assessed by overall survival (OS)
- 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
- Evaluate the efficacy of lenvatinib as assessed by OS
- 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)

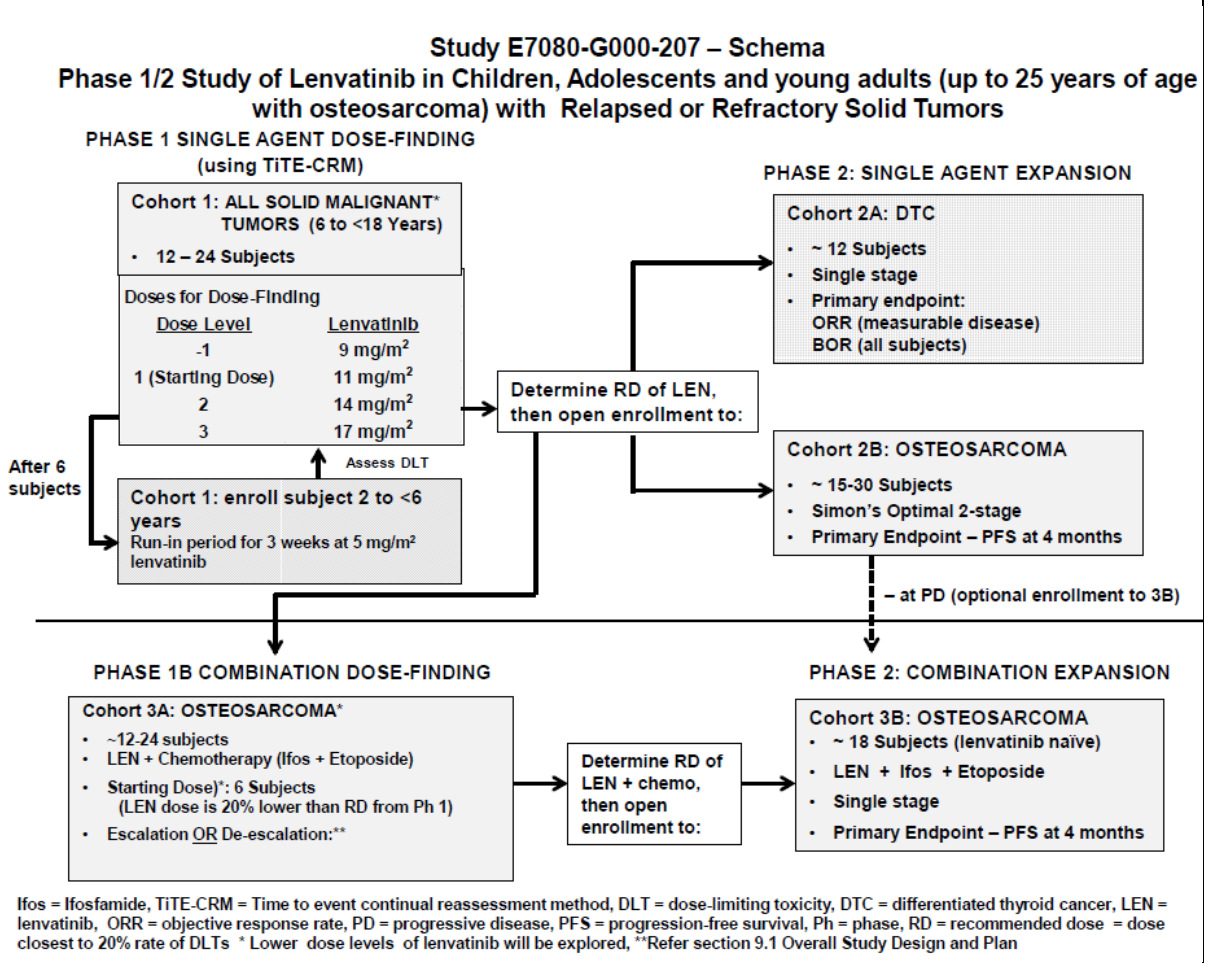
- Assess the safety and toxicity of lenvatinib in combination with ifosfamide and etoposide in children and adolescents, and young adults with relapsed or refractory osteosarcoma
- Evaluate the efficacy of lenvatinib as assessed by BOR, ORR, DOR, PFS, TTP, DCR and CBR
- Evaluate the efficacy of lenvatinib as assessed by OS
- 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

Exploratory Objective

- 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])

Study Design

This is a Phase 1/2, multicenter, open-label, study. The study will Need to update :



Cohort 1 (Single-Agent Dose-Finding): Dose-escalation to find the RD of lenvatinib using a Time to Event continual reassessment (TiTE-CRM) design in children and adolescents with relapsed or refractory solid malignant tumors (see **Study Treatment** below for dose-escalation scheme) (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).

Cohort 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). Cohort 2A and Cohort 2B will be open for enrollment 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 Cohort 1 or 2B and experienced progressive disease on lenvatinib as well as lenvatinib-naïve subjects with relapsed or refractory osteosarcoma will be candidates for enrollment in Cohort 3B.

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

Pretreatment Phase: Subjects will undergo screening evaluations to determine eligibility.

Treatment Phase:

In all cohorts, lenvatinib will be administered orally once daily (QD). One 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 is started after every 28 day period for Single-Agent Cohorts 1, 2A, and 2B or after a 21-day period for Combination-Treatment Cohorts 3A and 3B, irrespective of dose interruptions.

<u>Cohort 1 (Single-Agent Dose-Finding)</u>:

<u>Dose-Escalation in Cohort 1 Cycle 1:</u>

Subjects 6 to <18 years will enroll in Cohort 1 prior to subjects 2 to <6 years of age. The lenvatinib starting dose is 11 mg/m^2 QD (approximately 80% of the adult RD of 24 mg QD). 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). Doses of study drug administered during Cohort 1 of the study are displayed in the figure above. Dose-limiting toxicities (DLTs) that occur during Cycle 1 will be evaluated. A TiTE-CRM design will be used to drive dose-escalation and to determine the

RD of lenvatinib (Cheung and Chappell, 2000). Dose-limiting toxicities (DLTs) are defined in a table below. The RD in this study will be defined as the dose that has a DLT rate closest to the targeted 20% rate. The TiTE-CRM design allows continuous accrual throughout the study while using the 4 week toxicity endpoint as the basis for dose-escalation. At least 2 subjects should receive the full 4-week study treatment or report a DLT (at the starting dose) and complete evaluations before escalation to the next dose level. No intra-subject dose escalation will be allowed. Subjects who discontinue the study before the end of Cycle 1 (Cycle 1 Day 1 – Cycle 1 Day 28) due to reasons other than DLT will be replaced. Refer to the figure above for the study design.

Table 1: Lenvatinib Doses for Single-Agent Dose-Finding (Cohort 1)

Dose Level	Lenvatinib Once-Daily
-1	9 mg/m^2
1 (starting dose)	11 mg/m^2
2	14 mg/m^2
3	17 mg/m^2

Intrasubject dose-escalation prior to determining the RD will be allowed only for subjects 2 to <6 years of age from the Run-In Period to Cohort 1 Cycle 1 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. 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 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 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.

Cohort 2 (Single-Agent Expansion):

The efficacy of lenvatinib in children and adolescents,and young adults with osteosarcoma 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 primary efficacy endpoint in the DTC group is ORR (complete response [CR] plus partial response [PR]) for subjects with measurable disease and BOR for all subjects based on RECIST 1.1. The primary efficacy endpoint in the osteosarcoma group is PFS, assessed at 4 months based on RECIST 1.1.

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 osteosarcoma subjects as described below and in Table 2. Refer to Section 9.4.3 for dosing details.

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.

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 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 nonhematologic DLTs 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 experience nonhematologic 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 nonhematologic 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 the RD of the combination treatment.

This dose of lenvatinib will be used to treat additional subjects with osteosarcoma in Cohort 3B. Further dose de-escalation of lenvatinib or the chemotherapy dose may be considered (pending discussion with the Protocol Steering Committee [PSC]), if needed.

Cohort 3B (Combination Expansion):

Subjects with either lenvatinib-naïve relapsed osteosarcoma or osteosarcoma subjects who progress on single-agent lenvatinib in Cohorts 1 or 2B (optional enrollment) will receive the combination RD from Cohort 3A, provided the combination of lenvatinib, ifosfamide, and etoposide in Cohort 3A (Combination Dose-Finding) is judged to be safe and tolerable. Approximately 18 lenvatinib-naïve subjects will be enrolled in Cohort 3B, along with some

subjects from Cohorts 1 and 2B.

Osteosarcoma subjects who experience PD 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. For osteosarcoma subjects who experience PD in Cohort 2B and choose to receive the combination therapy of lenvatinib with ifosfamide and etoposide, prior to entering Cohort 3B (Combination Expansion), baseline tumor assessments by computed tomography/magnetic resonance imaging (CT/MRI) must be repeated on new images, unless the images confirming disease progression were performed within 28 days of Cycle 1 Day 1 in Cohort 3B. Subjects will undergo assessments as per the Schedule of Assessments provided for the combination treatment.

Subjects in Cohorts 3A and 3B will receive ifosfamide and etoposide for a maximum of 5 cycles. Subjects who discontinue ifosfamide and etoposide (eg, 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.

Subjects benefiting from the 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.

Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) in subjects treated with lenvatinib will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Appendix 2) 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)

Non-Hematologic 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 interruptions 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 PSC and medical monitor constitutes a DLT

All DLTs must be reported to the sponsor 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 the study treatment 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.

Post-treatment Follow-up: The Post-treatment Follow-up begins when the subject discontinues study treatment. All subjects who discontinue study treatment for reasons other than disease progression will be followed for documented disease progression for 1 year or until another anticancer therapy is initiated. Subjects will be followed for survival every 3 months until death or for 1 year unless the study is terminated or if the subject discontinues due to withdrawal of consent or is lost to follow-up.

Each cohort will have its own cut-off date for the final analysis for the CSR reporting purpose.

Cohorts 1 and 3A:

For purposes of the final analysis, 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.

Cohorts 2A, 2B, and 3B:

For DTC and osteosarcoma subjects, the cutoff will be after the completion of 6 cycles by the last subject enrolled in each cohort or early discontinuation before the end of Cycle 6, whichever occurs first (see figure above).

Number of Subjects

Approximately 69 to 108 subjects ages 2 to <18 years (≤25 years for osteosarcoma subjects)

are planned to be enrolled in this study.

Cohort 1 (Single-Agent Dose-Finding): Approximately 12 to 24 subjects with relapsed or refractory solid malignancies

Cohort 2 (Single-Agent Expansion): Approximately 27 to 42 subjects divided into 2 malignancy-type groups:

Cohort 2A: DTC group (approximately 12 subjects) and

Cohort 2B: Osteosarcoma group (15 to 30 subjects)

Cohort3A (Combination Dose-Finding): Approximately 12 to 24 subjects with osteosarcoma

Cohort 3B (Combination Expansion): Approximately 18 lenvatinib-naïve subjects with osteosarcoma (along with some subjects from Cohorts 1 and 2B after experiencing PD)

Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of solid malignant tumor
   a. Cohort 1: Any solid malignant tumor
   b. Cohort 2A: DTC with one of the following histologic subtypes:
      a. Papillary thyroid cancer (PTC)
         1. Follicular variant
         2. Other variants (including, but not limited to, tall cell, columnar cell, cribriform-morular, solid, oxyphil, Warthin's-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of papillary carcinoma, or poorly differentiated carcinomas)
      b. Follicular thyroid cancer (FTC)
         1. Hürthle cell
         2. Clear cell
         3. Insular
   c. Cohort 2B, 3A, and 3B: Relapsed or refractory osteosarcoma
2. Relapsed or refractory solid tumor malignancy that has progressed on standard anticancer therapy with no available curative options. (Note: Osteosarcoma subjects must be in first or subsequent relapse [≥ first relapse]). Only the osteosarcoma subjects enrolled to Cohorts 3A and 3B must be deemed candidates for ifosfamide and etoposide chemotherapy).
3. Evaluable or measurable disease that meets the following criteria
   a. Subjects must have evaluable or measurable disease based on RECIST 1.1 using computed tomography/magnetic resonance imaging (CT/MRI) (Appendix 1)
   b. Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must have subsequently grown

unequivocally to be deemed a target lesion

4. DTC subjects must be ^{131}I-refractory/relapsed as defined by at least one of the following:

   a. One or more evaluable or measurable lesions that do not demonstrate iodine uptake on any radioiodine scan OR
   b. One or more evaluable or measurable lesions that have progressed based on RECIST 1.1, within 12 months of ^{131}I therapy, despite demonstration of radioiodine avidity at the time of that treatment by pre- or post-treatment scanning. These subjects must not be eligible for possible curative surgery OR
   c. Cumulative activity of ^{131}I >400 millicuries (mCi) or 14.8 gigabecquerels (GBq), with the last dose administered at least 6 months prior to study entry

5. Subjects with DTC must be receiving thyroxine suppression therapy and levels of thyroid stimulating hormone (TSH) should not be elevated (TSH should be ≤5.50 mU/L). When tolerated by the subject, thyroxine dose should be changed to achieve TSH suppression (TSH <0.50 mU/L)

6. Subjects with known central nervous system (CNS) primary tumors or metastases who have completed brain therapy (such as radiotherapy, stereotactic radiosurgery, or surgical resection) and have remained clinically stable, asymptomatic, and off of steroids for 2 weeks prior to Cycle 1 Day 1 will be eligible

7. Male or female subjects age 2 years to <18 years (≤25 years for osteosarcoma subjects) at the time of informed consent

8. Lansky play score ≥50% or Karnofsky Performance Status score ≥50% (see Appendix 4 and Appendix 5, respectively). Use Karnofsky for subjects ≥16 years of age and Lansky for subjects <16 years of age

9. Life expectancy ≥ 3 months

10. Adequate bone marrow function as evidenced by:

    a. absolute neutrophil count (ANC) ≥1.0 × 10^9/L (for Cohorts 3A and 3B leucocyte count ≥2 × 10^9/L; subjects with bone marrow involvement should have ANC ≥0.8 × 10^9/L and leucocyte count ≥1 × 10^9/L)
    b. hemoglobin ≥8.0 g/dL (a hemoglobin <8.0 g/dL is acceptable if it is corrected by growth factor or transfusion before starting lenvatinib)
    c. platelet count ≥ 75 × 10^9/L

11. Adequate liver function as evidenced by:

    a. bilirubin ≤ 1.5 times the upper limit of normal (ULN)
    b. alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN (in the case of liver metastases ≤5 × ULN), unless there are bone metastases or bone primary tumor, in which case liver

specific alkaline phosphatase must be separated from the total and used to assess the liver function instead of the total alkaline phosphatase

12. Adequate renal function as evidenced by:
    a. Serum creatinine based on age/gender as below. If serum creatinine is greater than maximum serum creatinine for age/gender as shown in the table below, then creatinine clearance (or radioisotope glomerular filtration rate [GFR]) must be >70 mL/min/1.73 m^2 (Appendix 6).

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR (Schwartz, et al., 1985) using child length and stature data published by the CDC.

    b. Urine dipstick <2+ for proteinuria. Subjects who have ≥2+ proteinuria on dipstick urinalysis should undergo a spot protein-creatinine (P/C) ratio that should be Grade <2 per CTCAE v4.03, and if possible, perform a 24-hour urine collection (children and adolescents ≤12 years of age must have ≤500 mg of protein/24 hours, and subjects >12 years of age must have ≤1 g of protein/24 hours)
    c. No clinical evidence of nephrotic syndrome

13. Adequate cardiac function as evidenced by left ventricular ejection fraction (LVEF) ≥50%) at baseline as determined by echocardiography

14. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as:

    a. BP <95th percentile for sex, age, and height/length at screening (as per National Heart Lung and Blood Institute [NHLBI] guidelines; see Appendix 7 and Appendix 8) and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1. Osteosarcoma subjects 18 to 25 years should have BP ≤150/90 mm Hg at screening and no change in antihypertensive therapy within 1 week prior to Cycle 1/Day 1.

15. Washout of 3 weeks in case of prior chemotherapy, 6 weeks if treatment included nitrosoureas; 4 weeks for definitive radiotherapy, and 2 weeks for palliative radiotherapy; 3 months from high-dose chemotherapy and stem cell rescue; 3 weeks

from major surgery. Subjects must have recovered from the acute toxic effects of all prior anticancer therapy before enrollment into the study

16. Written and signed informed consent from the parent(s) or legal representative (guardian) and assent from the minor subject. Written informed consent from subjects ≥18 years.

17. Willing and able to comply with the protocol, scheduled follow-up, and management of toxicity as judged by the Investigator

Cohort 3B (Combination Expansion): Osteosarcoma subjects who progressed in Cohorts 1 or 2B and opt to receive combination therapy:

18. Osteosarcoma subjects receiving combination therapy of lenvatinib with ifosfamide and etoposide only need to meet Inclusion Criteria Numbers ~~7~~ 6 through 17 (after progression in Cohort 2B)

Exclusion Criteria

1. Any active infection or infectious illness unless fully recovered prior to dosing

2. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study

3. Other organ toxicity due to prior anticancer therapy (investigational agent, chemotherapy, or radiation therapy) except alopecia, and ototoxicity due to cisplatin not already covered in the inclusion/exclusion criteria, which has not recovered to Grade <2 per CTCAE v4.03

4. Known hypersensitivity to any component of the product (lenvatinib or ingredients)

5. Concurrent administration of any other antitumor therapy

6. Previous treatment with lenvatinib (except for subjects previously enrolled into Cohorts 1 or 2B of this study)

7. Two or more prior VEGF/VEGFR-targeted therapies

8. Currently receiving any investigational drug or device in another clinical trial or within 30 days preceding informed consent

9. A clinically significant ECG abnormality, including a marked baseline prolonged QT or QTc interval (eg, a repeated demonstration of a QTc interval >480 msec)

10. Gastrointestinal malabsorption or any other condition that in the opinion of the investigator might affect the absorption of lenvatinib

11. Gastrointestinal bleeding or active hemoptysis (bright red blood of at least ½ teaspoon)

within 3 weeks prior to the first dose of study drug

12. Active second malignancy within 2 years prior to enrollment (in addition to the primary tumor types specified by cohort in Inclusion Criterion Number 1), but not including definitively treated superficial melanoma, carcinoma in-situ, basal or squamous cell carcinoma of the skin)

13. Previous treatment with ifosfamide and grade ≥3 nephrotoxicity or encephalopathy (Cohorts 3A and 3B)

14. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] *(*human chorionic gonadotropin [hCG]*)* test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG *[* hCG*]*). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

    Females of childbearing potential who:

    - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device or intrauterine hormone-releasing system (IUS)
        - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 6 months after study drug discontinuation.) .
        - have a vasectomized partner with confirmed azoospermia.
    - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 6 months after study drug discontinuation.

    For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

    NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

    Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 5 times the half-life of the study drug plus 90 days after study drug discontinuation). No sperm donation is allowed during the study period and for 5 times the half-life of the study drug plus 90 days after study drug discontinuation.

Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 6 months after study drug discontinuation). If the female partner is pregnant, then males who do not agree to use condoms throughout the study period and for 6 months after study drug discontinuation. No sperm donation is allowed during the study period and for 6 months after study drug discontinuation.

Cohort 3B (Combination Expansion): Osteosarcoma subjects who progressed in Cohorts 1 or 2B and opt to receive combination therapy:

15. Osteosarcoma subjects receiving combination therapy of lenvatinib with ifosfamide and etoposide should meet all the exclusion criteria, with the exception of Criterion Number 6

Study Treatment

Additional details are provided in the Study Design section under Treatment Phase.

Test drug: Lenvatinib

Lenvatinib will be provided as hard capsules containing 1, 4, or 10 mg lenvatinib. Lenvatinib will be administered orally QD. The maximum dose administered during the study should not exceed 24 mg QD in any of the cohorts. An extemporaneous suspension of lenvatinib capsules should be used for children unable to swallow capsules, as detailed in Appendix 12.

Cohort 1 (Single-Agent Dose-Finding)

Subjects 6 to <18 years: Lenvatinib will be administered orally QD. Study drug doses for Cohort 1 are displayed in the table below. The starting dose is 11 mg/m^2 QD, which is 80% of the adult RD of 24 mg QD. The 80% starting dose is based on consensus reached for pediatric Phase 1 trials (Smith, et al., 1998; Lee, et al., 2005). If the dose of 11 mg/m^2 (Dose Level 1) is not safe and tolerable, subjects will receive lenvatinib at the lower de-escalation dose of 9 mg/m^2 (Dose Level -1).

Lenvatinib Doses for Single-Agent Dose-Finding (Cohort 1)

Dose Level	Lenvatinib Once-Daily
-1	9 mg/m^2
1 (starting dose)	11 mg/m^2
2	14 mg/m^2
3	17 mg/m^2

Body surface area (BSA) must be calculated on Day 1 of each cycle based on the subject's current height and body weight. BSA will be used to determine the amount of lenvatinib for

each subject. The dose should be rounded to the nearest whole number.

Subjects 2 to <6 years: Subjects will receive 5 mg/m^2 during the 21-day Run-In Period. If these subjects do not experience any DLT, they will enter Cohort 1 Cycle 1 Day 1 and intrasubject dose escalation will take place as detailed in the Study Design section (Treatment Phase: Cohort 1).

Cohorts 2A and 2B (Single-Agent Expansion)

Lenvatinib will be administered orally QD at the RD. 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.

Cohort 3A (Combination Dose Finding)

Lenvatinib will be administered in combination with ifosfamide and etoposide to osteosarcoma subjects as described in the Study Design section (Treatment Phase: Cohort 3A). Lower doses may be administered depending on the safety information.

Cohort 3B (Combination Expansion)

Subjects will receive lenvatinib at the RD determined to be safe and tolerable in Cohort 3A (Combination Dose-Finding) in combination with ifosfamide and etoposide.

The chemotherapy cycles in Cohorts 3A and 3B will be repeated every 21 days.

Lenvatinib Dose Reduction and Interruption Instructions

Dose adjustments will be made for subjects who experience treatment-related toxicity according to the guidelines provided in the table below. Doses in the Dose Adjustment column are based on a presumed starting dose of 11 mg/m^2.

Dose reductions will occur in succession based on the previous dose level. Each dose level reduction is a 20% reduction from the previous dose. Once the dose has been reduced, it cannot be increased at a later date.

Criteria for Temporary Discontinuation of Study Drug, Dose Reduction, and Resumption of Treatment

Treatment-Related Toxicity[a,b] including hepatic injury and thromboembolic events	**Management**	**Dose Adjustment**
Grade 1		
	Continue treatment	No change
Intolerable Grade 2[c] or Grade 3[e]		

First occurrence	Interrupt until resolved to Grade 0-1 or baseline	8.8 mg/m^2 (or 20% reduction of the starting dose) orally once daily (QD) (one-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	7.0 mg/m^2 (or 20% reduction of the previous dose) orally QD (one-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	5.6 mg/m^2 (or 20% reduction of the previous dose) orally QD (one-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Discuss with sponsor
Grade 4[d]: Discontinue Study Treatment		

Note: For grading see Common Terminology Criteria for Adverse Events version 4.0 (Appendix 2). Collect all CTC grades of adverse events, decreasing and increasing grade.

a: Interruption of lenvatinib treatment for more than 28 days (due to lenvatinib-related toxicities) will require a discussion with the sponsor before treatment can be resumed.

b: Initiate optimal medical management for nausea, vomiting, and/or diarrhea prior to any study treatment, interruption, or dose reduction.

c: Applicable only to Grade 2 toxicities judged by the subject and/or physician to be intolerable. Not applicable to abnormal clinical laboratory values that are not clinically relevant based on the judgment of the investigator.

d: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

e. Obese subjects with weight loss do not need to return to baseline or Grade 1 weight loss to restart lenvatinib. There should be no weight loss for at least 1 week, and subjects should be started at the lower dose and normal Body Mass Index (BMI) should be used for future dose reductions. Obesity is defined as body mass index (BMI) percentiles corresponding to 30 kg/m^2, related to the age of the children. (Cole TJ., et al 2000) or BMI $\geq$ the 95th percentile for children and teens of the same age and sex. (Ogden CL et al, 2002) (Appendix 9 and 10).

Blood Pressure

For children, blood pressure varies by sex and age of the child and is closely related to height and weight. Blood pressure will be assessed in terms of percentile for sex, age, and height/length. Guidelines to sex, age, and height-specific percentiles of blood pressure are provided in Appendix 7 and Appendix 8. Blood pressure that is consistently above the 95th [for subjects age 18-25 years BP >150/90 mm Hg] percentile for age and height/length requires further evaluation. A referral to a cardiologist is recommended for patients who develop hypertension during the study. Ideally, cardiovascular assessments and the management of hypertension should be supervised by a cardiologist. Exercise, excitement, coughing, crying, and struggling may raise the systolic pressure of children as much as 40 to 50 mmHg greater than their usual level. Variability in blood pressure in children of approximately the same age and body build should be expected and serial measurements should always be obtained when evaluating a patient with hypertension. **BP values for management of hypertension for subjects 18 to 25 years of age are included in parenthesis.**

Management of Hypertension

Hypertension is a recognized side-effect of treatment with drugs inhibiting vascular endothelial growth factor (VEGF) signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP <95th percentile [BP ≤150/90 mm Hg] for sex, age, and height/length at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1 Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥95th percentile or diastolic BP ≥95th percentile [BP ≥140 mm Hg or diastolic BP ≥90 mm Hg]) is confirmed on 2 assessments obtained 1 hour apart. One BP assessment is defined as the mean value of 3 measurements obtained at least 5 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when systolic BP ≥95th percentile [BP ≥140 mm Hg] or diastolic BP ≥95th percentile [BP ≥90 mm Hg] is first observed on 2 assessments obtained 1 hour apart. For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. For subjects with hypertension and proteinuria, treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist is preferred.

Lenvatinib should be withheld in any instances where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥99th percentile [BP ≥160/100 mm Hg], significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant comorbidities). Once the subject has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

During the Treatment Period, subjects with systolic BP ≥99th percentile [BP ≥160 mm Hg] or diastolic BP ≥99th percentile [BP ≥100 mm Hg] must have their BP monitored every 2 weeks (on Day 15 or more frequently as clinically indicated) until systolic BP has been <95th percentile [≤150 mm Hg] and diastolic BP has been <95th percentile [≤ 95 mm Hg] for 3 consecutive months. If a new event of systolic BP ≥99th percentile [BP ≥160 mm Hg] or diastolic BP ≥99th percentile [BP ≥100 mm Hg] occurs, the subject must resume the Day 15 evaluation until systolic BP has been <95th percentile [≤150 mm Hg] and diastolic BP has been <95th percentile [≤ 95 mm Hg] for 3 consecutive months.

