1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-A001-216	
Study Protocol Title:	A Phase 1/2 Study of Lenvatinib in Combination with Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including CNS Tumors	
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake New Jersey 07677 United States	
Investigational Product Name:	Lenvatinib (E7080), everolimus	
Indication:	Recurrent and refractory pediatric solid tumors, including central nervous system tumors	
Phase:	1/2	
Approval Date(s):	16 Mar 2017	Original Protocol
	24 Sep 2018	Amendment 01
	28 Apr 2020	Amendment 02
	16 Aug 2021	Amendment 03
IND Number:	072010	
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation 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 Statement:	This document is confidential. It contains proprietary information of 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

Amendment 03
Date: 16 Aug 2021

Change	Rationale	Affected Protocol Sections
Added text: "**Subjects will meet the criteria for being evaluable for an objective response, if they have measurable disease present at baseline and at least 1 post-baseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease. Subjects who are not evaluable for objective response will be replaced.**"	Clarified criteria for subjects to be considered evaluable for objective response.	• Synopsis (Study Design: Cohorts 1 – 3) • Section 9.1
Exclusion criterion 17 was added: **Males who have not had a successful vasectomy (confirmed azoospermia) or if 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 7 days after lenvatinib discontinuation or 4 weeks after discontinuation of everolimus). No sperm donation is allowed during the study period and for 7 days after lenvatinib discontinuation or 4 weeks after discontinuation of everolimus.**	Added contraception requirement for male participants.	• Synopsis (Study Design: Exclusion Criteria) • Section 9.3.2
Added the window for tumor assessment: performed ±1 week at the specified timepoints.	Clarified tumor assessments window.	• Synopsis; Assessments • Section 9.1.2 • Section 9.1.3 • Section 9.5.1.3.1 • Table 7 and Table 8; footnotes o and q

Added text: **Evaluable Analysis Set, defined as all subjects, who have measurable disease present at baseline and at least 1 post-baseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease. This will be the analysis set for efficacy.** Removed text: • "Full Analysis Set, defined as all subjects enrolled."	Clarified that the Evaluable Analysis Set is the analysis set for Phase 2 and for the efficacy analysis in Phase 1.	• Synopsis; Statistical Methods (Definitions of Analysis Sets / Statistical Analysis) • Section 9.7.1 • Section 9.7.1.2
Removed text: "All subjects who have measurable disease present at baseline will be included in the denominator for calculating the objective response rate."	Clarified criteria for subjects to be considered evaluable for objective response.	• Synopsis; Statistical Analysis • Section 9.7.1.6
Removed "for a cohort" and added "evaluable".	Clarified that the Evaluable Analysis Set is the analysis set for Phase 2 and for the efficacy analysis in Phase 1.	• Synopsis; Efficacy Analyses, Interim Analysis • Section 9.7.1.6 • Section 9.7.3
Moved and revised the following text: "Lenvatinib should be discontinued in any subject who develops gastrointestinal perforation of any Grade or ≥Grade 4 fistula." Added text: **Management of Fistula Formation and Gastrointestinal Perforation** **Lenvatinib should be discontinued in any subject who develops Grade 4 fistula (gastrointestinal or non-gastrointestinal), or gastrointestinal perforation of any grade.**	Added a new section and revised text to include nonGI G4 fistula in-line with lenvatinib safety management guidelines.	• Section 9.4.1.15

Added text: **Management of Osteonecrosis of the Jaw** **Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise study subjects regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in study subjects at higher risk. For study subjects requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of osteonecrosis of the jaw. Withhold lenvatinib if osteonecrosis of the jaw develops and restart based on clinical judgement of adequate resolution (see Section 9.4.7).**	Added a new section on management of osteonecrosis of the jaw in-line with lenvatinib safety management guidelines and label update.	• Section 9.4.1.16
Added text: **Management of QT Prolongation** **Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 msec. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to <480 msec or baseline. Monitor potassium, calcium and magnesium, and replenish as appropriate.**	Added new text on management of QT prolongation in-line with lenvatinib safety management guidelines and label update.	• Section 9.4.1.17
Changed "study drugs" to lenvatinib and added text: **Refer to everolimus prescribing information for recommended everolimus dosing information.**	Updated to reflect US label wording on missed dose administration.	• Section 9.4.5
Added text: • For scheduled dental surgery or invasive dental procedures: stop lenvatinib for at least 1 week before the procedure, then restart lenvatinib when deemed clinically appropriate.	Added text on scheduled dental surgery or invasive dental procedures.	• Section 9.4.7
Administrative changes	Revised for clarity	• Synopsis; Primary Efficacy Analysis • Section 9.7.1.6.1 • Section 9.7.1.6.2

Amendment 02
Date: 28 Apr 2020

Change	Rationale	Affected Protocol Sections
Updated abbreviation for ICH as per current definition.	Administrative change	• Title page • Section 4 • Section 5.1 • Section 5.2 • Investigator Signature page
The age subsets for PK data for subjects <12 years old were clarified by subset 2 to <6 years and ≥6 to <12 years with 6 subjects in each subset (changes are highlighted in bold in the below text): All subjects in the Phase 1 Dose Escalation phase will have samples taken for PK analysis with the intent at the end of Phase 1 of having evaluable PK data from minimally 6 subjects **aged 2 to <6 years old, 6 subjects ≥6 to** <12 years old, and 6 subjects ≥12 years old. Once the MTD or RP2D has been defined, 0 to 6 additional subjects will be enrolled to attain the goal of having evaluable PK data from minimally 6 subjects **aged 2 to <6 years old, 6 subjects aged ≥6 to** <12 years old, and 6 subjects ≥12 years old.	Clarification of the age subsets for PK data per FDA General Clinical Pharmacology Considerations for Pediatric Studies Guidance for Industry (2014).	• Synopsis; Study Design; Phase 1 Dose Escalation and Determination of the MTD • Section 9.1
It was clarified that the Sponsor will closely monitor enrollment to ensure that at least 50% of subjects enrolled in each cohort are <18 years of age at the time of informed consent.	Changes made as per requirement stated by FDA.	• Synopsis: Study Design (Cohorts 1-3) • Synopsis: Number of subjects • Section 9.1 • Section 9.3
Inclusion criterion 15 was added: • Adequate glycemic control defined as fasting serum glucose ≤160 mg/dL. Exclusion criteria 3, 4, and 5 were added: • Subjects having an active infection requiring systemic therapy • Subjects with a known history of active hepatitis B (defined as hepatitis B surface antigen reactive or hepatitis B virus-DNA detected) or known active	The selection criteria were updated in line with the Afinitor Product monograph, and as per recommendations from Health Canada.	• Synopsis: Inclusion criterion • Section 9.3.1 • Synopsis: Exclusion criterion • Section 9.3.2

hepatitis C virus (HCV, defined as HCV-RNA detected). Note: No testing for hepatitis B and hepatitis C is required unless mandated by the local health authority. • Known to be human immunodeficiency virus (HIV) positive. Note: HIV testing is required at screening only when mandated by the local health authority		
Exclusion criterion for untreated brain central nervous system (CNS) metastasis was updated to add exception for subjects with primary CNS tumors and leptomeningeal disease.	Further clarification of the exclusion criterion.	• Synopsis: Exclusion criterion • Section 9.3.2, Exclusion criterion
Current guidance, that for asymptomatic laboratory abnormalities (including Grade ≥3 abnormalities) that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with the sponsor, was added within the body text in addition to prior description within footnote 'f' of dose modification Table 5. Also, clarified that such abnormalities should be managed per institutional guidance.	Text was added for further clarity on management of laboratory abnormalities.	• Synopsis: Study Treatment • Section 9.4.1.1
Clarified that lenvatinib should be discontinued in any subject who develops gastrointestinal perforation of any Grade or ≥Grade 4 fistula.	Updated as per standard guidance for lenvatinib.	• Section 9.4.1.14
Clarified that for Phase 2 of the study, copies of scans for tumor assessments will be sent to an imaging core laboratory designated by the sponsor for quality assessment and archival and potential independent review. Also clarified that scans will not be sent to the imaging core lab after the data cutoff date.	Collection and archival of tumor assessment scans by an imaging core laboratory will enable potential future independent review of tumor responses to corroborate investigator assessments.	• Synopsis: Tumor Assessments, Primary Efficacy Analysis • Section 9.5.1.3.1 • Section 9.7.1.6.1
Clarified that only subjects with BSA >0.68 m^2 are eligible to consent (optional) to blood samples for plasma and serum studies for assessment of pharmacodynamic biomarkers.	Updated in order to comply with standard guidelines for pediatric blood draw volumes and as recommended by Health Canada.	• Synopsis: Pharmacodynamic Assessments • Section 9.5.1.4.2 • Section 9.5.2.1: Table 7 (footnote s) and Table 8 (footnote s)

Clarified that prior to ECG, subjects should be in recumbent position for 5 minutes, **if possible**.	Considering feasibility within pediatric age group, it was clarified that the requirement for subjects to remain in the recumbent position for 5 minutes prior to ECG is applicable, only if possible.	• Section 9.5.1.5.6 • Section 9.5.2.1: Table 7 (footnote j) and Table 8 (footnote j)
Typographical error in sentence 'For subjects with primary CNS tumors and no other known areas of disease only target and non-target lesions plus any areas of ~~nearly~~ **newly** suspected disease must be scanned'. 'nearly' was updated to 'newly'.	Correction of typographical error in text.	• Section 9.5.2.1: Table 7 (footnote o)
Dental examination was added at Baseline, every year on study, and at the Off-Treatment Visit.	This was added for monitoring of the dental development.	• Section 9.5.2.1: Table 7 (footnote r) and Table 8 (footnote r) • Section 9.5.1.5.7
Clarified that for CTCAE, version 4.03 will be used and not current version.	Correction made as 'current version' was mentioned in error.	• Synopsis (Safety Assessments) • Section 9.7.3
Provision of independent data monitoring committee (IDMC) was added for review of safety and efficacy data during the conduct of the study	This was added to facilitate independent review of safety and efficacy data.	• Synopsis (Interim Analyses) • Section 9.7.3
Period for retention of records was updated as per the latest protocol template to 15 years following the completion of the study. Also, for sites in Canada, the retention period of study records was updated to 25 years as per Health Canada requirement.	To align with latest template requirements, and requirements of Health Canada	• Section 11.6
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 guidelines 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	• Appendix 12

	the nasogastric tubing with undissolved granules.	

Revisions per Amendment 01

Date: 24 Sep 2018

Change	Rationale	Affected Protocol Sections
Changed "Conference" to "Council"	Administrative change	• Title page • Section 4, Section 5.1, Section 5.2 • Investigator Signature page
Removed text: "with the exception of Dose Level 2B which requires a minimum BSA of 1.33 m^2." Removed text "Dose Level 2 includes 2 sub dose levels, 2A and 2B, depending on the maximum daily dose of lenvatinib allowed and body surface area of the subjects. At Dose Level 2A, the maximum daily dose of lenvatinib will not exceed 18 mg daily with a minimum body surface area (BSA) of 0.6 m^2. At Dose Level 2B, the maximum daily dose of lenvatinib allowed will not exceed 24 mg and requires a minimum BSA of 1.33 m^2." Removed text "Dose Level 2 will include 2 sub dose levels, 2A and 2B, depending on the maximum daily dose of lenvatinib allowed." Changed text "-At Dose Levels ~~2A~~ **-1 and 1**, maximum daily dose of lenvatinib will not exceed 18 mg daily. At Dose Level 2~~B~~, maximum daily dose of lenvatinib allowed will not exceed 24 mg. Should Dose Level 2~~A and 2B~~ be well tolerated, Dose Level 3 may be considered to test lenvatinib at 14 mg/m^2 (capped at 24 mg) and escalate everolimus to 4.5 mg/m^2." Changed text "The actual dose to be administered is rounded to the nearest whole number. The total lenvatinib dose is capped at 18 mg daily (Dose Levels -1, **and** 1~~, and 2A~~), and at 24 mg daily (Dose Levels 2~~B~~ and 3)". Lenvatinib dose nomogram tables were updated accordingly.	Dose levels 2 and 3 have been adapted to explore the maximum daily dose of lenvatinib and everolimus respectively. Dose Level 2B was redundant and was therefore removed.	• Synopsis – Study Design, Table 1, Table 3, Table 4, Inclusion Criterion #15, Study Treatment • Section 9.1, Figure 1, Table 1, Table 3, Table 4, • Section 9.3.1 • Section 9.4.1

Change	Rationale	Affected Protocol Sections
Lenvatinib in "Planned Dose Escalation" Table 1 updated accordingly and footnotes corrected.		
Figure 1- Study Design updated	Figure updated for clarification and consistency with the body of the protocol.	• Section 9.1
Reduced maximum number of subjects in the dose levels -1, 1, 2 and 3 to 54 subjects in Phase 1 and 120 subjects in Phase 1 and 2. The projected maximum number of evaluable subjects required in Phase 1 was recalculated to 48 subjects.	Sample size was reduced since Dose level 2B was redundant and was therefore removed. Number of evaluable subjects was revised based on sample size calculations.	• Synopsis- Number of subjects, Sample Size Rationale • Section 9.3 • Section 9.7.2
Added "Subjects who on PSC review are not deemed evaluable for DLT assessment may be replaced."	Added for clarification	• Synopsis, Study Design • Section 9.1
Changed bullet o Grade 3 liver enzyme elevation, including alanine aminotransferase/aspartate aminotransferase (ALT/AST)/ gamma glutamyl transferase (GGT) /**bilirubin/alkaline phosphatase** that returns to Grade ≤1 or baseline within 7 days	The DLT criteria for Grade 3 liver enzyme elevation has been updated to reflect the liver function tests that are performed in this study.	• Synopsis – Study Design, • Section 9.1
Added bullet "Grade 3 headache <3 days duration responsive to optimal management."	The DLT criteria for Grade 3 non-hematological toxicities have been updated for clarification.	• Synopsis – Study Design • Section 9.1
Changed to "Subjects who discontinue the study treatment for any reason other than DLT (eg, early disease progression) during Cycle 1 (Day 1 to Day 28), **and have not received at least 75% of the prescribed dose prior to discontinuation**, will be replaced.	Clarification text was added regarding replacement of subjects prior to discontinuation.	• Synopsis – Study Design • Section 9.1
An antihypertensive tablet or capsule that contains up to 2 antihypertensive ingredient medications will ~~count as 1~~ **be considered a single** antihypertensive medication.	Updated for clarification	• Synopsis – Study Design • Section 9.1
Added to inclusion criterion #1a "Subjects with diffuse intrinsic pontine glioma, optic pathway glioma, or pineal tumors with	Update to the inclusion criteria to confirm that subjects with tumor types for	• Synopsis – Inclusion criteria • Section 9.3.1

Change	Rationale	Affected Protocol Sections
elevated tumor markers (alpha-fetoprotein [AFP] and beta-human chorionic gonadotropin [ß-hCG] [or hCG]) do not require histological or cytological confirmation of diagnosis."	which histological diagnosis is not possible due to inaccessibility of the tumor, do not require histological confirmation of diagnosis during Phase 1.	
Removed the following text from inclusion criterion #2a "If there is only one target lesion and it is a non-lymph node, it should have a longest diameter of ≥1.5 cm."	Removal of repetitive text.	• Synopsis – Inclusion criteria • Section 9.3.1
Changed inclusion criterion #5 "Male or female subjects must be ≥2 years and **<18 years of age for enrolment in Phase 1 or ≥2 years and** ≤21 years of age **for enrolment in Phase 2.**"	For the purpose of dose determination, subjects must be <18 years of age in Phase 1.	• Synopsis – Inclusion criteria • Section 9.3.1
Changed exclusion criterion #13 "**Must be on a stable dose of the same oral hormonal contraceptive product for at least 4 weeks before dosing with study drug, for the duration of the study, **and for at least 8 weeks after study drug discontinuation."**	Contraception requirements have been updated to include the 8-week period after study drug discontinuation, as per the everolimus label and the study ICF.	• Synopsis – Exclusion criteria • Section 9.3.2
Added text "For subjects with primary CNS tumors and no other known areas of disease, only target and non-target lesions plus any areas of newly suspected disease must be scanned."	Tumor assessment requirements have been updated for subjects with primary CNS tumors.	• Synopsis – Tumor assessments • Section 9.5.1.3.1 • Section 9.5.2, Table 7
Changed text "All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration of study drug on Cycle 1 Day 1 and within 48 hours ~~after~~ **prior to** dispensing study drug for all subsequent cycles." Updated text in footnote "l" of Clinical Chemistry and Hematology and added text "The results must be reviewed prior to administration of study drug on Cycle 1 Day 1 and within 48 hours prior to dispensing study drug for all subsequent cycles." to footnote "f"of Pregnancy test of Schedule of Assessments.	The review of laboratory measurement and pregnancy results have been clarified to reflect the timing in this study	• Synopsis-Pregnancy test • Section 9.5.1.5.3 • Section 9.5.2, Table 7 and Table 8
Added text "prior to Day 1 of each subsequent cycle" and to footnote "f" in Schedule of Assessments for pregnancy tests.	Pregnancy test schedule has been updated for consistency with the body of the protocol.	• Synopsis – Pregnancy Test • Section 9.5.1.6 • Section 9.5.2, Table 7 and Table 8

Change	Rationale	Affected Protocol Sections
"X's" added to the Schedule of Assessments tables to reflect pregnancy test prior to Day 1 of each subsequent cycle.		
Added text "In the event of nephrotic syndrome, lenvatinib must be discontinued."	Update to "Management of Proteinuria" to align with updates made to lenvatinib study protocols.	• Section 9.4.1.5
Added text "If a subject experiences an arterial thromboembolism event of any grade, lenvatinib must be discontinued."	Update to "Management of Thromboembolic Events" to align with updates made to lenvatinib study protocols.	• Section 9.4.1.11
Added text "Study treatment should be discontinued in any subject who develops gastrointestinal perforation or life-threatening fistula."	Update to "Management of Gastrointestinal Symptoms and Acute Abdominal Pain" to align with updates made to lenvatinib study protocols.	• Section 9.4.1.14
Changed text "Palliative radiotherapy of up to 2 painful pre-existing, non-target bone metastases will be permitted without being considered progressive disease ~~after determination of recommended dose~~. **In the Phase 1 part, palliative radiotherapy will be allowed after the completion of Cycle 1.**"	Clarification text has been added to confirm that palliative radiotherapy is permitted in Phase 1 after the completion of Cycle 1.	• Section 9.4.7
Expanded Footnotes in Table 7 and 8 (Schedule of Assessments, Phase 1 and Phase 2) to clarify the time window for echocardiogram (1 week prior to the scheduled visit).	Administrative change	• Section 9.5.2, Table 7 and Table 8

2 CLINICAL PROTOCOL SYNOPSIS

Compound No. E7080

Name of Active Ingredient: Lenvatinib and everolimus

Study Protocol Title

A Phase 1/2 Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including CNS Tumors

Investigator(s)

Principal Investigator: Filemon S. Dela Cruz, MD

Sites

Approximately 60 sites; 20 sites for the Phase 1 portion and additional 40 sites for the Phase 2 portion.

Study Period and Phase of Development

Approximately 4.5 years from the first subject providing signed informed consent in Phase 1 to the primary endpoint completion date for Phase 2 of the study. It is estimated that the Phase 2 portion will take 3 years in order to complete the final collection of data for the primary outcome analysis.

Phase 1/2, open-label, non-randomized

Objectives

- **Primary Objectives for Phase 1**

a. To determine a maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of lenvatinib administered in combination with everolimus, once daily to pediatric subjects with recurrent/refractory solid tumors.

b. To describe the toxicities of lenvatinib administered in combination with everolimus once daily to pediatric subjects with recurrent/refractory solid tumors.

- **Secondary Objectives for Phase 1**

a. To preliminarily define the antitumor activity of lenvatinib in combination with everolimus in pediatric subjects with recurrent/refractory solid tumors.

b. To characterize the pharmacokinetics (PK) of oral lenvatinib and everolimus, when administered in combination to pediatric subjects with recurrent/refractory solid tumors.