The following guidelines should be followed for the management of systolic BP ≥99th percentile [BP ≥160 mm Hg] or diastolic BP ≥99th percentile [BP ≥100 mm Hg] confirmed on repeat measurements after an hour:

- Continue lenvatinib and institute antihypertensive therapy for subjects not already receiving antihypertensive medication.

- For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added.

- If systolic BP ≥99th percentile [BP ≥160 mm Hg] or diastolic BP ≥99th percentile [BP ≥100 mm Hg] persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at a lower dose QD (one dose level reduction [20%] as specified in the table above) only when systolic BP <95th percentile [≤150 mm Hg] and diastolic BP <95th percentile [BP ≤95 mm Hg] and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

    - If systolic BP ≥99th percentile [BP ≥160 mm Hg] or diastolic BP ≥99th percentile [BP ≥100 mm Hg] recurs despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a lower dose QD (one dose level reduction [20%] as specified in the table above) only when systolic BP <95th percentile [BP ≤ 150 mm Hg] and diastolic BP <95th percentile [BP ≤95 mm Hg] and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

    - If systolic BP ≥99th percentile [BP ≥160 mm Hg] or diastolic BP ≥99th percentile [BP ≥100 mm Hg] recurs despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and a restart of lenvatinib should be discussed with the sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management
- Discontinue lenvatinib

Management of Posterior Reversible Leukoencephalopathy Syndrome (PRES)

A thorough medical history and a comprehensive physical examination, including a neurological examination, should be conducted as detailed in the Schedule of Assessments (Table 7, Table 8, and Table 9) and as clinically indicated.

Any subject with signs or symptoms of headache, confusion, seizure, or visual change combined with hypertension (usually but not always severe) should be immediately evaluated with brain MRI to evaluate the possibility of posterior reversible leukoencephalopathy syndrome (PRES), a Grade 4 hypertension adverse event per CTCAE v4.03. In subjects with suspected PRES, lenvatinib should be immediately withheld, and if the condition is confirmed by MRI, lenvatinib must be permanently discontinued (see Table 3). Appropriate measures should be taken to control blood pressure (see Section 9.4.1.4), and neurologic consultation is advised.

Management of Proteinuria

Regular assessment for proteinuria should be conducted as detailed in the Schedule of Assessments. Guidelines for assessment and management of proteinuria are summarized as follows:

- Initial episode of proteinuria: If proteinuria ≥2+ is detected on urine dipstick testing, study drug will be continued and a spot protein-creatinine ratio test and if possible a 24-hour urine collection for total protein will be obtained as soon as possible within 72 hours to verify the grade of proteinuria. Grading according to CTCAE v4.03 (Appendix 2) will be based on the protein-creatinine ratio, and whenever possible, also on the 24-hour urinary protein result per investigators discretion. Management of lenvatinib administration will be based on the grade of proteinuria according to the Treatment Related Toxicity table.
- During the Treatment Period, urine dipstick testing for subjects with proteinuria ≥2+ should be performed every 2 weeks (on Day 15 or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months. Any subsequent increases in the level of proteinuria ≥2+ on urine dipstick testing must be confirmed with a spot protein-creatinine ratio test, and if possible a 24-hour urinary protein test as per investigators discretion, which will be assessed and graded and managed according to the dose reduction and interruption instructions provided in the table above. If a new event of proteinuria ≥2+ occurs, the subject must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 3 consecutive months.

Management of Hepatotoxicity

Regular monitoring of liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the Schedule of Assessments and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in the table for dose reduction and interruptions of the protocol should be followed, "Study Treatment Dose Reduction and Interruption Instructions." Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, the study drug must be discontinued.

Management of Thromboembolic Events

Subjects should be advised to pay attention to symptoms suggestive of venous thromboembolic events which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, deep vein thrombosis (DVT) signs including lower-extremity swelling, redness, and warmth to touch or tenderness. In case any of these symptoms appear, subjects should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in the table for dose reduction and interruptions of the protocol should be followed, "Study Treatment Dose Reduction and Interruption instructions." Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, the study drug must be discontinued.

Management of Hypocalcemia
Serum calcium should be monitored monthly per the Schedule of Assessments. Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

Management of Gastrointestinal Symptoms and Acute Abdominal Pain
Initial management of acute abdominal pain in these study subjects should be focused on treating the underlying cause where possible, ensuring appropriate hydration/rehydration, and symptomatic pain improvement consistent with subject's age and in accordance to local and institutional standards of care. Appropriate supportive care should be provided together with close monitoring.

For adverse events of abdominal pain believed to be related to lenvatinib or more specific adverse events felt related to lenvatinib that result in the symptom of abdominal pain, instructions contained in the table Study Treatment Dose Reduction and Interruption instructions should be followed. For Grade 4 adverse events that result in abdominal pain, study drug must be discontinued.

Gastrointestinal (GI) symptoms including diarrhea should be managed by providing symptomatic treatment. If the symptoms persist (eg, diarrhea for more than 10 days), Study Treatment Interruption and Reduction guideline should be followed. Gastrointestinal symptoms should be monitored closely and evaluated using CT, Contrast-Enhanced MRI, ultrasound, or other diagnostic imaging if clinically indicated, per investigator's discretion. All GI symptoms should be recorded in the diary provided.

For additional information please refer to the current Investigator's Brochure (Lenvatinib Investigator's Brochure).

Management of Ifosfamide-Etoposide Associated Toxicity

All sites participating in this trial have had considerable experience with these chemotherapeutic agents. Blood counts should be closely monitored during and prior to the next cycle of chemotherapy. Chemotherapy-associated myelosuppression should be managed by G-CSF. It is recommended that pegylated G-CSF or G-CSF be administered at least 24 to 72 hours after completion of ifosfamide-etoposide chemotherapy; use of G-CSF is recommended until WBC counts are $\geq 1 \times 10^9$/L. Guidelines for dose modification for ifosfamide- and etoposide-associated toxicities are provided below.

- Neutropenia (Grade 4): Monitor ANC counts every 3 days until resolved to <Grade 3
- Febrile neutropenia (Grade 4): Reduce the next dose of ifosfamide and etoposide by 20% each
- Mucositis (repeated Grade 3 or Grade 4): Reduce etoposide by 20%
- Renal Toxicity: If serum creatinine >1.5 - 3 × ULN - interrupt ifosfamide and etoposide for 1 week
- Hematuria: Interrupt ifosfamide and etoposide if hematuria >50 RBC/high power field (hpf)

- Neurological Toxicity: Interrupt and reduce ifosfamide and etoposide each by 20% of the previous dose. After 2 dose reductions, the subject must discontinue the chemotherapy drugs, but if there is benefit, the subject can continue on single-agent lenvatinib at the investigator's discretion

Details of ifosfamide and etoposide dose interruption and reduction as well as management of toxicity can be found in the Summary of Product Characteristics (SmPC), and should be followed according to local and institutional guidelines. The SmPC will be provided to the study sites in the Investigator and Pharmacy files in the relevant local language. For additional information, investigators may refer to the SmPC or Euramos-1 protocol (ISRCTN67613327 EudraCT no. 2004-000242-20).

Duration of Treatment

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.

Concomitant Drug/Therapy

Prophylactic use of granulocyte colony-stimulating factors (G-CSFs) is not permitted during this study in Cohorts 1, 2A, and 2B. G-CSF use is recommended for Cohorts 3A and 3B to mitigate the toxicity of ifosfamide and etoposide).

The following concomitant treatments/procedures are allowed:

a. Removal of existing (not new) osteosarcoma metastatic lesion (surgical, radiofrequency ablation, etc) is allowed only:

   - After completion of the first 4 months of the Treatment Period without progression, and
   - Before the first 4 months of the Treatment Period only if there is disease progression assessed by the investigator and the subject will discontinue the study for progression

b. Palliative radiotherapy in Cohorts 2 and 3B is allowed for ≤2 significantly symptomatic nontarget lesions. For Cohorts 1 and 3A, palliative radiotherapy will be allowed after the RD is determined.

If a subject receiving treatment with lenvatinib requires surgery during the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.

- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 1 week after, once there is evidence of adequate healing and no risk of bleeding.

Any additional procedural or patient specific particularities should be discussed with the sponsor.

Assessments

Efficacy Assessments

Tumor assessments will be performed based on RECIST 1.1 (Appendix 1). Investigator-determined response assessments at each assessment time point will be entered onto the appropriate case report form (CRF).

At Screening

CT scans of the brain, neck (DTC only) chest, abdomen, pelvis, and other known sites of disease (bone metastases) plus any areas of newly suspected disease, will be performed at the Screening Visit. MRI may be used for brain, neck, abdomen, pelvis, and other sites of disease, but chest may only be evaluated with CT.

During Treatment Phase

For Cohort 1 only, CT/MRI scans of neck (DTC only), chest, abdomen, pelvis, and other known sites of disease plus any areas of newly suspected disease will be performed using the same methodology as at screening every 6 or 8 weeks per the appropriate tumor assessment schedule, or sooner if clinically indicated, beginning from the date of the first treatment dose, continuing during treatment cycles until documentation of disease progression.

For subjects with DTC (Cohort 2A) CT/MRI of the neck and other known sites of the disease plus any areas of newly suspected disease and CT chest will be performed. For osteosarcoma (Cohorts 2B, 3A and 3B), CT chest, and CT/MRI of other known sites of disease plus any areas of newly suspected disease will be performed. Tumor assessments should be performed using the same methodology as at screening every 6 or 8 weeks per the appropriate tumor assessment schedule, or sooner if clinically indicated, beginning from the date of the first treatment dose, continuing during treatment cycles until documentation of disease progression.

Brain scans should be performed at screening and during the study if clinically indicated. If protocol eligible brain metastases are present at screening, a CT/MRI of the brain must be performed at all tumor assessment time points. An initial assessment of CR or PR according to RECIST 1.1 must be confirmed not less than 4 weeks after the initial response. In subjects 2 to <6 years of age, CT/MRI scans must be performed at screening, Cycle 1 Day 1 (following the Run-In Period at investigator's discretion), and every 8 weeks during the Treatment Period as indicated in Table 7. For Cohorts 3A and 3B, CT/MRI scans should be

performed as indicated in Table 9.

During Post-treatment Follow-up

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

Palatability and Acceptability of Lenvatinib Suspension Formulation

The palatability and acceptability of lenvatinib suspension formulation will be assessed using the Palatability Questionnaire (see Appendix 13). All subjects who receive suspension formulation must complete the questionnaire according to the Schedule of Assessments. If the subject is unable to complete the questionnaire, this must be done by a parent or legal guardian. Measurement of palatability will be assessed using the Hedonic scale (Guinard, 2001) which is a Visual Analog Scale (VAS).

Pharmacokinetic Assessments

Blood samples for PK profiling of lenvatinib will be collected on Day 1 and Day 15 (single agent cohorts only-see Table 5) of Cycle 1 and on Day 1 of Cycle 2. For Cohort 1, Run-In Period blood samples will be collected on Day 15 (predose). PK blood samples for lenvatinib will also be drawn pretreatment on the day of tumor assessment. Exposure parameters such as area under the concentration × time curve (AUC) will be derived from posterior estimates of the PK parameters from the final population PK model.

Pharmacodynamic Assessments

Blood serum samples from study subjects will be collected at Baseline, Day 8 of Cycle 1 (Combination-Agent cohorts), Day 15 of Cycle 1 (Single-Agent cohorts), Day 1 of all subsequent cycles, and at the Off-treatment Visit. For subjects ongoing after the data cutoff date for the primary analysis, blood samples will be collected at the Off-Treatment Visit. For subjects 2 to <6 years, a blood serum sample will be collected in Cohort 1 at Day 1 of Cycle 1 (predose). Blood serum samples may be analyzed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, or other assays/methods and new technology in an effort to identify biomarkers. In addition, biomarkers identified in other lenvatinib clinical studies may also be assessed in samples collected from subjects enrolled in this study. Blood biomarker samples may be used for exploratory analysis for evaluation of response-related outcomes as well as for potential use in diagnostic development.

Pharmacogenomic/Pharmacogenetic Assessments

Archived, fixed tumor tissue will be collected (if available) for assessment of mutations and other genetic alterations or proteins that may be important in the development and progression of cancer as well as for potential use in diagnostic development.

A blood sample will be collected for pharmacogenomic analysis. The DNA may be analyzed for genes associated with lenvatinib absorption, distribution, metabolism, excretion (ADME) and to validate mutations suspected of functional relevance (using in silico prediction) to determine exclusivity to tumor sample. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have.

Data obtained from the PD and PG samples will be used for research. The PD and PG samples will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib and for potential diagnostic development. If the subject reaches 18 years of age prior to the date of final sample analyses they will be reconsented. No further analyses will be performed on these collected samples from subjects who either do not reconsent after their 18th birthday or cannot be reached for reconsenting and the sample will be destroyed.

When the subject reaches the age of 18 years (or 16 years in the UK) while on the study, and becomes competent to give informed consent, his/her consent will be obtained using separate ICFs to continue on the study.

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs; 12-lead ECGs; Lansky play score or Karnofsky performance status score; physical examinations; and height assessments. A diary will be provided to each subject to capture any abnormal gastrointestinal symptoms (e.g., diarrhea, abdominal discomfort, cramps, etc) experienced during the study. Fecal occult blood will be monitored regularly during the study.

Skeletal bone growth will be assessed by height measurements at the Baseline Visit, thereafter Day 1 of each cycle during the Treatment Phase for Cohort 1 (and Day 1 of every 3 cycles for cohorts 2A, 2B, 3A and 3B); at the Off-treatment Visit, and every 3 months during the Post-treatment Follow-up. Proximal tibial growth plates x-rays will be done at baseline and at the off-treatment visit. Postbaseline, only open growth plates will be further assessed.

Clinical and laboratory toxicities/symptomatology will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Appendix 2). Adverse events that are not reported in the CTCAE will be graded on a 4-point scale (mild, moderate, severe, and life-threatening).

Protocol Steering Committee

The sponsor will closely evaluate the risks and benefits of the study throughout its conduct,

along with the Protocol Steering Committee (PSC) as needed. The PSC may review available relevant data: DLT and safety data including laboratory assessments, 12-lead ECGs, dose administration, etc.

Bioanalytical Methods

Lenvatinib will be quantified using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method. Pharmacodynamic biomarker analysis will be performed as described in the separate analysis plan. Clinical laboratory tests will be performed at qualified local laboratories.

Statistical Methods

Cohort 1 (Single-Agent Dose-Finding)

Primary Endpoint

RD based on the TiTE-CRM design.

Secondary Endpoints

- Efficacy
  - BOR over the treatment period
  - ORR
  - DOR
  - 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 best overall response 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
  - PFS defined as the time from the date of the first administration of study drug until the date of first documentation of PD or death (whichever occurs first)
  - TTP defined as the time from the date of the first administration of study drug until the date of first documentation of disease progression
  - OS defined as the time from the date of the first administration 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).
- Safety
  - AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECG, urine dipstick,

occult blood in stool, Lansky Play Scores or Karnofsky performance status scores, physical examination findings, and height and closure of proximal tibial plates during treatment and follow-up

- Plasma lenvatinib exposure
- Assessment of blood or tumor biomarkers that correlate with clinical response to lenvatinib treatment or AEs associated with lenvatinib treatment
- Palatibility and acceptability of the suspension formulation of lenvatinib

Cohort 2

Primary Endpoints

- Cohort 2A: DTC: ORR (CR + 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 who are alive and free of disease progression at 4 months after the first dose based on RECIST 1.1

Secondary Endpoints

- Efficacy
  - BOR over the treatment period (osteosarcoma group)
  - ORR (measurable osteosarcoma group)
  - DOR (measurable DTC and osteosarcoma group)
  - 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 best overall response 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
  - PFS defined as the time from the date of first administration of study drug to the date of first documentation of disease progression or date of death, whichever occurs first
  - TTP defined as the time from the date of the first administration of study drug until the date of first documentation of disease progression
  - OS defined as the time from the date of the first administration 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).

- Safety
  - AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECGs, urine dipstick, occult blood in stool, Lansky play scores or Karnofsky performance status scores, physical examination findings, and height and closure of proximal tibial 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
- Palatibility and acceptability of the suspension formulation of lenvatinib

Cohort 3

Primary Endpoint

- Cohort 3A: RD of the combination treatment (lenvatinib + etoposide + ifosfamide)
- Cohort 3B: PFS-4, ie, the percentage of subjects who are alive and free of disease progression 4 months after the first dose based on RECIST 1.1

Cohorts 3A and 3B

Secondary Endpoints

- Efficacy
  - BOR over the treatment period
  - ORR (measurable osteosarcoma group)
  - DOR
  - 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 best overall response 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
  - PFS defined as the time from the date of first administration of study drug to the date of first documentation of disease progression or date of death, whichever occurs first

- TTP defined as the time from the date of the first administration of study drug until the date of first documentation of disease progression
- OS defined as the time from the date of the first administration 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).

- Safety
  - AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECGs, urine dipstick, occult blood in stool, Lansky play scores or Karnofsky performance status scores, physical examination findings, and height and closure of proximal tibial 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

Analysis Sets

The **Safety Analysis Set** is defined as subjects who receive any study drug.

The **Pharmacokinetic Analysis Set** is defined as subjects in Safety Analysis Set who have at least 1 measurable postdose plasma concentration with an adequately documented dosing history.

Statistical Analyses

Descriptive statistics will be used to summarize study endpoints. Categorical variables will be summarized by number and percentage. Continuous variables will be summarized using n (number of subjects with available data), mean, standard deviation, median, and range (minimum and maximum) unless otherwise specified. Pharmacokinetic data will be summarized using n, mean, standard deviation, coefficient of variation (% CV), geometric mean, median, minimum and maximum. Survival data (PFS and OS) will be estimated using Kaplan-Meier methods.

Efficacy will be evaluated based on the as-treated population (Safety Analysis Set). Safety data will be evaluated using the Safety Analysis Set. Pharmacokinetic data will be evaluated using the Pharmacokinetic Analysis Set on pooled data from both Cohort 1 and Cohort 2. Other study results for Cohort 1 and Cohort 2 will be reported separately.

Primary Endpoint Analyses

Cohort 1 (Single-Agent Dose-Finding)

Cohort 1 will be a lenvatinib single-agent dose-finding study including 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 the 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.

The RD will be defined as the dose that has a DLT rate closest to the targeted 20% rate.

Four experimental doses may be investigated in Cohort 1: Dose -1 (9 mg/m^2), Dose 1 (11 mg/m^2), Dose 2 (14 mg/m^2), and Dose 3 (17 mg/m^2). The starting dose will be Dose 1.

A one-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,α) 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; 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. Additional subjects will be allocated to the dose associated with the posterior probability of DLT closest to the target. At least 2 subjects will be required to complete 4-week treatment in Cycle 1 or report a DLT in Cycle 1 (at the starting dose) before a subject can be treated at the next dose level. It is further specified that dose levels cannot be skipped when escalating. The RD will be determined either when approximately 18 subjects have been tested, or when

futility is declared or when 10 subjects have been treated at the same dose. Futility is defined as having a low probability that any of the doses is safe.

Cohort 2 (Single-Agent Expansion)

DTC and osteosarcoma groups will be evaluated separately.

Cohort 2A: DTC

The primary efficacy endpoint is ORR for subjects with measurable disease and BOR for all subjects. All ORR or BOR will be based on RECIST 1.1 assessed every 8 weeks.

The analyses will be descriptively performed on the Safety Analysis Set.

Cohort 2B: Osteosarcoma

The primary efficacy endpoint is PFS-4 based on RECIST 1.1.

The null hypothesis that PFS-4 is ≤25% will be 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. PFS-4 will be presented with corresponding 2-sided, exact binomial 80% and 95% CIs. This analysis will be performed on the Safety Analysis Set.

Cohort 3: Combination Dose-Finding and Expansion)

Cohort 3A: Osteosarcoma Combination Dose-Finding

As in Cohort 1, the DLT will be assessed to determine the RD of lenvatinib in combination with chemotherapy (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 (refer to Section Study Design Treatment Phase: Cohort 3A).

Cohort 3B: Osteosarcoma Combination Expansion

The primary efficacy endpoint is PFS-4 based on RECIST 1.1.

The null hypothesis that PFS-4 is ≤25% will be 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. PFS-4 will be presented with corresponding 2-sided, exact binomial 80% and 95% CIs. This analysis will be performed on the lenvatinib-naïve subjects in Safety Analysis Set, while subjects enrolled from Cohorts 1 and 2B will only be summarized as appropriate.

Secondary Endpoint Analyses

The secondary endpoints of PFS and TTP will be analyzed using Kaplan-Meier product-limit estimates. Median PFS, and the cumulative probability of PFS at 4 and 12 months will be presented with 2-sided, 95% CIs when an adequate number of at risk subjects at those time

points warrant the estimate. The cumulative PFS and TTP probabilities will be plotted over time as appropriate.

The secondary endpoints of ORR, DCR, and CBRwill be calculated with exact binomial 95% CIs.

The endpoint of OS will be analyzed using Kaplan-Meier product-limit estimates. Median OS and the cumulative probability of OS at 12 months will be presented with 2-sided, 95% CIs when an adequate number of at risk subjects at those time points warrant the estimate.

The above analyses will be based on the lenvatinib-naïve subjects in Safety Analysis Set, while other subjects enrolled from Cohorts 1 and 2B will be summarized for these endpoints as appropriate.

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/Pharmacogenetic Analyses

Plasma concentrations of lenvatinib versus time data will be listed. Plasma concentrations of lenvatinib versus time data will be analyzed using a population PK approach to estimate population PK parameters. The analysis will be detailed in an analysis plan at a later date.

Correlation between clinical response to lenvatinib treatment and blood or tumor biomarkers may be examined using descriptive statistics and graphic displays as appropriate. If conducted, a detailed analysis plan will be provided in a separate document.

Exploratory/graphical analyses will be conducted for PK/PD evaluations, and may be followed by model based analyses. If conducted, a detailed analysis plan will be provided in a separate document at a later date.

Safety Analyses

The incidence of treatment-emergent adverse events (TEAEs) and SAEs will be summarized by study cohort, dose-level, and group. Laboratory test data, vital signs, 12-lead ECGs, urine dipstick, occult blood in stool, Lansky play scores or Karnofsky performance scores, physical examination, height, and proximal tibial growth plates at scheduled time points and their changes from baseline will be summarized by study cohort and group using descriptive statistics, as appropriate. Abnormal values will be flagged. Prior and concomitant medications, medical/surgical history, and subject demographics will be summarized and listed by study cohort and group.

Other Analyses

Measurement of palatability will be assessed using the Hedonic scale (Guinard, 2001) which is a Visual Analog Scale (VAS).

Interim Analyses

Interim analyses may be performed after consultation with the PSC.

The sponsor will closely evaluate the risks and benefits of the study throughout its conduct, along with the PSC as needed.

Sample Size Rationale

Approximately 69 to 108 subjects are planned for this study.

Cohort 1 (Single-Agent Dose-Finding)

Approximately 12 to 24 subjects based on TiTE-CRM algorithm (Cheung and Chappell, 2000).

Cohort 2 (Single-Agent Expansion)

Approximately 27 to 42 subjects: DTC group (12 subjects) and osteosarcoma group (15 to 30 subjects).

Cohort 2A: DTC Group

Approximately 12 subjects with evaluable or measurable disease are planned to be enrolled in Cohort 2A due to limited number of pediatric patients with DTC.

Cohort 2B: Osteosarcoma Group

A minimum of 15 PFS-4 evaluable subjects will be assessed in cohort 2B. The sample size estimates were based on Simon's Optimal Two-Stage Design (Simon, 1989). If fewer than 5 subjects who are alive and free of disease progression at 4 months after first dose date are observed 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, at least 5 subjects who are alive and free of disease progression at 4 months after first dose date are recorded among the 15 evaluable subjects, enrollment in the cohort will continue seamlessly for a total of approximately 27 evaluable subjects. If, at the end of the second stage for the cohort, at least 10 subjects who are alive and free of disease progression at 4 months are recorded among the 27 subjects in the cohort, study drug 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 $\leq 25\%$, and the alternative hypothesis PFS-4 (H_1) is $\geq 45\%$. One-sided Type I error (α) = 0.1, and power = 80%. To account for nonevaluable subjects, a total of 15-30 osteosarcoma subjects will be enrolled for Cohort 2B.