- **Primary Objective for Phase 2**

a. To estimate the antitumor activity of lenvatinib in combination with everolimus in pediatric subjects with selected recurrent/refractory solid tumors including Ewing sarcoma/peripheral primitive neuroectodermal tumor (pPNET), rhabdomyosarcoma, and high-grade glioma (HGG) using objective response rate (ORR) at Week 16 as the outcome measure.

- **Secondary Objectives for Phase 2**

a. To assess other response variables including ORR at the time of data cutoff, disease control rate (DCR), clinical benefit rate (CBR), and duration of response (DOR).

b. To evaluate the tolerability and safety profile of lenvatinib in combination with everolimus in pediatric subjects with recurrent/refractory Ewing sarcoma/pPNET, rhabdomyosarcoma, and HGG.

c. To characterize the PK of lenvatinib and everolimus, when administered in combination to children with recurrent/refractory Ewing sarcoma/pPNET, rhabdomyosarcoma, and HGG.

- **Exploratory Objectives for Phase 1 and Phase 2**

a. To evaluate blood, tumor, and safety (eg, hypertension) markers as correlative biomarkers of treatment effects and outcomes of lenvatinib in combination with everolimus.

b. To assess candidate alterations in genes and/or proteins that may contribute to tumor development and serve as predictive markers of response in archival tumor tissue from pediatric subjects.

c. To explore relationships between lenvatinib exposure and safety (eg, adverse events [AEs] of special interest).

Study Design

This is a multicenter, open-label, Phase 1/2 study of lenvatinib in combination with everolimus in pediatric subjects with relapsed or refractory solid tumors.

Phase 1 Dose Escalation and Determination of the MTD

The Phase 1 component is a dose escalation study with treatment in sequential cohorts of escalating doses of lenvatinib in combination with everolimus, each administered once daily in 28-day treatment cycles. Pediatric subjects with a relapsed/refractory solid malignancy, including primary brain tumors are eligible to participate. The initial dose level (Dose Level 1) for lenvatinib will be 11 mg/m^2, which is approximately 80% of lenvatinib single dose MTD in pediatric subjects determined in the ongoing Study E7080-G000-207. The initial dose of everolimus will be 3 mg/m^2, which is 66% of the Food and Drug Administration (FDA) approved dose and a dose previously found to be effective in subependymal giant cell astrocytoma (SEGA).

Dose Level 2 will escalate lenvatinib by approximately 25% to 14 mg/m^2 and maintain everolimus at the same dose of 3 mg/m^2. At Dose Level -1 and 1, the maximum daily dose of lenvatinib will not exceed 18 mg daily. At Dose Level 2, the maximum daily dose of lenvatinib allowed will not exceed 24 mg. Should Dose Level 2 be well tolerated, Dose Level 3 may be considered to test lenvatinib at 14 mg/m^2 (capped at 24 mg) and escalate everolimus to 4.5 mg/m^2. For everolimus dose levels of 3 mg/m^2 and 4.5 mg/m^2, the maximum daily dose of everolimus will not exceed 5 mg and 7 mg, respectively. If the MTD for combination of lenvatinib and everolimus has been exceeded at Dose Level 1, then the subsequent cohort of subjects will be treated at Dose Level -1 with dose of lenvatinib 8 mg/m^2 and dose of everolimus 3 mg/m^2 (Table 1). Intra-subject titration of everolimus will not be allowed on this study.

At study entry, subjects must have a minimum body surface area (BSA) of 0.6 m^2.

Table 1 Planned Dose-Escalation

Dose Level	Lenvatinib mg/m^2 (% Single-Agent MTD)	Everolimus (mg/m^2)
-1	8 (60% MTD)[a]	3[c]
1*	**11 (80% MTD)[a]**	**3[c]**
2	14 (100% MTD)[b]	3[c]
3[d]	14 (100% MTD)[b]	4.5[e]

MTD = maximum tolerated dose
*Starting dose level
a: Lenvatinib dose capped at 18 mg daily.
b: Lenvatinib dose capped at 24 mg daily.
c: Everolimus dose capped at 5 mg daily.
d: Dose Level 3 may be considered if Dose Level 2 is well tolerated
e: Everolimus dose capped at 7 mg daily.

The study will utilize a rolling 6 design (Skolnik, et al., 2008). Two to 6 subjects can be concurrently enrolled into a dose level cohort. Dose level assignment will be based on the following:

1. the number of subjects currently enrolled in the dose level cohort,
2. the number of dose-limiting toxicities (DLTs) observed, and
3. the number of subjects at risk for developing a DLT (ie, subjects enrolled but who are not yet assessable for toxicity).

For example, when 3 subjects are enrolled onto a dose cohort, if toxicity data is available for all 3 when the fourth subject entered and there are no DLTs, the dose is escalated and the fourth subject is enrolled to the subsequent dose level. If data is not yet available for one or more of the first 3 subjects and no DLT has been observed, or if one DLT has been observed, the new subject is entered at the same dose level. Lastly, if 2 or more DLTs have been observed, the dose level is de-escalated. This process is repeated for Subjects 5 and 6. In place of suspending accrual after every 3 subjects, accrual is only suspended when a cohort of 6 is filled (ie, subjects enrolled but are not yet assessable for toxicity) or when the study endpoints have been met. When subjects are not evaluable for toxicity, they will be replaced with the next available subject if escalation or de-escalation rules have not been fulfilled at the time the next available subject is enrolled onto the study.

The following table (Table 2) provides the decision rules for enrolling a subject at (i) the current dose level, (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

Table 2 The Rolling 6 Design

# Subjects Enrolled	# Subjects with DLT	# Subjects without DLT	# Subjects with Data Pending	Decision
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

DLT = dose-limiting toxicity
*If 6 subjects already entered at next lower dose level, the maximum tolerated dose (MTD) has been defined.
**If final dose level has been reached, the recommended dose has been reached.

If 2 or more of a cohort of up to 6 subjects experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped. In the event that 2 DLTs observed out of 6 evaluable subjects are of different classes of Adverse Effects (eg, hepatotoxicity and

myelosuppression), expansion of the cohort to 12 subjects will be considered (if one of the DLTs does not appear to be dose-related, the Adverse Effects are readily reversible, AND Protocol Steering Committee (PSC) AND sponsor all agree that expansion of the cohort is acceptable). Subjects who on PSC review are not deemed to be evaluable for DLT assessment may be replaced.

All subjects in the Phase 1 Dose Escalation phase will have samples taken for PK analysis with the intent at the end of Phase 1 of having evaluable PK data from minimally 6 subjects aged 2 to <6 years old, 6 subjects ≥6 to <12 years old, and 6 subjects ≥12 years old. Once the MTD or RP2D has been defined, 0 to 6 additional subjects will be enrolled to attain the goal of having evaluable PK data from minimally 6 subjects aged 2 to <6 years old, 6 subjects aged ≥6 to <12 years old, and 6 subjects ≥12 years old.

Protocol Steering Committee

The sponsor will closely evaluate the risks and benefits of the study throughout its conduct, along with the PSC as needed. The PSC may review available relevant data: DLT and safety data including laboratory assessments, 12-lead electrocardiograms (ECGs), dose administration, etc.

Toxicity Monitoring

The DLT observation period for the purposes of dose-escalation will be the first cycle of therapy. Routine Phase 1 monitoring for clinical and laboratory toxicities will be used. Blood pressure (BP) monitoring will occur at least weekly during the first 2 cycles.

Dose-limiting toxicity will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and is defined as any of the following events that are possibly, probably, or definitely attributable to lenvatinib or everolimus. Dose-limiting hematological and non-hematological toxicities are defined differently.

A. Non-hematological DLT:

- Any Grade 3 or greater non-hematological toxicity attributable to the investigational drug with the specific **exclusion** of:
  - Grade 3 nausea and vomiting <3 days duration
  - Grade 3 diarrhea <3 days duration
  - Grade 3 weight loss
  - Grade 3 liver enzyme elevation, including alanine aminotransferase/aspartate aminotransferase(ALT/AST)/ gamma glutamyl transferase (GGT)/ bilirubin/alkaline phosphatase that returns to Grade ≤1 or baseline within 7 days
  - Grade 3 asymptomatic elevation in amylase or lipase that returns to Grade ≤1 or baseline within 7 days
  - Grade 3 elevation in triglycerides that returns to Grade ≤1 or baseline within 7 days
  - Grade 3 or 4 fever <5 days duration
  - Grade 3 infection <5 days duration
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation
  - Grade 3 proteinuria (urine protein:creatinine [UPC]) ratio >1.9 unless confirmed with a second measurement within 72 hours
  - Grade 3 headache <3 days duration responsive to optimal management
- Any Grade 2 non-hematological toxicity that persists for ≥7 days and is considered sufficiently medically significant or sufficiently intolerable by subjects despite optimal supportive care that it requires treatment interruption.
- Any dose interruption or reduction due to toxicity which results in administration of less than 75% of the planned dosage of lenvatinib and/or everolimus.
- Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a DLT.

- **Dose-limiting hypertension**:
  - Any Grade 4 hypertension
  - Confirmed systolic or diastolic BP more than 25 mmHg above 95th percentile for sex, age, height/length, or an elevated diastolic BP (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 2 antihypertensive ingredient medications will be considered a single antihypertensive medication.

B. Hematological DLT:

- In subjects evaluable for hematological toxicity, DLT is defined as:
  - Grade 4 thrombocytopenia (platelet count <25,000/mm^3) or Grade 4 neutropenia, not due to malignant infiltration.
- Any ≥Grade 2 arterial thromboembolic events (including cerebrovascular ischemia, peripheral or visceral arterial ischemia).
- Note: Grade 3 or 4 febrile neutropenia will not be considered 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 the Eisai Medical Monitor in consultation with the PSC, as needed. Subjects who discontinue the study treatment for any reason other than DLT (eg, early disease progression) during Cycle 1 (Day 1 to Day 28) and have not received at least 75% of the prescribed dose prior to discontinuation will be replaced.

The sponsor and PSC will review all subjects' safety and clinical data to jointly determine the MTD/RP2D of the combination of lenvatinib with everolimus.

The Treatment Phase for each subject in Phase 1 ends after completing Cycle 1 of treatment unless subject discontinues early. Those subjects who discontinue study treatment in Cycle 1 transition to the Off-treatment Visit. Those who complete Cycle 1 will transition to the Extension Phase. Study treatment and tumor assessments will continue during the Extension Phase.

Phase 2 Cohorts

Once the MTD/RP2D of the combination of lenvatinib and everolimus in pediatric population has been determined in Phase 1, the Phase 2 portion of this pediatric study will commence with Cohort 1 (recurrent or refractory Ewing sarcoma/pPNET), Cohort 2 (recurrent or refractory rhabdomyosarcoma), and Cohort 3 (recurrent or refractory HGG), opening to accrual.

Cohorts 1 – 3

Phase 2 Cohorts 1-3 will use a 10+10 Simon's optimal 2-stage design for each cohort; 10 evaluable subjects will be enrolled to each stage. The Sponsor will closely monitor enrollment to ensure that at least 50% of subjects enrolled in each cohort are <18 years of age at the time of informed consent. The primary outcome measure for Ewing sarcoma/pPNET, rhabdomyosarcoma, and HGG will be ORR (complete or partial response) at 16 weeks. If there are no responses among the 10 subjects in Stage 1, then the enrollment to that disease cohort will stop and it will be concluded that the lenvatinib/everolimus combination therapy did not elicit a response in that disease cohort. If there is at least 1 response in the first stage, then the second stage will enroll 10 additional evaluable subjects. If there are 2 or fewer responses among the 20 evaluable subjects, then lenvatinib/everolimus combination therapy will be declared a failure for that disease cohort. Subjects will meet the criteria for being evaluable for an objective response, if they have measurable disease present at baseline and at least 1 post-baseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease. Subjects who are not evaluable for objective response will be replaced.

The Treatment Phase for each subject in Phase 2 ends after completing 4 cycles of treatment unless the subject discontinues early. Those who discontinue study treatment before completing 4 cycles transition to the Off-treatment Visit. Those who complete 4 cycles transition to the Extension Phase. Study treatment and tumor assessments will continue during the Extension Phase.

Dosing Nomogram

The dose nomogram in Table 3 provides dose of lenvatinib to be administered for BSA increments starting from 0.6 m^2. BSA must be calculated on Day 1 of each cycle based on the subject's current height and body weight. The actual dose to be administered is rounded to the nearest whole number. The total lenvatinib dose is capped at 18 mg daily (Dose Levels -1 and 1), and at 24 mg daily (Dose Levels 2 and 3).

Table 3 Total Lenvatinib Dose (mg): Body Surface Area (m^2) * Dose Level (mg/m^2)

Lenvatinib Dose Level							
8 mg/m^2 (Everolimus 3.0 mg/m^2) Dose Level -1		11 mg/m^2 (Everolimus 3.0 mg/m^2) Dose Level 1		14 mg/m^2 (Everolimus 3.0 mg/m^2) Dose Level 2		14 mg/m^2 (Everolimus 4.5 mg/m^2) Dose Level 3	
Body Surface Area (m^2)	Dose to be Administered (mg)	Body Surface Area (m^2)	Dose to be Administered (mg)	Body Surface Area (m^2)	Dose to be Administered (mg)	Body Surface Area (m^2)	Dose to be Administered (mg)
0.60 - 0.68	5	0.60 - 0.68	7	0.60 - 0.60	8	0.60 - 0.60	8
0.69 - 0.81	6	0.69 - 0.77	8	0.61 - 0.67	9	0.61 - 0.67	9
0.82 - 0.93	7	0.78 - 0.86	9	0.68 - 0.74	10	0.68 - 0.74	10
0.94 - 1.06	8	0.87 - 0.95	10	0.75 - 0.82	11	0.75 - 0.82	11
1.07 - 1.18	9	0.96 - 1.04	11	0.83 - 0.89	12	0.83 - 0.89	12
1.19 - 1.31	10	1.05 - 1.13	12	0.90 - 0.96	13	0.90 - 0.96	13
1.32 - 1.43	11	1.14 - 1.22	13	0.97 - 1.03	14	0.97 - 1.03	14
1.44 - 1.56	12	1.23 - 1.31	14	1.04 - 1.10	15	1.04 - 1.10	15
1.57 - 1.68	13	1.32 - 1.40	15	1.11 - 1.17	16	1.11 - 1.17	16
1.69 - 1.81	14	1.41 - 1.49	16	1.18 - 1.24	17	1.18 - 1.24	17
1.82 - 1.93	15	1.50 - 1.59	17	1.25 - 1.32	18	1.25 - 1.32	18
1.94 - 2.06	16	≥1.60	18	1.33 - 1.39	19	1.33 - 1.39	19
2.07 - 2.18	17			1.40 - 1.46	20	1.40 - 1.46	20
≥2.19	18			1.47 - 1.53	21	1.47 - 1.53	21
				1.54 - 1.60	22	1.54 - 1.60	22
				1.61 - 1.67	23	1.61 - 1.67	23
				≥1.68	24	≥1.68	24

The dose nomogram in Table 4 provides dose of everolimus to be administered for BSA increments starting from 0.6 m^2. The total everolimus dose is capped at 5 mg daily for Dose Levels -1, 1, and 2, and at 7 mg daily for Dose Level 3.

Table 4 Total Everolimus Dose (mg): Body Surface Area (m^2) * Dose Level (mg/m^2)

Everolimus Dose Level			
3 mg/m^2 Dose Levels -1, 1, and 2		4.5 mg/m^2 Dose Level 3	
Body Surface Area (m^2)	Dose to be Administered (mg)	Body Surface Area (m^2)	Dose to be Administered (mg)
0.60 – 0.83	2	0.60 – 0.77	3
0.84 – 1.16	3	0.78 – 0.99	4
1.17 – 1.49	4	1.00 – 1.22	5
≥1.50	5	1.23 – 1.44	6
		≥1.45	7

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.

Number of Subjects

A maximum accrual of 120 subjects in Phase 1 and Phase 2 portions of the study is expected.

- Phase 1: 4 to 48 evaluable subjects. In the event that each of the 4 dose levels (-1, 1, 2, and 3) are expanded to 12 subjects and 6 additional subjects need to be enrolled in the PK Cohort, a maximum of 54 subjects (allowing for 20% to be non-evaluable and including the additional 6 subjects for PK analysis) will be enrolled.
- Phase 2 Cohorts 1 - 3: 10 to 20 evaluable subjects per cohort (maximum 22 subjects enrolled per cohort allowing for 10% to be non-evaluable). A maximum of 66 subjects will be enrolled in Phase 2. In each cohort, at least 50% of the subjects enrolled will be <18 years old at the time of informed consent.

Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of the following tumor types:
   a. Phase 1: Recurrent or refractory solid tumors (excluding hepatoblastoma and lymphomas), including primary central nervous system (CNS) tumors; subjects must have either measurable or evaluable disease. Subjects with diffuse intrinsic pontine glioma, optic pathway glioma, or pineal tumors with elevated tumor markers (alpha-fetoprotein [AFP] and beta-human chorionic gonadotropin [ß-hCG] [or hCG]) do not require histological or cytological confirmation of diagnosis.
   b. Phase 2: Recurrent or refractory tumors; subjects must have measurable disease
      - Cohort 1: Ewing sarcoma/pPNET
      - Cohort 2: Rhabdomyosarcoma
      - Cohort 3: HGG (subjects with Diffuse Intrinsic Pontine Glioma are not eligible)
2. Measurable disease that meets the following criteria (Phase 2):
   a. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (for all tumor types except HGG)
      - At least 1 lesion of ≥1.0 cm in the longest diameter for a non lymph node or ≥1.5 cm in the short-axis diameter for a lymph node which is serially measurable according to RECIST 1.1 using computed tomography /magnetic resonance imaging (CT/MRI).
   b. Response Assessment in Neuro-Oncology (RANO) for HGG (Wen, et al., 2010)
      - At least one lesion must be measurable as defined as a bi-dimensionally contrast-enhancing lesion with clearly defined margins by CT or MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are preferably at most 5 mm apart with 0 mm skip.

Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.

3. Karnofsky performance score ≥50 for subjects >16 year of age and Lansky play score ≥50 for subjects ≤16 years of age. Note: Neurologic deficits in subjects with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. Subjects who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
4. Subjects must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to

enrollment. If after the required timeframe, the numerical eligibility criteria are met, eg, blood count criteria, the subject is considered to have recovered adequately.

a. Cytotoxic chemotherapy or other chemotherapy known to be myelosuppressive: ≥21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).
b. Anti-cancer agents not known to be myelosuppressive (eg, not associated with reduced platelet or absolute neutrophil counts): ≥7 days after the last dose of agent.
c. Monoclonal antibodies: ≥21 days or 3 half-lives (whichever is shorter) of the antibody must have elapsed after the last dose of a monoclonal antibody (including checkpoint inhibitors). Toxicity related to prior antibody therapy must be recovered to Grade ≤1.
d. Corticosteroids: If used to modify immune AEs related to prior therapy, ≥14 days must have elapsed since last dose of corticosteroid. Subjects receiving corticosteroids, who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment, are not eligible.
e. Hematopoietic growth factors: ≥14 days after the last dose of a long-acting growth factor (eg, Neulasta) or 7 days for short-acting growth factor. For agents that have known AEs occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs are known to occur.
f. Interleukins, interferons, and cytokines (other than hematopoietic growth factors): ≥21 days after the completion of interleukins, interferons or cytokines (other than hematopoietic growth factors).
g. Stem cell infusions (with or without total body irradiation):
   - Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including donor leukocytes infusion or boost infusion: ≥84 days after infusion and no evidence of graft versus host disease.
   - Autologous stem cell infusion including boost infusion: ≥42 days
h. Cellular Therapy: ≥42 days after the completion of any type of cellular therapy (eg, modified T cells, natural killer cells, dendritic cells, etc).
i. Radiotherapy (XRT)/External Beam Irradiation including Protons: ≥14 days after local XRT; ≥150 days after total body irradiation, craniospinal XRT or if radiation to ≥50% of the pelvis; ≥42 days if other substantial bone marrow radiation.
j. Radiopharmaceutical therapy (eg, radiolabeled antibody, iodine-131 metaiodobenzylguanidine [^{131}I-MIBG]): ≥42 days after systemically administered radiopharmaceutical therapy.
k. Vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR)-targeted or mammalian target of rapamycin (mTOR)-targeted therapies:
   - Must not have received prior exposure to lenvatinib
   - May have previously progressed on an mTOR inhibitor
   - No more than 2 prior VEGF/VEGFR-targeted therapies (For Phase 2 only)
   - Must not have received prior VEGF/VEGFR-targeted therapy in combination with an mTOR inhibitor (For Phase 2 only)

5. Male or female subjects must be ≥2 years and <18 years of age for enrolment in Phase 1 or ≥2 years and ≤21 years of age for enrolment in Phase 2.
6. Adequate bone marrow function:
   - For subjects with solid tumors without known bone marrow involvement:
     - Peripheral absolute neutrophil count (ANC) ≥1000/mm^3
     - Platelet count ≥100,000/mm^3

- Hemoglobin ≥8.0 g/dL at baseline (may receive red blood cell transfusions)

- For subjects with known bone marrow metastatic disease:
  - Peripheral ANC ≥1000/mm^3
  - Platelet count ≥100,000/mm^3 (and with no platelet transfusions for at least 7 days prior to enrollment)
  - May receive transfusions provided they are not known to be refractory to red cell or platelet transfusions. These subjects will not be evaluable for hematologic toxicity. At least 5 of every cohort of 6 subjects with a solid tumor must be evaluable for hematologic toxicity, for the dose-escalation part of the study. If dose-limiting hematologic toxicity is observed, all subsequent subjects enrolled must be evaluable for hematologic toxicity.