Cohort 3 (Combination Dose-Finding and Expansion)

Cohort 3A (Combination Dose-Finding)

Approxinately 12 to 24 osteosarcoma subjects for whom ifosfamide and etoposide are

considered a treatment option

Cohort 3B (Combination Expansion)

With the following assumptions: p_0=25%, p_1=50%, 1-sided α=10%, β=20%, where p_0 is an unacceptable rate of PFS, p_1 is the target rate of PFS, α is the probability of declaring lenvatinib effective when the true rate is p_0, and β 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 for Cohort 3B, along with some subjects enrolled from Cohorts 1 and 2B.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
^{131}I	radioiodine
ACE	angiotensin converting enzyme
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AJCC	American Joint Committee on Cancer
AST	aspartate aminotransferase
ANC	absolute neutrophil count
ATC	Anatomical-Therapeutic-Chemical
AUC	area under the concentration x time curve
bFGF	basic fibroblast growth factor
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BOR	best overall response
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CA	competent authorities
CBR	clinical benefit rate
CEP	circulating endothelial progenitor cell
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
C_{max}	maximum drug or metabolite concentration
CPM	cyclophosphamide
CR	complete response
CRA	Clinical Research Associate
CRF	case report form

CRM	continual reassessment method
CRO	Clinical Research Organization
CSR	clinical study report
CT	computerized tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae/coefficient of variation
CYP/CYP3A4	Cytochrome P450/cytochrome P4503A4
DCR	disease control rate
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DTC	differentiated thyroid cancer
EBRT	external bean radiotherapy
EC	European Communities
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EEG	electroencephalogram
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FGF	fibroblast growth factor
Flt-1	fms-like tyrosine kinase-1
FS	fractional shortening
FTC	follicular thyroid cancer
GBq	Gigabequerels
GCP	Good Clinical Practice
h	Hour
HIV	human immunodeficiency virus
HR	hazard ratio/heart rate

IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
IHC	immunohistochemical
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IVRS/IWRS	interactive voice/web response system
KDR	kinase insert domain receptor
KM	Kaplan-Meier
LC/MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEN	multiple endocrine neoplasia
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
MTD_0	prior maximum tolerated dose
N/n	number
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NYHA	New York Heart Association

ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics(s) or progressive disease
PDGFR	platelet-derived growth factor receptor
PDGFRβ	platelet-derived growth factor receptor beta
PFS	progression-free survival
PFS-4	progression free survival at 4 months
PI	principal investigator
PK	pharmacokinetic(s)
pNET	primitive neuroectodermal tumors
PR	partial response
PRES	Posterior Reversible Leukoencephalopathy Syndrome
PSC	Protocol Steering Committee
PT	preferred term
PTC	papillary thyroid cancer
QD	once daily
RBC	red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors
RD	recommended dose
RET	rearranged during transfection
RF	radiofrequency
RR	respiratory rate
RTK	receptor tyrosine kinase
QTc	QT interval corrected for heart rate
SAE	serious adverse event
SD	stable disease
SEER	Surveillance Epidemiology and End Result
SmPC	summary of product characteristics
SOC	system organ class
SOP	standard operating procedure

SUSARs	suspected unexpected serious adverse reactions
^{99}m-Tc	^{99}m-technetium
$t_{1/2}$	terminal elimination half-life
T4	thyroxine
TEAEs	treatment-emergent adverse events
TiTE-CRM	Time To Event-Continual Reassessment Method
TEAV	treatment-emergent abnormal laboratory value
T_{max}	time to reach maximum (peak) concentration following administration
TNM	tumor-node metastasis
TSH	thyroid stimulating hormone
TTP	time to progression
UK	United Kingdom
ULN	upper limit of normal
US/USA	United States of America
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF)/assent, and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with ICH E6 (Good Clinical Practice), Section 3, and any local regulations (eg, European Union [EU] Clinical Trials Directive 2001/20/EC or Code of Federal Regulations, Title 21 CFR Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in Clinical Research Associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The definition for end of the study is the time of data cutoff for the final analysis or the time of last subject/last treatment, whichever occurs later. It is estimated that the study duration will be 36 months.

In the case of early termination/temporary halt of the study, the investigator should notify the IEC and competent authority (CA) within 15 days and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki, 2008

- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

- US 21 CFR, including parts 50 and 56 concerning Informed Patient Consent and IRB regulations, and applicable sections of US 21 CFR Part 312

All studies that are conducted within any EU country will comply with the European Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the CA of all involved EU member states.

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject (or subject's parent(s) or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject and the legally authorized representative must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a subject's parent or legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent/assent form and any other written information to be provided to subjects is read and explained to the subject, the subject's parent(s) or legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form.

The subject and/or the subject's parent(s) or legally authorized representative(s) will be asked to sign an informed consent/assent form at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. Informed consent from the parents or subject's legally acceptable representative and informed consent (or assent) from the subject must be obtained prior to any study specific procedures are performed.

An unsigned copy of an IRB/IEC-and sponsor approved written ICF/assent must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (eg, EU Clinical Trials Directive 2001/20/EC or Code of Federal Regulations, Title 21, CFR Part 50) and provided to the sponsor. Each subject and the subject's parent(s) or legally acceptable

representative must sign an approved informed consent/assent form before study participation. The form must be signed and dated by the appropriate parties. The original, signed and dated informed consent/assent form for each subject will be verified by the sponsor and kept in the investigator site file and a copy must be given to the subject

The subject or the subject's parent(s) or legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

When the subject reaches the age of 18 years (or 16 years in the UK) while on study, and becomes competent to give informed consent, his/her consent will be obtained using separate ICFs to continue on the study.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 12 investigational site(s) in the European Union (EU) and the US.

The name and telephone and fax numbers of the Eisai Medical Monitor and other contact personnel at the sponsor will be listed in the Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Pediatric Cancers

Cancer occurs rarely in children and adolescents (incidence of 10 to 15 cases per 100,000 individuals <19 years of age) and the incidence is comprised mainly of leukemias (approximately 30% of all cases) and solid tumors (Ries, et al., 1999). Current treatments for malignant solid tumors in pediatric patients involve a combination of chemotherapy, surgery, and in certain cases, radiotherapy. This multidisciplinary treatment approach leads to an overall cure rate of 80%. Nevertheless, cancer mortality remains the leading cause of disease-related death in children and adolescents between 1 and 19 years of age. This mortality rate is due to diseases with a poor prognosis (3-year overall survival <30%), such as metastatic neuroblastoma, multi-metastatic bone sarcomas (osteosarcomas and Ewing's sarcomas), metastatic medulloblastomas, and refractory disease and relapses of most of the pediatric solid tumors.

7.1.1 Epidemiology and Etiology of Pediatric Thyroid Cancer

Pediatric thyroid cancer is rare, with less than 15% of differentiated thyroid cancer (DTC) cases diagnosed at age <18 years. However, it does account for approximately 10% of malignant tumors and approximately 35% of carcinomas in children (Bernstein and Gurney, 1999). In the US, approximately 350 people younger than 20 years of age are diagnosed with thyroid carcinoma each year (Bernstein and Gurney, 1999). In Europe, annual numbers of new pediatric cases are similar to the US with the exception of the geographic areas close to

the 1986 nuclear plant accident in Chernobyl, where much higher incidence rates are observed (Steliarova-Foucher, et al., 2006).

Differentiated thyroid cancer comprises 90% to 95% of all childhood thyroid cancers. Medullary thyroid cancer (MTC) is diagnosed in 5% to 8% of childhood thyroid cancer patients (Bernstein and Gurney, 1999; Harach and Williams, 1995). Undifferentiated thyroid tumors, ie, insular and anaplastic cancers, are extremely rare in the pediatric population (Hassoun, et al., 1997). Juvenile DTC is classified as sporadic or radiation induced. These 2 forms do not appear to have major clinical differences (Samaan, et al., 1987).

Juvenile DTC appears to have several notable differences when compared to DTC in adults. DTC in childhood is often more advanced at presentation and there is a higher risk of disease recurrence. In addition, a higher propensity for lymph node and distant lung metastases is observed in childhood DTC.

In papillary thyroid cancer (PTC), which constitutes the main histologic type of DTC diagnosed in children, there are 2 major initiating events, rearranged transformation/papillary thyroid carcinoma (RET/PTC) and BRAF point mutation T1799A, both activating the mitogen activated protein kinase (MAPK) signaling pathway (Santoro, et al., 2006). RET/PTC is a chimeric gene generated by the fusion of the tyrosine kinase domain of the rearranged during transfection gene (RET) to the 5′terminal region of genes that are constitutively expressed in thyroid follicular cells and result in constitutively active tyrosine kinase. There are at least 10 different types of RET/PTC of which RET/PTC1 and RET/PTC3 are the most common types, accounting for >90% of all rearrangements (Xing, 2005). The frequency of RET/PTC rearrangement differs substantially in various populations, the most important factor seems to be age: RET/PTC rearrangements are much more frequent in younger patients (aged 6 to 21 years of age) with PTC and especially in children <8 years of age. The T1799A BRAF point mutation is the more common mutation in sporadic papillary carcinomas seen in adult patients. It occurs in approximately 40% to 60% of all cases (Kumagai, et al., 2004). In contrast to adult papillary carcinomas, pediatric tumors (both sporadic and radiation-induced) have a low (0% to 12%) prevalence of BRAF mutations (Giordano, et al., 2005).

7.1.2 Epidemiology and Etiology of Pediatric Osteosarcoma

Osteosarcoma is the most commonly diagnosed primary malignancy of the bone, particularly in children and adolescents. Malignancies of the bone, with an average annual incidence rate of 8.7 per million children younger than 20 years of age, comprise about 6% of childhood cancers reported by the Surveillance, Epidemiology, and End Results (SEER) program area from 1975 to 1995 (Gurney, et al., 1997). In the US, between 650 and700 children and adolescents younger than 20 years of age are diagnosed with bone tumor each year of which approximately 400 are osteosarcomas and 200 are Ewing's sarcomas (Gurney, et al., 1997). There is a bimodal age distribution of osteosarcoma incidence. A primary peak in osteosarcoma incidence occurs in children and adolescents ages 0 to 24 years, the incidence plateaus for ages 25 to 59 years, with a second peak in the elderly (ages 60 to >85). Current

treatment utilizes multi-agent chemotherapy and surgical resection of all clinically detectable disease.

An extensive list of genetic abnormalities and environmental exposures, including vascular endothelial growth factor receptor (VEGFR) platelet-derived growth factor receptor (PDGFR) overexpression, c-fos overexpression, and radiation exposure, has been associated with the development of osteosarcoma in laboratory models as well as humans (Gorlick and Khanna, 2010). A single recurrent genetic event does not seem to define this cancer. The vast majority of abnormal oncogenes and tumor-suppressor genes associated with osteosarcoma are also common in the most prevalent cancers (Gorlick and Khanna, 2010). The use of ionizing radiation for the treatment of childhood solid tumors has been well implicated in the development of a second malignancy, with osteosarcoma being the most likely to develop within the first 2 decades following treatment (Le Vu, et al., 1988).

7.1.3 Current Therapeutic Options

Recurrent Pediatric DTC Which is Refractory/Resistant to Radioiodine

The current standard management of pediatric DTC is total or near total thyroidectomy (often with central lymph node dissection) followed by radioiodine (^{131}I) ablation and then thyroid hormone treatment, with further surgery and ablation for recurrences. Despite pediatric cases having large initial tumors, common involvement of cervical lymph node at presentation, and high recurrence rates, this approach is highly successful with a 5 year survival rate of 96% to 100% and a 20 year survival rate of over 90%.

A subset of these pediatric/adolescent patients with recurrent relapsed DTC may become refractory and/or resistant to radioiodine.

Cytotoxic chemotherapy in the setting of ^{131}I-refractory/resistant DTC in any patient age group offers little to no benefit and is associated with significant toxicity. In fact, the 2012 ESMO Clinical Practice Guidelines for thyroid cancer state that "chemotherapy is no longer indicated [for treatment of advanced ^{131}I-refractory DTC] because of lack of effective results and should be replaced by enrollment of the patients in experimental trials with targeted therapy (Pacini, et al., 2014)."

Recurrent Pediatric and Adolescent Osteosarcoma

About 30% of patients with localized disease and 80% of those presenting with metastatic disease will relapse (NCCN Bone Cancer Guidelines, 2014). Complete removal of all sites of metastases must be attempted as the disease is otherwise almost universally fatal (ESMO, 2012).

The role of second-line chemotherapy for recurrent osteosarcoma is much less well defined that of surgery and there is no accepted standard regimen (ESMO, 2012). Choice may take into account the prior disease-free interval, and often includes ifosfamide +/- etoposide +/- carboplatin, and other active drugs (ESMO, 2012). In the two largest reported series, the use of second-line chemotherapy correlated with limited prolongation of survival in patients with

inoperable metastatic recurrences, while a positive correlation in operable disease was observed in only one of the two (Ferrari, et al., 2003; Kempf-Bielack, et al., 2005).

The combination of etoposide with cyclophosphamide (CPM) or ifosfamide has been evaluated in at least 2 clinical trials of >20 patients (Berger, et al., 2009; Gentet, et al., 1997). The French Society of Paediatric Oncology conducted a Phase 2 trial of high-dose ifosfamide and moderate-dose etoposide in 27 patients with relapsed or refractory childhood osteosarcoma (Gentet, et al., 1997). The chemotherapy regimen was 2 courses (3-4 weeks apart) of ifosfamide 3 g/m^2/day and etoposide 75 mg/m^2/day, each given daily for 4 days with mesna uroprotection. The response rate was 48% (95% confidence interval, 29-67%). Response rate was equivalent in the sub-group of 22 patients who had previously received ifosfamide (4 CR, 6 PR).

In another Phase II trial by Italian investigators led by Berger (Berger, et al., 2009), the activity of 2 courses of cyclophosphamide and etoposide was evaluated in 26 relapsed high-risk osteosarcoma patients with a median age of 18.5 years. The chemotherapy regimen consisted of cyclophosphamide 4 g/m^2 IV over 3 hours on Day 1 and etoposide 100 mg/m^2 IV over 1 hour twice daily for 3 days on Days 2, 3, and 4 (total dose: 600 mg/m^2) with mesna uroprotection. This resulted in a 19% response rate (2 CR, 3 PR). Progression-free survival at 4 months (PFS-4) was 42%.

In a smaller Phase 2 study reported by Rodríguez-Galindo, 14 children with refractory osteosarcoma were given fractionated cyclophosphamide (500 mg/m^2/day for 5 days) and etoposide (100 mg/m^2/day for 5 days) with granulocyte colony-stimulating factor every 21 to 28 days (Rodriguez-Galindo, et al., 2002). A total of 47 courses were given (median 3 per patient [range: 1 to 12]). The response rate was 28.5% (1 CR, 3 PR, in 11 evaluable subjects).

In general, despite second-line treatment, the prognosis of recurrent disease in osteosarcoma has remained poor, with long-term post-relapse survival of <20% (NCCN Bone Cancer Guidelines, 2014).

In light of this, the use of newer targeted therapies either alone or in combination with chemotherapy for bone sarcoma subjects is an area under intensive study in clinical trials. Gaspar, Di Giannatale, Geoerger, and colleagues have published a detailed review summarizing these efforts (Gaspar, et al., 2012).

One published Phase 2 trial conducted by the Italian Sarcoma Group explored the activity of the multikinase inhibitor sorafenib as single-agent therapy (400-mg dose twice daily) in 35 patients aged >14 years with relapsed and unresectable osteosarcoma (Grignani, et al., 2012). The PFS-4 (primary endpoint) was 46% with a median follow-up of 3.6 months. The objective response rate was 9% (3 PR, no CR). Based on these results, the 2014 NCCN Bone Cancer Guidelines have included sorafenib as a systemic therapy option for osteosarcoma patients with relapsed disease (NCCN Bone Cancer Guidelines, 2014).

Lenvatinib

Lenvatinib is an oral, multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (kinase domain receptor [KDR]), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor (PDGF) receptor PDGFRα; KIT; and RET. Lenvatinib inhibits VEGF-driven KDR phosphorylation and suppresses proliferation and tube formation in human umbilical vein endothelial cell (HUVEC) models. It has demonstrated antiangiogenic activity and has shown antitumor effects against various human cancer xenograft models in mice (Lenvatinib Investigator's Brochure, 2014). In combination with paclitaxel or platinum-based anticancer agents, it showed enhanced antitumor activity in gastric cancer, non-small cell lung cancer, and melanoma xenografts in athymic mice (Lenvatinib Investigator's Brochure, 2014). In view of these properties, it is being developed as an anticancer therapy as a single agent or in combination with other anticancer agents. It has exhibited anti-tumor activity in Phase 1 and 2 clinical trials in adults; based on which, several Phase 3 clinical trials were initiated. Preliminary data have shown promising results in DTC patients in a Phase 2 trial and a Phase 3 trial in adult DTC patients (Schlumberger M, et al. 2015).

7.1.3.1 Angiogenesis and Pediatric Tumors - Mechanism of Action

Angiogenesis and Vasculogenesis in Pediatric Solid Tumors

Pediatric tumors are highly vascularized. As with normal tissue, the growing tumor requires an extensive network of capillaries to provide the necessary nutrients and oxygen. Moreover, the new intratumor blood vessels offer a way for tumor cells to enter the circulation and metastasize to distant organs and thus play an indispensable role in solid tumor growth and metastasis. Angiogenesis, which is the growth of new capillaries from pre-existing blood vessels, and vasculogenesis, which is the differentiation of precursor cells into endothelial cells, are the fundamental processes by which new blood vessels are formed. Angiogenesis is the result of a dynamic balance between proangiogenic factors, VEGF and platelet-derived growth factor (PDGF), and factors that inhibit angiogenesis such as thrombospondin-1 and angiostatin (Bid and Houghton, 2011). VEGF, through its binding to the RTK vascular endothelial growth factor receptor 2 (VEGFR2), is the most potent and specific promoter of angiogenesis known. The PDGFR and their cognate RTK PDGFR have potent implications in modulating endothelial cell proliferation and angiogenesis in solid tumors (Geoerger, et al., 2003). Vasculogenesis is mainly dependent on VEGFA/VEGFR2 for migration of the bone marrow-derived progenitor cells and Notch signaling (DLL4) for their differentiation into pericytes and vascular smooth muscle cells (Stewart and Kleinerman, 2011).

Growth Factor Receptors in Pediatric Solid Tumors

VEGF receptor signaling plays a regulatory role in pediatric cancer angiogenesis via both a paracrine mechanism through 2 specific tyrosine kinase VEGF receptors, VEGFR1 (or Flt-1) and VEGFR2 (or KDR) at the surface of the endothelial cells, and a VEGF autocrine loop

involved in pediatric tumor growth (mainly rhabdomyosarcomas [RMS] (Gee, et al., 2005) and high-grade gliomas [HGG]) (Tuettenberg, et al., 2006). Both angiogenesis and vasculogenesis appeared to be correlated with metastatic status of the disease and poor outcome. VEGFR plays a significant role in osteosarcoma, a highly vascularized tumor, and in DTC. VEGF expression and serum levels correlated with increased tumor vascularity, metastatic potential and poorer prognosis (Bid and Houghton, 2011). These results advocate a role for inhibition of tumor angiogenesis using anti-VEGF methods.

Fibroblast growth factors (especially FGF2), FGF3, and vascular endothelial growth factor (VEGF) are some of the genes acting in multistep bone development. Fibroblast growth factor receptors (FGFR1, 2, 3, and 4) seem to play a major role, the latter particularly in RMS (Cao, et al., 2010; Hirotsu, et al., 2009; Taylor, et al., 2009). FGFR1 is upregulated in 70 % of human osteosarcomas and involved in the malignant transformation (Guagnano and Kauffmann, 2012). FGF2/FGFR1 activation has been shown to induce growth inhibition, neuronal differentiation, and apoptosis in primitive neuroectodermal tumors [PNET] and Ewing's sarcoma (Sturla, et al., 2000; Kim, et al., 2004). Basic fibroblast growth factor (bFGF)/FGFR1 strongly induced the motility and invasion of Ewing's sarcoma cells (Kamura, et al., 2010). Embryonal RMS patient biopsy specimens were found to over-express FGFR3 (Bodo, et al., 2002). An autocrine role of βFGF endogenous release controlled the different osteosarcoma phenotypes (Bodo, et al., 2002).

High expression of the PDGFR and its ligands PDGFα and PDGFβ highlight the role of the PDGF pathway in several pediatric tumors (eg., osteosarcoma, [Kubo, 2008] glioma, [Mauro, et al., 1991] diffuse pontine glioma, [Zarghooni, et al., 2010] nephroblastoma, [Ghanem, et al., 2010] Ewing sarcoma [Schaefer, et al., 2008]). PDGFR expression is associated with clinical stage (nephroblastoma [Ghanem, et al., 2010]), with the metastatic status (eg., Ewing's sarcomas, [Schaefer, et al., 2008] medulloblastoma), and correlates with event-free survival (eg., osteosarcoma [Kubo, et al., 2008]).

The RET protooncogene, a member of the cadherin superfamily, encodes an RTK with a crucial role in neural crest development. Different activating mutations in the RET gene are associated with disorders like multiple endocrine neoplasia (MEN) type 2A (MEN2A is characterized by MTC, pheochromocytoma, and primary hyperparathyroidism), MEN type 2B (MEN2B is characterized by clinically aggressive MTC, pheochromocytoma, a Marfanoid body habitus, mucosal and other neuromas, and intestinal tumors mostly ganglioneuromas), Hirschsprung disease, and MTC.

Antiangiogenic Therapies in Pediatric Solid Tumors

Inhibition of single or multiple angiogenic factors have demonstrated antitumor efficacy in nonclinical pediatric tumor models (eg, NB [Pacini, et al., 2012; NCCN Bone Cancer Guidelines, 2014], 3ES [ESMO, 2012], HGG [Tuettenberg, et al., 2006]). Vascular normalization allows reoxygenation and hence increased radiation sensitivity or increased uptake of drugs into tumor tissue, including brain tumors (Tuettenberg, et al., 2006). Drugs such as cediranib (Ferrari, et al., 2003), sorafenib (Kempf-Bielack, et al., 2005), and sunitinib (Berger, et al., 2009), exhibited growth inhibitory activity, inducing significant prolongation

of the time to event in pediatric solid tumor models. Complete responses were rare in soft tissue sarcoma, Ewing's sarcoma, osteosarcoma, Wilms' tumor, hepatoblastoma, ependymoma, and high- and low-grade glioma (Gentet, et al., 1997).

Tyrosine kinase inhibitor (TKI) class toxicity has been similar to adults, with an apparent lower incidence of hypertension in the pediatric population and fewer than anticipated reports of growth plate toxicity.

Inhibition of multiple angiogenic related factors by multitargeted RTK inhibitors:

RTK inhibitors suppress several angiogenic factors but also other TK proto-oncogenes involved in tumor growth and might be useful in tumors with complex genetic abnormalities such as osteosarcoma. Several molecules are available and are currently in early clinical trials in children and adolescents with relapsed or refractory cancer. Phase 1 trials have been completed for sunitinib (inhibitor of PDGFR, VEGFR1-3, c-kit, RET, CSF1R, Flt3) with observed cardiac toxicity (shortened ejection fraction) for pediatric patients with solid tumors with prior anthracycline or radiation exposure, (Rodriguez-Galindo, et al., 2002) and for pazopanib (inhibitor of VEGFR1-3, PDGFRα/β, c kit) with 1 partial response in hepatoblastoma and 3 stable disease (Zarghooni, et al., 2010). A pediatric Phase 2 trial is ongoing for sorafenib (inhibitor of VEGFR1-3, PDGFR, RET, BRAF, c-kit; NCT01445080), that has demonstrated clinical activity in an osteosarcoma Phase 3 study in adults (Ghanem, et al., 2010). A vandetanib (inhibitor of VEGFR2-3, EGFR, RET) Phase 1/2 trial in children and adolescents with hereditary medullary thyroid carcinoma started recruiting in 2007 and is expected to continue recruiting up to 2014 (Schaefer, et al., 2008).

All these molecules are well tolerated with a similar toxicity profile (eg, arterial hypertension, proteinuria, fatigue, gastrointestinal discomfort) due to VEGF pathway inhibition.

7.1.3.2 Clinical Experience with Lenvatinib

As of 27 Apr 2013, 13 studies in Phase 1/1b have been completed in the adult population; 5 in healthy volunteers, 1 bioavailability, 1 QTc effect, 1 food effect, 2 drug-drug interaction (DDI), 2 studies in renally or hepatically impaired subjects, and a mass balance study. Lenvatinib is rapidly absorbed with t_{max} typically from 1 to 4 hours postdose. The capsule form of lenvatinib is about 10% to 14% less bioavailable than the tablet (E7080-A001-001). The terminal elimination half-life ($t_{½}$) of lenvatinib is about 28 hours for both the tablet and the capsule. Serum protein binding of lenvatinib is high (96.6% to 98.2%) and is almost constant in the concentration range of 26 ng/mL to 574 ng/mL (Study E7080-J081-103). Systemic exposure of lenvatinib increases slightly (15% to 19%) upon coadministration with ketoconazole; a CYP3A4 and P glycoprotein inhibitor (P-gp) (E7080-A001-004). Food did not have any significant effect on absorption, indicating that lenvatinib may be administered with or without food (E7080-A001-003). A bioavailability study was conducted in adult healthy volunteers to evaluate the relative bioavailability and palatability of a lenvatinib suspension compared to the capsule formulation (E7080-A001-009).

Pharmacokinetic analysis demonstrated that lenvatinib is rapidly absorbed with maximum concentrations observed from 1 to 3 hours postdose. Exposure to lenvatinib, as measured by AUC and Cmax, increased proportionally with increasing lenvatinib. Steady-state plasma concentrations were achieved within 5 days. Lenvatinib elimination occurred with a bi-exponential decline composed of an initial rapid decline followed by a slower decline. The terminal half-life is approximately 30 hours and steady state is achieved within 5 days. A dose dependent increase in soluble VEGF, consistent with an anti-angiogenic effect was observed during 2 weeks of continuous dosing.

Lenvatinib does not exert a clinically relevant effect on QTcF. Hepatic impairment did not impact the excretion of lenvatinib in urine. Continuous lenvatinib administration at 25 mg once daily (QD) allowed the targeting of higher exposures compared to 10 mg BID and was recommended for ongoing and future studies.

Eight ongoing Phase 2 studies are exploring the safety and efficacy of lenvatinib in subjects with DTC and MTC (E7080-G000-201), HCC (E7080-J081-202), malignant glioma (E7080-G000-203), endometrial cancer (E7080-G000-204), melanoma (E7080-G000-206), thyroid cancer (E7080-J081-208), adenocarcinoma of the lung (E7080-G000-209), and NSCLC (E7080-703) (O'Day, et al., 2013; Funahashi, et al., 2013; Vergote, et al., 2013). Hypertension and proteinuria were the most common dose-limiting toxicities (DLTs). A dose of 25 mg QD was found to be the maximum tolerated dose (MTD) for the QD continuous dosing schedule.

There are 2 ongoing Phase 3 studies, E7080-G000-303, comparing the PFS of subjects treated with lenvatinib versus placebo who have ^{131}I-refractory DTC and E7080-G000-304 comparing the efficacy and safety of lenvatinib versus sorafenib as a first-line systemic treatment in subjects with unresectable HCC.

7.1.3.3 Lenvatinib Clinical Experience in Thyroid Cancer

The most common DLTs reported in the Phase 1b studies were hypertension (31%) and proteinuria (25%). TEAEs commonly reported during Phase 1/1b studies included diarrhea, nausea, hypertension, fatigue, anorexia, constipation, vomiting, proteinuria, and stomatitis. In general, it appears that the incidence of TEAEs increased with increasing doses. The majority of events were ≤Grade 3. In the Phase 2 program, overall, 97% of subjects experienced at least 1 TEAE. The most frequently reported TEAEs included hypertension, fatigue, diarrhea, nausea, and decreased appetite. More than half of the TEAEs were Common Terminology Criteria for Solid Tumors (CTCAE) Grade 3 events, with some CTCAE Grade 4 or Grade 5 events.