7. Adequate renal function:
   - Creatinine clearance or radioisotope glomerular filtration rate (GFR) ≥70 mL/min/1.73 m^2 or
   - A serum creatinine based on age/gender as follows:

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 utilizing child length and stature data published by the Centers for Disease Control and Prevention (CDC).

   - 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).

8. Adequate liver function:
   - Bilirubin (sum of conjugated + unconjugated) ≤1.5 × upper limit of normal (ULN) for age, except for unconjugated hyperbilirubinemia of Gilbert's syndrome.
   - ALT and AST ≤3 × ULN
   - Serum albumin ≥2 g/dL

9. Adequate cardiac function:
   - Adequate cardiac function as evidenced by left ventricular shortening fraction of ≥27% by echocardiogram or left ventricular ejection fraction (LVEF) ≥50% at baseline as determined by echocardiography/multigated acquisition (MUGA) scan.
   - QT interval corrected for heart rate using Fridericia's formula (QTcF) ≤480 msec.

10. Adequate neurologic function:
    - Subjects with seizure disorder may be enrolled if on non-enzyme-inducing anticonvulsants and well controlled.
    - Nervous system disorders (CTCAE v4.03) resulting from prior therapy and not tumor-induced must be ≤ Grade 2.

11. Adequate BP control with or without antihypertensive medications, defined as:
    - A BP < the 95th percentile for sex, age and height/length (≤150/90 mmHg for subjects aged 18 - 21 years) at Screening (as per National Heart Lung and Blood Institute [NHLBI] guidelines) and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1.
12. Adequate coagulation:
    - International Normalized Ratio (INR) ≤1.5
13. Adequate pancreatic function:
    - Serum amylase ≤1.5 × ULN
    - Serum lipase ≤1.5 × ULN
14. Adequate metabolic function:
    - Serum triglycerides ≤300 mg/dL
15. Adequate glycemic control defined as:
    - Fasting serum glucose ≤160 mg/dL
16. Subjects must have a minimum BSA of 0.6 m^2 at study entry.

Exclusion Criteria

1. Subjects who have had or are planning to have the following invasive procedures:
    - Major surgical procedure, laparoscopic procedure, open biopsy or significant traumatic injury within 28 days prior to enrollment.
    - Central line placement or subcutaneous port placement is not considered major surgery. External central lines must be placed at least 3 days prior to enrollment and subcutaneous ports must be placed at least 7 days prior to enrollment.
    - Fine needle aspirate within 7 days prior to enrollment.
    - Surgical or other wounds must be adequately healed prior to enrollment.

NOTE: For purposes of this study, bone marrow aspirate and biopsy are not considered surgical procedures and therefore are permitted within 14 days prior to start of protocol therapy.

2. Subjects who have non-healing wound, unhealed or incompletely healed fracture, or a compound (open) bone fracture at the time of enrollment
3. Subjects having an active infection requiring systemic therapy.
4. Subjects with a known history of active hepatitis B (defined as hepatitis B surface antigen reactive or hepatitis B virus-DNA detected) or known active hepatitis C virus (HCV, defined as HCV-RNA detected). Note: No testing for hepatitis B and hepatitis C is required unless mandated by the local health authority.
5. Known to be human immunodeficiency virus (HIV) positive. Note: HIV testing is required at screening only when mandated by the local health authority
6. Clinical evidence of nephrotic syndrome prior to enrollment
7. Gastrointestinal bleeding or active hemoptysis (bright red blood of at least half teaspoon) within 21 days prior to enrollment
8. Thrombotic/ thromboembolic event requiring systemic anticoagulation within 90 days prior to enrollment
9. Evidence of new intracranial hemorrhage of more than punctate size on MRI assessment obtained within 28 days prior to study enrollment for subjects with HGG
10. Diagnosis of lymphoma

11. Radiographic evidence of major blood vessel invasion/infiltration.
12. Evidence of untreated CNS metastases (exception: subjects with primary CNS tumors and leptomeningeal disease).
13. Subjects who are currently receiving enzyme-inducing anticonvulsants
14. Subjects chronically receiving strong cytochrome P450 3A4 (CYP3A4)/P-glycoprotein (P-gp) inhibitors or inducers within 7 days prior to study enrollment (See Appendix 15 for a list of strong inhibitors and inducers).
15. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive ß-hCG [or hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or 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.
16. Females of childbearing potential* who:
    - do not agree to use a highly effective method of contraception for the entire study period and for 8 weeks after study drug discontinuation, ie,:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device (IUD) or hormone releasing system (IUS)
        - a contraceptive implant
        - an oral contraceptive** (with additional barrier method)

    OR
    - do not have a vasectomized partner with confirmed azoospermia.

For sites outside of the European Union (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.

NOTES:
*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), or are pre-menarcheal (Tanner Stage 1-3).

Must be on a stable dose of the **same oral hormonal contraceptive product for at least 4 weeks before dosing with study drug, for the duration of the study, and for at least 8 weeks after study drug discontinuation.

17. Males who have not had a successful vasectomy (confirmed azoospermia) or if 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 7 days after lenvatinib discontinuation or 4 weeks after discontinuation of everolimus). No sperm donation is allowed during the study period and for 7 days after lenvatinib discontinuation or 4 weeks after discontinuation of everolimus.

Study Treatment

Study drugs: Lenvatinib will be provided as hard capsules containing 1 mg, 4 mg, or 10 mg lenvatinib. An extemporaneous suspension of lenvatinib capsules should be used for children unable to swallow capsules.

Everolimus will be provided as 2 mg, 3 mg, and 5 mg dispersible tablet formulations (everolimus tablets for oral suspension).

Lenvatinib and everolimus will be administered orally on a once daily schedule in continuous 28-day cycles. The sequence of administration is not important. Dosing nomograms based on BSA and dose level will be used to prescribe lenvatinib and everolimus for subjects to minimize inter-subject dosing variability. The maximum daily dose of lenvatinib administered during the study should not exceed 18 mg in Dose Levels -1, and 1, and 24 mg in Dose Levels 2 and 3. The maximum daily dose of everolimus should not exceed 5 mg in Dose Levels -1, 1, and 2, and 7 mg in Dose Level 3. Intra-subject titration of everolimus will not be allowed on this study. Intra-subject dose escalation will not be allowed.

Comparator Drug (if applicable): Not Applicable

Study Drug Dose Interruption and Reduction Instructions:

Dose reductions and interruptions for subjects who experience lenvatinib-everolimus combination therapy-related toxicity will be managed as described in Table 5. Investigators will decide the probability of the event being related to protocol therapy as to whether dose modification of drug therapy is required.

Asymptomatic laboratory abnormalities, including Grade ≥3 abnormalities (eg, elevations of amylase and lipase) that are not considered clinically relevant by the investigator, should be managed per institutional guidelines; continuation of treatment should be discussed with the sponsor.

Doses in the Dose Adjustment column are based on a presumed starting dose of 11 mg/m^2 lenvatinib and 3 mg/m^2 everolimus. Dose reductions will occur in succession based on the previous dose level. Each dose level reduction due to toxicity at a given BSA is approximately 25% reduction from the previous dose. Once the study drug dose has been reduced, it may not be increased at a later date, unless the dose was mistakenly decreased; in this situation, the sponsor's approval is required to increase the dose.

Table 5 Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity

Treatment-Related Toxicity[a,b]	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d, e] or Grade 3[f]		
First occurrence	Interrupt lenvatinib and everolimus until resolved to Grade 0-1 or tolerable Grade 2	Reduce lenvatinib dose to 8 mg/m^2 (or approximately 25% reduction of the starting dose) orally once a day (one-level reduction) and resume everolimus at the same dose as prior to dose interruption
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and everolimus until resolved to Grade 0-1 or tolerable Grade 2	Reduce lenvatinib dose to 6 mg/m^2 (or approximately 25% reduction from the previous dose level) once a day (one-level reduction). Dose reduction of everolimus to 3 mg/m^2 every other day may be considered for Grade 3 toxicity[e]

Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and everolimus until resolved to Grade 0-1 or tolerable Grade 2	Reduce lenvatinib dose to 4.5 mg/m^2 (or approximately 25% reduction from the previous dose level) orally once a day (1-level reduction). Dose reduction of everolimus for Grade 3 toxicity: i) if 3 mg/m^2 daily everolimus at event onset, reduce to 3 mg/m^2 every other day or ii) if 3 mg/m^2 every other day everolimus at event onset, discontinue
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and everolimus	Discuss with sponsor
Grade 4[g]: Discontinue Study Treatment		

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

a: An interruption of study treatment for more than 28 days will require sponsor`s approval before treatment can be resumed.
b: Initiate optimal medical management for nausea, vomiting, hypothyroidism 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.
d: Obese subjects with weight loss do not need to return to the baseline weight or within10% of baseline weight (ie, Grade 1weight loss). These subjects will restart the study drug(s) at a lower dose once their weight remains stable for at least 1 week and they reached the normal body mass index (BMI; if the weight loss occurred, but it is still above normal BMI, they can restart the study treatment at a lower dose once the weight has been stable for at least 1 week). Normal BMI should be used as the new baseline for further dose reductions.
e: For Grade 2 toxicity, resume everolimus at the same dose as prior to dose interruption. For Grade 3 toxicity, investigator will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required.
f: For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with the sponsor.
g: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

Duration of Treatment

Study duration for each subject is estimated to be:

- **Pretreatment Phase:** 4 weeks
- **Treatment Phase:** 1 cycle (4 weeks) in Phase 1, 4 cycles (16 weeks) in Phase 2.
- **Extension Phase:** Estimated maximum time of treatment is 2 years (24 cycles)

Subjects may remain on study treatment as long as they do not meet any of the following criteria: 1) experience objective progression of disease (according to RECIST 1.1 or RANO criteria, as appropriate); 2) exhibit no clinical benefit (in the opinion of the investigator); 3) experience unacceptable toxicity leading to withdrawal from the study; 4) withdraw or are withdrawn from the study for any reason, or; 5) termination of the study program.
As long as the subject has not experienced intolerable toxicity, he or she can continue to receive study treatment. A 28-day follow-up visit from last date of receiving investigational drug will be performed for subjects who discontinue study treatment.

Concomitant Drug/Therapy

Treatment (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs, etc.) of complications of AEs or therapy to ameliorate symptoms may be administered at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study medication.
An anti-diarrheal agent should be recommended to the subject at the start of study treatment and subjects should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the subject's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in the Dose Modification Guidelines should be followed.
Administration of corticosteroids for progressive disease is not permitted. Administration of corticosteroids will be limited to premedication or the short-term treatment of acute medical conditions in accordance with approved indications, institutional, or national guidelines.

Further information on the prohibited concomitant therapies for lenvatinib and everolimus is included in the respective package inserts.

Assessments

Tumor Assessments:

For all tumor types except HGG: Tumor assessments will be performed using RECIST 1.1. Investigator-determined response assessments will be performed at each assessment time point and entered onto case report form. Tumor assessments (CT chest and CT/MRI of abdomen, pelvis and other areas of known disease at screening plus any areas of suspected disease) should be performed at Screening and, for Phase 1 of the study, at Week 4 ±1 week, Week 12 ±1 week, Week 24 ±1 week and every12 weeks ±1 week thereafter, or as clinically indicated. For subjects with primary CNS tumors and no other known areas of disease only CNS target and non-target lesions plus any areas of newly suspected disease must be scanned. For Phase 2 of the study, tumor assessments should be performed at Screening, Week 8 ±1 week, Week 16 ±1 week, Week 24 ±1 week, and then every 12 weeks ±1 week thereafter, or as clinically indicated. All responses are to be confirmed at a follow-up examination after ≥28 days following the initial indication of response. A brain scan (CT with contrast or MRI pre-and post-contrast) will be performed at Screening, and during the study if clinically indicated.

For HGG: Tumor assessments will be performed using RANO Criteria. A standard MRI imaging protocol will be performed for use in the assessments. Investigator-determined response assessments at each assessment time point will be entered onto the appropriate CRFs. Tumor assessments will be carried out during Screening and for Phase 1 of the study, at Week 4 ±1 week, Week 12 ±1 week, Week 24 ±1 week, and then every 12 weeks ±1 week thereafter, or as clinically indicated. For Phase 2 of the study, tumor assessments should be performed at Screening, Week 8 ±1 week, Week 16 ±1 week, Week 24 ±1 week, and every 12 weeks ±1 week thereafter, or as clinically indicated.

For Phase 2, copies of scans for tumor assessments will be sent to an imaging core laboratory designated by the sponsor for quality assessment and archival and potential future independent review.

The imaging methodology for tumor assessments for all tumor types, including solid tumors and HGG, will be provided in an appendix to the study protocol.

Pharmacokinetic Assessments: Blood samples for plasma concentrations of lenvatinib and whole blood concentrations of everolimus will be collected from all subjects as described in the Schedule of Assessments.

Pharmacodynamic (PD) Assessments: Blood samples for plasma and serum studies will be collected from consenting subjects (optional) at Baseline and on Cycle 1 Day 15, Cycle 2 Day 1,

and then matched with tumor assessments and at the Off-treatment Visit, as specified in the Schedule of Assessments. Only subjects with BSA >0.68 m^2 are eligible to consent (optional) to blood samples for plasma and serum studies. Biomarker discovery and/or validation will be performed to identify blood or tumor biomarkers that may be useful to predict subject response to study drug as well as for potential use in diagnostic development. Blood samples may undergo global proteomic and/or single analyte enzyme-linked immunosorbent assays (ELISA) or multiplex immunoassays based on the amount of sample available. Potential blood biomarkers to be explored include, FGF ligands (eg, FGF2/bFGF, FGF19, FGF21, FGF23), and angiogenesis related markers (eg, VEGF, Ang 1/2, sTie-2, HGF, PlGF). In addition, biomarkers identified in other lenvatinib clinical studies may also be assessed in samples collected from subjects enrolled in this study. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

Pharmocokinetic/Pharmacodynamic Assessments: Relationships between lenvatinib exposure and safety will be explored graphically. Pending the outcome of graphical assessments, modeling of potential relationships will be explored. Details of exposure-safety analyses will be provided in a separate analysis plan.

Pharmacogenomic/Pharmacogenetic Assessments: Archived, fixed tumor tissue will be collected (if available) for potential assessment of mutations and other genetic alterations in genes and/or proteins that may be important in the development and progression of tumor biology relevant to the tumor types being explored, to evaluate response to study drug treatment as well as for potential use in diagnostic development. Genetic alterations in target genes include lenvatinib targets (eg, FGF ligands and FGF receptors 1 to 4), angiogenesis-relevant targets (such as expression levels of VEGF, Ang 1/2, Tie-2, HGF and cMET) and markers associated with cell differentiation and tumorigenesis (eg, WNT/β-catenin pathway, hedgehog/PTCH pathway, and BMP/TGF signaling pathway). Appropriate analytical technology/methodologies, such as next generation sequencing (NGS)-based whole exome sequencing (WES), whole transcriptome analysis or targeted re-sequencing using targeted gene panels (eg, ThermoFisher Oncomine Comprehensive Assay (OCA)) for gene alterations, targeted gene expression panels (eg, Nanostring PanCancer Pathway, PanCancer Immune) for gene expression analysis, single analyte or multiplex IHC, etc may be used based on the amount of tumor tissue available.

Blood plasma samples will be collected (optional) for analysis of cell free nucleic acid (cf-nucleic acid). Cell free nucleic acid isolated from plasma samples may be used to explore tumor genetic alterations such as mutations and other genetic alterations observed in archival tumor samples (using NGS-based targeted gene panels), as well as those which develop during drug treatment to monitor response to study drug.

A blood sample will be collected for pharmacogenomic (PG) analysis (optional). Variation in study drug exposure or the occurrence of AEs observed in the study population may be evaluated by correlating single–nucleotide polymorphisms with PK, safety, or PD data. Genomic DNA extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA extracted from tumor material are limited to the tumor.

Data obtained will be used for research to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. 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 after study completion to assist in research scientific questions related to cancer biology or for potential diagnostic development.

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

Safety Assessments: Routine Phase 1 monitoring for clinical and laboratory toxicities will be used. CTCAE v 4.03 will be used for grading toxicities and recording of all AEs and serious adverse events (SAEs). Regular performance of physical examinations, laboratory evaluation for hematology, blood chemistry, and urine dipstick values, periodic measurement of vital signs, 12-lead ECGs, echocardiography/MUGA scan, Lansky play score and Karnofsky performance score, baseline and periodic assessments of pancreatic enzymes, thyroid-stimulating hormone (TSH) levels and physeal dysplasia will be performed. BP monitoring will occur at least weekly during the first 2 cycles. BP will be assessed in terms of percentile for sex, age and height/length. Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥95th percentile [BP ≥140 mmHg for adult subjects] or diastolic BP ≥95th percentile [BP ≥90 mmHg for adult subjects]) is confirmed on 2 assessments obtained 1 hour apart. For subjects with hypertension and proteinuria, treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist is preferred. Cardiac systolic function and corrected QT interval (QTc) will be assessed at screening, prior to Cycles 2 and 5, and every sixth cycle thereafter by echocardiography/MUGA scan and ECG.

Other Assessments

Pregnancy Test: A serum β-hCG test will be performed for females of childbearing potential (see definition included in the Inclusion/Exclusion criteria). 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), prior to Day 1 of each subsequent cycle and at the Off-treatment Visit in females of childbearing potential. The results must be reviewed prior to administration of study drug on Cycle 1 Day 1 and within 48 hours prior to dispensing study drug for all subsequent cycles. Blood and urine samples will be taken at designated time points as specified in the Schedule of Assessments.

Bioanalytical Methods

Lenvatinib in plasma and everolimus in whole blood will be quantified using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods.

Statistical Methods

Study Endpoints

Primary Endpoints for Phase 1

- MTD and RP2D of lenvatinib in combination with everolimus
- Safety and toxicity of lenvatinib in combination with everolimus

Primary Endpoint for Phase 2

- ORR, defined as the proportion of subjects who have the best overall response (BOR) of complete response (CR) or partial response (PR) at Week 16

Secondary Endpoints for Phase 1 and Phase 2

- ORR at the time of data cutoff
- DCR, defined as the proportion of subjects who have the BOR of CR or PR or stable disease (SD) (SD duration ≥7 weeks since the first dose of the study treatment)
- CBR, defined as the proportion of subjects who have the BOR of CR or PR or durable SD (SD duration ≥23 weeks since the first dose of the study treatment)
- DOR, defined as the time from the date of the first documented CR or PR to the date of the disease progression objectively documented or death (whichever occurs first)

- Plasma PK of lenvatinib and trough concentrations of everolimus when administered in combination
- Safety and toxicity of lenvatinib in combination with everolimus in Phase 2

Exploratory Endpoints

- Assess candidate alterations in genes and/or proteins that may contribute to tumor development and predictive marker of response in archival tumor tissue
- Correlative blood and tumor biomarkers of treatment effects and outcomes

Definitions of Analysis Sets

- **Evaluable Analysis Set**, defined as all subjects, who have measurable disease present at baseline and at least 1 post-baseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease. This will be the analysis set for efficacy.
- **Safety Analysis Set**, defined as all subjects who received at least 1 dose of the study drug (lenvatinib or everolimus).
- **Pharmacokinetic (PK) Analysis Set**, defined as subjects in Safety Analysis Set who had at least 1 measurable postdose plasma concentration with an adequately documented dosing history.
- **Pharmacodynamic (PD) Analysis Set**, defined as all subjects in Safety Analysis Set who had evaluable PD data.

Statistical Analysis

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, Q1, Q3, and range (minimum and maximum), unless otherwise specified.

Efficacy data will be analyzed using the Evaluable Analysis Set, safety data will be analyzed using the Safety Analysis Set, PK data will be analyzed using the PK Analysis Set, and PD data will be analyzed using the PD Analysis Set. All analyses will be performed by dose level in Phase 1 (if appropriate) and for each study cohort in Phase 2, unless otherwise specified.

Efficacy Analyses

Data cut-off for the primary study analysis in Phase 2 will occur when all subjects have completed at least 4 treatment cycles and, if applicable, a confirmatory scan has been performed (in case of a PR or CR at Week 16), or have discontinued study drug early.

The following are evaluability criteria for objective response and non-target disease response analysis:

- **Evaluable for objective response:** Only those subjects who have measurable disease present at baseline and have their disease re-evaluated at post-baseline visits will be considered evaluable for objective response. These subjects will have their response classified according to RECISIT 1.1 (for Ewing sarcoma/pPNET and rhabdomyosarcoma) or RANO (for HGG).
- **Evaluable for non-target disease response:** Subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease and have had their disease re-evaluated at post-baseline visits will be considered evaluable for non-target disease. Subjects with only non-target disease will be summarized by their best overall response. The response will be classified according to RECIST 1.1 defined categories for subjects with non-target disease only.

Primary Efficacy Analysis

Phase 1:

The study will utilize the rolling 6 design. The primary objective of Phase 1 is to determine the MTD and to establish the RP2D.

Phase 2:

The primary efficacy endpoint in Phase 2 is ORR at 16 weeks. Objective responses will count only confirmed CR and PR. Estimated ORR and its exact 95% confidence interval (CI) using the method of Clopper and Pearson will be presented.

Secondary Efficacy Analyses for Phase 1 and Phase 2

The secondary efficacy endpoints will be ORR at the time of data cutoff, DCR, CBR and DOR. These endpoints in Phase 1 will be summarized if appropriate and listed by dose level, and ORR will be based only on subjects with measureable disease at screening/baseline. For Phase 2, the ORR, DCR and CBR will be provided with exact 95% CIs using the method of Clopper and Pearson, and the DOR will be analyzed for responders using Kaplan-Meier approach.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analysis

Lenvatinib and everolimus concentration versus time data will be tabulated and summarized and graphically presented.

Plasma concentrations of lenvatinib from the intense sampling in Phase 1 will be used to determine the following PK parameters: area under the plasma concentration time course profile (AUC), maximum observed concentration (C_{max}), and time from dosing to the maximum observed concentration (T_{max}). Other PK parameters may be determined as data permit.

For both lenvatinib and everolimus, data from both Phase 1 and 2 of the study will be pooled with available data from other studies and subjected to population PK analysis. For each drug, the PK model will be parameterized in terms of clearance and volume of distribution. Details of the population PK analysis will be provided in a separate analysis plan.

Pharmacodynamic, Pharmacokinetic/Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Correlation between clinical response to treatment associated with a combination of lenvatinib and everolimus and blood or tumor biomarkers will be examined using descriptive statistics and graphic displays as appropriate. Details will be provided in a separate analysis plan.

Pharmacokinetic/PD exposure-safety relationships will be explored. Safety endpoints will be most frequent AEs of special interest and dose reductions. Exploratory/graphical analyses will be conducted for PK/PD evaluations, and may be followed by model-based analyses. A detailed analysis plan will be provided separately.

Safety Analyses

A descriptive summary of all toxicities will be provided.

The following are evaluability criteria for toxicity analysis:

- **Evaluable for toxicity:** All subjects who received at least 1 dose of study treatment are evaluable for toxicity. For Phase 1, toxicities during Cycle 1 will be used for the purpose of dose escalations according to the rolling 6 design. Subjects who developed a DLT or received at least 75% of the prescribed dose during Cycle 1 are considered fully evaluable for toxicity for the purpose of dose escalation.

The incidence of treatment-emergent adverse events (TEAEs) and SAEs will be summarized by system organ class and preferred term. Laboratory test data, vital signs, 12-lead ECGs, cardiac function by echocardiography/MUGA scan, urine dipstick, and Lansky play scores or Karnofsky

performance scores, and their changes or shifts from baseline will be summarized using descriptive statistics, as appropriate. Summary of study drug exposure will be provided. Prior and concomitant medications, medical/surgical history and subject demographics will be summarized.

Interim Analyses

For each disease cohort (Ewing sarcoma/pPNET, rhabdomyosarcoma, and HGG) in Phase 2, there will be 1 futility analysis: this is planned for after the first 10 evaluable subjects have completed the Week 16 tumor assessment (or discontinued before Week 16). At the futility analysis, if there are no responders (CR/PR), then the enrollment for that cohort will be discontinued for lack of efficacy. If 1 or more responses are observed, the accrual will continue.

Independent data monitoring committee (IDMC)

Safety monitoring will be conducted by an independent data monitoring committee (IDMC). The frequency of safety reviews will be defined in the IDMC charter. Minutes from the open meetings of the IDMC will be provided if requested by regulatory agencies. The function and membership of the IDMC will be described in the IDMC charter.

Sample Size Rationale

Phase 1 – Determination of the Maximum Tolerated Dose: The total number of subjects required for the Phase 1 portion of this study will depend upon the toxicities observed as the study progresses. The minimum number of evaluable subjects required is 4. The projected maximum number of evaluable subjects required is 48. Once the MTD or RP2D has been defined, up to 6 additional subjects with recurrent or refractory solid tumors may be enrolled to acquire PK data in a representative number of young subjects. Therefore, a maximum of 54 subjects are expected to be enrolled in the 4 dose escalation levels, and PK expansion. The Phase 1 part of the study is expected to be completed within 18 months. In the event that each of Dose Levels -1, 1, 2, and 3 are expanded to 12 subjects, an absolute maximum of 54 subjects would be required allowing for 20% to be non-evaluable and including up to 6 additional subjects for PK analysis.

Phase 2: Phase 2 will require a minimum of 10 evaluable subjects per disease cohort and a maximum of 20 (10 evaluable subjects in each stage of Simon's optimal 2-stage design). Therefore, a maximum of 22 subjects per cohort will be enrolled to allow for a 10% non-evaluable rate. This design has 88% power to detect a 20% increase in the response rate at the significance level of one-sided alpha = 0.07 assuming a null response rate of 5% and alternative response rate ≥25%.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ß-hCG	beta-human chorionic gonadotropin
BOR	best overall response
BP	blood pressure
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
IDMC	Independent Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
FDA	Food and Drug Administration
FGF(R)	fibroblast growth factor (receptor)
GCP	Good Clinical Practice
HGG	high grade glioma
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

Abbreviation	Term
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MUGA	multigated acquisition
ORR	objective response rate
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
pPNET	peripheral primitive neuroectodermal tumor
PR	partial response
PRES/RPLS	Posterior Reversible Leukoencephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome
PSC	Protocol Steering Committee
QTc	corrected QT interval
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RTK(I)	receptor tyrosine kinase (inhibitor)
SAE	serious adverse event
SD	stable disease
SmPC	Summary of Product Characteristics
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor (receptor)
XRT	radiotherapy

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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP), Section 3, and any local regulations (eg, Code of Federal Regulations, Title 21 CFR Part 56 or European Union [EU] Clinical Trials Directive 2001/20/EC). 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(s) [CRA(s)], 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 within 90 days. The definition for end of the study is the date of data cutoff for the final analysis or last subject/last visit including discontinuation from the study for any reason, whichever occurs later. Subjects who remain on treatment at the cutoff for the final analysis will continue receiving the same treatment in consecutive cycles as long as they do not meet any of the study discontinuation criteria as detailed in the protocol.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar 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, 2013
- 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 Harmonisation of of Technical Requirements for Pharmaceuticals for Human Use

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities 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 (or subject's parent[s] or 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 should be given by means of a standard written statement, written in nontechnical language. The subject (or subject's parent[s] or legally authorized representative) 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, Title 21 CFR Part 50 or EU Clinical Trials Directive 2001/20/EC) 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 while on study, and becomes competent to give informed consent, his/her consent will be obtained using separate ICFs to continue on the study.

With regard to the pharmacogenomic assessments described in Section 9.5.1.4.2, an informed consent for collection of samples during the study for gene analysis will be prepared separately. Subjects may still be eligible to enroll in the study if they do not give informed consent for gene analysis.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 60 sites: 20 sites for the Phase 1 portion and an additional 40 sites for the Phase 2 portion.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organizations (CROs) are listed in Investigator Study File provided to each site.

7 INTRODUCTION

Solid tumors make up about 30% of all cancers in children. Current strategies for treatment of solid tumors in children have greatly improved in the last few decades. The success of curing nearly 80% of children diagnosed with cancer is tempered by the inability to cure the remaining 20% with conventional approaches. There remains a significant unmet medical

need for more effective treatment options with a manageable safety profile and for identifying biomarkers to more accurately diagnose these tumors and determine the level of risk in pediatric patients with solid tumors.

Some of the most common types of solid tumors found in children are brain tumors, rhabdomyosarcoma, and Ewing sarcoma/peripheral primitive neuroectodermal tumor (pPNET).

High grade gliomas (HGGs) represent approximately 8–12% of all pediatric central nervous system (CNS) tumors. The overall total incidence of HGG (including anaplastic astrocytoma, anaplastic oligodendrioglioma, glioblastoma, mixed glioma, and malignant glioma) among children 0-19 years old is approximately 0.85 per 100,000 (CBTRUS 2012). The distribution of HGGs between males and females is relatively equal (Finlay, et al., 2005). Pediatric HGGs are very aggressive and malignant lesions. Initial treatment strategies typically consist of a gross total resection when feasible followed by focal radiotherapy combined with chemotherapy. Despite improvements in neurosurgery, radiotherapy, and chemotherapy, the outcome for children with HGG remains poor. No effective chemotherapy regimens have been identified for any pediatric HGG (MacDonald, et al., 2011). Two-year survival rates range from 10% to 30%.

Rhabdomyosarcoma is the most common soft tissue sarcoma in children, with approximately 350 new cases diagnosed each year in the US among the population age group between 0 and 19 years (Linet, et al., 1999). There is slight male predominance, and approximately two-thirds of the cases are diagnosed in children younger than 6 years of age (Dasgupta, et al., 2012). Rhabdomyosarcoma usually manifests as an expanding mass in different body locations. The most common primary tumor sites include the head and neck region (35%), followed by the genitourinary and extremity primaries (Pappo, et al., 1995). In patients with localized disease, overall 5-year survival rates are over 80% with the combined use of surgery, radiation therapy, and 3-drug chemotherapy of vincristine, actinomycin D, and cyclophosphamide (VAC). However, in patients with metastatic disease, little progress has been made in survival rates, with a 5-year, failure-free survival rate of less than 30% (Egas-Bejar, et al., 2014).

Ewing's sarcoma/pPNET also called Ewing's sarcoma family of tumors (ESFT) constitutes 5% to 10% of primary bone tumors (Gurney, et al., 1999). It occurs predominantly in children and young adults and shows a slight predominance for males. Ewing's sarcoma/pPNET is very rare with an incidence of just less than 3 per 1 million people under 20 years of age (Esiashvili, et al., 2008). It occurs most frequently in the pelvis, long bones of the legs or arms, chest wall, spine and the skull. The first line treatment consists of neoadjuvant chemotherapy followed by local control surgery (which frequently involves limb-sparing surgery with prosthetic reconstruction) with or without radiation, followed by adjuvant chemotherapy. Chemotherapy involves a 5-drug regimen of vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide in 2-3 weeks intervals (VDC-IE). Presence of metastases is the most prominent adverse prognostic factor in Ewing's sarcoma/pPNET. Metastases at diagnosis are detected in 15% to 33% of patients,

with survival rates from 9% to 41%, as compared with the survival expectancy of patients with localized disease of approximately 70% (Ladenstein, et al., 2010).

7.1 Scientific Rationale for the Combination of Lenvatinib with Everolimus

Angiogenesis is vital for the growth and metastatic behavior of malignant solid tumors. Vascular endothelial growth factor (VEGF) is critical to both physiologic and pathologic angiogenesis, and ligand-binding to VEGF receptor (VEGFR1-3) has been shown to drive tumor growth and facilitate metastasis (Ferrara, et al., 2002). VEGFR-predominating receptor tyrosine kinase inhibitors (RTKIs) have emerged as successful anticancer agents, with numerous Food and Drug Administration (FDA) approved drugs in class, and several indications for renal and hepatic carcinomas, thyroid cancer and soft tissue sarcoma (Brose, et al., 2014; van der Graaf, et al., 2012; Llovet, et al., 2008; Escudier, et al, 2007; Motzer, et al., 2007). RTKIs have consistently demonstrated anti-tumor activity in preclinical models of pediatric solid tumors, notably rhabdomyosarcoma, Ewing sarcoma, and neuroblastoma models (Maris, (a) et al., 2008; Maris, (b) et al., 2008). Factors limiting the clinical efficacy of RTKIs in pediatric tumors to date may include the early acquisition of drug resistance, tumor heterogeneity, and utilization of alternative survival pathways in tumors. Classic resistance to RTKIs include secondary mutations that disrupt target binding, increased RTK expression, increased ligand expression, increased drug efflux, and altered drug metabolism pathways (Engelman, et al., 2008), and altered energy (glucose) metabolism (Hudson, et al., 2014).

Lenvatinib is a potent multiple RTKI that selectively inhibits VEGFRs (VEGFR1 [FLT1], VEGFR2 [KDR], VEGFR3 [FLT4]) in addition to other pro-angiogenic and oncogenic pathway-related RTKs, including fibroblast growth factor (FGF) receptors FGFR1-4, platelet-derived growth factor (PDGF) receptor α, KIT, and RET. Lenvatinib has potent anti-angiogenic properties not only towards VEGF-driven angiogenesis and lymphangiogenesis but also towards FGF-driven angiogenesis. Through established VEGF- and FGF-dependent angiogenesis mouse models, lenvatinib significantly inhibited both VEGF- and FGF-induced in vivo angiogenesis in a dorsal air sac assay at doses of 10 and 30 mg/kg (Ichikawa, et al., 2015; Yamamoto, et al., 2014). A subset of glioblastomas harbor oncogenic chromosomal translocations involving the in-frame fusion of the tyrosine kinase domains of FGFR1 or FGFR3 with TACC genes which result in constitutive kinase activity (Parker, et al., 2013; Singh, et al., 2012). Treatment of in vivo models harboring the FGFR-TACC fusions with an FGFR inhibitor prolongs survival suggesting a role for FGFR-targeted therapies in high grade CNS tumors. The studies also demonstrated activating recurrent hotspot mutations and intragenic duplications of the tyrosine kinase domain of FGFR1 in pediatric pilocytic astrocytomas and diffuse pediatric gliomas respectively providing further rationale for exploring agents targeting FGFR (Zhang, et al., 2013; Jones, et al., 2013).

In addition to the anti-proliferative activity of lenvatinib, target engagement of the FGFR signaling pathway has been evaluated in both in vitro and in vivo models (Tohyama, et al., 2014). Lenvatinib treatment at doses as low as 3 mg/kg and 10 mg/kg demonstrated a

decrease in phosphorylation of FRS2 levels in the RO82-W-1 xenograft model (Tohyama, et al., 2014). These results demonstrate that lenvatinib effectively engages and inhibits the FGFR signaling pathway in vitro and in vivo which contributes to the observed anti-tumor activity of lenvatinib. Further in vitro and in vivo studies confirm the inhibition of FGFR1 and downstream targets including MEK and Erk (Nakazawa, et al., 2015).

FGF ligand levels, such as FGF23, may be useful biomarkers for FGFR inhibition by lenvatinib (Ichikawa, et al., 2015). FGF23, a protein hormone regulating mineral metabolism, is a potential pharmacodynamics (PD) marker for FGFR inhibition in vivo, since plasma levels are elevated as a compensatory response to FGFR inhibition (Wohrle, et al., 2011; Kim, et al., 2011). Plasma FGF23, was significantly increased (2.6-fold, compared to vehicle control) in mice 24 hours after a single oral administration of lenvatinib mesylate (10 mg/kg) (Ichikawa, et al., 2015). Inhibition of multiple receptors is also postulated as a mechanism to decrease the rate of drug resistance to anti-angiogenic therapy (Sonpavde, et al., 2012).

Lenvatinib showed a favorable profile for combination in preclinical studies on 5 human osteosarcoma tumor xenograft models demonstrating that lenvatinib enhances the anti-tumor activity of conventional cytotoxic chemotherapy with ifosfamide and etoposide (IE) (Matsuki, et al., 2016). Lenvatinib also appears to be effective in sensitizing chemo-resistant osteosarcoma models. Gene expression profiling studies (RNAseq analysis) conducted on 5 human pediatric osteosarcoma xenograft models identified genes and signaling pathways associated with tumor response to the combination treatment (Lenvatinib + Ifosfamide + Etoposide) (Dezso, et al., 2016). Genes included in these pathways were related to cell differentiation, RTKs, and angiogenic and pro-oncogenic pathways. These genes and signaling pathways may be relevant targets of lenvatinib and everolimus, and have all been demonstrated to play key roles in the pathogenesis of pediatric sarcomas and HGGs (Pressey, et al., 2011; Oue, et al., 2010; Matushansky, et al., 2008). For example, activation of Wnt/β-catenin, SHH/PTCH/GLI1, BMP/TGF, and the HGF/MET axes have all been implicated in the development and progression of several soft tissue sarcomas and gliomas (Lin and Chen, 2014; Graveel, et al., 2013; Yoshikawa, et al., 2004;). The hyperactivation and overexpression of these pathways may also play critical roles in the development of chemoresistance (WNT5A) and can serve as prognostic biomarkers (FGF23, BMP2/4) (Hung, et al., 2014; Yoshikawa, et al., 2004;).

An alternative angiogenic pathway is mediated by mammalian target of rapamycin (mTOR). mTOR is a serine/threonine kinase involved in integrating growth factor-activated and nutrient-sensing signals which regulate diverse cellular processes including growth, survival, differentiation, autophagy and metabolism (Shimobayashi, et al., 2014). Deregulation of mTOR signaling has been described for numerous cancer types and familial cancer syndromes. mTOR activation can result from the overexpression or presence of activating mutations in RTKs such as insulin like growth factor 1 receptor (IGF-1R), FGFR, or epidermal growth factor receptor (EGFR) and has been described in different solid tumors including various sarcoma subtypes and gliomas (Wan, et al., 2005). Similarly, downstream mutations or overexpression of PI3K and Akt, or loss of tumor suppressor protein function,

have been associated with various tumors and cancer predisposition syndromes due to the aberrant activation of the TSC-Rheb-mTOR axis (Engelman, et al., 2006).