As of 27 Apr 2013, 1046 serious adverse events (SAEs) have been reported, including deaths. Of these reported SAEs, 444 were reported as related to test drug and 602 were reported as unrelated to test drug. Of the 187 deaths, 34 (18.2%) were considered related to study drug and 153 (81.8%) were considered not related to study drug. These 187 deaths represent the entire lenvatinib program and include ongoing, blinded studies, which may include deaths in subjects randomized to placebo.

In the randomized, double-blind, placebo-controlled, Phase 3 study that compares the safety and efficacy of lenvatinib in subjects with ^{131}I-refractory DTC, a total of 354 SAEs have been reported (includes active and blinded arms, excludes placebo arm) of which 151 SAEs (42.7%) were reported as related to study drug and 203 SAEs (57.3%) were not related to study drug. The most frequently reported SAEs were hypertension, cerebral vascular accident, pneumonia, dehydration, pulmonary embolism, and vomiting.

For additional information please refer to the current Investigator's Brochure (Lenvatinib Investigator's Brochure).

7.1.3.4 Pediatric Studies

There is no prior experience with lenvatinib in children.

7.2 Study Rationale

Although DTC is rare in children, subjects with DTC have a higher frequency of relapse and their tumors are generally aggressive and advanced at initial presentation. Chemotherapy in the setting of radio-resistant cases offers little or no benefit. Novel therapies, like lenvatinib, with its antiangiogenic activity via the VEGF pathway, may potentially offer therapeutic benefit. However, one of the challenges is that pediatric DTC is rare and it is rarer still to find radio-iodine refractory DTC patients. Osteosarcoma is another pediatric malignancy that uses the VEGF regulatory pathway and merits further exploration of new treatment options. Lenvatinib in combination with conventional chemotherapy for pediatric osteosarcoma potentially could improve clinical results and warrants clinical study.

8 STUDY OBJECTIVES

8.1 Primary Objective(s)

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

8.2 Secondary Objective(s)

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, disease control rate (DCR), and clinical benefit rate (CBR)
- Evaluate the efficacy of lenvatinib as assessed by overall survival (OS)
- 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
- Evaluate the efficacy of lenvatinib as assessed by OS
- 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
- Evaluate the efficacy of lenvatinib as assessed by OS
- 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

8.3 Exploratory Objective

The exploratory objective of this study is 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])

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

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

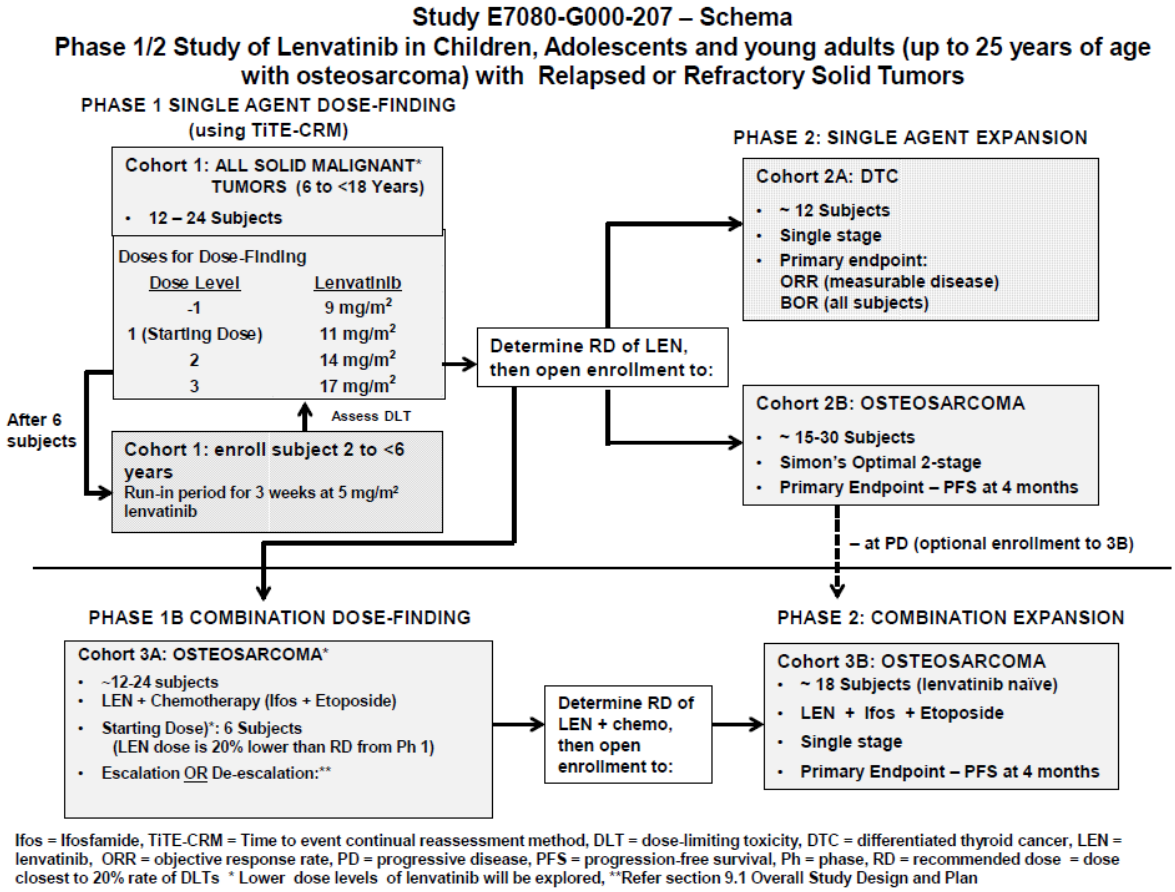


Figure 1 Overall Study Design

Cohort 1 (Single-Agent Dose-Finding): Dose-escalation to find the RD of lenvatinib using a TiTE-CRM design in children and adolescents with relapsed or refractory solid malignant tumors (see **Study Treatment** for dose-escalation scheme; Section 9.1.2.1) (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.

9.1.1 Pretreatment Phase (All Cohorts)

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

9.1.1.1 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. (Procedures to be followed when obtaining informed consent are detailed in Section 5.3.)

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]) as detailed in the Inclusion Criteria (Section 9.3.1).

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.

9.1.1.2 Baseline (All Cohorts)

The purpose of the Baseline Period is to confirm protocol eligibility as specified in the inclusion/exclusion criteria (as detailed in 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 (Table 6), 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 (as detailed in Section 9.3.1 and Section 9.3.2) will begin the Treatment Phase of this study.

9.1.2 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 Section 9.4.1 for rules regarding the calculation of lenvatinib dose based on body surface area (BSA).

9.1.2.1 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 Statistical Methods, Section 9.7.1.5. 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 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.

Intrasubject 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.

9.1.2.2 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.

9.1.2.3 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 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.

9.1.2.4 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.

9.1.3 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 (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 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.
- 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.

9.2 Discussion of Study Design, Including Choice of Control Groups

This study is the first study of lenvatinib in the pediatric population. The primary objective is to identify the RD, and evaluate the activity of lenvatinib as single-agent or in combination with chemotherapy (ifosfamide and etoposide). The study will be conducted in 5 cohorts:

- Cohort 1, a single-agent dose-finding study of lenvatinib in children and adolescents with relapsed or refractory solid tumors to determine the RD;
- Cohort 2, an assessment of the efficacy of lenvatinib at the RD in subjects with either
  - ^{131}I-refractory DTC (Cohort 2A) or
  - relapsed or refractory osteosarcoma (Cohort 2B);
- Cohort 3A, a combination dose-finding study of lenvatinib in combination with ifosfamide and etoposide in subjects with osteosarcoma to determine the RD of the combination; and
- Cohort 3B, a combination expansion study with lenvatinib at the RD, in combination with ifosfamide and etoposide in subjects with osteosarcoma who had either disease progression on lenvatinib (from Cohorts 1 or 2B) or who are lenvatinib-naïve.

In Cohort 1, the Time-to-Event Continuous Reassessment Method (TiTE-CRM [Cheung and Chappell, 2000]) will be used to identify the RD of lenvatinib. TiTE-CRM is an accepted adaptive design that is statistically robust to evaluate RD in most dose-escalation Phase 1 studies (Doussau, et al., 2012). Single agent lenvatinib will be administered at the RD in Cohort 2 of the study. The 80% starting dose is based on consensus reached for pediatric Phase 1 trials (Smith, et al., 1998).

Cohort 2 will evaluate the efficacy of lenvatinib in subjects (1) with relapsed or ^{131}I refractory DTC (Cohort 2A) based upon ORR for subjects with measurable disease and BOR for all subjects as assessed by RECIST 1.1; and (2) with osteosarcoma (Cohort 2B) based upon PFS-4, as assessed by RECIST 1.1. Tumors under study in Cohort 2 may be modified based on preliminary safety and efficacy signals observed in Cohort 1 of the study.

Cohort 3A will determine the RD and safety and toxicity of the combination of lenvatinib, ifosfamide, and etoposide.

Osteosarcoma subjects receiving combination treatment in Cohort 3B will be evaluated for efficacy based upon PFS-4, as assessed by RECIST 1.1.

Secondary objectives of the study will assess safety, toxicity, and tumor response (BOR (osteosarcoma), DOR (measurable DTC and osteosarcoma), PFS, TTP, ORR [osteosarcoma only], DCR and CBR), determine and PK parameters and palatability and acceptability of the suspension formulation.

The study will also collect blood and tumor biomarkers to correlate PK and pharmacodynamics (PD) biomarkers with tumor response or AEs associated with lenvatinib treatment. Dose-limiting toxicities are defined based on known lenvatinib and chemotherapy drug toxicities, but also include any unexpected toxicities.

9.3 Selection of Study Population

Approximately 69 to 108 subjects between 2 and <18 years of age (≤25 years for osteosarcoma subjects) will be enrolled at approximately 12 sites in Europe and US. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Histologically or cytologically confirmed diagnosis of solid malignant tumor
    a. Cohort 1: Any solid malignant tumor
    b. Cohort 2A: DTC with one of the following histological subtypes:
        b. Papillary thyroid cancer (PTC)
            1. Follicular variant
            2. Other variants (including but not limited to tall cell, columnar cell, cribriform-morular, solid, oxyphil, Warthin's-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of papillary carcinoma, or poorly differentiated carcinomas)
        c. Follicular thyroid cancer (FTC)
            1. Hürthle cell
            2. Clear cell
            3. Insular
    c. Cohort 2B, 3A, and 3B: Relapsed or refractory osteosarcoma
2. Relapsed or refractory solid tumor malignancy that has progressed on standard anticancer therapy with no available curative options. (Note: Osteosarcoma subjects must be in first

or subsequent relapse [≥ first relapse]). Only the osteosarcoma subjects enrolled to Cohorts 3A and 3B must be deemed candidates for ifosfamide and etoposide chemotherapy).

3. Evaluable or measurable disease per RECIST 1.1 that meets the following criteria

    a. Subjects must have evaluable or measurable disease based on RECIST 1.1 using computed tomography/magnetic resonance imaging (CT/MRI) (Appendix 1)

    b. Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must have subsequently grown unequivocally to be deemed a target lesion

4. DTC subjects must have ^{131}I-non-avid/refractory progressive disease and no effective anticancer therapy options available.

    a. One or more evaluable or measurable lesions that do not demonstrate iodine uptake on any radioiodine scan OR
    b. One or more evaluable or measurable lesions that have progressed based on RECIST 1.1, within 12 months of ^{131}I therapy, despite demonstration of radioiodine avidity at the time of that treatment by pre- or post-treatment scanning. These subjects must not be eligible for possible curative surgery OR
    c. Cumulative activity of ^{131}I >400 millicuries (mCi) or 14.8 gigabecquerels (GBq), with the last dose administered at least 6 months prior to study entry

5. Subjects with DTC must be receiving thyroxine suppression therapy and levels of thyroid stimulating hormone (TSH) should not be elevated (TSH should be ≤5.50 mU/L). When tolerated by the subject, thyroxine dose should be changed to achieve TSH suppression (TSH <0.50 mU/L)

6. Subjects with known central nervous system (CNS) primary tumors or metastases who have completed brain therapy (such as radiotherapy, stereotactic radiosurgery or surgical resection), and have remained clinically stable, asymptomatic and off of steroids for 2 weeks prior to Cycle 1 Day 1 will be eligible

7. Male or female subjects age 2 years to <18, (≤25 years for osteosarcoma subjects) at the time of informed consent

8. Lansky play score ≥50% or Karnofsky Performance Status score ≥50% (Appendix 4 and Appendix 5, respectively). Use Karnofsky for subjects ≥16 years of age and Lansky for subjects <16 years of age

9. Life expectancy ≥3 months

10. Adequate bone marrow function as evidenced by:

    a. absolute neutrophil count (ANC) ≥1.0 × 10^9/L

b. (for Cohorts 3A and 3B leucocyte count ≥2 × 10^9/L; subjects with bone marrow involvement should have ANC ≥ 0.8 × 10^9/L and leucocyte count ≥1 ×x 10^9/L)
c. hemoglobin ≥8.0 g/dL (a hemoglobin <8.0 g/dL is acceptable if it is corrected by growth factor or transfusion before starting lenvatinib)
d. platelet count ≥75 × 10^9/L

11. Adequate liver function as evidenced by:

a. bilirubin ≤1.5 times the upper limit of normal (ULN)
b. alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN (in the case of liver metastases ≤5 × ULN), unless there are bone metastases or bone primary tumor, in which case liver specific alkaline phosphatase must be separated from the total and used to assess the liver function instead of the total alkaline phosphatase

12. Adequate renal function as evidenced by:

a. Serum creatinine based on age/gender as below. If serum creatinine is greater than maximum serum creatinine for age/gender as shown in the table below, then creatinine clearance (or radioisotope glomerular filtration rate [GFR]) must be >70 mL/min/1.73 m^2 (Appendix 6).

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz, et al., 1985) using child length and stature data published by the CDC.

b. Urine dipstick <2+ for proteinuria. Subjects who have ≥2+ proteinuria on dipstick urinalysis should undergo a spot protein-creatinine (P/C) ratio test that should be Grade <2 per CTCAE v4.03 and if possible perform a 24-hour urine collection (children and adolescents ≤12 years of age must have ≤500 mg of protein/24 hours and subjects >12 years of age must have ≤ 1 g of protein/24 hours)
c. No clinical evidence of nephrotic syndrome

13. Adequate cardiac function as evidenced by left ventricular ejection fraction ≥50%) at baseline as determined by echocardiography

14. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as:

BP <95th percentile for sex, age, and height/length at screening (as per National Heart Lung and Blood Institute guidelines; see Appendix 7 and Appendix 8) and no change in antihypertensive medications within 1 week prior to Cycle 1/Day 1. Osteosarcoma subjects age 18 to 25 years should have BP ≤150/90 mm Hg at screening and no change in antihypertensive therapy within 1 week prior to Cycle 1 Day 1.

15. Washout of 3 weeks in case of prior chemotherapy, 6 weeks if treatment included nitrosoureas; 4 weeks for definitive radiotherapy, and 2 weeks for palliative radiotherapy; 3 months from high-dose chemotherapy and stem cell rescue; 3 weeks from major surgery. Subjects must have recovered from the acute toxic effects of all prior anticancer therapy before enrollment into the study

16. Written and signed informed consent from the parent(s) or legal guardian and assent from the minor subject. Written informed consent from subjects ≥18 years.

17. Willing and able to comply with the protocol, scheduled follow-up, and management of toxicity as judged by the Investigator

Cohort 3B (Combination Expansion): Osteosarcoma subjects who progressed in Cohorts 1 or 2B and opt to receive combination therapy:

18. Osteosarcoma subjects receiving combination therapy of lenvatinib with ifosfamide and etoposide should meet only Inclusion Criteria Numbers ~~7~~ 6 through 17 (after progression in Cohort 2B)

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any active infection or infectious illness unless fully recovered prior to dosing

2. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study

3. Other organ toxicity due to prior anticancer therapy (investigational agent, chemotherapy, or radiation therapy) except alopecia, and ototoxicity due to cisplatin not already covered in the inclusion/exclusion criteria, which has not recovered to Grade <2 per CTCAE v4.03

4. Known hypersensitivity to any component of the product (lenvatinib or ingredients)

5. Concurrent administration of any other antitumor therapy

6. Previous treatment with lenvatinib (except for subjects previously enrolled into Cohorts 1 or 2B of this study)

7. Two or more prior VEGF/VEGFR-targeted therapies

8. Currently receiving any investigational drug or device in another clinical trial or within 30 days preceding informed consent

9. A clinically significant ECG abnormality, including a marked baseline prolonged QT or QTc interval (eg, a repeated demonstration of a QTc interval >480 msec).

10. Gastrointestinal malabsorption or any other condition that in the opinion of the investigator might affect the absorption of lenvatinib.

11. Gastrointestinal bleeding or active hemoptysis (bright red blood of at least ½ teaspoon) within 3 weeks prior to the first dose of study drug.

12. Active second malignancy within 2 years prior to enrollment ([in addition to the primary tumor types specified by cohort in Inclusion Criterion Number 1], but not including definitively treated superficial melanoma, in-situ, basal or squamous cell carcinoma of the skin).

13. Previous treatment with ifosfamide and grade ≥3 nephrotoxicity or encephalopathy (Cohorts 3A and 3B).

14. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG], human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG / hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

    Females of childbearing potential who:

    - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device or intrauterine hormone-releasing system (IUS)
        - an oral contraceptive. Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 6 months after study drug discontinuation.) .
        - have a vasectomized partner with confirmed azoospermia.
    - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 6 months after study drug discontinuation.

    For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 5 times the half-life of the study drug plus 90 days after study drug discontinuation). No sperm donation is allowed during the study period and for 5 times the half-life of the study drug plus 90 days after study drug discontinuation.

Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 6 months after study drug discontinuation). If the female partner is pregnant, then males who do not agree to use condoms throughout the study period and for 6 months after study drug discontinuation. No sperm donation is allowed during the study period and for 6 months after study drug discontinuation.

Cohort 3B (Combination Expansion): Osteosarcoma subjects who progressed in Cohorts 1 or 2B and opt to receive combination therapy:

15. Osteosarcoma subjects receiving combination therapy of lenvatinib with etoposide and ifosfamide should meet all the exclusion criteria, with the exception of Criterion Number 6

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. If a subject discontinues study treatment, the subject will enter the Post-treatment Follow-up Period and complete protocol-specified off-treatment visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents. The Discontinuation From Treatment, case report form (CRF) page will be completed indicating the primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from treatment. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing CRF page.

During the Follow-Up Period, subjects who discontinue study treatment without progression should have tumor assessments every 6 or 8 weeks (per the appropriate tumor assessment schedule) for up to 1 year or sooner if clinically indicated, until disease progression is

documented or until another anticancer therapy is initiated. After data cutoff, tumor assessments may be performed as clinically indicated per institutional guidelines, following the prevailing local standard of care.

All subjects will be followed for survival for 1 year or until death, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up after completion of the primary study analysis.

9.4 Treatment

9.4.1 Treatment(s) Administered

Lenvatinib will be provided by Eisai as hard capsules containing 1, 4, or 10 mg lenvatinib. An extemporaneous suspension of lenvatinib capsules should be used for children unable to swallow capsules, as detailed in Appendix 12.

Cohort 1 (Single-Agent Dose-Finding): Lenvatinib will be administered orally QD on Days 1 to 28 of each 28-day cycle (Table 1).

Cohort 2 (Single-Agent Expansion): Lenvatinib will be administered orally QD at the Single-Agent RD (identified in Cohort 1) on Days 1 to 28 of each 28-day cycle.

Cohort 3A (Combination Dose-Finding): Lenvatinib will be administered orally QD on Days 1 to 21 of each 21-day cycle (Table 2)

Cohort 3B (Combination Expansion): Lenvatinib will be administered orally QD at the RD (identified in Cohort 3A) on Days 1 to 21 of each 21-day cycle. Ifosfamide and etoposide will be administered on Days 1 to 3 of each 21-day cycle.

Before dose administration on Day 1 of each cycle and prior to a change in dose due to dose reduction, the amount of lenvatinib needed for each subject must be calculated as follows:

Scheduled dose (mg/m^2) x body surface area (BSA) (m^2) = lenvatinib dose (mg)

BSA will be calculated using the method that is accepted and customarily used by the clinical site. BSA must be calculated on Day 1 of each cycle based on the subject's current height and body weight. BSA will be used to determine the amount of lenvatinib for each subject. BSA should not be corrected for amputation. The dose should be rounded to the nearest whole number. After adjustment for BSA, the daily dose of lenvatinib should not exceed 24 mg daily.

9.4.1.1 Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) in subjects treated with lenvatinib will be assessed according to CTCAE v4.03 (Appendix 2) 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 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)

Non-Hematologic 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 the Eisai Medical Monitor, in consultation with the PSC, as needed. Subjects who discontinue the study treatment for any reason other than DLT during Cycle 1 (Day 1 through Day 28 for Cohort 1, and Day 1 through Day 21 for Cohort 3A) will be replaced.

9.4.1.2 Lenvatinib Dose Reduction and Interruption Instructions

Dose adjustments will be made for subjects who experience treatment-related toxicity according to the instructions provided in the Table 3. Doses in the Dose Adjustment column are based on a presumed starting dose of 11 mg/m^2.

Dose reductions occur in succession based on the previous dose level. Each dose level reduction is a 20% reduction from the previous dose. Once the dose has been reduced, it cannot be increased at a later date.

Table 3 Criteria for Temporary Discontinuation of Study Drug, Dose Reduction, and Resumption of Treatment

Lenvatinib Related Toxicity[a, b] including hepatic injury and thromboembolic events	**Management**	**Dose Adjustment**
Grade 1		
	Continue treatment	No change
Intolerable Grade 2[c] or Grade 3[e]		
First occurrence	Interrupt until resolved to Grade 0 - 1 or baseline	8.8 mg/m^2 (or 20% reduction of the starting dose) orally QD (one-level reduction)
Second occurrence		
(same toxicity or new toxicity)	Interrupt until resolved to Grade 0 - 1 or baseline	7.0 mg/m^2 (or 20% reduction of the previous dose) orally QD (one-level reduction)
Third occurrence		
(same toxicity or new toxicity)	Interrupt until resolved to Grade 0 - 1 or baseline	5.6 mg/m^2 (or 20% reduction of the previous dose) orally QD (one-level reduction)
Fourth occurrence		
(same toxicity or new toxicity)	Interrupt until resolved to Grade 0 - 1 or baseline	Discuss with sponsor
Grade 4[d]: Discontinue Study Treatment		

For grading, see Common Terminology Criteria for Adverse Events (CTCAE v4.03) (Appendix 2). Collect all CTC grades of adverse events, decreasing and increasing grade.

a. Interruption of lenvatinib treatment for more than 28 days (due to lenvatinib-related toxicities) will require a discussion with the sponsor before treatment can be resumed.

b. Initiate optimal medical management for nausea, vomiting, and/or diarrhea before any lenvatinib interruption or dose reduction.

c. Applicable only to those Grade 2 toxicities judged by the subject and physician to be intolerable. Not applicable to abnormal clinical laboratory values that are not clinically relevant based on the judgment of the investigator.

d. Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

e. Obese subjects with weight loss do not need to return to baseline or Grade 1 weight loss to restart lenvatinib. There should be no weight loss for at least 1 week, and subjects should be started at the lower dose and normal BMI should be used for future dose reductions. Obesity is defined as body mass index (BMI) percentiles corresponding to 30 kg/m², related to the age of the children. (Cole T.J., et al 2000) or BMI ≥ the 95th percentile for children and teens of the same age and sex (Ogden CL et al, 2002)(Appendix 9 and 10).

9.4.1.3 Blood Pressure

For children, blood pressure varies by the sex and age of the child and it is closely related to height and weight. Blood pressure will be assessed in terms of percentile for sex, age and height/length. Guidelines to sex, age, and height-specific percentiles of blood pressure is provided in Appendix 7 and Appendix 8. Blood pressure that is consistently above the 95th percentile [for subjects age 18-25 years BP ≤140/90 mm Hg] for age and height/length requires further evaluation. A referral to a cardiologist is recommended for patients who develop hypertension during the study. Ideally, cardiovascular assessments and the management of hypertension should be supervised by a cardiologist. Exercise, excitement, coughing, crying and struggling may raise the systolic pressure of children as much as 40 to 50 mmHg greater than their usual level. Variability in blood pressure in children of approximately the same age and body build should be expected and serial measurements should always be obtained when evaluating a patient with hypertension. **BP values for management of hypertension for subjects 18 to 25 years of age are included in parenthesis.**

9.4.1.4 Management of Hypertension

Hypertension is a recognized side-effect of treatment with drugs inhibiting vascular endothelial growth factor (VEGF) signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP <95th percentile [BP ≤150/90 mm Hg] for sex, age, and height/length at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1 Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥95th percentile [BP ≥140 mm Hg] or diastolic BP ≥95th percentile [BP ≥90 mm Hg]) is confirmed on 2 assessments obtained 1 hour apart. One BP assessment is defined as the mean value of 3 measurements obtained at least 5 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when systolic BP ≥95th percentile [BP ≥140 mm Hg] or diastolic BP ≥95th percentile [BP ≥90 mm Hg] is first observed on 2 assessments obtained 1 hour apart. For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. For subjects with hypertension and proteinuria, treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist is preferred.

Lenvatinib should be withheld in any instances where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥99th percentile [BP ≥160/100 mm Hg], significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant comorbidities). Once the subject has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

During the Treatment Period, subjects with systolic BP ≥99th percentile [BP ≥160 mm Hg] or diastolic BP ≥99th percentile [BP ≥100 mm Hg] must have their BP monitored every 2 weeks (on Day 15 or more frequently as clinically indicated) until systolic BP has been <95th percentile [≤ 150 mm Hg] and diastolic BP has been <95th percentile [≤ 95 mm Hg] for 3 consecutive months. If a new event of systolic BP ≥99th percentile [BP ≥160 mm Hg] or diastolic BP ≥99th percentile [BP ≥100 mm Hg] occurs, the subject must resume the Day 15 evaluation until systolic BP has been <95th percentile [≤ 150 mm Hg] and diastolic BP has been <95th percentile [≤ 95 mm Hg] for 3 consecutive months.

The following guidelines should be followed for the management of systolic BP ≥99th percentile [BP ≥160 mm Hg] or diastolic BP ≥99th percentile [BP ≥100 mm Hg] confirmed on repeat measurements after an hour:

- Continue lenvatinib and institute antihypertensive therapy for subjects not already receiving antihypertensive medication.

- For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added.

- If systolic BP ≥99th percentile [BP ≥160 mm Hg] or diastolic BP ≥99th percentile [BP ≥100 mm Hg] persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at a lower dose QD (one dose level reduction [20%] as specified in Table 2) only when systolic BP <95th percentile [BP ≤150 mm Hg] and diastolic BP <95th percentile [BP ≤95 mm Hg] and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

    - If systolic BP ≥99th percentile [BP ≥160 mm Hg] or diastolic BP ≥99th percentile [BP ≥100 mm Hg] recurs despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a lower dose QD (one dose level reduction [20%] as specified in the table above) only when systolic BP <95th percentile [BP ≤150 mm Hg] and diastolic BP <95th percentile [BP ≤ 95 mm Hg] and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

    - If systolic BP ≥99th percentile [BP ≥160 mm Hg] or diastolic BP ≥99th percentile [BP ≥100 mm Hg] recurs despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and a restart of lenvatinib should be discussed with the sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management
- Discontinue lenvatinib

Figure 2 shows the procedures associated with the management of hypertension.

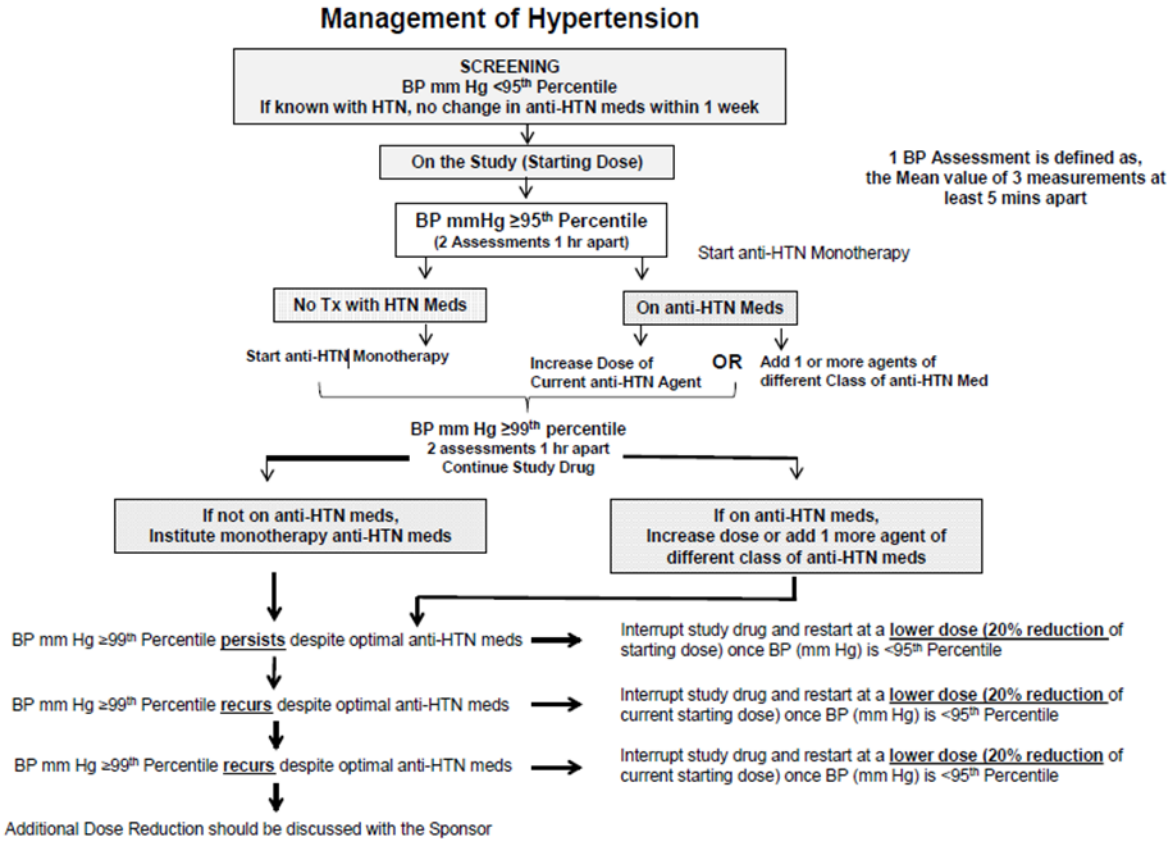


Figure 2 Management of Hypertension

BP = blood pressure, HTN = hypertension, Tx = treatment.

9.4.1.5 Management of Posterior Reversible Leukoencephalopathy Syndrome (PRES)

A thorough medical history and a comprehensive physical examination, including a neurological examination, should be conducted as detailed in the Schedule of Assessments (Table 7, Table 8, and Table 9) and as clinically indicated.

Any subject with signs or symptoms of headache, confusion, seizure, or visual change combined with hypertension (usually but not always severe) should be immediately evaluated with brain MRI to evaluate the possibility of posterior reversible leukoencephalopathy syndrome (PRES), a Grade 4 hypertension adverse event per CTCAE v4.03. In subjects with suspected PRES, lenvatinib should be immediately withheld, and if the condition is confirmed by MRI, lenvatinib must be permanently discontinued (see

Table 3). Appropriate measures should be taken to control blood pressure (see Section 9.4.1.4), and neurologic consultation is advised.

9.4.1.6 Management of Proteinuria

Regular assessment for proteinuria should be conducted as detailed in the Schedule of Assessments (Table 7, Table 8, and Table 9). Guidelines for assessment and management of proteinuria are summarized as follows:

- Initial episode of proteinuria: If proteinuria ≥ 2+ is detected on urine dipstick testing, study drug will be continued and a spot protein-creatinine ratio test and if possible a 24-hour urine collection for total protein will be obtained as soon as possible within 72 hours to verify the grade of proteinuria. Grading according to CTCAE v4.03 (Appendix 2) will be based on the protein-creatinine ratio. And wherever possible also on the 24-hour urinary protein result per investigators discretion. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 3.

- During the Treatment Period, urine dipstick testing for subjects with proteinuria ≥ 2+ should be performed every 2 weeks (on Day 15 or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months. Any subsequent increases in the level of proteinuria ≥ 2+ on urine dipstick testing must be confirmed with a spot protein-creatinine ratio test and if possible a 24-hour urinary protein test per investigators discretion which will be assessed and graded and managed according to the dose reduction and interruption instructions provided in the table above. If a new event of proteinuria ≥ 2+ occurs, the subject must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 3 consecutive months.

9.4.1.7 Management of Hepatotoxicity

Regular monitoring of liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the Schedule of Assessments (Table 7, Table 8, and Table 9) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in the table for dose reduction and interruptions of the protocol should be followed (see Table 3), for Study Treatment Dose Reduction and Interruption Instructions). Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study drug must be discontinued.

9.4.1.8 Management of Thromboembolic Events

Subjects should be advised to pay attention to symptoms suggestive of venous thromboembolic events which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, deep vein thrombosis signs including lower-extremity swelling, redness and warmth to touch or tenderness. In case any of these symptoms appear, subjects should be instructed to report such symptoms promptly to the

treating physician. If a thromboembolic event is confirmed, instructions contained in the table for dose reduction and interruptions of the protocol should be followed, (see Table 3), for Study Treatment Dose Reduction and Interruption Instructions). Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, the study drug must be discontinued.

9.4.1.9 Management of Hypocalcemia

Serum calcium should be monitored monthly per the Schedule of Assessments. Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

9.4.1.10 Management of Gastrointestinal Symptoms and Acute Abdominal Pain

Initial management of acute abdominal pain in these study subjects should be focused on treating the underlying cause where possible, ensuring appropriate hydration/rehydration, and symptomatic pain improvement consistent with subject's age and in accordance to local and institutional standards of care. Appropriate supportive care should be provided together with close monitoring.

For adverse events of abdominal pain believed related to lenvatinib or more specific adverse events believed related to lenvatinib that result in the symptom of abdominal pain, instructions contained in Table 3 regarding study treatment dose reduction and interruption instructions. For Grade 4 adverse events that result in abdominal pain, study drug must be discontinued.

Gastrointestinal (GI) symptoms including diarrhea should be managed by providing symptomatic treatment. If the symptoms persist (eg, diarrhea for more than 10 days), Study Treatment Interruption and Reduction guideline should be followed. Gastrointestinal symptoms should be monitored closely and evaluated using CT, Contrast-Enhanced MRI, ultrasound, or other diagnostic imaging if clinically indicated, at the investigator's discretion. All GI symptoms should be recorded in the diary provided.

9.4.1.11 For additional information please refer to the current Investigator's Brochure (Lenvatinib Investigator's Brochure). Management of Ifosfamide-Etoposide Associated Toxicity

All sites participating in this trial have had considerable experience with these chemotherapeutic agents. Blood counts should be closely monitored during and prior to the next cycle of chemotherapy. Chemotherapy-associated myelosuppression should be managed by G-CSF. It is recommended that pegylated G-CSF or G-CSF be administered at least 24 to 72 hours after completion of ifosfamide-etoposide chemotherapy; use of G-CSF is recommended until WBC counts are $\geq 1 \times 10^9$/L. Guidelines for dose modification for ifosfamide and etoposide associated toxicities are provided in the Table 4 below.

Details of ifosfamide and etoposide dose interruption and reduction as well as management of toxicity can be found in the Summary of Product Characteristics (SmPC), and may be followed as per local and institutional guidelines. The SmPC will be provided to the study sites in the Investigator and Pharmacy files in the relevant local language. For additional information investigators may refer to the SmPC or Euramos-1 protocol (ISRCTN67613327 EudraCT no. 2004-000242-20).

Table 4 Criteria for Dose Modification of Chemotherapy Dose

Toxicity	Grade	Action
Neutropenia	Grade 4	Monitor ANC counts every 3 days until resolved to < Grade 3
Febrile neutropenia	Grade 4	Reduce the next dose of ifosfamide and etoposide by 20%
Mucositis	Repeated grade 3 or Grade 4	Reduce etoposide by 20%
Renal Toxicity	Serum creatinine is 1.5 – 3 × ULN maximum serum creatinine for age and gender	Interrupt ifosfamide and etoposide for 1 week
Hematuria	>50 RBC/ high power field (hpf)	Interrupt ifosfamide for 1 week
Neurological Toxicity	≥ Grade 2	Interrupt and reduce ifosfamide and etoposide each by 20% of the previous dose. After 2 dose reductions subject must discontinue the chemotherapy drugs, but if benefiting, can continue on single-agent lenvatinib at the investigator's discretion

9.4.2 Identity of Investigational Product(s)

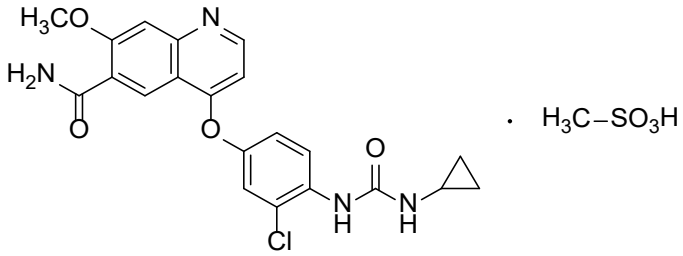
Lenvatinib

Lenvatinib will be supplied by the sponsor in labeled containers. The sponsor will package lenvatinib as open-label supplies. Lenvatinib will be provided to the sites as #4 size hydroxypropyl methylcellulose (HPMC) capsules in 3 strengths differentiated by color (iron oxide red and iron oxide yellow); 1-mg capsule (yellowish red cap and white body, containing 1 mg E7080 anhydrous-free base), 4 mg capsule (yellowish-red cap and body, containing 4 mg E7080 anhydrous-free base); and 10 mg capsule (yellowish-red cap with yellow body, containing 10 mg E7080 anhydrous-free base). Excipients of the E7080 formulation will be calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, talc, hypromellose, titanium dioxide, iron oxide yellow, and iron oxide red. Lenvatinib capsules may be suspended in water or apple juice for children unable to swallow capsules. Appendix 12 provides instructions for the preparation of the lenvatinib suspension.

9.4.2.1 Chemical Name, Structural Formula of Lenvatinib

- Study drug code: E7080

- Generic name: lenvatinib
- Chemical name: 4-[3-Chloro-4-(*N*'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate
- Molecular formula: $C_{21}H_{19}ClN_4O_4 \bullet CH_4O_3S$
- Molecular weight: 522.96
- Structural formula:



9.4.2.2 Comparator Drug

Not applicable.

9.4.3 Cytotoxic Chemotherapy: Ifosfamide and Etoposide

The cytotoxic chemotherapy drugs (used in combination with lenvatinib) in this study will be ifosfamide and etoposide. These chemotherapy drugs will be provided by the sponsor. The administration procedure should follow the approved prescribing information in each country/region. The chemotherapy regimen schedule and dosing details are provided below.

The chemotherapy regimen schedule will consist of ifosfamide 3000 mg/m^2/day IV infusion over 30 minutes for 3 consecutive days (Day 1 to Day 3 of each cycle) and etoposide 100 mg/m^2/day IV infusion for 3 consecutive days (Day 1 to Day 3 of each cycle). Chemotherapy administration should be accompanied by vigorous hydration and administration of mesna according to the institutional guidelines. Each chemotherapy cycle will be 21 days for a total of 5 cycles.

Pegylated G-CSF or G-CSF will be administered at least 24 to 72 hours after completion of ifosfamide-etoposide chemotherapy until WBC counts are $\geq 1 \times 10^9$/L or at the investigator's discretion.

9.4.3.1 Labeling for Study Drug

Lenvatinib and the combination chemotherapy drugs, ifosfamide and etoposide, will be labeled centrally for all countries except for Germany and US in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

The following information will be provided (but not limited to):

- For clinical trial use only

- Name and address of the sponsor
- Chemical name / drug identifier
- Lot number/Batch number
- Storage conditions, expiration date if necessary

9.4.3.2 Storage Conditions

Lenvatinib will be stored in accordance with the labeled storage conditions. The expiry date for lenvatinib will be established based on the date that manufacturing/packing is completed or will be based on formulation testing, and will therefore be described in the "Procedures for Handling Investigational Drug." The sponsor will prepare the "Procedures for Handling Investigational Drug," which will be provided to the investigator and the designated pharmacist.

Ifosfamide and etoposide will be stored in accordance with the labeled storage conditions.

Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained. The temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.4 Method of Assigning Subjects to Treatment Groups

This is an open-label study. All subjects who provide signed informed consent and/or assent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to 1 of 5 dosing cohorts. Enrollment will start with Cohort 1. Approximately 12 to 24 subjects with solid tumors will be enrolled.

After identifying the Single-Agent RD of lenvatinib in Cohort 1, Cohorts 2A, 2B, and 3A will begin enrollment in parallel. Osteosarcoma subjects will be assigned to either Cohort 2B or Cohort 3A. Approximately 27 to 42 subjects divided into the 2 malignancy groups (approximately 12 subjects with ^{131}I refractory DTC and 15 to 30 subjects with osteosarcoma) will be enrolled in Cohort 2. Approximately 12 to 24 subjects with osteosarcoma will be enrolled in Cohort 3A (Dose-Finding combination).

Enrollment in Cohort 3B will start after Combination RD of lenvatinib is identified in Cohort 3A. After defining the RD of lenvatinib in combination with chemotherapy (ifosfamide and etoposide) 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 will enroll approximately 18 lenvatinib–naïve subjects with osteosarcoma, along with some subjects who progressed in Cohorts 1 or 2B.

9.4.5 Selection of Doses in the Study

The starting dose of lenvatinib for Cohort 1 is 11 mg/m^2 QD, which is 80% of the adult RD of 24 mg QD. The 80% starting dose is based on the consensus reached for pediatric Phase 1 trials (Smith, et al., 1998). The starting dose of lenvatinib used in Cohort 3A will be 20% lower than the RD of lenvatinib identified in Cohort 1.

9.4.6 Selection and Timing of Lenvatinib Dose for Each Subject

Lenvatinib capsules are to be taken orally once a day at approximately the same time in the morning without regard to food intake for 28 days from Cycle 1 onward. If a subject misses a dose, it may be taken within the 12 hours following the usual time of the morning dose. If more than 12 hours have elapsed from the time of the usual daily dose, lenvatinib should be taken the next day at the usual time in the morning. In the event a subject vomits after study drug administration, the subject should not take another dose until the next scheduled dose.

Study drug(s) should be administered at the clinic on PK sampling days. All scheduled visits must be conducted as per protocol, irrespective of treatment interruption. If holidays or personal schedules make administration impossible on the scheduled days, then administration should be resumed as soon as possible.

9.4.7 Blinding

Not applicable.

9.4.8 Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with lenvatinib may be continued during the study.

Drugs that are not prohibited for concomitant use include drugs used to treat complications or adverse events or drugs used to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) lenvatinib.

Aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and low-molecular-weight heparin (LMWH) are permissible but should be used with caution. Erythropoietic stimulating agents (ESAs) may be used according to the American Society of Clinical Oncology (ASCO),

institutional, or national guidelines and according to the SmPC or local labeling instructions, but the subject should be carefully monitored for increases in red blood cell (RBC) counts.

If concomitant medication/therapy is administered for an adverse event, investigators will record that AE on the Adverse Events CRF.

9.4.8.1 Drug-Drug Interactions

The weak inhibitory effect on CYP enzymes (in vitro) exhibited by lenvatinib suggests a low risk of lenvatinib interference with the PK of other drugs co-administered in usual clinical practice. Simultaneous CYP3A4/P-gp inhibitions by ketoconazole slightly (15% – 19%) increased systemic exposure to lenvatinib after oral administration as measured by AUC and C_{max} in humans. Since no change was observed in half-life, t_{max}, or t_{lag}, the slight increase in systemic exposure is probably related to a decrease in first pass metabolism. However, since the magnitude of the change is small, coadministration of lenvatinib with CYP3A4/P-gp inhibitors is not of clinical concern. Similarly, PK data did not suggest any major effects of rifampin on the exposure or disposition of lenvatinib. Following administration of a single dose of lenvatinib with a single dose of rifampin, lenvatinib exposure increased about 31%. In contrast, following administration of multiple doses of rifampin, free lenvatinib exposure was reduced about 9% and about 18% for total lenvatinib. These findings suggest that there is no clinically meaningful influence of either P-gp inhibition (single dose of rifampin) or simultaneous P-gp and CYP3A4 induction (multiple doses of rifampin) on lenvatinib PK.

The locally approved product label or applicable SmPC for ifosfamide and etoposide should be referenced for any concomitant therapy use with ifosfamide and etoposide.

9.4.8.2 Prohibited Concomitant Therapies and Drugs

Subjects should not receive other antitumor therapies while on study. If subjects receive additional antitumor therapies, such as chemotherapy, hormone therapy with well-known direct antitumor activity against the subject's malignancy, palliative radiotherapy (other than as described below), or immunotherapy, this will be judged to represent evidence of disease progression, and study medication will be discontinued. These subjects should complete all off-treatment assessments and continue to be followed for survival in the Post-treatment Follow-Up.

Prophylactic use of G-CSF is not permitted during this study for Cohorts 1, 2A, and 2B. G-CSF is recommended for Cohorts 3A and 3B to mitigate the toxicity of ifosfamide and etoposide).

9.4.8.3 Permitted Concomitant Treatment/Procedures

The following concomitant treatments/procedures are allowed:

a. Removal of existing (not new) osteosarcoma metastatic lesion (surgical, radiofrequency ablation, etc) as follows:

   - After the completion of first 4 months of the Treatment Period without progression, and
   - Before the first 4 months of the Treatment Period only if there is disease progression assessed by the investigator and the subject will discontinue the study for progression

b. Palliative radiotherapy in Cohort 2 and 3B is allowed for ≤2 significantly symptomatic nontarget lesions. For Cohorts 1 and 3A, it will be allowed after the RD is determined.

If a subject receiving treatment with lenvatinib requires surgery during the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 1 week after, once there is evidence of adequate healing and no risk of bleeding.

9.4.9 Any additional procedural or patient specific particularities should be discussed with the investigator and the sponsor. Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Clinical research associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

9.4.10 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study

- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted *(if required)*, and the Import License *(if required)*

The investigator, study staff, and the designated pharmacist will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to Good Clinical Practice (GCP) guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study other than the parent, guardian, or authorized legal representative of a study subject.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to the site but not dispensed to the subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, MHRA). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator or the designated pharmacist by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will

only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

For subjects continuing study treatment at the time of the data cutoff date for the primary analysis, the study drugs will be ordered and dispensed manually, and IxRS dispensing will be closed out once the procedure for reconciliation of study drugs is complete for the purpose of the clinical study report.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity (recorded in accordance with prevailing regulations).

9.5.1.2 Baseline Assessments

Baseline assessments will be performed at Day -1 or at Cycle 1 Day 1 prior to treatment. Assessments will include confirmation of subject eligibility with the inclusion and exclusion criteria, medical and surgical history, prior medications and procedures, pregnancy test (serum or urine) within 72 hours of the first dose of study medication), Lansky play score (see Appendix 4) or Karnofsky performance status score (see Appendix 5), TNM Staging (at initial diagnosis of the disease), vital signs, clinical chemistry and hematology, urine dipstick testing, height, hand/wrist x-ray, proximal tibial growth plates, guaiac fecal occult blood test, guaiac fecal occult blood test, PD biomarkers and optional biomarkers, and blood sample collection for pharmacogenomics (PG) analysis.

A comprehensive physical examination, including a neurological examination, will be performed at baseline if the screening physical examination was performed >7 days prior to Cycle 1 Day 1. Subjects 2 to <6 years of age must complete Screening/ Baseline assessments and all the assessments during the Run-In Period as indicated in Table 7 from Day 1 to Day 21 of Cycle 1 prior to entering Cycle 1.

MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history and current medical conditions will be recorded at the Screening and Baseline Visits. All medical and surgical history must be noted in the Medical History and Current Medical Conditions CRF.

Physical examinations (comprehensive or symptom directed) will be performed as designated in the Schedule of Assessments (Table 7, Table 8, and Table 9). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.3 Efficacy Assessments

TUMOR RESPONSE ASSESSMENTS

Tumor assessment will be performed based on RECIST 1.1 (Appendix 1). Investigator-determined response assessments at each assessment time point will be entered onto the appropriate CRF. Subjects must have evaluable disease or measurable disease based on RECIST 1.1.

At Screening

CT/MRI scans of the brain, neck (DTC only) chest, abdomen, pelvis, and other known sites of disease (bone), plus any areas of newly suspected disease will be performed at screening. Historical scans (within prior 28 days) that do not follow the guidelines completely may be used to demonstrate eligibility. For subjects with ^{131}I refractory DTC, historical scans (within prior 12 months) that do not follow the guidelines completely may be used to demonstrate eligibility.

During Treatment Phase

For Cohort 1 only, CT/MRI scans of neck (DTC only), chest, abdomen, pelvis, and other known sites of disease plus any areas of newly suspected disease will be performed using the same methodology as at screening every 8 weeks per the appropriate tumor assessment schedule, or sooner if clinically indicated, beginning from the date of the first treatment dose, continuing during treatment cycles until documentation of disease progression.

For subjects with DTC (Cohort 2A) CT/MRI of the neck and other known sites of the disease and CT chest plus any areas of newly suspected disease will be performed. For subjects with osteosarcoma (Cohorts 2B, 3A and 3B), CT chest, and CT/MRI of other known sites of disease plus any areas of newly suspected disease will be performed. Tumor assessments

will be performed based on RECIST 1.1 every 6 or 8 weeks per the appropriate tumor assessment schedule (or sooner, if clinically indicated) beginning from the date of the first treatment dose, continuing during treatment cycles until documentation of disease progression.

In subjects 2 to <6 years of age, CT/MRI scans must be performed at screening, Cycle 1 Day 1 (following the Run-In Period at investigator's discretion) and every 8 weeks during the Treatment Period as indicated in Table 7. For Cohorts 3A and 3B CT/MRI scans should be performed every 6 weeks. This schedule for tumor assessments will be maintained irrespective of treatment delays.

An initial assessment of CR or PR according to RECIST 1.1 must be confirmed not less than 4 weeks after the initial response. The same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as was used for the screening assessments should be utilized across all time points to allow consistent comparison of lesions. After treatment discontinuation for a reason other than disease progression, tumor assessments should continue to be performed every 8 weeks (for Single-Agent Cohorts) or 6 weeks (for Combination-Cohorts) until documentation of progression or start of a new anticancer agent. Screening CT scans should be performed with oral and iodinated IV contrast and MRI scans should be performed with IV gadolinium chelate. Post-screening scans may be performed without contrast if a medical contraindication develops while on study treatment. If iodinated IV contrast is contraindicated, chest CT should be done without IV contrast. MRI should be performed for all other body regions (with gadolinium unless contraindicated (eg, severe renal dysfunction).

CT scans should be diagnostic quality spiral/multidetector CT with oral and iodinated IV contrast, and the MRI scans should be performed with IV gadolinium chelate. Scans of the neck, abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. Spiral/multidetector CT should be performed with a t-mm contiguous slice reconstruction algorithm. If body MRI scans are performed, contiguous slices of 5 mm should also be performed. If a subject develops a contraindication to CT contrast during the study, the chest evaluation should be done with non-contrast CT, and the other body scans should be done with MRI with gadolinium chelate IV.

The same imaging modality and image-acquisition protocol (including use or non-use of contrast) should be used consistently across all time points to allow consistent comparison of lesions. Low-dose non-contrast CT transmission scans from a positron emission tomography-CT (PET-CT) combination scanner are not acceptable. Ultrasound should not be used for radiographic tumor assessment. A chest x-ray or skeletal x-ray which clearly demonstrates a new metastatic lesion may be used to document progression in lieu of the CT/MRI scans.

If subcutaneous masses or nodes are palpable (eg, bulky) and are assessable by both clinical and radiographic techniques, the radiographic (CT/MRI) technique should be used for the assessment of target and non-target lesions.

Brain scans by MRI with and without contrast enhancement or CT with contrast enhancement will be performed at screening, and as clinically indicated. If protocol eligible brain metastases are present at screening, a CT/MRI of the brain must be performed at all tumor assessment time points (eg, every 6 or 8 weeks).

During Post-treatment Follow-up

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.