Everolimus is an oral rapamycin analogue that forms a complex with FK506 Binding Protein-12 (FKBP12) and acts as a highly selective allosteric inhibitor of the mTOR complex 1 (mTORC1) causing the dissociation of regulatory-associated protein of mTOR (Raptor) and loss of mTORC1 substrate interactions (Chiarini, et al., 2015). Everolimus has been FDA-approved for the treatment of various cancers including advanced renal carcinoma, unresectable neuroendocrine pancreatic adenocarcinoma, and advanced estrogen receptor-positive/HER2$^-$ breast carcinoma. Most notably, everolimus has a pediatric specific approval for the treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (Franz, et al., 2012; Krueger, et al., 2010;). The anti-tumor effects of everolimus have also been demonstrated in a number of in vitro and in vivo models of sarcomas including synovial sarcoma, osteosarcoma, chondrosarcoma, and leiomyosarcoma (Yasui, et al., 2014; Pignochino, et al., 2013; Perez, et al., 2012; Hernando, et al., 2007). These results provide a strong biologic rationale for further evaluating the role of everolimus in pediatric solid tumors.

Proangiogenic signaling pathways (VEGF, FGF) cooperate with mTOR-mediated regulation of cell growth and maintenance to drive the development of pediatric solid tumors. The agents that target both the proangiogenic pathways and mTOR signaling are attractive candidate agents for study. Combinations of molecularly targeted agents guided by the genetics and biology of sarcoma may aid in overcoming the resistance that is inevitable with single-agent therapy by blocking several pathways critical to cancer progression. This can be achieved by simultaneous inhibition of several mediators (eg, simultaneous inhibition of VEGF, FGF, platelet derived growth factor) or targeted inhibition at several levels within the same pathway (eg, inhibition of VEGF/mTOR/HIF). Thus, a multi-target therapeutic approach may help overcome drug resistance leading to enhanced and prolonged efficacy. Indeed, combined VEGF and mTOR pathway inhibition has shown promise in preclinical solid tumor models (Molhoek, et al., 2008; Ikezoe, et al., 2006).

Combination of the multi-RTKI sorafenib and the mTOR inhibitor, everolimus, has shown enhancement of the anti-angiogenic, anti-proliferative, and pro-apoptotic effects of RTK inhibition in various in vitro and in vivo solid tumor models including pancreatic cancer, hepatocellular carcinoma, mesothelioma, and osteosarcoma (Pignochino, et al., 2015; Pignochino, et al., 2013; Pawaskar, et al., 2013; Piguet, et al., 2011;).

The combination of lenvatinib with everolimus has also been shown to exert a significantly higher anti-tumor effect compared to either agent alone in mouse models of renal cell carcinoma (Adachi, et al., 2016). In xenograft models of Ewing sarcoma and osteosarcoma, the lenvatinib-everolimus combination was more potent in abrogating tumor growth than either agent alone (Eisai Co. Ltd. Data on File).

Overcoming RTKI-induced resistance has been shown to be effectively accomplished by inhibiting alternative survival pathways. In preclinical studies, sensitivity of lenvatinib-resistant tumor xenograft models was restored after sequential treatment with the

dual-RTKI, golvatinib which targets not only VEGFR, but also c-MET (Nakagawa, et al., 2014). mTOR inhibition is anticipated to abrogate several alternative survival pathways providing biologic rationale for combined treatment with lenvatinib and everolimus (Yasui, et al., 2014; Etnyre, et al., 2014; Imura, et al., 2014).

A preclinical study of lenvatinib plus everolimus demonstrates enhanced inhibition of VEGF and FGF-induced angiogenesis than for either agent alone in human endothelial cell models (Mitsuhashi, et al., 2016). The combination also showed synergistic enhancement against bFGF-driven angiogenesis, distinguishing this from other VEGFR2 tyrosine kinase inhibitors (TKIs). Effects of lenvatinib, everolimus, and its combination on VEGF or bFGF activated intracellular signaling were analyzed in human umbilical vein endothelial cells (HUVEC) by western blotting. Lenvatinib inhibited the VEGF or bFGF-driven phosphorylation of Erk1/2 (Thr202/Tyr204), S6K (Thr389), and S6K (Thr421/Ser424), and S6 (Ser235/Ser236), indicating the inhibition of both the MAPK pathway and the mTOR-S6K-S6 pathway. Everolimus inhibited the phosphorylation of S6K (Thr389), S6K (Thr421/Ser424), and S6 (Ser235/Ser236), but not Erk1/2. The combination showed greater inhibition for the phosphorylation of S6K (Thr421/Ser424) and S6 (Ser235/Ser236) than each single agent. Combination effects of lenvatinib and everolimus on VEGF and bFGF-induced proliferation or tube formation of human umbilical vein endothelial cells (HUVEC) were examined using combination indexes. Inhibitory activity of the combination at several molar ratios was mostly additive for VEGF-driven proliferation (combination index: 0.799-1.167) and mostly synergistic for bFGF-driven tube formation (combination index: 0.469-0.741). Antitumor activities were tested in the KP-1/VEGF or KP-1/FGF models, where VEGF or FGF-induced tumor angiogenesis and tumor growth were enhanced in nude mice due to overexpressed VEGF or FGF in human pancreatic cancer KP-1cells (Mitsuhashi, et al., 2016). In the KP-1/VEGF or KP-1/FGF xenograft models, lenvatinib, everolimus, and the combination (orally, once daily x 14) significantly inhibited tumor growth compared to vehicle. In addition the combination of lenvatinib (7.5 mg/kg) and everolimus (15 mg/kg) showed significantly greater antitumor activity than higher dose of either lenvatinib (10 mg/kg) or everolimus (30 mg/kg) monotherapy. The vertical inhibition of angiogenic signaling pathways with lenvatinib (RTK) and everolimus (mTOR) may contribute to enhanced antiangiogenic activity by dual targeting of the mTOR-S6K-S6 pathway.

In addition to the results obtained in the extensive in vitro and in vivo pre-clinical studies, the strong rationale for pediatric evaluation of the combination of lenvatinib and everolimus is the positive randomized trial in renal cell carcinoma resulting in FDA approval of lenvatinib combination with everolimus for patients with advanced renal cell carcinoma following 1 prior antiangiogenic therapy.

7.2 Clinical Results Obtained with Combination Lenvatinib plus Everolimus Treatment

The safety and efficacy of lenvatinib and everolimus combination treatment was investigated in the randomized, multi-center, open-label trial E7080-G000-205 (Study 205) in subjects with unresectable, advanced or metastatic RCC. In the Phase 1b portion the recommended

Phase 2 dose (RP2D) for the lenvatinib/everolimus combination was determined as lenvatinib 18 mg plus everolimus 5 mg administered daily.

The Phase 2 portion enrolled subjects with advanced or metastatic, clear-cell, renal cell carcinoma who had a history of receiving one prior VEGF agent. A total of 153 subjects were randomized in a 1:1:1 ratio to receive treatment with lenvatinib (18 mg) plus everolimus (5 mg), lenvatinib (24 mg), or everolimus (10 mg) administered once daily.

The primary analysis demonstrated median PFS for lenvatinib of 7.4 months (5.6-10.2, 95% confidence interval [CI]) vs everolimus 5.5 months (3.5-7.1) vs combination 14.6 months (5.9-20.1) with a hazard ratio (HR) of combination vs everolimus of 0.40 (0.24-0.68; p = 0.0005) and HR of lenvatinib vs everolimus of 0.61 (0.38-0.98; p = 0.0479). The objective response rate (ORR) for lenvatinib was 27% (16-41), everolimus 6% (1-17%), and combination 43% (29-58%) with a median duration of objective response of lenvatinib 7.5 months (3.8-not estimable), everolimus 8.5 months (7.5-9.4), and combination 13.1 months (3.8-not estimable). The ORR ratio between combination vs everolimus was 7.2 (2.3-22.5; p <0.0001) and lenvatinib vs everolimus was 4.5 (1.4-14.7; p = 0.0067). Updated overall survival analysis suggests a survival benefit for the combination over everolimus with an overall survival for lenvatinib of 19.1 months (13.6-26.2), everolimus 15.4 months (11.8-19.6), and the combination of 25.5 months (16.4-not estimable). The HR for combination vs everolimus is 0.51 (0.30-0.88; p = 0.024) and 0.68 for lenvatinib vs everolimus (0.41-1.14; p = 0.118) in support of a potential survival benefit with combination therapy (Motzer, et al., 2015).

The average duration of therapy for lenvatinib was 7.4 months (range 0.1-23.0), everolimus 4.1 months (0.3-20.1), and combination 7.6 months (0.7-22.6). The reported Grade 3/4 AEs included diarrhea, fatigue/asthenia, vomiting, nausea, hypertension, decreased weight and dyspnea. Discontinuations due to AEs were as follows: lenvatinib 25%, everolimus 12%, and combination 24%. The rates of AEs were generally higher for the combination arm, but they were predictable and generally managed with concomitant medication and dose modifications.

7.3 Pediatric Studies with Lenvatinib

The safety, tolerability, and activity of lenvatinib in pediatric population is being evaluated in an ongoing Phase 1/2 study E7080-G000-207 (Study 207) of lenvatinib in children and adolescents with refractory or relapsed solid malignancies. During Phase 1 portion of the study, the maximum tolerated dose (MTD) and a recommended dose of lenvatinib as a single agent in this subject population was identified. The Time-to-Event Continuous Reassessment Method (TiTE-CRM) was used to identify the recommended dose of lenvatinib (Cheung, et al., 2000). Twenty three subjects were enrolled across 3 dose groups. Three of those subjects were treated at 11 mg/m^2, 9 subjects were treated at 14 mg/m^2, and 11 subjects were treated at 17 mg/m^2. Twenty of 23 enrolled subjects were evaluable for dose-limiting toxicity (DLT) assessment. Three DLTs were reported at dose level 14 mg/m^2, including alanine aminotransferase (ALT) increase (Grade 3), hypertension (Grade 3), and hypertension (Grade 4). The Protocol Steering Committee (PSC) confirmed that the 14

mg/m^2 was the recommended dose for single agent lenvatinib in children and adolescents with refractory or relapsed solid tumors (Eisai Co Ltd Data on File). Phase 2 portion of Study 207 evaluating lenvatinib as a single agent or lenvatinib in combination with ifosfamide and etoposide in children and adolescents with osteosarcoma and ^{131}I-refractory differentiated thyroid cancer is ongoing.

7.4 Study Rationale

There remains a significant unmet medical need for more effective treatment options for pediatric subjects with solid tumors. Overall solid tumors make up to 30% of all cancers in children. Approximately 80% of these tumors are cured with conventional approaches. This study will be performed on pediatric subjects with solid tumors, which were resistant to conventional therapy, and for whom there are no alternative therapies that might lead to cure.

The proposed multicenter, Phase 1/2 study (E7080-G000-216) will determine (in Phase 1 portion) a MTD and RP2D of lenvatinib administered in combination with everolimus. Phase 2 portion will estimate the antitumor activity, safety and tolerability of the lenvatinib and everolimus combination in pediatric subjects with recurrent/refractory solid tumors including HGG, rhabdomyosarcoma, and Ewing's sarcoma/pPNET.

The initial dose level (Dose Level 1) for lenvatinib will be 11 mg/m^2, which is approximately 80% of lenvatinib single dose MTD in pediatric subjects determined in the ongoing Study 207. The initial dose of everolimus will be 3 mg/m^2, which is 66% of the FDA approved dose and a dose previously found to be effective in subependymal giant cell astrocytoma (SEGA), as per everolimus package insert (Afinitor package insert).

Due to a lower starting dose determined for adult subjects with hepatocellular cancer (HCC): 12 mg (baseline body weight [BW] ≥60 kg) or 8 mg (baseline BW <60 kg) given once daily for the Phase 3 study in subjects with HCC, as opposed to the approved dose of lenvatinib monotherapy in adult subjects with differentiated thyroid cancer, which is 24 mg once daily, subjects with hepatoblastoma will be excluded from participation in this study.

8 STUDY OBJECTIVES

8.1 Primary Objectives

- **Primary Objectives for Phase 1**
  a. To determine maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of lenvatinib administered in combination with everolimus, once daily to pediatric subjects with recurrent/refractory solid tumors.
  b. To describe the toxicities of lenvatinib administered in combination with everolimus once daily to pediatric subjects with recurrent/refractory solid tumors.
- **Primary Objective for Phase 2**
  a. To estimate the antitumor activity of lenvatinib in combination with everolimus in pediatric subjects with selected recurrent/refractory solid tumors including Ewing

sarcoma/pPNET, rhabdomyosarcoma, and HGG using objective response rate (ORR) at Week 16 as the outcome measure.

8.2 Secondary Objectives

- **Secondary Objectives for Phase 1**
  a. To preliminarily define the antitumor activity of lenvatinib in combination with everolimus in pediatric subjects with recurrent/refractory solid tumors.
  b. To characterize the pharmacokinetics (PK) of oral lenvatinib and everolimus, when administered in combination to pediatric subjects with recurrent/refractory solid tumors.
- **Secondary Objectives for Phase 2**
  a. To assess other response variables including ORR at the time of data cutoff, disease control rate (DCR), clinical benefit rate (CBR), and duration of response (DOR).
  b. To evaluate the tolerability and safety profile of lenvatinib in combination with everolimus in pediatric subjects with recurrent/refractory Ewing sarcoma/pPNET, rhabdomyosarcoma, and HGG.
  c. To characterize the PK of lenvatinib and everolimus, when administered in combination to children with recurrent/refractory Ewing sarcoma/pPNET, rhabdomyosarcoma, and HGG.

8.3 Exploratory Objectives

- **Exploratory Objectives for Phase 1 and Phase 2**
  a. To evaluate blood, tumor, and safety (eg, hypertension) markers as correlative biomarkers of treatment effects and outcomes of lenvatinib in combination with everolimus.
  b. To assess candidate alterations in genes and/or proteins that may contribute to tumor development and serve as predictive markers of response in archival tumor tissue from pediatric subjects.
  c. To explore relationships between lenvatinib exposure and safety (eg, AEs of special interest).

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, open-label, Phase 1/2 study of lenvatinib in combination with everolimus in pediatric subjects with relapsed or refractory solid tumors. The overall study design is depicted in Figure 1.

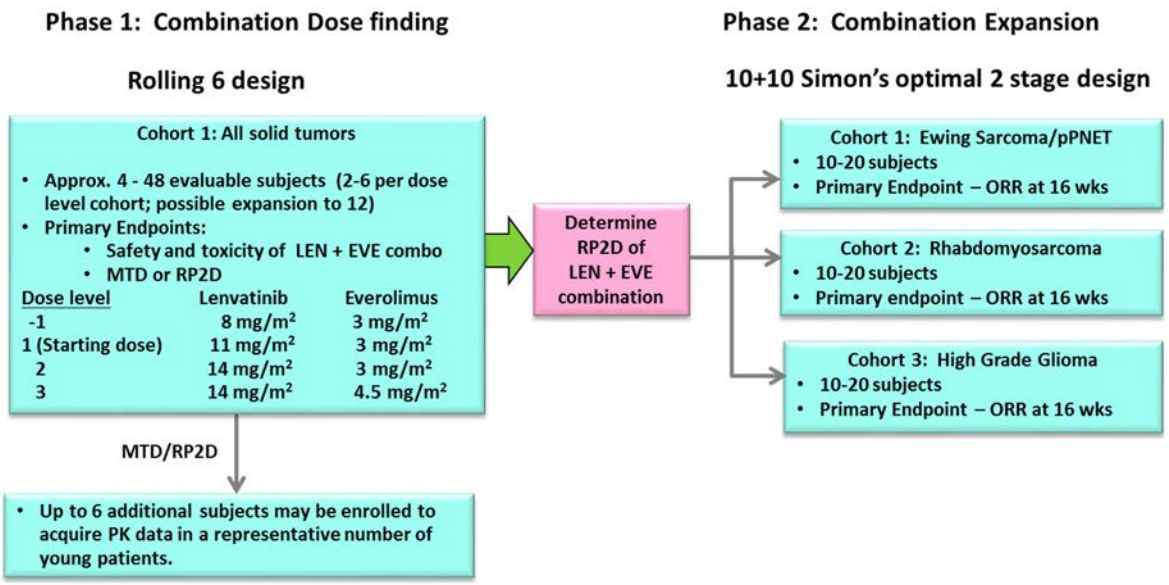


Figure 1 Study Design

EVE = everolimus, LEN = lenvatinib, MTD = maximum tolerated dose, ORR = objective response rate, PK = pharmacokinetic, pPNET = peripheral primitive neuroectodermal tumor, RP2D = recommended Phase 2 dose.

Phase 1 Dose Escalation and Determination of the MTD

The Phase 1 component is a dose escalation study with treatment in sequential cohorts of escalating doses of lenvatinib in combination with everolimus, each administered once daily in 28-day treatment cycles. Pediatric subjects with a relapsed/refractory solid malignancy, including primary brain tumors are eligible to enroll. The initial dose level (Dose Level 1) for lenvatinib will be 11 mg/m^2. The initial dose of everolimus will be 3 mg/m^2. Dose Level 2 will escalate lenvatinib by approximately 25% to 14 mg/m^2 and maintain everolimus at the same dose of 3 mg/m^2. At Dose Levels -1 and 1, maximum daily dose of lenvatinib will not exceed 18 mg daily. At Dose Level 2, maximum daily dose of lenvatinib allowed will not exceed 24 mg. Should Dose Level 2 be well tolerated, Dose Level 3 may be considered to test lenvatinib at 14 mg/m^2 (capped at 24 mg) and escalate everolimus to 4.5 mg/m^2. For everolimus dose levels of 3 mg/m^2 and 4.5 mg/m^2, the maximum daily dose of everolimus will not exceed 5 mg and 7 mg, respectively. If the MTD for combination of lenvatinib and everolimus has been exceeded at Dose Level 1, then the subsequent cohort of subjects will be treated at Dose Level -1 with dose of lenvatinib 8 mg/m^2 and dose of everolimus 3 mg/m^2 (Table 1). Intra-subject titration of everolimus will not be allowed on this study.

At study entry, subjects must have a minimum BSA of 0.6 m^2.

Table 1 Planned Dose-Escalation

Dose Level	Lenvatinib mg/m^2 (% Single-Agent MTD)	Everolimus (mg/m^2)
-1	8 (60% MTD)[a]	3[c]
1*	**11 (80% MTD)[a]**	**3[c]**
2	14 (100% MTD)[b]	3[c]
3[d]	14 (100% MTD)[b]	4.5[e]

MTD = maximum tolerated dose
*Starting dose level
a: Lenvatinib dose capped at 18 mg daily.
b: Lenvatinib dose capped at 24 mg daily.
c: Everolimus dose capped at 5 mg daily.
d: Dose Level 3 may be considered if Dose Level 2 is well tolerated.
e: Everolimus dose capped at 7 mg daily.

The Phase 1 portion of the study will utilize a rolling 6 design (Skolnik, et al., 2008). Two to 6 subjects can be concurrently enrolled into a dose level cohort.

Dose level assignment will be based on:

1. the number of subjects currently enrolled in the dose level cohort,
2. the number of DLTs observed, and
3. the number of subjects at risk for developing a DLT (ie, subjects enrolled but who are not yet assessable for toxicity).

For example, when 3 subjects are enrolled onto a dose cohort, if toxicity data is available for all 3 when the fourth subject entered and there are no DLTs, the dose will be escalated and the fourth subject will be treated at the subsequent dose level. If data is not yet available for 1 or more of the first 3 subjects and no DLT has been observed, or if one DLT has been observed, the new subject will be treated at the same dose level. Lastly, if 2 or more DLTs have been observed, the dose level will be de-escalated. This process will be repeated for Subjects 5 and 6. In place of suspending accrual after every 3 subjects, accrual will be suspended when a cohort of 6 potentially evaluable subjects has enrolled (ie, subjects enrolled but are not yet assessable for toxicity) or when the study endpoints have been met. When subjects are not evaluable for toxicity, they will be replaced with the next available subject if escalation or de-escalation rules have not been fulfilled at the time the next available subject is enrolled in the study.