For osteosarcoma subjects who experience PD in Cohort 2B and choose to receive the combination therapy of lenvatinib with ifosfamide and etoposide, prior to entering Cohort 3B (Combination Expansion), baseline tumor assessments must be re-established on new images (unless the images confirming disease progression were performed within 28 days of Cycle 1 Day 1 in Cohort 3B). Subjects will undergo assessments as per the Schedule of Assessments provided for the combination treatment. After data cutoff, tumor assessments may be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care. All subjects will be followed for survival for 1 year or until death, unless the study is terminated.

PALATABILITY AND ACCEPTABILITY OF LENVATINIB SUSPENSION FORMULATION

The palatability and acceptability of lenvatinib suspension formulation will be assessed using the Palatability Questionnaire (see Appendix 13). All subjects who receive suspension formulation must complete the questionnaire according to the Schedule of Assessments. If the subject is unable to complete the questionnaire, this must be done by a parent or legal guardian. Measurement of palatability will be assessed using the Hedonic scale (Guinard, 2001) which is a Visual Analog Scale (VAS).

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

PHARMACOKINETIC ASSESSMENTS

Blood samples (2 mL each) will be collected from all subjects at the time points shown in Table 5. PK blood samples will also be drawn pretreatment on the day of tumor assessment as described in the Table 5. Actual time and date of PK blood collection as well as time of drug administration will be recorded on the appropriate page of the CRF. Exposure parameters such as area under the concentration × time curve (AUC) will be derived from posterior estimates of the PK parameters from the final population PK model. For the time points shown in Table 5, subjects or their parents will be instructed not to take the dose of lenvatinib prior to arriving at the study site. Lenvatinib capsule administration will be recorded in the eCRF. The Cycle 1 Day 1 and Day 15 (single agent cohorts only), and Cycle 2 Day 1 doses of lenvatinib will be administered at the study site at approximately the same time of day as the Cycle 1 Day 1 dose was administered in order to accommodate PK sample

collection timing. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in a separate Laboratory Manual.

Table 5 Lenvatinib Pharmacokinetic Sampling Time Points

Time Point[a]	Time (h)
Run-In Day 15	Predose[b]
Cycle 1 Day 1	Postdose: 0.5-4 and 6-10
Cycle 1 Day 15[c]	Predose Postdose: 0.5-4 and 6-10
Cycle 2 Day 1	Predose Postdose: 2-12

Note: PK blood samples should be drawn on day of tumor assessments (predose). If the tumor assessments fall on the same day as study treatment PK samples, they need not be collected again to avoid duplicate samples.

h = hour(s).

a. If dose interruption is necessary in these time points, only predose sample should be collected, if possible.

b. Sample to be collected during the Run-in Period (Cohort 1).

c. Samples not required for Cohorts 3A and 3B

Only the samples from all subjects receiving active treatment will be analyzed. Lenvatinib will be quantified using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method.

PHARMACODYNAMIC ASSESSMENTS

Blood serum samples from study subjects will be collected at Baseline, Day 8 of Cycle 1 (Combination-Agent cohorts 3A and 3B), Day 15 of Cycle 1 (Single-Agent cohorts), Day 1 of all subsequent cycles, and at the Off-Treatment Visit. For subjects ongoing after the data cutoff date for the primary analysis, blood samples will be collected at the Off-Treatment Visit. For subjects 2 to <6 years, blood serum sample will be collected in Cohort 1 at Cycle 1 Day 1 (predose). Blood serum samples may be analyzed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, or other assays/methods and new technology in an effort to identify biomarkers. In addition, biomarkers identified in other lenvatinib clinical studies may also be assessed in samples collected from subjects enrolled in this study. Blood biomarker samples may be used for exploratory analysis for evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. (see Appendix 11)

Pharmacodynamic biomarker analysis will be performed as described in an analysis plan provided separately.

PHARMACOGENOMIC/PHARMACOGENETIC ASSESSMENTS

Archived, fixed tumor tissue will be collected (if available) for assessment of mutations and other genetic alterations or proteins that may be important in the development and progression of cancer as well as for potential use in diagnostic development.

A blood sample will be collected for pharmacogenomic analysis. The DNA may be analyzed for genes associated with lenvatinib absorption, distribution, metabolism, excretion (ADME) and to validate mutations suspected of functional relevance (using in silico prediction) to determine exclusivity to tumor sample. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have.

Data obtained from the PD and PG samples will be used for research. The PD and PG samples will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib and for potential diagnostic development. If the subject reaches 18 years of age prior to the date of final sample analyses they will be reconsented. No further analyses will be performed on these collected samples from subjects who either do not reconsent after their 18th birthday or cannot be reached for reconsenting and the sample will be destroyed.

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

When the subject reaches the age of 18 years (or 16 years in the UK) while on the study, and becomes competent to give informed consent, his/her consent will be obtained using separate ICFs to continue the study.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grades (for both increasing and decreasing severity), and serious adverse events (SAEs); regular laboratory evaluation of hematology, blood chemistry, and urine values; periodic measurement of vital signs and 12-lead ECGs; and echocardiograms, Lansky play score or Karnofsky performance status score, physical examinations, and height assessments as detailed in the Schedule of Assessments (Table 7, Table 8, and Table 9). A diary will be provided to each subject to capture any abnormal gastrointestinal symptoms (eg, diarrhea, abdominal discomfort, cramps) experienced during the study. Fecal occult blood will be monitored regularly during the study.

Skeletal bone growth will be assessed by height measurements at the Baseline Visit, thereafter at Day 1 of each cycle during the Treatment Phase for Cohort 1 (and Day 1 of every 3 cycles for cohorts 2A, 2B, 3A and 3B), at the Off-treatment Visit, and every 3 months during the Post-treatment Follow-up for 1 year. Proximal tibial growth plate x-rays will be done at Baseline and at the Off-treatment Visit. Postbaseline, only open growth plates will be further assessed.

Clinical and laboratory toxicities/symptomatology will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (see Appendix 2).

ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation in a subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug(s) are lenvatinib, etoposide, and ifosfamide.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not.

A laboratory result should be considered by the investigator to be an AE if it:

- Results in the withdrawal of study drug
- Results in withholding of study drug pending some investigational outcome
- Results in an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia)
- Is an out-of-range laboratory value that in the investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile

All AEs observed during the clinical study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study informed consent form until 30 days after the last dose of study treatment. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality

considered to constitute an AE should be reported on the Adverse Event CRF. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is >480 or a QTc increase of ≥60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Progression of malignant disease under study should not be recorded as an AE in studies where it is included as an endpoint for underlying disease. Signs and symptoms clearly related to the progression of disease should not be captured as an AE. If the progression leads to an untoward medical occurrence, then this medical occurrence should be recorded as an AE.

All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study consent through the last visit and for 30 days following study drug discontinuation.

All AEs must be followed for 30 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded according to Common Terminology Criteria for Adverse Event (CTCAE v4.03) (Appendix 2).

Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity). All adverse events reported using CTCAE classification and graded as 4 or 5 are to be considered serious. Adverse events that are not reported in the CTCAE will be graded on a 4-point scale (mild, moderate, severe, and life-threatening).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments

- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility

Related: A causal relationship between the study treatment and the AE is a reasonable possibility. The investigator must further qualify the degree of certainty as "possible" or "probable."

Serious Adverse Events and Other Events of Interest

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events should also be considered SAEs. These events may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest include pregnancy overdose, misuse, abuse, or medication error; and any treatment-emergent significant laboratory abnormality (TEAV). These events of interest are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with events of interest are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care

- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug

LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 6. Subjects should be in a seated or supine position during blood collection. The Schedule of Assessments (Table 7, Table 8, and Table 9) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 6 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), MCH, MCHC, MCV
Chemistry	
Electrolytes	Bicarbonate, chloride, potassium, sodium
Liver function tests	ALT, alkaline phosphatase, aspartate AST, conjugated (direct) bilirubin[a], total bilirubin
Renal function tests	BUN or urea, creatinine
Other chemistries	Albumin, amylase, calcium, glucose, LDH, lipase, magnesium, phosphorus, total protein, uric acid, Guaiac fecal occult blood test (FOBT)
Urinalysis for microscopy[b]	RBCs/high-power-field (HPF)
Urine dipstick testing[b,c]	Blood, protein, glucose
Other	Pregnancy test (serum or urine β–hCG), TSH, free T4 levels, thyroglobulin[d]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; β hCG = beta-human chorionic gonadotropin; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cells; T4 = thyroxine; TSH = thyroid stimulating hormone; WBC = white blood cells.

a: Direct bilirubin should be assessed if total bilirubin is elevated.

b: If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory

c: If urine protein is ≥ 2+, then a spot test for protein-creatinine ratio and if possible, a 24-hour urine collection should be done to quantify the 24 hour urine protein excretion.

d: For DTC subjects, TSH, free T4, and thyroglobulin should be tested. TSH should be assessed for all subjects.

All clinical laboratory tests during the study will be performed by local laboratories. All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis

samples are to be obtained prior to study drug administration and sent to the local laboratory on the day of collection unless otherwise instructed.

Clinical chemistry and hematology results must be reviewed prior to administration of study drug on Cycle 1 Day 1 and within 48 hours after dispensing study drug for all subsequent cycles. Scheduled assessments may be performed within 72 hours prior to the visit. If ≥ Grade 3 hematologic or clinical chemistry toxicity, repeat laboratory test and AEs assessment at least every 3 days (until improvement to < Grade 3). Refer to Study Drug Dose Reduction and Interruption Instructions, Table 3 for the management of clinically significant laboratory abnormalities. Every effort should be made to collect samples for analysis at the local laboratory at the same time.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

For laboratory abnormalities meeting the criteria of SAEs (Section 9.5.1.5), the site must send the SAE report including the laboratory report (as regionally required) to the SAE fax number or email provided in the Investigator File.

VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute]), body temperature (in centigrade), weight [kg]), and height (cm) will be obtained at the visits designated in the Schedule of Assessments (Table 7, Table 8, and Table 9) by a validated method. Blood pressure and pulse will be measured after the subject has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person. For subjects with an elevated BP (≥95th percentile for sex, age, and height/length) it should be confirmed by 2 assessments obtained 1 hour apart. One BP assessment is defined as the mean value of 3 measurements obtained at least 5 minutes apart. Subjects with elevated BP (≥99th percentile for sex, age and height/length) must have their BP monitored every 2 weeks (on Day 15 or more frequently as clinically indicated) until BP has been <95th percentile for 3 consecutive months. If a new event of elevated BP occurs, the subject must resume the Day 15 evaluation until BP has been <95th percentile for 3 consecutive months.

PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Assessments (Table 7, Table 8, and Table 9). A comprehensive physical examination (including a neurological examination) will be performed at Screening, Baseline (only if screening physical examination was performed >7 days prior to Cycle 1 Day 1), Cycle 1 Day 8 (Cohorts 3A and 3B), Cycle 1 Day 15 (Single-Agent), Day 1 of each subsequent cycle, and at the off-treatment assessment. A symptom-directed physical examination will be performed on Cycle 1 Day 1 and at any time during the study, as clinically indicated. Documentation of the physical examination will be included in the source documentation at the site. Only

changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Assessments (Table 7, Table 8 and Table 9). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Serious Adverse Events and Other Events of Interest), the study site must fax the SAE report including the ECG report to the number indicated in the Investigator File using the SAE reporting form (see Section 9.5.4.1).

OTHER SAFETY ASSESSMENTS

Pregnancy Test

A serum β-hCG test will be performed for females of childbearing potential (see definition included in the Inclusion/Exclusion criteria, Sections 9.3.1and 9.3.2). A serum or urine pregnancy test will be performed at Screening and Baseline (or within 72 hours prior to the first dose of study medication) and at the Off-treatment Visit in women of childbearing potential. Blood and urine samples will be taken at designated time points as specified in the Schedule of Assessments Table 7, Table 8, and Table 9).

Echocardiogram

An echocardiogram to assess left ventricular ejection fraction (LVEF) will be performed during the screening phase, every 16 weeks following the first dose of study drug while the subject is on treatment or sooner, if clinically indicated, and at (or within 1 week following) the off-treatment assessment. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

9.5.2 Schedule of Assessments

9.5.2.1 Schedule of Assessments

Table 7, Table 8, and Table 9 present the Schedules of Assessments for the cohorts in this study.

Table 7 Schedule of Assessments – Cohort 1

Phase	**Pretreatment**					**Treatment[a] (All cycles are 28 days in duration)**																			**Post-Tx**
Period	**Screening[b]**	**Baseline[c]**	**Run-In Period**			**Treatment Phase[d]**																		**Off-Tx**	**Follow-up[e]**
Visit	1	2	3-5			6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23, etc	99	
Cycle			**21 Days**			**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4**				**Cycle 5 - Last**			
Day	-28 to -2	-1	1	8	15	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22	1	15		
Procedures/Assessments																									
Informed consent	X																								
Inclusion/exclusion	X	X																							
Demographic data	X																								
Medical/surgical history	X	X																							
Prior medication/procedures	X	X																							
Pregnancy test[f]	X	X																						X	
Lansky play score/ Karnofsky PS[g]	X	X				X[g]				X				X				X				X			
TNM Staging	X																								
Physical examination[h]	X	X				X[h]		X		X				X				X				X		X	
Vital signs[i]	X	X			X	X[i]		X	X	X		X		X		X		X		X		X	X	X	
12-lead ECG[j]	X					X[j]				X				X				X				X		X	
Echocardiogram[k]	X				X	Performed every 16 weeks following the first dose of study drug or sooner, if clinically indicated																		X	
Clinical chemistry and hematology[l]	X	X			X	X[l]		X		X		X		X		X		X				X		X	
Guaiac Fecal occult blood test[l]	X					X				X				X				X				X		X	
Urine dipstick testing[m]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	
PK blood samples[n]					X	X		X		X															
Study treatment			Once Daily (lenvatinib) [based on BSA calculations at Day 1 of each Cycle]																						
Palatability Questionnaire						X																			
	X					X[o]	CT/MRI of neck, chest, abdomen, pelvis, and other areas of known disease at Screening plus any																	X	

Table 7 Schedule of Assessments – Cohort 1

Phase	**Pretreatment**					**Treatment[a] (All cycles are 28 days in duration)**																		**Post-Tx**
Period	**Screening[b]**	**Baseline[c]**	**Run-In Period**			**Treatment Phase[d]**																		**Follow-up[e]**
Visit	1	2	3-5			6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23, etc	99	
Cycle			**21 Days**			**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4**				**Cycle 5 - Last**			
Day	-28 to -2	-1	1	8	15	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22	1	15		
Tumor assessments: CT/MRI[o]						areas of newly suspected disease should be performed every 8 weeks (during week 8) or sooner if clinically indicated until documentation of disease progression																			
Brain CT/MRI[p]	X					Brain scans will be performed at screening and, if clinically indicated during treatment. For subjects with protocol-eligible, treated brain metastases at screening, brain scans should be performed at all tumor assessment time points.																			
Height[q]		X				X				X				X				X				X		X	X
Proximal Tibial growth plates x-ray[q]		X																						X	
Pharmacodynamic biomarkers[r]		X				X		X		X				X				X				X		X	
Archival tumor block or slides[s]			X																						
Blood sample for pharmacogenetic/ pharmacogenomic analysis[t]		X																							
Survival[u]						X																		X	
Concomitant medications[v]			Throughout																					X	
AEs/SAEs[w]			Throughout																					X	
Safety Monitoring (call at C1D8)							X																		

AE = adverse event, BP = blood pressure, C1D1 = Cycle 1/Day 1, C1D2 = Cycle 1/Day 2, C1D8 = Cycle 1/Day 8, C1D15 = Cycle 1/Day 15, CR = complete response, CT = computerized tomography, ECG = electrocardiogram, h = hour, HR = heart rate, MRI = magnetic resonance imaging, PK =pharmacokinetics, PR = partial response, PS = performance score, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1, RR = respiratory rate, SAE = serious adverse event, TNM = tumor-node-metastasis, Tx = treatment. Note: Subjects 2 to <6 years of age must complete Screening/ Baseline assessments, all the assessments during the Run-In period, and all the cycles as indicated in Table 7. All subjects who receive suspension formulation must complete the Palatability Questionnaire according to the Schedule of Assessments. If the subject is unable to complete the questionnaire, this must be done by a parent or legal guardian (Appendix 13).

a. Efforts should be made to conduct study visits on the day scheduled (±1 day).
b. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Baseline Visit. Informed consent may be obtained up to 4 weeks prior to C1D1.
c. Baseline assessments can be performed on Day -1 or on C1D1 prior to treatment.
d. Subjects benefiting from study treatment in the opinion of the investigator will continue 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.
e. Subjects will be followed every 3 months for 1 year or until death, whichever occurs first, as per the protocol.
f. A serum or urine pregnancy test will be performed at Screening and Baseline (or within 72 hours prior to the first dose of study medication) and at the off visit in women of childbearing potential.
g. A Lansky play score or Karnofsky performance status score will be obtained at the screening, baseline, C1D1 (subjects 2 to <6 years), Cycle 2 Day 1 visits, and every subsequent cycle visit thereafter.
h. A comprehensive physical examination (including a neurological examination) will be performed at the screening, baseline (only if screening physical examination was performed > 7 days prior to C1D1), C1D1 (subjects 2 to <6 years), C1D15, and Day 1 visits of each subsequent cycle, and at the Off-treatment visits. A symptom-directed physical examination will be performed on C1D1 and at any time during the study, as clinically indicated.
i. Assessments will include vital signs (resting BP, HR, RR, and body temperature), and weight. Blood pressure that is consistently above the 95th percentile for sex, age, and height/length requires further evaluation. For blood pressure management, please refer to Section 9.4.1.3 and Figure 2 in the protocol. Vitals should also be performed at Run-In Period D15, C1D1 and C1D22 for subjects 2 to <6 years.
j. Single 12-lead ECG. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. It should also be performed at C1D1 for subjects 2 to <6 years.
k. An echocardiogram is performed during screening, every 16 weeks, and at the end of treatment visit, or sooner if clinically indicated.
l. Clinical chemistry and hematology results must be reviewed prior to administration of study drug on C1D1 (should be performed for subjects 2 to <6 years) and within 48 hours after dispensing study drug for all subsequent cycles. Scheduled assessments may be performed within 72 hours prior to the visit. If ≥ Grade 3 hematologic or clinical chemistry toxicity, repeat laboratory test and AEs assessment at least every 3 days (until improvement to < Grade 3). Guaiac fecal occult blood test (FOBT) should be performed. TSH should be assessed for all subjects, free T4 and thyroglobulin should be assessed only for RR-DTC subjects. See Table 6.
m. Urine dipstick testing should be performed on Days 1, 8, 15, and 22 for Cycles 1-3, bi-weekly thereafter, or more frequently as clinically indicated. and at the Off-treatment Visit. For subjects with history of proteinuria ≥2+, urine dipstick testing should be performed until the results have been 1+ or negative for 3 consecutive months. If a new event of proteinuria ≥2+ occurs, the subject must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 3 consecutive months. Subjects who have ≥2+ proteinuria on dipstick urinalysis should perform a spot P/C test and if possible undergo a 24-hour urine collection. Please refer to the guidelines in the protocol. Urine glucose should be performed as shown in Table 7 as part of urine dipstick. Also, see Table 6.
n. PK blood samples drawn 0.5-4 hours and 6-10 hours postdose on C1D1 and predose, 0.5-4 hours and 6-10 hours postdose on C1D15 and predose and 2-12 hours postdose on C2D1. A PK sample should also be collected during the Run-In Period of D15 (predose), for subjects 2 to <6 years. Study Treatment PK blood samples should be drawn also on the day of tumor assessment (predose). If the tumor assessments fall on the same day as study treatment PK samples, they need not be collected again to avoid duplicate samples. If dose interruption is necessary at these time points, only a predose sample should be collected, if possible.
o. **Screening**: Tumor assessments using CT of the neck (DTC only)/chest/abdomen/pelvis and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1. Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans should be performed with IV gadolinium chelate.
Treatment Phase: Tumor assessments of the neck (DTC only)/chest/abdomen/pelvis and other areas of known disease at Screening or newly suspected disease should be performed every 8 weeks (within week 8) from C1D1 during the Treatment Phase (or sooner if there is evidence of progressive disease) and should utilize the same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as was used for the screening assessments. Tumor response will be assessed according to RECIST 1.1. For subjects 2 to <6 years tumor assessment must also be performed at C1D1 at the investigator's discretion. Any CR or PR must be

confirmed not less than 4 weeks after initial achievement of the response. After treatment discontinuation, tumor assessments should continue to be performed every 8 weeks until documentation of progression for 1 year or start of a new anticancer agent (refer to Section 9.5.1.3).

p. Brain CT with contrast or MRI pre- and post- gadolinium contrast will be performed at the Screening Visit, and as clinically indicated. For subjects with protocol-eligible treated brain metastases, brain CT/MRI will be performed at all tumor assessment time points.
q. Height will be assessed at the Baseline Visit, Day 1 of each cycle during the Treatment Phase, at the Off-treatment Visit and every 3 months during the Post-treatment Follow-up. Proximal tibial growth plates x-rays should be conducted at baseline and at the Off-treatment Visit.
r. Blood samples will be collected at the Baseline Visit, C1D1 (predose for subjects 2 to <6 years), C1D15, Day 1 of all subsequent cycles, and at the Off-treatment Visit for assessment for blood serum sample to measure factors implicated in angiogenesis. For subjects ongoing after the data cutoff date for the primary analysis, blood samples will be collected at the Off-Treatment Visit.
s. An archival tumor sample from the most recent surgery or biopsy for identification of predictive biomarkers and pathology review may be collected at any time during the study, unless no such material is available.
t. Collection of whole blood to obtain genomic DNA will be performed at the Baseline Visit. If sampling is not performed predose, sampling may occur at any subsequent visit in which other blood sampling is scheduled to occur. Pharmacogenetic markers of drug metabolism and drug transport may be assessed.
u. Survival data will be collected every 3 months until death or 1 year as per the protocol. All anticancer therapies will be collected.
v. Concomitant medications will be recorded throughout the study and for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of survival follow-up.
w. AEs will be recorded from the date of signed informed consent, throughout the study, and for 30 days after the last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 hours. A diary will be provided to the subject to capture any abnormal gastrointestinal symptoms (eg, diarrhea, abdominal discomfort, cramps) experienced during the study.

Table 8 Schedule of Assessments – Cohort 2A – Differentiated Thyroid Cancer and Cohort 2B - Osteosarcoma

Phase	**Pretreatment**		**Treatment[a] (All cycles are 28 days in duration)**																			**Post-Treatment**
Period	**Screening[b]**	**Baseline[c]**	**Treatment[d]**																		**Off-Tx**	**Follow-up[e]**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	99	
Cycle			**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4**				**Cycle 5-Last**			
Day	-28 to -2	-1	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22	1	15		
Procedures/Assessments																						
Informed consent	X																					
Inclusion/exclusion	X	X																				
Demographic data	X																					
Medical/surgical history	X	X																				
Prior medication/ procedures	X	X																				
Pregnancy test[f]	X	X																			X	
Lansky play score/ Karnofsky PS[g]	X	X					X				X				X				X			
TNM Staging	X																					
Physical examination[h]	X	X			X		X				X				X				X		X	
Vital signs[i]	X	X	X		X		X		X		X		X		X		X		X	X	X	
12-lead ECG[j]	X						X				X				X				X		X	
Echocardiogram[k]	X	Performed every 16 weeks following the first dose of study drug or sooner, if clinically indicated																			X	
Clinical chemistry and hematology[l]	X	X			X		X		X		X		X		X				X		X	
Guaiac Fecal occult blood test[l]	X	X					X				X				X				X		X	
Urine dipstick testing[m]	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	
PK blood samples[n]			X		X		X															
Study treatment			Once Daily (lenvatinib) [based on BSA calculations at Day 1 of each Cycle]																			
Palatability Questionnaire			X																			
Tumor assessments: CT/MRI[o]	X		CT chest, CT/MRI of neck (DTC only), and other areas of known disease at Screening plus any areas of newly suspected disease should be performed every 8 weeks (during week 8) or sooner if clinically indicated until documentation of disease progression																		X	

Table 8 Schedule of Assessments – Cohort 2A – Differentiated Thyroid Cancer and Cohort 2B - Osteosarcoma

Phase	**Pretreatment**		**Treatment[a] (All cycles are 28 days in duration)**																			**Post-Treatment**
Period	**Screening[b]**	**Baseline[c]**	**Treatment[d]**																		**Off-Tx**	**Follow-up[e]**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	99	
Cycle			**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4**				**Cycle 5-Last**			
Day	-28 to -2	-1	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22	1	15		
Brain CT/MRI[p]	X		Brain scans will be performed at screening and, if clinically indicated during treatment. For subjects with protocol-eligible, treated brain metastases at screening, brain scans should be performed at all tumor assessment time points.																			
Height[q]		X	X												X						X	X
Proximal Tibial growth plates x-ray[q]		X																			X	
Pharmacodynamic biomarkers[r]		X			X		X				X				X				X		X	
Archival tumor block or slides[s]	X																					
Blood sample for pharmacogenomic analysis[t]		X																				
Survival[u]			X																			X
Concomitant medications[v]	Throughout																					X
AEs/SAEs[w]	Throughout																					X
Safety Monitoring (call at C1D8)				X																		

AE = adverse event, BP = blood pressure, C1D1 = Cycle 1/Day 1, C1D2 = Cycle 1/Day 2, C1D8 = Cycle 1/Day 8, C1D15 = Cycle 1/Day 15, CR = complete response, CT = computerized tomography, ECG = electrocardiogram, h = hour, HR = heart rate, MRI = magnetic resonance imaging, PK = pharmacokinetics, PR = partial response, PS = performance score, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1, RR = respiratory rate, SAE = serious adverse event, TNM = tumor-node-metastasis, Tx = treatment. Note: All subjects who receive suspension formulation must complete the Palatability Questionnaire according to the Schedule of Assessments. If the subject is unable to complete the questionnaire, this must be done by a parent or legal guardian (Appendix 13).

a. Efforts should be made to conduct study visits on the day scheduled (±1 day).
b. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Baseline Visit. Informed consent may be obtained up to 4 weeks prior to C1D1.
c. Baseline assessments can be performed on Day -1 or on C1D1 prior to treatment.
d. Subjects benefiting from study treatment in the opinion of the investigator will continue 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.

e. Subjects will be followed every 3 months for 1 year or until death whichever occurs first**,** as per the protocol.
f. A serum or urine pregnancy test will be performed at the Screening and Baseline Visits (or within 72 hours prior to the first dose of study medication) and at the off visit in women of childbearing potential.
g. A Lansky play score or Karnofsky performance status score will be obtained at the Screening, Baseline, and Cycle 2 Day 1 visits, and every subsequent cycle visit thereafter.
h. A comprehensive physical examination (including a neurological examination) will be performed at the Screening and Baseline Visits (only if screening physical examination was performed >7 days prior to C1D1), C1D15, Day 1 visit of each subsequent cycle, and at the Off-treatment Visit. A symptom-directed physical examination will be performed on C1D1 and at any time during the study, as clinically indicated.
i. Assessments will include vital signs (resting BP, HR, RR, and body temperature, and weight. Blood pressure that is consistently above the 95th percentile for sex, age, and height/length requires further evaluation. For blood pressure management, please refer to Section 9.4.1.3 and Figure 2 in the protocol.
j. Single 12-lead ECG. Subject must be in the recumbent position for a period of 5 minutes prior to the ECG.
k. An echocardiogram is performed during screening, every 16 weeks, and at end of treatment visit, or sooner if clinically indicated.
l. Clinical chemistry and hematology results must be reviewed prior to administration of study drug on C1D1 and within 48 hours after dispensing study drug for all subsequent cycles. Scheduled assessments may be performed within 72 hours prior to the visit. If ≥Grade 3 hematologic or clinical chemistry toxicity, repeat laboratory test and AEs assessment at least every 3 days (until improvement to <Grade 3). Guaiac fecal occult blood test (FOBT) should be performed. TSH should be assessed for all subjects, free T4 and thyroglobulin should be assessed only for RR-DTC subjects. See Table 6.
m. Urine dipstick testing should be performed every on Day 1, 8, 15 and 22 for cycles 1-3, bi-weekly thereafter or more frequently as clinically indicated and at the off-treatment visit. For subjects with history of proteinuria ≥2+, urine dipstick testing should be performed until the results have been 1+ or negative for 3 consecutive months. If a new event of proteinuria ≥2+ occurs, the subject must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 3 consecutive months. Subjects who have ≥2+ proteinuria on dipstick urinalysis should perform a spot P/C test and if possible undergo a 24-hour urine collection. Urine glucose should be performed as shown in Table 8 as part of urine dipstick. Also see Table 6.
n. PK blood samples drawn 0.5-4 hours and 6-10 hours postdose on C1D1 and predose, 0.5-4 hours and 6-10 hours postdose on C1D15 and predose and 2-12 hours postdose on C2D1. Study Treatment PK blood samples drawn also on the day of tumor assessment (Predose). If the tumor assessments fall on the same day as study treatment PK samples, they need not be collected again to avoid duplicate samples. If dose interruption is necessary at these time points, only a predose sample should be collected, if possible.
o. **Screening:** Tumor assessments using CT/MRI of the neck (DTC only), CT chest, abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1. Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans should be performed with IV gadolinium chelate.
Treatment Phase: Tumor assessments of the neck (DTC only), chest, and other areas of known disease at Screening or newly suspected disease should be performed every 8 weeks (within week 8) from C1D1 during the Treatment Phase (or sooner if there is evidence of progressive disease) and should use the same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as was used for the screening assessments. Tumor response will be assessed according to RECIST 1.1. An initial assessment of CR or PR must be confirmed not less than 4 weeks after achievement of the initial response. After treatment discontinuation, tumor assessment should continue to be performed every 8 weeks until documentation of progression for 1 year or start of a new anticancer agent (refer to Section 9.5.1.3).
p. Brain CT with contrast or MRI pre- and post- gadolinium contrast will be performed at the Screening Visit, and as clinically indicated. For subjects with protocol-eligible treated brain metastases, brain CT/MRI will be performed at all tumor assessment time points.
q. Height will be assessed at the Baseline Visit, Day 1 of every 3 cycles during the Treatment Phase, at the Off-treatment Visit, and every 3 months during the Post-treatment Follow-up. Proximal tibial growth plates x-rays should be conducted at baseline, and at the Off-treatment visit.
r. Blood samples will be collected at the Baseline Visit, C1D15, Day 1 of all subsequent cycles, at the Off-treatment Visit for blood serum sample to measure factors implicated in angiogenesis. For subjects ongoing after the data cutoff date for the primary analysis, blood samples will be collected at the Off-Treatment Visit.
s. An archival tumor sample from the most recent surgery or biopsy for identification of predictive biomarkers and pathology review may be collected at any time during the study, unless no such material is available.
t. Collection of whole blood to obtain genomic DNA will be performed at the Baseline Visit. If sampling is not performed predose, sampling may occur at any subsequent visit in which other blood sampling is scheduled to occur. Pharmacogenomic markers of drug metabolism and drug transport may be assessed.
u. Survival data will be collected every 3 months until death or 1 year as per the protocol. All anticancer therapies will be collected.

v. Concomitant medications will be recorded throughout the study and for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of Survival Follow-up.
w. AEs will be recorded from the date of signed informed consent, throughout the study, and for 30 days after last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 hours. A diary will be provided to the subject to capture any abnormal gastrointestinal symptoms (e.g., diarrhea, abdominal discomfort, cramps, etc) experienced during the study.

Table 9 Schedule of Assessments – Cohorts 3A and 3B – Osteosarcoma

Phase	**Pretreatment**		**Treatment[a] (All cycles are 21 days in duration)**																**Post-Treatment**
Period	**Screening[b]**	**Baseline[c]**	**Treatment[d]**															**Off-Tx**	**Follow-up[e]**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	99	
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**				
Day	-28 to -2	-1	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15		
Procedures/Assessments																			
Informed consent	X																		
Inclusion/exclusion	X	X																	
Demographic data	X																		
Medical/surgical history	X	X																	
Prior medication/ procedures	X	X																	
Pregnancy test[f]	X	X																X	
Lansky play score/ Karnofsky PS[g]	X	X				X			X			X			X				
TNM Staging	X																		
Physical examination[h]	X	X		X		X			X			X			X			X	
Vital signs[i]	X	X	X	X	X	X			X			X			X			X	
12-lead ECG[j]	X		X			X			X			X			X			X	
Echocardiogram[k]	X	Performed every 16 weeks following the first dose of study drug or sooner, if clinically indicated.																	
Clinical chemistry and hematology[l]	X	X		X	X	X			X			X			X			X	
Guaiac Fecal occult blood test[l]	X	X				X			X			X			X			X	
Urine dipstick testing[m]	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	
PK blood samples[n]			X			X													
Study treatment			Combination of lenvatinib (QD) + ifosfamide + etoposide (Days 1-3 of Cycles 1-5 only) [based on BSA calculations at Day 1 of each Cycle]																
Palatability Questionnaire			X																
Tumor assessments: CT/MRI[o]	X		CT chest and CT/MRI of other areas of known disease at Screening plus any areas of newly suspected disease should be performed every 6 weeks (during Week 6) or sooner if clinically indicated until documentation of disease progression.															X	
Brain CT/MRI[p]	X		Brain scans will be performed at screening and, if clinically indicated during treatment. For subjects																

Table 9 Schedule of Assessments – Cohorts 3A and 3B – Osteosarcoma

Phase	**Pretreatment**		**Treatment[a] (All cycles are 21 days in duration)**																**Post-Treatment**
Period	**Screening[b]**	**Baseline[c]**	**Treatment[d]**															**Off-Tx**	**Follow-up[e]**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	99	
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**				
Day	-28 to -2	-1	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15		
			with protocol-eligible, treated brain metastases at screening, brain scans should be performed at all tumor assessment time points.																
Height[q]		X	X									X						X	X
Proximal Tibial growth plates x-ray		X																X	
Pharmacodynamic biomarkers[r]		X		X		X			X			X			X				
Archival tumor block or slides[s]	X																		
Blood sample for pharmacogenetic/ pharmacogenomic analysis[t]		X																	
Survival[u]			X																X
Concomitant medications[v]	Throughout																		X
AEs/SAEs[w]	Throughout																		X
Safety Monitoring (call at C1D8)				**X**															

AE = adverse event, BP = blood pressure, C1D1 = Cycle 1/Day 1, C1D2 = Cycle 1/Day 2, C1D8 = Cycle 1/Day 8, C1D15 = Cycle 1/Day 15, CR = complete response, CT = computerized tomography, ECG = electrocardiogram, h = hour, HR = heart rate, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cells, PK = pharmacokinetics, PR = partial response, PS = performance score, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1, RR = respiratory rate, SAE = serious adverse event, TNM = tumor-node-metastasis, Tx = treatment. All subjects who receive suspension formulation must complete the Palatability Questionnaire according to the Schedule of Assessments. If the subject is unable to complete the questionnaire this must be done by their parents or their legal guardian (Appendix 13).

a. Efforts should be made to conduct study visits on the day scheduled (±1 day).
b. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Baseline Visit. Informed consent may be obtained up to 4 weeks prior to C1D1.
c. Baseline assessments can be performed on Day -1 or on C1D1 prior to treatment.
d. Subjects benefiting from study treatment in the opinion of the investigator will continue 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.
e. Subjects will be followed every 3 months for 1 year or until death as per the protocol.
f. A serum or urine pregnancy test will be performed at the Screening and Baseline Visits (or within 72 hours prior to the first dose of study medication) and at the Off-treatment Visit in women of childbearing potential.
g. A Lansky play score or Karnofsky performance status score will be obtained at the Screening, Baseline, and Cycle 2 Day 1 Visits, and Day 1 of every subsequent cycle visit thereafter.
h. A comprehensive physical examination (including a neurological examination) will be performed at the Screening and Baseline Visits (only if screening physical examination was performed >7 days prior to C1D1), C1D8, and Day 1 visit of each subsequent cycle, and at the Off-treatment Visit. A symptom-directed physical examination will be performed on C1D1 and at any time during the study, as clinically indicated.
i. Assessments will include vital signs (resting BP, HR, RR, and body temperature), and weight. Blood pressure that is consistently above the 95th percentile for sex, age, and height/length requires further evaluation. For blood pressure management, please refer to Section 9.4.1.3 and Figure 2 in the protocol.
j. Single 12-lead ECG. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.
k. An echocardiogram is performed during screening, every 16 weeks, and at end of treatment visit, or sooner if clinically indicated.
l. Clinical chemistry and hematology results must be reviewed prior to administration of study drug on C1D1 and within 48 hours after dispensing study drug for all subsequent cycles. Scheduled assessments may be performed within 72 hours prior to the visit. If ≥ Grade 3 hematologic or clinical chemistry toxicity, repeat laboratory test and AEs assessment at least every 3 days (until improvement to < Grade 3). Guaiac fecal occult blood test (FOBT) should be performed. TSH should be assessed for all subjects, See Table 6.
m. Urine dipstick testing should be performed on Day 1 or more frequently as clinically indicated for 4 cycles, biweekly thereafter, and at the Off-treatment Visit. For subjects with a history of proteinuria ≥2+, urine dipstick testing should be performed until the results have been 1+ or negative for 3 consecutive months. If a new event of proteinuria ≥2+ occurs, the subject must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 3 consecutive months. Subjects who have ≥2+ proteinuria on dipstick urinalysis should perform a spot P/C test and if possible undergo a 24-hour urine collection. Urine glucose should be performed as shown in Table 9 as part of the urine dipstick. Also, see Table 6.
n. Study Treatment PK blood samples drawn 0.5-4 hours and 6-10 hours postdose on C1D1, and predose and 2-12 hours postdose on C2D1. Study Treatment PK blood samples drawn also on the day of tumor assessment (predose). If the tumor assessments fall on the same day as study treatment PK samples, they need not be collected again to avoid duplicate samples. If dose interruption is necessary at these time points, only a predose sample should be collected, if possible.
o. **Screening**: Tumor assessments of the chest, abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1. Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans should be performed with IV gadolinium chelate
Treatment Phase: Tumor assessments of the chest, and other areas of known disease at Screening or newly suspected disease should be performed every 6 weeks (within Week 6) from C1D1 during the Treatment Phase (or sooner if there is evidence of progressive disease) and should utilize the same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as was used for the screening assessments. Tumor response will be assessed according to RECIST 1.1. Subjects who discontinue must complete the off-treatment tumor assessment. Any CR or PR must be confirmed not less than 4 weeks following the initial achievement of the response. After treatment discontinuation, tumor assessment should continue to be performed every 6 weeks until documentation of progression for 1 year or start of a new anticancer agent (refer to Section 9.5.1.3).
p. Brain CT with contrast or MRI pre- and post- gadolinium contrast will be performed at the Screening Visit, and as clinically indicated. For subjects with protocol-eligible treated brain metastases, brain CT/MRI will be performed at all tumor assessment time points.

q. Height will be assessed at the Baseline Visit, Day 1 of every 3 cycles during the Treatment Phase, at the Off-treatment Visit and every 3 months during the Post-treatment Follow-up for 1 year. Proximal tibial growth plates x-rays should be conducted at baseline and at the Off-treatment Visit**.** Hand and wrist x-rays and tibial growth plate x-rays will be optional for Germany.
r. Blood samples will be collected at the Baseline Visit, C1D8, Day 1 of all subsequent cycles, and at the Off-Treatment assessment for blood serum sample to measure factors implicated in angiogenesis. For subjects ongoing after the data cutoff data for the primary analysis, blood samples will be collected at the Off-Treatment Visit.
s. An archival tumor sample from the most recent surgery or biopsy for identification of predictive biomarkers and pathology review may be collected at any time during the study, unless no such material is available.
t. Collection of whole blood to obtain genomic DNA will be performed at the Baseline Visit. If sampling is not performed predose, sampling may occur at any subsequent visit in which other blood sampling is scheduled to occur. Pharmacogenetic markers of drug metabolism and drug transport may be assessed.
u. Survival data will be collected every 3 months until death or 1 year as per the protocol. All anticancer therapies will be collected.
v. Concomitant medications will be recorded throughout the study and for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of Survival Follow-up.
w. AEs will be recorded from the date of signed informed consent, throughout the study, and for 30 days after last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 hours. A diary will be provided to the subject to capture any abnormal gastrointestinal symptoms (eg, diarrhea, abdominal discomfort, cramps) experienced during the study.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of relapsed or refractory solid tumors.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, radiologic studies, and assessment of AEs, are standard evaluations to ensure subject safety. The use of RECIST 1.1 for tumor assessments of solid tumors is widely accepted (see Appendix 1) (Eisenhauer, et al., 2009).

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the time the investigator becomes aware of the event.

Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 24 hours by emailing or faxing the completed SAE form.

Serious adverse events, regardless of causality assessment, must be collected through the last visit and for 30 days after the subject's last dose, whichever occurs first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator should notify his/her IRB/IEC of the occurrence of the SAE, in writing, in accordance with local requirements. A copy of this communication must be forwarded to the sponsor and/or the designated CRO monitor and filed in the Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the time the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the time the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Associated with Special Situations

REPORTING OF ADVERSE EVENTS ASSOCIATED WITH STUDY DRUG OVERDOSE, MISUSE, ABUSE, OR MEDICATION ERROR

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

REPORTING OF SIGNIFICANT LABORATORY ABNORMALITY

Any significant treatment-emergent laboratory abnormality that meets the criteria described below and is observed during the clinical study should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the laboratory abnormality does not meet serious criteria. If the significant laboratory abnormality does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

A laboratory result should be considered a treatment-emergent significant abnormality if the result:

- Is within normal limits at baseline and has increased in severity to meet the sponsor's grading criteria for laboratory values of Grade 3 or above
- Is outside normal limits at baseline and increases in severity to the sponsor's grading criteria for laboratory values of Grade 4 or above. These abnormalities are automatically considered to be serious, with the exception of expected and reproducible hematologic abnormalities.
- Is otherwise considered by the investigator to meet serious criteria as defined in Section 9.5.1.5

Significant laboratory abnormalities should not be listed as separate AEs or SAEs if they are considered to be part of the clinical syndrome that is being reported as an AE or SAE.

REPORTING OF STUDY-SPECIFIC EVENTS

Study-specific events should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet serious criteria. If the event does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject (or subject's parent or guardian) may elect to discontinue study drug at any time for safety, medical, or personal reasons. Subjects who choose to discontinue study drug prior to disease progression will be followed in the post-study treatment follow-up period and continue to undergo regularly scheduled disease assessment until documentation of disease progression or start of an alternative anticancer treatment. All subjects who discontinue study drug will be followed for overall survival and all post progression cancer treatments administered will be recorded. Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Assessments (Table 7, Table 8, and Table 9).

The investigator will promptly explain to the subject (or subject's parent or guardian) involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, progression of disease, withdrawal of consent, pregnancy, study terminated by sponsor, or administrative/other. In addition to

the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory

requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study data cut-off and the database is locked and released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of the study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

PRIMARY ENDPOINT(S)

Cohort 1 (Single-Agent Dose-Finding)

- RD based on the TiTE-CRM design.

Cohort 2 (Single-Agent Expansion)

- Cohort 2A: DTC Group: ORR (CR + PR) for subjects with measurable disease and BOR for all subjects based on RECIST 1.1
- Cohort 2B: Osteosarcoma Group: PFS-4, ie, the percentage of subjects who are alive and free of disease progression 4 months after the first dose based on RECIST 1.1

Cohort 3A (Combination Dose-Finding)

- RD of the combination treatment (lenvatinib + ifosfamide + etoposide)

Cohort 3B (Combination Expansion)

- PFS-4, ie, the percentage of subjects who are alive and free of disease progression 4 months after the first dose based on RECIST 1.1

SECONDARY ENDPOINTS

Cohort 1 (Single-Agent Dose-Finding)

- Efficacy
    - BOR over the treatment period

- ORR
- DOR
- 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 best overall response 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
- PFS defined as the time from the date of the first administration of study drug to the date of first documentation of disease progression or date of death, whichever occurs first
- TTP defined as the time from the date of the first administration of study drug until the date of first documentation of disease progression
- OS defined as the time from the date of the first administration 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).

- Safety

  - AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECG, urine dipstick, occult blood in stool, Lansky play scores or Karnofsky performance scores, physical examination findings, and height and closure of proximal tibial 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

Cohorts 2A and 2B

- Efficacy

  - BOR over the treatment period (osteosarcoma group)
  - ORR (measurable osteosarcoma group)
  - DOR (measurable DTC and osteosarcoma group)
  - 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 best overall response 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
- PFS defined as the time from the date of the first administration of study drug to the date of first documentation of disease progression or date of death, whichever occurs first
- TTP defined as the time from the date of the first administration of study drug until the date of first documentation of disease progression
- OS defined as the time from the date of the first administration 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).

- Safety
  - AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECGs, urine dipstick, occult blood in stool, Lansky play scores or Karnofsky performance scores, physical examination findings, and height and closure of proximal tibial 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

Cohorts 3A and 3B

- Efficacy
  - BOR over the treatment period
  - ORR (osteosarcoma group)
  - DOR
  - 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 best overall response 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

- PFS defined as the time from the date of the first administration of study drug to the date of first documentation of disease progression or date of death, whichever occurs first
- TTP defined as the time from the date of the first administration of study drug until the date of first documentation of disease progression
- OS defined as the time from the date of the first administration 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).

- Safety
  - AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECGs, urine dipstick, occult blood in stool, Lansky play scores or ECOG performance scores, physical examination findings, and height and closure of proximal tibial 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

9.7.1.2 Definitions of Analysis Sets

The Safety Analysis Set is defined as all subjects who received any study drug and had at least one post-baseline safety evaluation.

The Pharmacokinetic Analysis Set is defined as all subjects who received any study drug and have evaluable PK data.

9.7.1.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the safety analysis set will be summarized using descriptive statistics. Continuous demographic and baseline variables include age, sex, race, height, and weight will be summarized using n (number of subjects with available data), mean, standard deviation (SD), median, and range (minimum and maximum) unless otherwise specified. Categorical variables will be summarized by number and percentage.

9.7.1.4 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) class indicating therapeutic classification. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were

continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. All medications will be will be summarized and listed by drug and drug class and by cohort.

9.7.1.5 Efficacy Analyses

Efficacy will be evaluated based on the as-treated population (Safety Analysis Set).

Each cohort will have its own cutoff date for the final analysis for CSR reporting purpose.

Cohorts 1 and 3A: For purposes of the final analysis, data cutoff will occur when the RD is determined and the last enrolled subject completes 6 cycles of treatment or discontinue before the end of Cycle 6, whichever occurs first or pending discussion with the PSC.

Cohorts 2A, 2B, and 3B: For DTC and osteosarcoma subjects, the cutoff will be after the completion of 6 cycles by the last subject enrolled in each cohort or early discontinuation before the end of Cycle 6, whichever occurs first.

PRIMARY EFFICACY ANALYSIS

Primary Endpoint Analyses

Cohort 1 (Single-Agent Dose-Finding)

Cohort 1 will be a lenvatinib single-agent dose-finding study including 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.

The RD will be defined as the dose that has DLT rate closest to the targeted a 20% rate.

Four experimental doses may be investigated in Cohort 1: Dose -1 (9 mg/m^2), Dose 1 (11 mg/m^2), Dose 2 (14 mg/m^2), and Dose 3 (17 mg/m^2). The starting dose will be Dose 1.

A one-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,α) 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. Additional subjects will be allocated to the dose associated with the posterior probability of DLT closest to the target (ie, having a DLT rate closest to 20%). A least 2 subjects will be required to complete 4 weeks of treatment in Cycle 1 or report a DLT during Cycle 1 (at the starting dose) before a subject can be treated at the next dose level (dose-escalation). It is further specified that dose levels cannot be skipped when escalating. The RD will be determined either when approximately 18 subjects have been tested, or when futility is declared or when 10 subjects have been treated at the same dose. Futility is defined as having <25% probability that any of the doses is safe.

Cohort 2 (Single-Agent Expansion)

DTC and osteosarcoma groups will be evaluated separately.

Cohort 2A: DTC

The primary efficacy endpoint is ORR for subjects with measurable disease and BOR for all subjects. All ORR or BOR will be based on RECIST 1.1 assessed every 8 weeks.

The analyses will be descriptively performed on the Safety Analysis Set.

Cohort 2B: Osteosarcoma

The primary efficacy endpoint is PFS-4 based on RECIST 1.1.

The null hypothesis that PFS-4 is ≤25% will be 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. PFS-4 will be presented with corresponding 2-sided, exact binomial 80% and 95% CIs. This analysis will be performed on the Safety Analysis Set.

Cohort 3 (Combination Dose-Finding and Expansion)

Cohort 3A: Osteosarcoma Combination Dose-Finding

As in Cohort 1, the DLT will be assessed to determine the RD of lenvatinib in combination with ifosfamide plus 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 9.1.2.3 Treatment Phase: Cohort 3A).

This dose of lenvatinib will be used to treat additional osteosarcoma subjects in Cohort 3B.

Cohort 3B (Osteosarcoma Combination Expansion)

The primary efficacy endpoint is PFS-4 based on RECIST 1.1.

The null hypothesis that PFS-4 is ≤25% will be 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. PFS-4 will be presented with corresponding 2-sided, exact binomial 80% and 95% CIs. This analysis will be performed on the lenvatinib-naïve subject in Safety Analysis Set, while subjects enrolled from Cohorts 1 and 2B will be summarized only as appropriate.

SECONDARY EFFICACY ANALYSES

Secondary endpoints PFS and TTPwill be analyzed using Kaplan-Meier product-limit estimates. Median PFS and the cumulative probability of PFS at 4, and 12 months will be presented with 2-sided, 95% CIs when an adequate number of at risk subjects at those time points warrant the estimate. The cumulative PFS and TTP probabilities will be plotted over time as appropriate.

Secondary endpoints ORR, DCR, and CBRwill be calculated with exact binomial 95% CIs.

The endpoint of OS will be analyzed using Kaplan-Meier product-limit estimates. Median OS and the cumulative probability of OS at 12 months will be presented with 2-sided, 95% CIs when an adequate number of at risk subjects at those time points warrant the estimate.

The above analyses will be based on the lenvatinib-naïve subjects in the Safety Analysis Set, while subjects enrolled from Cohorts 1 and 2B will be summarized only as appropriate.

9.7.1.6 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

PHARMACOKINETIC ANALYSES

Plasma concentration of lenvatinib versus time data will be listed. 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 an analysis plan at a later date.

Pharmacokinetic data will be summarized using n, mean, SD, percent coefficient of variation (% CV), geometric mean, median, minimum and maximum. Survival data (PFS and OS) will be estimated using Kaplan-Meier methods.

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.

Exploratory/graphical analyses will be conducted for PK/PD evaluations, and may be followed by model based analyses. If conducted, a detailed analysis plan will be provided in a separate document at a later date.

9.7.1.7 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. The incidence of treatment-emergent adverse events (TEAEs) and SAEs will be summarized by study cohort, and dose-level, if appropriate. Laboratory test data, vital signs, 12-lead ECGs, urine dipstick, occult blood in stool, Lansky play scores or Karnofsky performance scores, physical examination, height, and closure of proximal tibial plates at scheduled time points and their changes from baseline will be summarized by study cohort and group using descriptive statistics, as appropriate. Abnormal values will be flagged. Prior and concomitant medications, medical/surgical history and subject demographics will be summarized and listed by study cohort and group.

EXTENT OF EXPOSURE

The number of cycles/days on treatment, quantity of study drug administered, and the number of subjects requiring dose reductions, treatment interruption, and treatment discontinuation due to adverse events will be summarized.

ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 16.1 or higher)

lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment (and within 30 days of the last study treatment), having been absent at pretreatment (Baseline), or

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

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

An overview table, including the incidence of and the number of subjects with treatment-emergent adverse events (TEAEs), SAEs, deaths, and TEAEs that led to discontinuation, dose modification, or dose interruption will be provided.

The TEAEs will be summarized by study cohort and dose level, as appropriate. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT.

LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For quantitative parameters, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) 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 and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be 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. Shift tables for baseline CTC grade to worst post-baseline grade may be provided.

VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight, height) and changes from baseline will be presented by study cohort and group. Descriptive summary statistics for vital sign parameters and their changes from baseline will be calculated.

ELECTROCARDIOGRAMS AND ECHOCARDIOGRAMS

ECG results will be evaluated on an individual basis by subject. Abnormal readings will be identified as those outside (above or below) the reference range. ECG findings will be summarized.

Echocardiograms (including LVEFs) will be summarized using descriptive statistics.