The following table (Table 2) provides the decision rules for enrolling a subject at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

Table 2 The Rolling 6 Design

# Subjects Enrolled	# Subjects with DLT	# Subjects without DLT	# Subjects with Data Pending	Decision
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

DLT = dose-limiting toxicity
*If 6 subjects already entered at next lower dose level, the maximum tolerated dose (MTD) has been defined.
**If final dose level has been reached, the recommended dose has been reached.

If 2 or more of a cohort of up to 6 subjects experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped. In the event that 2 DLTs observed out of 6 evaluable subjects are of different classes of Adverse Effects (eg, hepatotoxicity and myelosuppression), expansion of the cohort to 12 subjects will be considered (if one of the DLTs does not appear to be dose-related, the Adverse Effects are readily reversible, **AND** Protocol Steering Committee (PSC) **AND** sponsor all agree that expansion of the cohort is acceptable). Subjects who on PSC review are not deemed to be evaluable for DLT assessment may be replaced.

All subjects in the Phase 1 Dose Escalation phase will have samples taken for PK analysis with the intent at the end of Phase 1 of having evaluable PK data from minimally 6 subjects aged 2 to <6 years old, 6 subjects ≥6 to <12 years old, and 6 subjects ≥12 years old. Once the MTD or RP2D has been defined, 0 to 6 additional subjects will be enrolled to attain the goal of having evaluable PK data from minimally 6 subjects aged 2 to <6 years old, 6 subjects ≥6 to <12 years old, and 6 subjects ≥12 years old.

Protocol Steering Committee

The sponsor will closely evaluate the risks and benefits of the study throughout its conduct, along with the PSC as needed. The PSC may review available relevant data: DLT and safety data including laboratory assessments, 12-lead electrocardiograms (ECGs), dose administration, etc.

Toxicity Monitoring

The DLT observation period for the purposes of dose-escalation will be the first cycle of therapy. Routine Phase 1 monitoring for clinical and laboratory toxicities will be used. Blood pressure (BP) monitoring will occur at least weekly during the first 2 cycles.

Dose-Limiting Toxicity

Dose-limiting toxicity will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and is defined as any of the following events that are possibly, probably, or definitely attributable to lenvatinib or everolimus. Dose-limiting hematological and non-hematological toxicities are defined differently.

A. Non-hematological DLT:

- Any Grade 3 or greater non-hematological toxicity attributable to the investigational drug with the specific **exclusion** of:
  - Grade 3 nausea and vomiting <3 days duration
  - Grade 3 diarrhea <3 days duration
  - Grade 3 weight loss
  - Grade 3 liver enzyme elevation, including ALT/aspartate aminotransferase (AST)/ gamma glutamyl transferase (GGT)/ bilirubin/alkaline phosphatase that returns to Grade ≤1 or baseline within 7 days
  - Grade 3 asymptomatic elevation in amylase or lipase that returns to Grade ≤1 or baseline within 7 days
  - Grade 3 elevation in triglycerides that returns to Grade ≤1 or baseline within 7 days
  - Grade 3 or 4 fever <5 days duration
  - Grade 3 infection <5 days duration
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation
  - Grade 3 proteinuria (UPC) ratio >1.9 unless confirmed with a second measurement within 72 hours
  - Grade 3 headache <3 days duration responsive to optimal management.

- Any Grade 2 non-hematological toxicity that persists for ≥7 days and is considered sufficiently medically significant or sufficiently intolerable by subjects despite optimal supportive care that it requires treatment interruption.
- Any dose interruption or reduction due to toxicity which results in administration of less than 75% of the planned dosage of lenvatinib and/or everolimus.
- Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a DLT.
- **Dose-limiting hypertension**:
  - Any Grade 4 hypertension

Confirmed systolic or diastolic BP more than 25 mmHg above 95th percentile for sex, age, height/length, or an elevated diastolic BP (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 2 antihypertensive ingredient medications will be considered a single antihypertensive medication.

B. Hematological DLT:

- In subjects evaluable for hematological toxicity, DLT is defined as:
  - Grade 4 thrombocytopenia (platelet count <25,000/mm^3) or Grade 4 neutropenia, not due to malignant infiltration.
- Any ≥Grade 2 arterial thromboembolic events (including cerebrovascular ischemia, peripheral or visceral arterial ischemia).
- Note: Grade 3 or 4 febrile neutropenia will not be considered 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 the Eisai Medical Monitor in consultation with the PSC, as needed. Subjects who discontinue the study treatment for any reason other than DLT (eg, early disease progression) during Cycle 1 (Day 1 to Day 28), and have not received at least 75% of the prescribed dose prior to discontinuation, will be replaced.

The sponsor and PSC will review all subjects' safety and clinical data to jointly determine the MTD/RP2D of the combination of lenvatinib with everolimus. The Treatment Phase for each subject in Phase 1 ends after completing Cycle 1 of treatment unless subject discontinues early. Those subjects who discontinue study treatment in Cycle 1 transition to the Off-treatment Visit. Those who complete Cycle 1 will transition to the Extension Phase. Study treatment and tumor assessments will continue during the Extension Phase.

Phase 2 Cohorts

Once the MTD/RP2D of the combination of lenvatinib and everolimus in pediatric population has been determined in Phase 1, the Phase 2 portion of this pediatric study will commence with Cohort 1 (recurrent or refractory Ewing sarcoma/pPNET), Cohort 2 (recurrent or refractory rhabdomyosarcoma), and Cohort 3 (recurrent or refractory HGG), opening to accrual.

Cohorts 1 – 3

Phase 2 Cohorts 1 to 3 will use a 10+10 Simon's optimal 2-stage design for each cohort; 10 evaluable subjects will be enrolled to each stage. The Sponsor will closely monitor enrollment to ensure that at least 50% of subjects enrolled in each cohort are <18 years of age at the time of informed consent. The primary outcome measure for Ewing sarcoma/pPNET, rhabdomyosarcoma, and HGG will be ORR (complete or partial response) at 16 weeks. If there are no responses among the 10 subjects in Stage 1, then the enrollment to that disease cohort will stop and conclude that the lenvatinib/everolimus combination therapy does not elicit a response in that disease cohort. If there is at least 1 response in the first stage, then the second stage will enroll 10 additional evaluable subjects. If there are 2 or fewer responses among the 20 evaluable subjects, then lenvatinib/everolimus combination therapy will be declared a failure for that disease cohort. Subjects will meet the criteria for being evaluable for an objective response if they have measurable disease present at baseline and at least 1 post-baseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease. Subjects who are not evaluable for objective response will be replaced.

The Treatment Phase for each subject in Phase 2 ends after completing 4 cycles of treatment unless subject discontinues early. Those subjects who discontinue study treatment before completing 4 cycles transition to the Off-treatment Visit. Those who complete 4 cycles will transition to the Extension Phase. Study treatment and tumor assessments will continue during the Extension Phase.

Dosing Nomogram

The dose nomogram in Table 3 provides the dose of lenvatinib to be administered for BSA increments starting from 0.6 m^2. BSA must be calculated on Day 1 of each cycle based on the subject's current height and body weight. The actual dose to be administered is rounded to the nearest whole number. The total lenvatinib dose is capped at 18 mg daily (Dose Levels -1 and 1), and at 24 mg (Dose Levels 2 and 3).

Table 3 Total Lenvatinib Dose (mg): Body Surface Area (m^2) * Dose Level (mg/m^2)

Lenvatinib Dose Levels							
8 mg/m^2 Everolimus 3.0 mg/m^2) Dose Level -1		**11 mg/m^2 Everolimus 3.0 mg/m^2) Dose Level 1**		**14 mg/m^2 (Everolimus 3.0 mg/m^2) Dose Level 2**		**14 mg/m^2 (Everolimus 4.5 mg/m^2) Dose Level 3**	
Body Surface Area (m^2)	**Dose to be Administered (mg)**	**Body Surface Area (m^2)**	**Dose to be Administered (mg)**	**Body Surface Area (m^2)**	**Dose to be Administered (mg)**	**Body Surface Area (m^2)**	**Dose to be Administered (mg)**
0.60 – 0.68	5	0.60 – 0.68	7	0.60 – 0.60	8	0.60 – 0.60	8
0.69 – 0.81	6	0.69 – 0.77	8	0.61 – 0.67	9	0.61 – 0.67	9
0.82 – 0.93	7	0.78 – 0.86	9	0.68 – 0.74	10	0.68 – 0.74	10
0.94 – 1.06	8	0.87 – 0.95	10	0.75 – 0.82	11	0.75 – 0.82	11
1.07 – 1.18	9	0.96 – 1.04	11	0.83 – 0.89	12	0.83 – 0.89	12
1.19 – 1.31	10	1.05 – 1.13	12	0.90 – 0.96	13	0.90 – 0.96	13
1.32 – 1.43	11	1.14 – 1.22	13	0.97 – 1.03	14	0.97 – 1.03	14
1.44 – 1.56	12	1.23 – 1.31	14	1.04 – 1.10	15	1.04 – 1.10	15
1.57 – 1.68	13	1.32 – 1.40	15	1.11 – 1.17	16	1.11 – 1.17	16
1.69 – 1.81	14	1.41 – 1.49	16	1.18 – 1.24	17	1.18 – 1.24	17
1.82 – 1.93	15	1.50 – 1.59	17	1.25 – 1.32	18	1.25 – 1.32	18
1.94 – 2.06	16	≥1.60	18	1.33 – 1.39	19	1.33 – 1.39	19
2.07 – 2.18	17			1.40 – 1.46	20	1.40 – 1.46	20
≥2.19	18			1.47 – 1.53	21	1.47 – 1.53	21
				1.54 – 1.60	22	1.54 – 1.60	22
				1.61 – 1.67	23	1.61 – 1.67	23
				≥1.68	24	≥1.68	24

The dose nomogram in Table 4 provides the dose of everolimus to be administered for BSA increments starting from 0.6 m^2. The total everolimus dose is capped at 5 mg daily for Dose Levels -1, 1, and 2, and at 7 mg daily for Dose Level 3.

Table 4 Total Everolimus Dose (mg): Body Surface Area (m^2) * Dose Level (mg/m^2)

Everolimus Dose Level			
3 mg/m^2 Dose Levels -1, 1, and 2		4.5 mg/m^2 Dose Level 3	
Body Surface Area (m^2)	Dose to be Administered (mg)	Body Surface Area (m^2)	Dose to be Administered (mg)
0.60 – 0.83	2	0.60 – 0.77	3
0.84 – 1.16	3	0.78 – 0.99	4
1.17 – 1.49	4	1.00 – 1.22	5
≥1.50	5	1.23 – 1.44	6
		≥1.45	7

Study Duration

Approximately a total of 4.5 years from the first subject providing signed informed consent in Phase 1 to the primary endpoint completion date for Phase 2 of the study. It is estimated that the Phase 2 portion will take 3 years in order to complete the final collection of data for the primary outcome analysis.

Study duration for each subject is estimated to be:

- **Pretreatment Phase:** 4 weeks
- **Treatment Phase:** 1 cycle (4 weeks) in Phase 1; 4 cycles (16 weeks) in Phase 2.
- **Extension Phase:** Estimated maximum time of treatment is 2 years (24 cycles). Subjects may remain on study treatment as long as they do not meet any of the following criteria: 1) experience objective progression of disease (according to RECIST 1.1 or RANO, as appropriate), 2) exhibit no clinical benefit (in the opinion of the investigator), 3) experience unacceptable toxicity leading to withdrawal from the study, 4) withdraw or are withdrawn from the study for any reason, or, 5) termination of the study program. As long as the subject has not experienced intolerable toxicity, he or she can continue to receive study treatment. A 28-day follow up visit from last date of receiving investigational drug will be performed for subjects who discontinue study treatment.

9.1.1 Pretreatment Phase

The Pretreatment Phase will last up to 28 days and will include a Screening Period and a Baseline Period.

9.1.1.1 Screening Period

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 after the study has been fully explained to each subject and before the conduct of

any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

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

The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Baseline Visit.

9.1.1.2 Baseline Period

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 treatment (Cycle 1 Day 1). Baseline assessments can be performed on Day –1 or on Cycle 1 Day 1 prior to start of study treatment.

Subjects who complete the baseline assessments and continue to meet the criteria for inclusion/exclusion (Sections 9.3.1 and 9.3.2) will begin the Treatment Phase.

9.1.2 Treatment Phase

The Treatment Phase will begin with the first dose of study drug administration in Cycle 1. The duration of the Treatment Phase is 1 cycle (4 weeks of treatment) in Phase 1 of the study, and 4 cycles (16 weeks of treatment) in Phase 2 of the study. Subjects will receive study treatment in 28-day cycles. Tumor assessments will be performed during the Treatment Phase at Week 4 ±1 week (Phase 1) and at Week 8 ±1 week and Week 16 ±1 week (Phase 2).

Subjects who discontinue study treatment during Cycle 1 (Phase 1), or before completing 4 cycles of treatment (Phase 2), will transition to the Off-treatment Visit.

9.1.3 Extension Phase

All subjects who are still on study treatment following completion of Cycle 1 in Phase 1, or after completing 4 cycles in Phase 2 of the study, will transition to the Extension Phase. During the Extension Phase, subjects will continue to receive the same study treatment in 28-day cycles. Tumor assessments will be performed during the Extension Phase at Week 12 ±1 week and Week 24 ±1 week, and every 12 weeks ±1 week thereafter (Phase 1) and at Week 24 ±1 week, and every 12 weeks ±1 week thereafter (Phase 2).

9.1.4 Treatment Discontinuation Criteria

Subjects may remain on study treatment as long as they do not meet any of the following criteria: 1) experience objective progression of disease (according to Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 or Response Assessment in Neuro-Oncology

[RANO] criteria, as appropriate), 2) exhibit no clinical benefit (in the opinion of the investigator), 3) experience unacceptable toxicity leading to withdrawal from the study, 4) withdraw or are withdrawn from the study for any reason, or, 5) termination of the study program.

As long as the subject has not experienced intolerable toxicity, he or she can continue to receive study treatment.

9.1.5 Off-Treatment Visit

After subject discontinues treatment, an Off-Treatment Visit and the procedures noted in the Schedule of Assessments (Table 7 and Table 8) should be completed within 28 days after the last dose of study treatment.

9.1.6 Post-Treatment Phase

9.1.6.1 Follow-Up Period

The post-treatment follow up will begin when the subject discontinues study treatment and all off-treatment assessments have been completed. 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 whichever occurs first. Subjects will be followed for survival every 3 months until death or for 1 year, whichever occurs first, unless the study is terminated or if the subject discontinues due to withdrawal of consent or is lost to follow up.

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 is planned to begin in April 2017 and to end in March 2022.
- The maximum estimated period for each subject on study is anticipated to be approximately 2 years (24 treatment cycles). However, subjects will continue to receive study treatment as long as they demonstrate clinical benefit.

9.2 Discussion of Study Design

This multicenter, open-label, Phase 1/2 study will investigate safety, tolerability and antitumor activity of lenvatinib in combination with everolimus in pediatric subjects with relapsed or refractory solid tumors.

The Phase 1 portion of the study utilizes dose-finding rolling 6 design (Skolnik, et al., 2008), which allows enrollment of more than 3 subjects at the particular dose level, unlike the traditional 3+3 Phase 1 study design. If there is no DLTs in the first 3 subjects enrolled under rolling 6 design, then the fourth subject can be allocated to the next higher dose level. If toxicity data are not available on the first 3 subjects, or if one DLT is observed, in which

case the new subject will be kept at the same dose level. The main advantage of the rolling 6 design is the reduction of the overall study duration as it aims to decrease the number of times the study is suspended to accrual.

The Simon-optimal 2-stage design utilized for Phase 2 portion of the study allows for interim evaluation for futility. The traditional single-stage study designs evaluate drug response rate on the predetermined number of subjects, possibly unnecessarily exposing children to the risk of ineffective new agents. For ethical reasons, Simon's 2-stage design utilizes a small number of subjects to determine drug activity and allows early termination of the study if activity criteria are not met. This prevents exposure of too many pediatric subjects to an inactive study drug.

Toxicity will be assessed according to National Cancer Institute's CTCAE v4.03. In this study, the subjects will remain on treatment as long as they do not experience progression of disease or unacceptable toxicity. This will allow evaluation of short-term toxicity, as well as, side effects after prolonged use of combination of lenvatinib and everolimus, which is particularly important for pediatric population where physical growth and tissue maturation continues.

9.3 Selection of Study Population

A maximum accrual of 120 subjects in Phase 1 and Phase 2 portions of the study is expected at approximately 60 sites (20 sites for the Phase 1 portion and an additional 40 sites for the Phase 2 portion).

Phase 1: 4 to 48 evaluable subjects. In the event that each of the Dose Levels -1, 1, 2 , and 3 is expanded to 12 subjects, a maximum of 54 subjects (allowing for 20% to be non-evaluable and including the additional 6 subjects for PK analysis) will be enrolled.

Phase 2 Cohorts 1 to 3: 10 to 20 evaluable subjects per cohort (maximum 22 subjects per cohort allowing for 10% to be non-evaluable). A maximum of 66 subjects will be enrolled in Phase 2. In each cohort, at least 50% of the subjects enrolled will be <18 years old at the time of informed consent.

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 treatment.

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 the following tumor types:
   a. Phase 1: Recurrent or refractory solid tumors (excluding hepatoblastoma and lymphomas), including primary CNS tumors; subjects must have either measurable or evaluable disease. Subjects with diffuse intrinsic pontine glioma, optic pathway glioma, or pineal tumors with elevated tumor markers (alpha-fetoprotein [AFP] and

beta-human chorionic gonadotropin [ß-hCG] [or hCG]) do not require histological or cytological confirmation of diagnosis.

b. Phase 2 : Recurrent or refractory tumors; subjects must have measurable disease
   - Cohort 1: Ewing sarcoma/pPNET
   - Cohort 2: Rhabdomyosarcoma
   - Cohort 3: HGG (subjects with Diffuse Intrinsic Pontine Glioma are not eligible)

2. Measurable disease that meets the following criteria (Phase 2):
   a. RECIST 1.1 (for all tumor types except HGG)
      - At least 1 lesion of ≥1.0 cm in the longest diameter for a non lymph node or ≥1.5 cm in the short-axis diameter for a lymph node which is serially measurable according to RECIST 1.1 using computed tomography /magnetic resonance imaging (CT/MRI).
   b. Response Assessment in Neuro-Oncology (RANO) for high grade glioma (HGG) (Wen, et al., 2010)
      - At least one lesion must be measurable as defined as a bi-dimensionally contrast-enhancing lesion with clearly defined margins by CT or MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are preferably at most 5 mm apart with 0 mm skip.

Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.

3. Karnofsky performance score ≥50 for subjects >16 year of age and Lansky play score ≥50 for subjects ≤16 years of age. Note: Neurologic deficits in subjects with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. Subjects who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
4. Subjects must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the numerical eligibility criteria are met, eg, blood count criteria, the subject is considered to have recovered adequately.
   a. Cytotoxic chemotherapy or other chemotherapy known to be myelosuppressive: ≥21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).
   b. Anti-cancer agents not known to be myelosuppressive (eg, not associated with reduced platelet or absolute neutrophil counts): ≥7 days after the last dose of agent.
   c. Monoclonal antibodies: ≥21 days or 3 half-lives (whichever is shorter) of the antibody must have elapsed after the last dose of a monoclonal antibody (including immune checkpoint inhibitors). (Appendix 3). Toxicity related to prior antibody therapy must be recovered to Grade ≤1.
   d. Corticosteroids: If used to modify immune adverse events (AEs) related to prior therapy, ≥14 days must have elapsed since last dose of corticosteroid. Subjects

receiving corticosteroids, who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment, are not eligible.

e. Hematopoietic growth factors: ≥14 days after the last dose of a long-acting growth factor (eg, Neulasta) or 7 days for short-acting growth factor. For agents that have known AEs occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs are known to occur.

f. Interleukins, interferons, and cytokines (other than hematopoietic growth factors): ≥21 days after the completion of interleukins, interferons or cytokines (other than hematopoietic growth factors).

g. Stem cell infusions (with or without total body irradiation [TBI]):
   - Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including donor leukocytes infusion or boost infusion: ≥84 days after infusion and no evidence of graft versus host disease (GVHD).
   - Autologous stem cell infusion including boost infusion: ≥42 days

h. Cellular Therapy: ≥42 days after the completion of any type of cellular therapy (eg, modified T cells, natural killer cells, dendritic cells, etc).

i. Radiotherapy (XRT)/External Beam Irradiation including Protons: ≥14 days after local XRT; ≥150 days after total body irradiation, craniospinal XRT or if radiation to ≥50% of the pelvis; ≥42 days if other substantial bone marrow radiation.

j. Radiopharmaceutical therapy (eg, radiolabeled antibody, iodine-131 metaiodobenzylguanidine [^{131}I-MIBG]): ≥42 days after systemically administered radiopharmaceutical therapy.

k. VEGF/VEGFR-targeted or mTOR-targeted therapies:
   - Must not have received prior exposure to lenvatinib
   - May have previously progressed on an mTOR inhibitor
   - No more than 2 prior VEGF/VEGFR-targeted therapies (For Phase 2 only)
   - Must not have received prior VEGF/VEGFR-targeted therapy in combination with an mTOR inhibitor (For Phase 2 only)

5. Male or female subjects must be ≥2 years and <18 years of age for enrolment in Phase 1 or ≥2 years and ≤21 years of age for enrolment in Phase 2.
6. Adequate bone marrow function:
   - For subjects with solid tumors without known bone marrow involvement:
     - Peripheral absolute neutrophil count (ANC) ≥1000/mm^3
     - Platelet count ≥100,000/mm^3
     - Hemoglobin ≥8.0 g/dL at baseline (may receive red blood cell transfusions)
   - For subjects with known bone marrow metastatic disease:
     - Peripheral ANC ≥1000/mm^3
     - Platelet count ≥100,000/mm^3 (and with no platelet transfusions for at least 7 days prior to enrollment)
     - May receive transfusions provided they are not known to be refractory to red cell or platelet transfusions. These subjects will not be evaluable for hematologic

toxicity. At least 5 of every cohort of 6 subjects with a solid tumor must be evaluable for hematologic toxicity, for the dose-escalation part of the study. If dose-limiting hematologic toxicity is observed, all subsequent subjects enrolled must be evaluable for hematologic toxicity.

7. Adequate renal function:
   - Creatinine clearance or radioisotope glomerular filtration rate (GFR) ≥70 mL/min/1.73 m^2 or
   - A serum creatinine based on age/gender as follows:

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 utilizing child length and stature data published by the Centers for Disease Control and Prevention (CDC).

   - 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).
8. Adequate liver function:
   - Bilirubin (sum of conjugated + unconjugated) ≤1.5 × upper limit of normal (ULN) for age, except for unconjugated hyperbilirubinemia of Gilbert's syndrome.
   - ALT and AST ≤3 × ULN
   - Serum albumin ≥2 g/dL
9. Adequate cardiac function:
   - Adequate cardiac function as evidenced by left ventricular shortening fraction of ≥27% by echocardiogram or left ventricular ejection fraction (LVEF) ≥50% at baseline, as determined by echocardiography/multigated acquisition (MUGA) scan.
   - QT interval corrected for heart rate using Fridericia's formula (QTcF) ≤480 msec.
10. Adequate neurologic function:
   - Subjects with seizure disorder may be enrolled if on non-enzyme-inducing anticonvulsants and well controlled.
   - Nervous system disorders (CTCAE v4.03) resulting from prior therapy and not tumor-induced must be ≤Grade 2.
11. Adequate BP control with or without antihypertensive medications, defined as: A BP < the 95th percentile for sex, age and height/length (≤150/90 mmHg for subjects aged 18 - 21 years) at Screening (as per National Heart Lung and Blood Institute [NHLBI] guidelines; Appendix 7 and Appendix 8) and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1.

12. Adequate coagulation:
    - International Normalized Ratio (INR) ≤1.5
13. Adequate pancreatic function:
    - Serum amylase ≤1.5 × ULN
    - Serum lipase ≤1.5 × ULN
14. Adequate metabolic function:
    - Serum triglycerides ≤300 mg/dL
15. Adequate glycemic control defined as:
    - Fasting serum glucose ≤160 mg/dL
16. Subjects must have a minimum BSA of 0.6 m^2 at study entry.

9.3.2 Exclusion Criteria

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

1. Subjects who have had or are planning to have the following invasive procedures:
    - Major surgical procedure, laparoscopic procedure, open biopsy or significant traumatic injury within 28 days prior to enrollment.
    - Central line placement or subcutaneous port placement is not considered major surgery. External central lines must be placed at least 3 days prior to enrollment and subcutaneous ports must be placed at least 7 days prior to enrollment.
    - Fine needle aspirate within 7 days prior to enrollment.
    - Surgical or other wounds must be adequately healed prior to enrollment.

NOTE: For purposes of this study, bone marrow aspirate and biopsy are not considered surgical procedures and therefore are permitted within 14 days prior to start of protocol therapy.

2. Subjects who have non-healing wound, unhealed or incompletely healed fracture, or a compound (open) bone fracture at the time of enrollment
3. Subjects having an active infection requiring systemic therapy
4. Subjects with a known history of active hepatitis B (defined as hepatitis B surface antigen reactive or hepatitis B virus-DNA detected) or known active hepatitis C virus (HCV, defined as HCV-RNA detected). Note: No testing for hepatitis B and hepatitis C is required unless mandated by the local health authority.
5. Known to be human immunodeficiency virus (HIV) positive. Note: HIV testing is required at screening only when mandated by the local health authority
6. Clinical evidence of nephrotic syndrome prior to enrollment
7. Gastrointestinal bleeding or active hemoptysis (bright red blood of at least half teaspoon) within 21 days prior to enrollment
8. Thrombotic/ thromboembolic event requiring systemic anticoagulation within 90 days prior to enrollment
9. Evidence of new intracranial hemorrhage of more than punctate size on MRI assessment obtained within 28 days prior to study enrollment for subjects with high-grade glioma
10. Diagnosis of lymphoma
11. Radiographic evidence of major blood vessel invasion/infiltration.

12. Evidence of untreated CNS metastases (exception: subjects with primary CNS tumors and leptomeningeal disease).
13. Subjects who are currently receiving enzyme-inducing anticonvulsants
14. Subjects chronically receiving strong cytochrome P450 3A4 (CYP3A4)/ P-glycoprotein (P-gp) inhibitors or inducers within 7 days prior to study enrollment (See Appendix 15 for a list of strong inhibitors and inducers).
15. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive ß-hCG [or hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or 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.
16. Females of childbearing potential* who:
    - do not agree to use a highly effective method of contraception for the entire study period and for 8 weeks after study drug discontinuation, ie,:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device (IUD) or hormone releasing system (IUS)
        - a contraceptive implant
        - an oral contraceptive** (with additional barrier method)

    OR
    - do not have a vasectomized partner with confirmed azoospermia.

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.

NOTES:
*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), or are pre-menarcheal (Tanner Stage 1-3).

Must be on a stable dose of the **same oral hormonal contraceptive product for at least 4 weeks before dosing with study drug, for the duration of the study, and for at least 8 weeks after study drug discontinuation.

17. Males who have not had a successful vasectomy (confirmed azoospermia) or if 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 7 days after lenvatinib discontinuation or 4 weeks after discontinuation of everolimus). No sperm donation is allowed during the study period and for 7 days after lenvatinib discontinuation or 4 weeks after discontinuation of everolimus.

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 Follow-Up Period and complete 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 Subject Disposition CRF 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 Medication CRF.

9.4 Treatment

9.4.1 Treatment Administered

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

Everolimus will be provided as 2 mg, 3 mg, and 5 mg dispersible tablet formulations (everolimus tablets for oral suspension).

Lenvatinib and everolimus will be administered orally on a once daily schedule in continuous 28-day cycles. The sequence of administration is not important. Dosing nomograms based on BSA and dose level will be used to prescribe lenvatinib and everolimus for subjects to minimize inter-subject dosing variability. The maximum daily dose of lenvatinib administered during the study should not exceed 18 mg in Dose Levels -1, and 1, and 24 mg in Dose Levels 2 and 3. The maximum daily dose of everolimus should not exceed 5 mg in Dose Levels -1, 1, and 2, and 7 mg in Dose Level 3. Intra-subject titration of everolimus will not be allowed on this study. Intra-subject dose escalation of both lenvatinib and everolimus will not be allowed.

Subjects benefiting from study treatment in the opinion of the investigator will continue treatment until disease progression, development of unacceptable toxicity, withdrawal of consent or are withdrawn from the study for any reason, or termination of the study by the sponsor.

9.4.1.1 Study Treatment Dose Reduction and Interruption Instructions

Dose reduction and interruptions for subjects who experience lenvatinib-everolimus combination therapy-related toxicity will be managed as described in Table 5. Investigators will decide the probability of the event being related to protocol therapy as to whether dose modification of drug therapy is required.

Doses in the Dose Adjustment column are based on a presumed starting dose of 11 mg/m^2 lenvatinib and 3 mg/m^2 everolimus. Dose reductions will occur in succession based on the previous dose level. Each dose level reduction due to toxicity at a given BSA is

approximately 25% reduction from the previous dose. Once the study drug dose has been reduced, it may not be increased at a later date, unless the dose was mistakenly decreased; in this situation, the sponsor's approval is required to increase the dose.

Asymptomatic laboratory abnormalities, including Grade ≥3 abnormalities (eg, elevations of amylase and lipase) that are not considered clinically relevant by the investigator, should be managed per institutional guidelines; continuation of treatment should be discussed with the sponsor.

Table 5 Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity

Treatment-Related Toxicity[a,b]	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d, e] or Grade 3[f]		
First occurrence	Interrupt lenvatinib and everolimus until resolved to Grade 0-1 or tolerable Grade 2	Reduce lenvatinib dose to 8 mg/m^2 (or approximately 25% reduction of the starting dose) orally once a day (one-level reduction) and resume everolimus at the same dose as prior to dose interruption
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and everolimus until resolved to Grade 0-1 or tolerable Grade 2	Reduce lenvatinib dose to 6 mg/m^2 (or approximately 25% reduction from the previous dose level) once a day (one-level reduction). Dose reduction of everolimus to 3 mg/m^2 every other day may be considered for Grade 3 toxicity[e]
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and everolimus until resolved to Grade 0-1 or tolerable Grade 2	Reduce lenvatinib dose to 4.5 mg/m^2 (or approximately 25% reduction from the previous dose level) orally once a day (1-level reduction). Dose reduction of everolimus for Grade 3 toxicity: i) if 3 mg/m^2 daily everolimus at event onset, reduce to 3 mg/m^2 every other day or

		ii) if 3 mg/m^2 every other day everolimus at event onset, discontinue
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and everolimus	Discuss with sponsor
Grade 4[g]: Discontinue Study Treatment		

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

a: An interruption of study treatment for more than 28 days will require sponsor`s approval before treatment can be resumed.
b: Initiate optimal medical management for nausea, vomiting, hypothyroidism 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.
d: Obese subjects with weight loss do not need to return to the baseline weight or 10% of baseline weight (ie, Grade 1weight loss). These subjects will restart the study drug(s) at a lower dose once their weight remains stable for at least 1 week and they reached the normal body mass index (BMI; if the weight loss occurred but it is still above normal BMI, they can restart the study treatment at a lower dose once the weight has been stable for at least 1 week). Normal BMI should be used as the new baseline for further dose reductions. See BMI charts for boys (Appendix 9) and girls (Appendix 10).
e: For Grade 2 toxicity, resume everolimus at the same dose as prior to dose interruption. For Grade 3 toxicity, investigator will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required.
f: For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with the sponsor.
g: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

9.4.1.2 Blood Pressure

For children, BP varies by the sex and age of the child and it is closely related to height and weight. BP will be assessed in terms of percentile for sex, age and height/length. Guidelines to sex, age, and height-specific percentiles of BP are provided in Appendix 7 and Appendix 8. BP that is consistently above the 95th percentile [for subjects age 18-21 years BP ≥140/90 mmHg] for age and height/length requires further evaluation. A referral to a cardiologist is recommended for subjects 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 BP in children of approximately the same age and body build should be expected and serial measurements should always be obtained when evaluating a subject with hypertension. **BP values for management of hypertension for subjects 18 to 21 years of age are included in parenthesis.**

9.4.1.3 Management of Hypertension

Hypertension is a recognized side-effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP <95th percentile [BP ≤150/90 mmHg] 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 dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥95th percentile [BP ≥140 mmHg] or diastolic BP ≥95th percentile [BP ≥90 mmHg]) 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 mmHg] or diastolic BP ≥95th percentile [BP ≥90 mmHg] 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.

Study treatment 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 mmHg], 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, study treatment should be resumed as described below.

During the Treatment Period, subjects with systolic BP ≥99th percentile [BP ≥160 mmHg] or diastolic BP ≥99th percentile [BP ≥100 mmHg] 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 mmHg] and diastolic BP has been <95th percentile [≤95 mmHg] for 3 consecutive months. If a new event of systolic BP ≥99th percentile [BP ≥160 mmHg] or diastolic BP ≥99th percentile [BP ≥100 mmHg] occurs, the subject must resume the Day 15 evaluation until systolic BP has been <95th percentile [≤150 mmHg] and diastolic BP has been <95th percentile [≤95 mmHg] for 3 consecutive months.

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

- Continue study treatment 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 mmHg) or diastolic BP ≥99th percentile (BP ≥100 mmHg) persists despite maximal antihypertensive therapy, then study treatment administration should be interrupted and restarted at a lower dose once daily (one dose level reduction as specified in Table 5) only when systolic BP <95th percentile (BP ≤150 mmHg) and diastolic BP <95th percentile (BP

≤95 mmHg) and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

- If systolic BP ≥99th percentile (BP ≥160 mmHg) or diastolic BP ≥99th percentile (BP ≥100 mmHg) recurs despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then study treatment administration should be interrupted and restarted at a lower dose once daily (one dose level reduction as specified in the Table 5) only when systolic BP <95th percentile (BP ≤150 mmHg) and diastolic BP <95th percentile ([BP ≤95 mmHg] and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

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

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

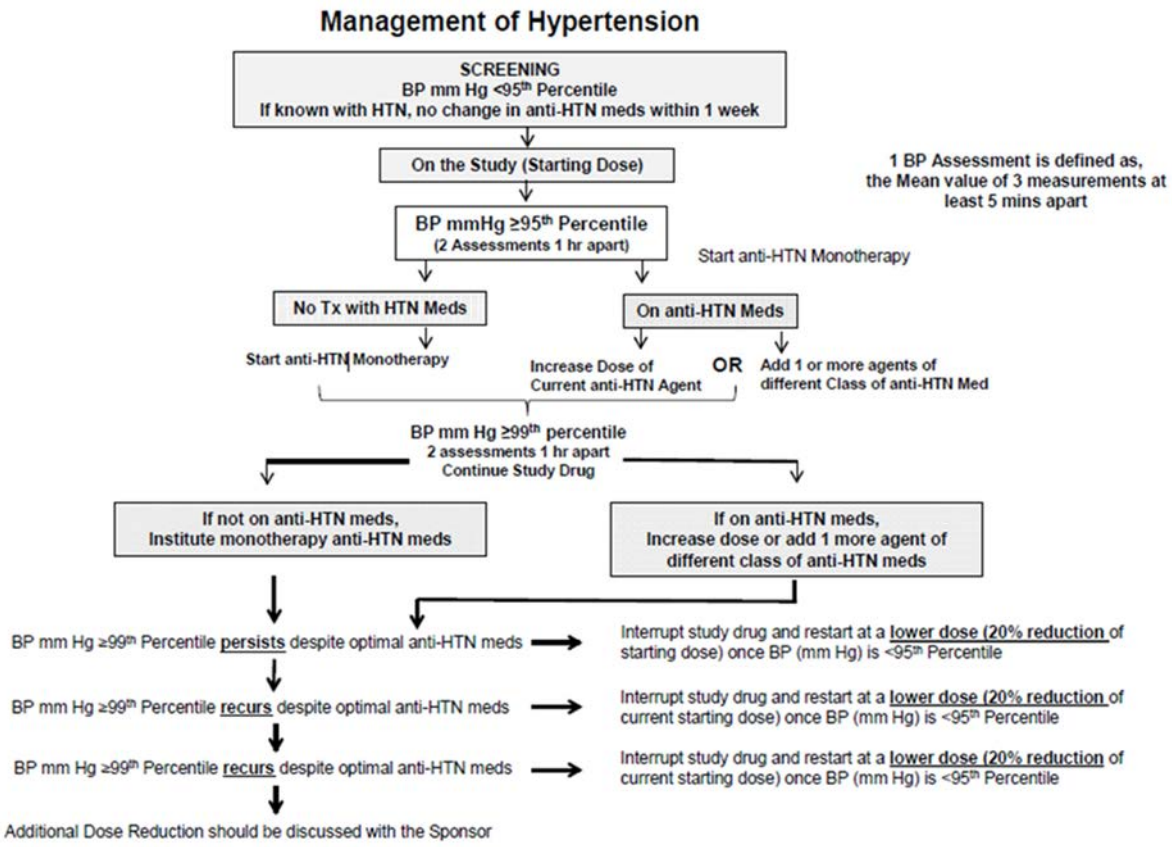


Figure 2 Management of Hypertension

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

9.4.1.4 Management of Posterior Reversible Leukoencephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome

Posterior Reversible Leukoencephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome (PRES/RPLS) is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES/RPLS, the Dose Modification Guidelines (Table 5) should be followed.

9.4.1.5 Management of Proteinuria

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

1. Grading according to CTCAE v4.03 will be based on the protein-creatinine ratio, and whenever possible, also on the 24-hour urinary protein result per investigator's

discretion. Management of study treatment administration will be based on the grade of proteinuria according to the Dose Modification Guidelines.

2. A spot protein-creatinine ratio test, and if possible a 24-hour urinary protein test as per investigator's discretion, to verify the grade of proteinuria is required in the following situations:
   - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study treatment
   - A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib/everolimus dose level
   - When there has been a lenvatinib/everolimus dose reduction and at the new dose level the urine protein dipstick result is 2+, 3+, or 4+
3. Urine dipstick testing for subjects with proteinuria ≥2+ should be performed every 2 weeks (or on Day 1 and Day 15 or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months.

4. In the event of nephrotic syndrome, lenvatinib must be discontinued.

9.4.1.6 Management of Diarrhea

An anti-diarrheal agent should be recommended to the subject at the start of study treatment and subjects should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the subject's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in the Dose Modification Guidelines should be followed.

9.4.1.7 Management of Non-Infectious Pneumonitis

Non-infectious pneumonitis is a recognized class effect of rapamycin derivatives, including everolimus. Non-infectious pneumonitis was described in 19% of subjects taking everolimus (Afinitor package insert). Some cases were severe and on rare occasions, a fatal outcome was observed. Investigators should therefore consider a diagnosis of non-infectious pneumonitis in subjects presenting with non-specific respiratory signs and symptoms and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations.

Subjects who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1) may continue study dosing without dose adjustments.

1. If symptoms are moderate (CTCAE Grade 2):
   - Study treatment (lenvatinib-everolimus combination) should be interrupted and the use of corticosteroids may be indicated until symptoms abate (resolved to CTCAE Grade 0-1) and may then be restarted at the same doses prior to study treatment interruption.

- If Grade 2 non-infectious pneumonitis recurs despite optimal management, then study treatment administration should be interrupted and the use of corticosteroids may be indicated until symptoms abate (resolved to CTCAE Grade 0-1).

2. If symptoms are severe (CTCAE Grade 3):
   - Study treatment should be interrupted and the use of corticosteroids may be indicated until clinical symptoms resolve (to CTCAE Grade 0-1).
3. If symptoms are life-threatening (CTCAE Grade 4):
   - Study medications should be discontinued.