9.7.1.8 Other Analyses

Palatability and Acceptability Questionnaire

Measurement of palatability will be assessed using the Hedonic scale (Guinard, 2001) which is a Visual Analog Scale (VAS).

Expansion Phase Analyses

Safety data for Cohort 3B (Combination Expansion) will be reported at a later date.

9.7.2 Determination of Sample Size

Approximately 69 to 108 subjects are planned for this study as follows:

Cohort 1 (Single-Agent Dose-Finding): Approximately 12 to 24 subjects based on TiTE-CRM algorithm.

Cohort 2 (Single-Agent Expansion): Approximately 27 to 42 subjects: Cohort 2A: DTC group (12 subjects) and Cohort 2B: osteosarcoma group (15 to 30 subjects).

Cohort 2A: DTC Group

Approximately 12 subjects with evaluable or measurable disease are planned to be enrolled in Cohort 2A due to limited number of pediatric patients with DTC.

Cohort 2B: Osteosarcoma Group

A minimum of 15 PFS-4 evaluable subjects will be assessed in cohort 2B. The sample size estimates were based on Simon's Optimal Two-Stage Design (Simon, 1989). If fewer than 5 subjects who are alive and free of disease progression at 4 months after first dose date are observed among the first 15 evaluable subjects in Stage I, accrual in the cohort will be suspended. Otherwise, if at any time during Stage I of the cohort, at least 5 subjects who are alive and free of disease progression at 4 months after first dose date are recorded among the first 15 evaluable subjects, enrollment in the cohort will continue seamlessly for a total of approximately 27 evaluable subjects. If, at the end of the second stage for the cohort, at least 10 subjects who are alive and free of disease progression at 4 months are recorded among the 27 subjects in the cohort, study drug 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 (α) = 0.1, and power = 80%. To account for nonevaluable subjects, a total of 15-30 osteosarcoma subjects will be enrolled for Cohort 2B.

Cohort 3A (Combination Dose-Finding)

Approximately 12 to 24 osteosarcoma subjects for whom ifosfamide and etoposide are considered a treatment option

Cohort 3B (Combination Expansion)

With the following assumptions: p_0=25%, p_1=50%, 1-sided α=10%, β=20%, where p_0 is an unacceptable rate of PFS, p_1 is the target rate of PFS, α is the probability of declaring lenvatinib effective when the true rate is p_0, and β 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 for Cohort 3B, along with some subjects from Cohorts 1 and 2B.

9.7.3 Interim Analysis

Interim analyses may be performed after consultation with the PSC.

The sponsor will closely evaluate the risks and benefits of the study throughout its conduct, along with the PSC as needed.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required by local regulations. Per 21 CFR 312.30, a protocol change intended to eliminate an immediate hazard may be implemented immediately, provided FDA is subsequently notified by protocol amendment.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail

11.5 Identification of Source Data

Not applicable.

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years

after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

Lenvatinib will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Ifosfamide and etoposide will be supplied by the study sites from commercially available sources. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at

protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Tumor response assessments in this clinical trial will use Response Evaluation Criteria in Solid Tumors (RECIST 1.1) based on the 2009 article by Eisenhauer et al entitled *New Response Evaluation Criteria in Solid Tumors: revised RECIST guideline (version 1.1*) (Eisenhauer, et al., 2009).

The sole modification to RECIST 1.1 to be implemented in this trial is that chest x-rays may not be used to follow disease; only CT scans may be used to follow chest disease. As required by RECIST 1.1, the protocol states that the minimum duration of stable disease is 7 weeks following the date of first dose of study drug.

Appendix 2 Common Terminology Criteria for Adverse Events (v4.0)

The National Cancer Institute's Common Terminology Criteria for Adverse Events provides descriptive terminology to be used for adverse event reporting in clinical trials. An updated version (4.03) is now in use as of 14 Jun 2010. Version 4.03 includes clarifications for a select few grading scales and adverse event term definitions. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE version 4.03 have been correlated with single-concept, Medical Dictionary for Regulatory Activities (MedDRA®) terms.

CTCAE v4.03 grading refers to the severity of the AE. CTCAE grades 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

Grade	CTCAE Status
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).[a]
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL.[b]
4	Life-threatening consequences: urgent intervention indicated.
5	Death related to adverse event.

CTCAE = Common Terminology Criteria for Adverse Events.
a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Adapted from the Cancer Therapy Evaluation Program, NCI. CTCAE v4.03. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03 [Accessed 11 Jan 2015]

Appendix 3 Papillary or Follicular Thyroid Carcinoma Staging

Papillary or Follicular Carcinoma			
Stage Group[a]	**T Stage**	**N Stage**	**M Stage**
Under 45 Years			
I	Any T	Any N	M0
II	Any T	Any N	M1

a. Separate stage groupings are recommended for papillary or follicular, medullary, and anaplastic (undifferentiated) carcinoma.

Adapted from AJCC: Thyroid. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 87-96.

Appendix 4 Lansky Score

The Lansky score should be used for children <16 years of age.

100 - Fully active, normal

90 - Minor restrictions in physically strenuous activity

80 - Active, but tires more quickly

70 - Both greater restriction of and less time spent in play activity

60 - Up and around, but minimal active play; keeps busy with quieter activities

50 - Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.

40 - Mostly in bed; participates in quiet activities

30 - In bed; needs assistance even for quiet play

20 - Often sleeping; play entirely limited to very passive activities

10 - No play; does not get out of bed

0 - Unresponsive

Adapted from: Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. Cancer. 1987 Oct 1;60(7):1651-6.

Appendix 5 Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Crooks V, Waller S, Smith T, Hahn TJ. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991;46(4):M139-44.
Hollen PJ, Gralla RJ, Kris MG, Cox C, Belani CP, Grunberg SM, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies: Psychometric assessment of the Lung Cancer Symptom Scale. Cancer. 1994;73(8):2087-98.
O'Toole DM, Golden AM. Evaluating cancer patients for rehabilitation potential. West J Med. 1991;155:384-7.

Appendix 6 Schwartz Formula

The pediatric Schwartz equation is:

GFR (mL/min/1.73 m^2) = (0.41 x Height) / S_{cr} were S_{cr} is serum/plasma creatinine in mg/dL

Related references

Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009a;20:629-37.

Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009b;4(11):1832-43.

Selistre L, De Souza V, Cochat P et al. GFR estimation in adolescents and young adults. J Am Soc Nephrol 2012; 23: 989–996.

See more at: http://nkdep.nih.gov/lab-evaluation/gfr-calculators/children-conventional-unit.asp#sthash.FRfNtBFs.dpuf.

Francis at al: Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer; The American Thyroid Association Guidelines Task Force on Pediatric Thyroid Cancer. THYROID, Volume 25, Number 7, 2015.

and

Kumagai at al: Childhood thyroid cancers and radioactive iodine therapy: necessity of precautious radiation health risk management. Endocr J. 2007 Dec;54(6):839-47.

Appendix 7 Blood Pressure Levels for Boys by Age and Height Percentile

	BP	Systolic BP (mmHg)							Diastolic BP (mmHg)						
AGE	Percentile	Percentile of Height							Percentile of Height						
(Year)	Ð	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63

	BP	Systolic BP (mmHg)							Diastolic BP (mmHg)						
AGE	Percentile	Percentile of Height							Percentile of Height						
(Year)	Ð	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.
Guidelines to sex, age, and height-specific percentiles of blood pressure can be accessed at http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm.

Appendix 8 Blood Pressure Levels for Girls by Age and Height Percentile

		Systolic BP (mmHg)							Diastolic BP (mmHg)						
AGE	BP Percentile	Percentile of Height							Percentile of Height						
(Year)	Ð	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

	BP	Systolic BP (mmHg)							Diastolic BP (mmHg)						
AGE	Percentile	Percentile of Height							Percentile of Height						
(Year)	Ð	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

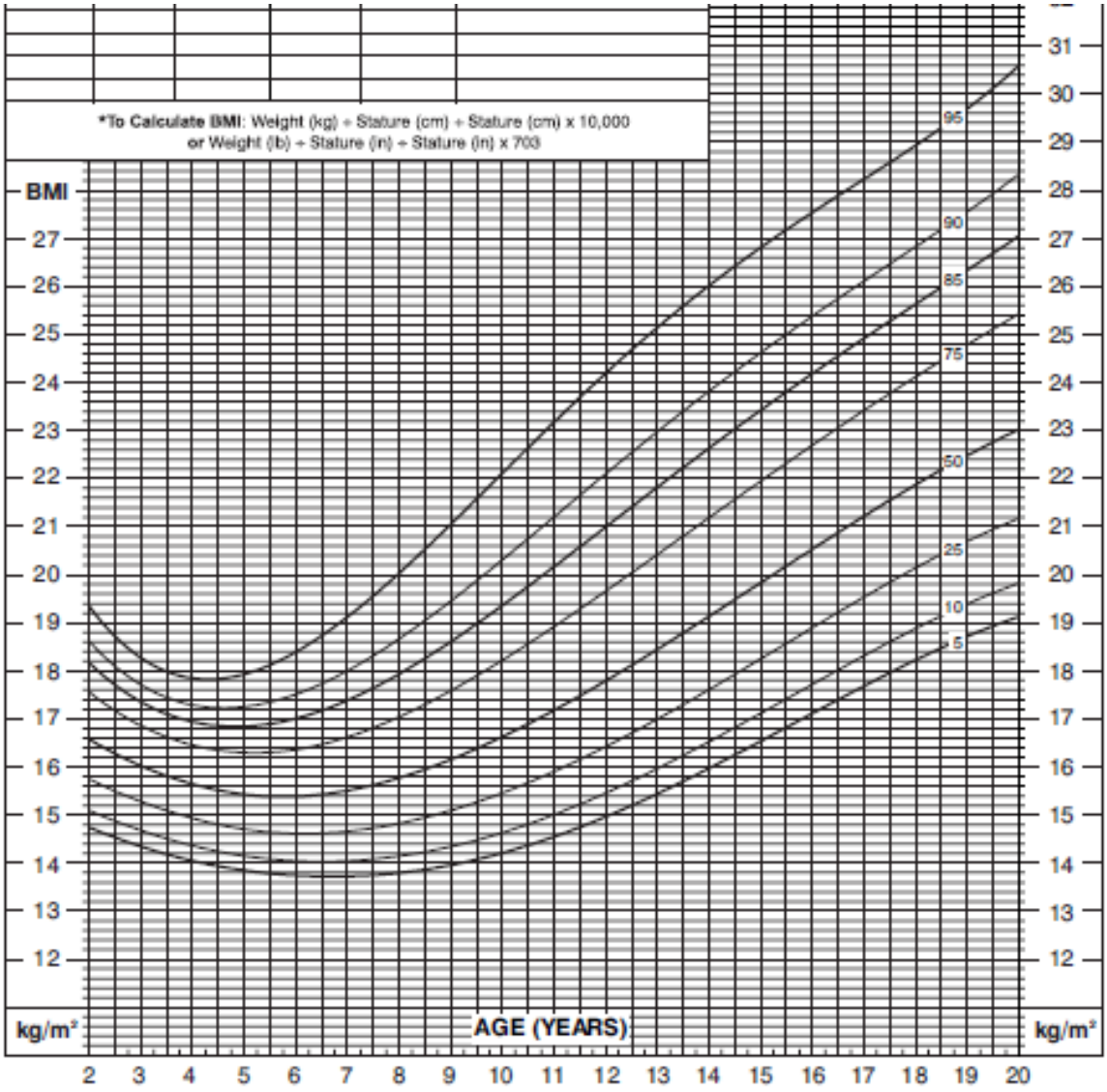
BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

Guidelines to sex, age, and height-specific percentiles of blood pressure can be accessed at http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm.

Appendix 9 Body Mass Index-For-Age Percentiles

2 to 20 years: Boys



SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

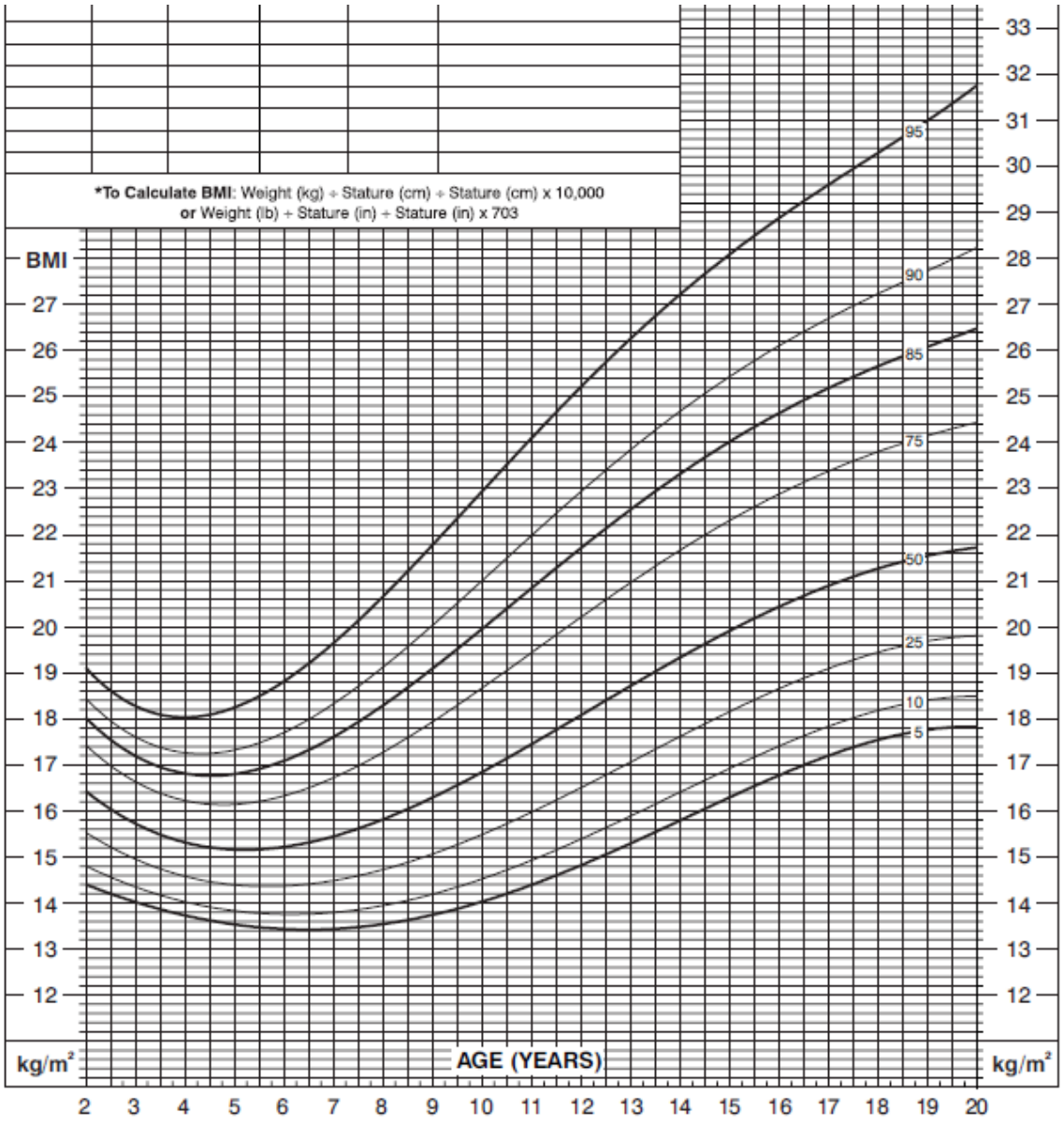
http://www.cdc.gov/growthcharts

Link for the charts is provided below

http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html.

Appendix 10 Body Mass Index-For-Age Percentiles

2 to 20 years: Girls



SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

http://www.cdc.gov/growthcharts

Link for the charts is provided below

http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.htm.

Appendix 11 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic (PD), pharmacogenomic (PG), and other biomarker analysis. These samples may be used for discovery or validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PG samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

Collection of the PD, PG, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PG, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the sponsor
- Independent ethics committees or institutional review boards that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PG, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PG, and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments (CLIA)-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

Appendix 12 Preparation of Lenvatinib Suspension

Wash hands thoroughly with soap and water both before putting on and after removing gloves. Double gloves should be worn at all times during preparation and administration of lenvatinib.

Young and other children in the home should not be near the area of where lenvatinib suspension is being prepared or administered.

Ensure proper disposal of all the materials for administration by disposing directly into the designated waste container, to protect from children or anyone who may handle the trash.

Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

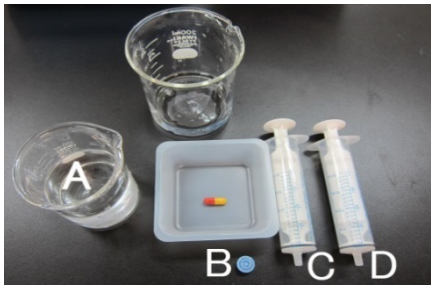
If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

All unused products and packaging from used products should be returned to the site by the patient or caregiver at the next visit. Do not throw away any medicines via wastewater or household waste.

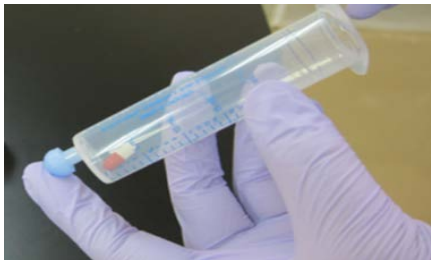
Preparation of suspension

Prepare the suspension as illustrated below by either the oral method (a) or by a nasogastric tube (b). Prepare the suspension with water or apple juice. The suspension should be directly administered into the mouth of the subject and washed down with additional fluid added to the syringe after the medication is administered; likewise for nasogastric (NG) administration. The suspension should be administered immediately after preparation.

a. Procedure for suspension administration by syringe orally:



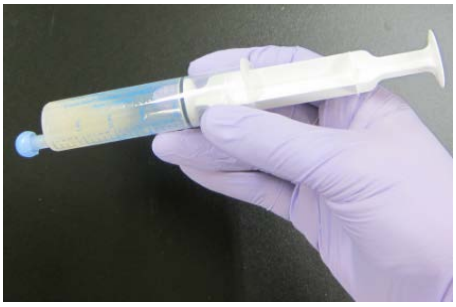
A: Water or apple juice
B: Cap
C: Syringe (20 mL, Baxa preferred)
D: Syringe for rinse (20 mL, Baxa preferred)



Place 1 capsule* into a syringe. Close the tip port of the syringe with a cap.
* One to 5 capsules are allowed to be placed into a 20 mL syringe.

Add 3 mL of water or apple juice into the syringe using another (new) 20 mL syringe.

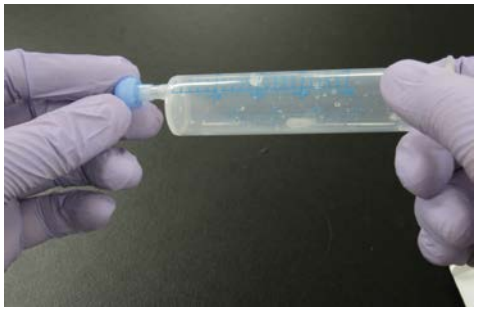
Insert the plunger into the syringe (cylinder) about 2 cm from the end. Leave the syringe upright in a flask for not less than 10 minutes.



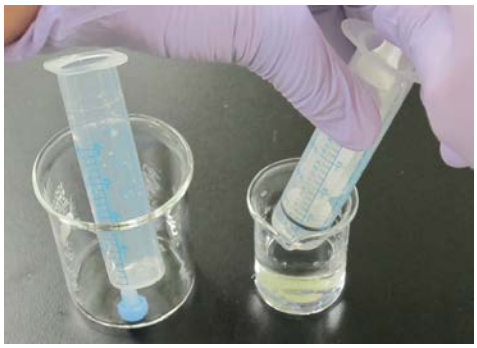
After 10 minutes, shake the syringe for not less than 3 minutes to dissolve the capsule shell completely to make a suspension of the granules (the capsule shell needs to be dissolved and the granules well suspended).

Remove the cap from the syringe.
Slide the plunger toward the solution to remove air from the syringe, and then administer the 3mL of suspension into the mouth of the subject.

Rinse step

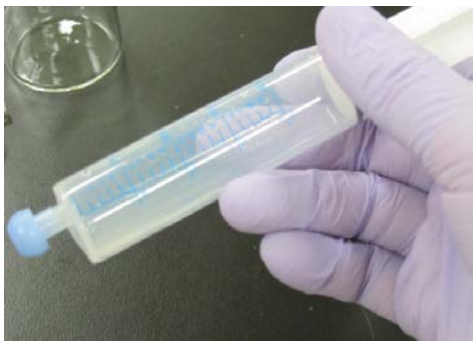


After the administration of the 3 mL suspension from the syringe, recap the syringe for reuse.



Draw up 2 mL of water or apple into a new syringe.

Insert the 2 mL of water or apple juice into the first syringe (which was used for the 3 mL suspension).



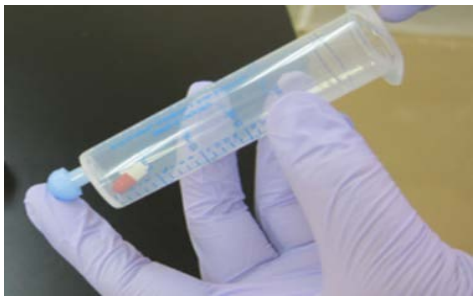
Shake the syringe 10 times to dissolve the remaining granules.

Remove the cap from the syringe and push the air out of the syringe with the plunger, and then insert the syringe into the mouth and administer the 2 mL of rinse liquid.

Total volume of suspension to be administrated is 5 ml (=3 mL for suspension + 2 mL of water of apple juice for rinse) for 1 to 5 capsules.

b. Procedure of suspension administering by syringe with nasogastric tube

A: Water or apple juice
B: NG tube (Vygon, 6FR)
C: Cap
D: Syringe (20 mL, Baxa, preferred)
E: Syringe for rinse (20 mL, Baxa preferred)



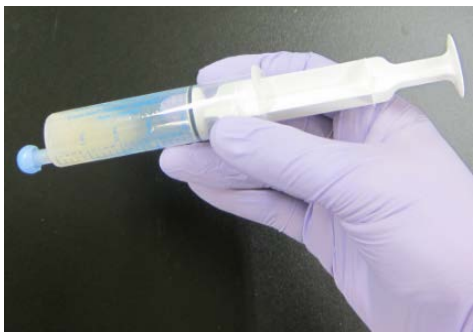
Place 1 capsule* into a syringe with the tip of the port of the syringe closed with a cap and place into a flask.

* One to 5 capsules are allowed to be placed in a 20 mL syringe.

Use a new 20 mL syringe and draw up 3 mL of water or apple juice and insert it into the medication syringe.

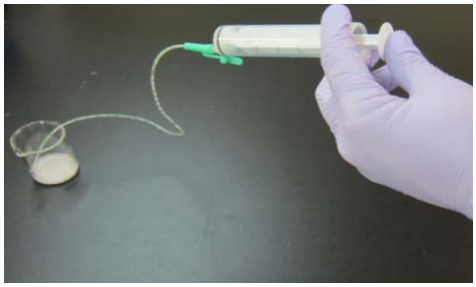
Insert the plunger into the syringe about 2 cm from the end.

Leave the syringe upright in the flask for not less than 10 minutes.



After 10 minutes, shake the syringe for not less than 3 minutes to dissolve the capsule shell completely and to suspend the granules (the capsule shell needs to be dissolved and the granules well suspended).

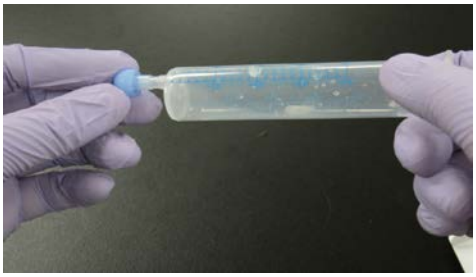
Remove the cap from the syringe and slide the plunger to remove the air from the syringe.



Connect the syringe to an NG tube and administer the 3 mL of suspension through the NG tube. It is recommended where possible, that the syringe is held in the horizontal position while administering the suspension to avoid the possibility of blocking the nasogastric tubing with undissolved granules..

Rinse step

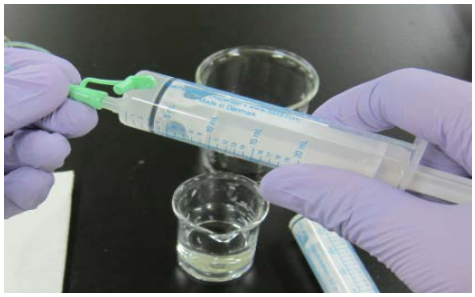
After inserting the suspension,disconnect the NG tube from the syringe.



Reconnect the cap (reuse) of the syringe.

Draw up 2 mL of water or apple juice in a new 20 mL syringe and insert the liquid into the medication syringe.

Reinsert the plunger to about 2 cm from the end and, shake the syringe for 10 times.



Remove the cap and slide the plunger to about 2 mL from the end to remove the air from the syringe.

Reconnect the NG tube to the to the syringe and insert the 2 mL of rinse liquid through the NG tube.

Total volume of suspension to be administered is 5 ml (=3 mL for suspension + 2 mL of water of apple juice for rinse) for 1 to 5 capsules.

Appendix 13 Palatability Questionnaire

Study E7080-G000-207- Palatability Questionnaire

Subject ID:

1	0	0	1				

Treatment Dose:

Visit Cycle:

Date:

Taste

(Please circle according to your experience)

Please provide reasons for your rating:

……

Appearance

(Please circle according to your experience)

Please provide reasons for your rating:

……

Smell

(Please circle according to your experience)

Mouth Feel (how does it feel in your mouth?)	 *(Please circle according to your experience)*
Overall Acceptability	 *(Please circle according to your experience)*

PROTOCOL SIGNATURE PAGE

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

Investigational Product Name: Lenvatinib

EudraCT Number: 2013-005534-38

SIGNATURES

Authors:

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27 NOV 2019
Date

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Nov 27th, 2019
Date

Oncology Business Group, Eisai Inc.

PPD

4 Dec. 2019
Date

Oncology Business Group, Eisai Inc.

PPD

Nov. 26, 2019
Date

Oncology Business Group, Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

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
Investigational Product Name:	Lenvatinib
EudraCT Number:	2013-005534-38

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date