9.4.1.8 Management of Infections

Everolimus has immunosuppressive properties and may predispose subjects to infections. It is important therefore to monitor for signs and symptoms of infection, and treat promptly. Dose alterations of everolimus may be required in accordance with everolimus prescribing information, ie, Afinitor Disperz package insert or Votubia Summary of Product Characteristics (SmPC).

9.4.1.9 Management of Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia and hypertriglyceridemia are recognized class effects of rapamycin derivatives, including everolimus. Glycemic and lipid control should be optimized before starting a subject on this study. Blood glucose will be monitored as specified in the Schedule of Procedures/Assessments. For subjects with blood glucose >ULN, a fasting (>6 hour, water only) blood glucose sample will be obtained. Grading will be based on the fasting blood glucose result. The choice of hypoglycemic agent should be individualized to the subject's clinical circumstances and follow standard medical practice.

Dose alterations of everolimus may be required in accordance with everolimus prescribing information, ie, Afinitor Disperz package insert or Votubia SmPC.

9.4.1.10 Management of Hepatotoxicity

Regular monitoring of liver function tests (ALT, AST, bilirubin levels) should be conducted as detailed in the Schedule of Assessments (Table 7 and Table 8) 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 5), for Study Treatment Dose Reduction and Interruption Instructions). Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study treatment must be discontinued.

9.4.1.11 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 5), 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 treatment must be discontinued. If a subject experiences an arterial thromboembolism event of any grade, lenvatinib must be discontinued.

9.4.1.12 Management of Hypocalcemia

Serum calcium should be monitored per the Schedule of Assessments. Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v 4.03, using the following formula:

Corrected calcium = ([4 – serum albumin in g/dL] x 0.8 + serum calcium)

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

9.4.1.13 Management of Hemorrhage

For subjects with hemorrhage, either resume at a reduced dose or discontinue study treatment depending on the severity and persistence of hemorrhage.

9.4.1.14 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 AEs of abdominal pain believed related to lenvatinib or more specific AEs believed related to lenvatinib that result in the symptom of abdominal pain, instructions contained in Table 5 regarding study treatment dose reduction and interruption instructions. For Grade 4 AEs that result in abdominal pain, study treatment must be discontinued.

Gastrointestinal 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. It is recommended that all gastrointestinal symptoms should be recorded in the diary provided.

9.4.1.15 Management of Fistula Formation and Gastrointestinal Perforation

Lenvatinib should be discontinued in any subject who develops Grade 4 fistula (gastrointestinal or non-gastrointestinal), or gastrointestinal perforation of any grade.

9.4.1.16 Management of Osteonecrosis of the Jaw

Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise study subjects regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in study subjects at higher risk. For study subjects requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of osteonecrosis of the jaw. Withhold lenvatinib if osteonecrosis of the jaw develops and restart based on clinical judgement of adequate resolution (see Section 9.4.7).

9.4.1.17 Management of QT Prolongation

Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 msec. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to <480 msec or baseline. Monitor potassium, calcium and magnesium, and replenish as appropriate.

9.4.2 Identity of Investigational Products

The study drugs under evaluation in this study are lenvatinib in combination with everolimus. The sponsor will provide the study drugs packaged as open-label supplies.

Lenvatinib

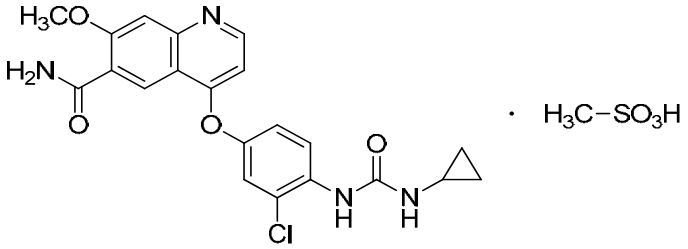
Lenvatinib will be supplied by the sponsor in labeled containers. The sponsor will package lenvatinib as open-label supplies. Lenvatinib will be provided to the sites as #4 size hydroxypropyl methylcellulose (HPMC) capsules in 3 strengths differentiated by color (iron oxide red and iron oxide yellow); 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.

Everolimus

Everolimus dispersible tablets for oral suspension will be provided as commercial drug product such as ‘Afinitor Disperz’ or ‘Votubia dispersible tablets’ in strengths of 2 mg, 3 mg, and 5 mg. Note that everolimus tablets contain lactose.

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: $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$
- Molecular weight: 522.96
- Structural formula:



9.4.2.2 Chemical Name, Structural Formula of Everolimus

- Generic name: everolimus
- Chemical name: -O-(2-hydroxyethyl)-rapamycin
- Molecular formula: $C_{53}H_{83}NO_{14}$

Refer to the latest everolimus prescribing information, ie, Afinitor Disperz package insert or Votubia SmPC.

9.4.2.3 Comparator Drug

Not applicable

9.4.2.4 Labeling for Study Drug

Lenvatinib and everolimus will be labeled 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.

9.4.2.5 Storage Conditions

Study drug 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 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.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to receive lenvatinib in combination with everolimus in 28-day treatment cycles. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

The purpose of the Phase 1 portion of the study is to determine the MTD and the RP2D of lenvatinib administered in combination with everolimus in this pediatric population. The dose levels of lenvatinib and everolimus to be evaluated in the study are pre-specified. The starting dose level of lenvatinib is 11 mg/m^2, which is approximately 80% of lenvatinib single dose MTD in pediatric subjects determined in the ongoing Study E7080-G000-207. The initial dose of everolimus is 3 mg/m^2, which is 66% of the FDA approved dose and dose previously found effective in subependymal giant cell astrocytoma.

9.4.5 Selection and Timing of Dose for Each Subject

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

Refer to everolimus prescribing information for recommended everolimus dosing information.

Study drugs 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.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) administered 28 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 28 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 the study medication may be continued during the study.

Aspirin, nonsteroidal anti-inflammatory 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 counts.

Treatment (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs, etc) of complications of AEs or therapy to ameliorate symptoms may be administered at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study medication.

An anti-diarrheal agent should be recommended to the subject at the start of study treatment and subjects should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the subject's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in the Dose Modification Guidelines should be followed.

Administration of corticosteroids for progressive disease is not permitted. Administration of corticosteroids will be limited to premedication or the short-term treatment of acute medical conditions in accordance with approved indications, institutional, or national guidelines.

Palliative radiotherapy of up to 2 painful pre-existing, non-target bone metastases will be permitted without being considered progressive disease. In the Phase 1 part, palliative radiotherapy will be allowed after the completion of Cycle 1.

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.
- For scheduled dental surgery or invasive dental procedures: stop lenvatinib for at least 1 week before the procedure, then restart lenvatinib when deemed clinically appropriate.

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

9.4.7.1 Drug-Drug Interactions

Lenvatinib's weak in vitro inhibitory and induction potential on CYP enzymes (Study No. XT063020) suggests a low risk of lenvatinib interference with the PK of other drugs metabolized by CYP enzymes which are co-administered in usual clinical practice. Nonclinical studies identify CYP3A4 as the important CYP isozyme responsible for human hepatic metabolism of lenvatinib. However, clinical studies conducted showed that coadministration of lenvatinib with CYP3A4/P-gp inhibitors or inducers is not of clinical concern. The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes (Lenvima® package insert).

For subjects receiving everolimus, drugs or substances (including herbal supplements or grapefruit juice) known to be potent inhibitors of CYP3A4/P-gp should not be used. Potent inducers of CYP3A4/P-gp should not be used unless there is no alternative treatment available. Dose increase of everolimus may be considered when co-administering strong CYP3A4 or P-gp inducers. Moderate/ weak inhibitors or inducers or substrates of CYP3A4 and/or P-gp should be used with caution. Dose reduction of everolimus may be considered when co-administering moderate CYP3A4 or P-gp inhibitors. For further information, please refer to everolimus prescribing information.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this study:

- Concurrent anticancer therapies such as chemotherapy, TKIs, radiotherapy (with the exception of palliative radiotherapy as specified in Section 9.4.7), antitumor interventions (surgical resection, surgical debulking of tumor, etc), or cancer immunotherapy
- Concurrent other investigational drugs
- Live vaccines are prohibited while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed.

For subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of the study medication and further participation in the study must be discussed and agreed upon with the sponsor.

If subjects receive additional anticancer therapies, 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 Follow-Up Period.

Further information on the prohibited concomitant therapies for lenvatinib and everolimus is included in the respective prescribing information.

9.4.8 Treatment Compliance

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

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) 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 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 and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to 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 site but not dispensed to 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/study supplies 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 if regionally required, the head of the medical institution 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.

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, and race/ethnicity.

9.5.1.2 Baseline Assessments

Baseline assessments will be performed at Day -1 or at Cycle 1 Day 1 prior to treatment. The screening assessment can serve as the baseline assessment, if performed within 72 hours of the first dose of study 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 prior to the first dose of study treatment, Lansky play score (see Appendix 4) or Karnofsky performance status score (see Appendix 5), tumor staging (as appropriate) at the time of initial diagnosis, vital signs, clinical chemistry and hematology, urine dipstick testing, echocardiogram/MUGA scan, proximal tibial growth plates x-ray, PD biomarkers and optional biomarkers, and blood sample collection for pharmacogenomics analysis.

9.5.1.2.1 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 and Table 8). 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. 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

9.5.1.3.1 Tumor Assessments

For all tumor types except HGG: Tumor assessments will be performed using RECIST 1.1 (Appendix 1). Investigator-determined response assessments will be performed at each assessment time point and entered onto the CRF. Tumor assessments (CT chest and CT/MRI of abdomen, pelvis and other areas of known disease at screening plus any areas of suspected disease) should be performed at Screening and, for Phase 1 of the study, at Week 4 ±1 week, Week 12 ±1 week, Week 24 ±1 week, and every 12 weeks ±1 week thereafter, or as clinically indicated. For subjects with primary CNS tumors and no other known areas of disease only target and non-target lesions plus any areas of newly suspected disease must be scanned. For Phase 2 of the study, tumor assessments should be performed at Screening, Week 8 ±1 week, Week 16 ±1 week, Week 24 ±1 week, and then every 12 weeks ±1 week thereafter, or as clinically indicated. All responses are to be confirmed at a follow-up examination after ≥28 days following the initial indication of response. Historical scans (within 28 days prior) that do not follow the guidelines completely may be used.

A brain scan (CT with contrast or MRI pre- and post-contrast) will be performed at Screening and during the study if clinically indicated.

For Phase 1 of the study, subsequent tumor assessments will occur at Week 4 ±1 week, Week 12 ±1 week, Week 24 ±1 week and every 12 weeks ±1 week thereafter, or as clinically indicated. For Phase 2 of the study, tumor assessments should be performed at Week 8 ±1

week, Week 16 ±1 week, Week 24 ±1 week, and then every 12 weeks ±1 week thereafter, or as clinically indicated. Tumor assessments will be performed based on RECIST 1.1 beginning from the date of first dose, continuing during treatment cycles until documentation of disease progression. This schedule for tumor assessments will be maintained irrespective of treatment delays. All responses are to be confirmed at a follow-up examination after ≥28 days following the initial indication of response. The same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of intravenous 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 12 weeks until documentation of progression or start of a new anticancer agent. Please see Appendix 13 for imaging methodology for tumor assessment.

If protocol eligible brain metastases are present at Screening, a CT/MRI of the brain must be performed at all tumor assessment time points.

For HGG: Tumor assessments will be performed using RANO Criteria (Appendix 14). A standard MRI-imaging protocol will be performed for use in the assessments. Investigator-determined response assessments at each assessment time point will be entered onto the appropriate CRFs. Tumor assessments will be carried out during Screening and for Phase 1 of the study, at Week 4 ±1 week, Week 12 ±1 week, Week 24 ±1 week, and then every 12 weeks ±1 week thereafter, or as clinically indicated. For Phase 2 of the study, tumor assessments should be performed at Screening, Week 8 ±1 week, Week 16 ±1 week, Week 24 ±1 week, and every 12 weeks ±1 week thereafter, or as clinically indicated.

For Phase 2, copies of scans for tumor assessments will be sent to an imaging core laboratory designated by the sponsor for quality assessment and archival and potential future independent review.

After data cutoff, tumor assessments may be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care and scans will not be sent to the imaging core laboratory.

The imaging methodology for tumor assessments for all tumor types, including solid tumors and HGG, is provided in Appendix 13.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 Pharmacokinetic Assessments

Blood samples (2 mL each) for plasma concentrations of lenvatinib and whole blood concentrations of everolimus will be collected from all subjects as described in the Schedule of Assessments (Table 7 and Table 8). Instructions for the collection, handling, and shipping procedures of the plasma and blood PK samples will be provided in a separate laboratory manual.

If dose interruption is necessary at the PK time points, the sponsor should be consulted.

Lenvatinib in plasma and everolimus in whole blood will be quantified using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods.

9.5.1.4.2 Pharmacodynamic, Pharmacokinetic/Pharmacodynamic, Pharmacogenomic, and Other Biomarker, Assessments

Pharmacodynamic Assessments: Blood samples for plasma and serum studies will be collected from consenting subjects (optional) at Baseline and on Cycle 1 Day 15, Cycle 2 Day 1, and then matched with tumor assessments and at the Off-treatment Visit, as specified in the Schedule of Assessments (Table 7 and Table 8). Only subjects with BSA >0.68 m^2 are eligible to consent (optional) to blood samples for plasma and serum studies. Biomarker discovery and/or validation will be performed to identify blood or tumor biomarkers that may be useful to predict subject response to study drug as well as for potential use in diagnostic development (see Appendix 11). Blood samples may undergo global proteomic and/or single analyte enzyme-linked immunosorbent assays (ELISA) or multiplex immunoassays based on the amount of sample available. Potential blood biomarkers to be explored include FGF ligands (eg, FGF2/bFGF, FGF19, FGF21, FGF23), and angiogenesis related markers (eg, VEGF, Ang 1/2, sTie-2, HGF, PlGF). In addition, biomarkers identified in other lenvatinib clinical studies may also be assessed in samples collected from subjects enrolled in this study. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

Pharmocokinetic/Pharmacodynamic Assessments: Relationships between lenvatinib exposure and safety will be explored graphically. Pending the outcome of graphical assessments, modeling of potential relationships will be explored. Details of exposure-safety analyses will be provided in a separate analysis plan.

Pharmacogenomic/Pharmacogenetic Assessments: Archived, fixed tumor tissue will be collected (if available), as specified in the Schedule of Assessments (Table 7 and Table 8), for potential assessment of mutations and other genetic alterations in genes and/or proteins that may be important in the development and progression of tumor biology relevant to the tumor types being explored, to evaluate response to study drug treatment, as well as for potential use in diagnostic development. Genetic alterations in target genes include lenvatinib targets (eg, FGF ligands and FGF receptors 1-4), angiogenesis-relevant targets (such as expression levels of VEGF, Ang 1/2, Tie-2, HGF and cMET) and markers associated with cell differentiation and tumorigenesis (eg, WNT/β-catenin pathway, hedgehog/PTCH pathway, and BMP/TGF signaling pathway). Appropriate analytical technology/methodologies, such as next generation sequencing (NGS)-based whole exome sequencing (WES), whole transcriptome analysis or targeted re-sequencing using targeted gene panels (eg, ThermoFisher Oncomine Comprehensive Assay (OCA)) for gene alterations, targeted gene expression panels (eg, Nanostring PanCancer Pathway, PanCancer Immune) for gene expression analysis, single analyte or multiplex IHC, etc may be used based on the amount of tumor tissue available.

Blood plasma samples will be collected (optional) for analysis of cell-free nucleic acid (cf-nucleic acid). Cell-free nucleic acid isolated from plasma samples may be used to explore tumor genetic alterations such as mutations and other genetic alterations observed in archival tumor samples (using NGS-based targeted gene panels), as well as those which develop during drug treatment to monitor response to study drug.

A blood sample will be collected for PG analysis (optional). Variation in study drug exposure or the occurrence of AEs observed in the study population may be evaluated by correlating single–nucleotide polymorphisms with PK, safety, or PD data. Genomic DNA extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA extracted from tumor material are limited to the tumor.

Data obtained will be used for research to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. 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 after study completion to assist in research scientific questions related to cancer biology or for potential diagnostic development.

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

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs) using CTCAE v4.03; regular laboratory evaluation for hematology, blood chemistry, and urine dipstick values; regular performance of physical examinations; periodic measurement of vital signs, 12-lead ECGs, echocardiography/MUGA scan, Lansky play score and Karnofsky performance score as detailed in the Schedule of Assessments (Table 7 and Table 8).

BP monitoring will occur at least weekly during the first 2 cycles. BP will be assessed in terms of percentile for sex, age and height/length. Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥95th percentile [BP ≥140 mmHg for adult subjects] or diastolic BP ≥95th percentile [BP ≥90 mmHg for adult subjects]) is confirmed on 2 assessments obtained 1 hour apart. For subjects with hypertension and proteinuria, treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist is preferred. Cardiac systolic function and QTc will be assessed at screening, prior to Cycles 2 and 5, and every sixth cycle thereafter by echocardiography/MUGA scan and electrocardiogram.

9.5.1.5.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal

relationship with the medicinal product. For this study, the study drugs are lenvatinib and everolimus.

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 (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- 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, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the 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 ICF through the last visit and for 28 days after the last dose of study treatment. Serious AEs (SAEs) will be collected for 28 days after the last dose of study treatment.

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. 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. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (corrected QT interval [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 more than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed for 28 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

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Adverse events will be graded on a 5-point scale according to CTCAE v4.03 (Appendix 2). Investigators will report CTCAE grades for all AEs.

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

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related)	A causal relationship between the study drug and the AE is a reasonable possibility.
No (not related)	A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

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 AE 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 that 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 should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations. In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding, AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations 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 special situations 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
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 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 and Table 8) 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, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils) International Normalized Ratio[a]
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, potassium, sodium, magnesium, phosphorus
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin[b], total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function tests[c]	Thyroid stimulating hormone, free thyroxine (T4) level
Other chemistries	Albumin, amylase, calcium, glucose[d], lactate dehydrogenase, lipase, total protein, triglycerides, cholesterol
Urinalysis for microscopy[e]	RBCs/high-power-field (HPF)
Urine dipstick testing[e]	Blood, protein, glucose
Other	Pregnancy test (serum or urine beta-human chorionic gonadotropin)

a: INR should only be performed as part of the screening assessment and when clinically indicated.
b: Direct bilirubin should be assessed if total bilirubin is elevated.
c: Thyroid function will be assessed every cycle
d: For subjects with blood glucose>ULN, a fasting (>6h, water only) blood glucose sample will be obtained.
e: 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. 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.

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.

All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration of study drug on Cycle 1 Day 1 and within 48 hours prior to dispensing study drug for all subsequent cycles. 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 Table 5 for the management of clinically significant laboratory abnormalities.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 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 9.5.1.5.2), 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.

9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse rate [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) and height (cm) will be obtained at the visits designated in the Schedule of Assessments (Table 7 and Table 8) by a validated method. BP and pulse rate 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. BP that is consistently above the 95th percentile for sex, age, and height/length requires further evaluation.

9.5.1.5.5 Physical Examinations

Physical examinations will be performed as designated in the Schedule of Assessments (Table 7 and Table 8). 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.

9.5.1.5.6 Electrocardiograms

Electrocardiograms will be obtained as designated in the Schedule of Assessments (Table 7 and Table 8). Complete, standardized, single 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. If possible, subjects should 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 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

Cardiac systolic function and QTc will be assessed using echocardiography and ECG. See Table 7 and Table 8 for test schedules.

9.5.1.5.7 OTHER SAFETY ASSESSMENTS

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 and at the Off-treatment Visit.

Proximal tibial growth plates x-rays will be taken at baseline and at the Off-treatment Visit (for subjects with open plates at the Baseline Visit).

Information from studies in animals suggest that there is a risk of delayed tooth formation and/or physical growth and development. Therefore, dental examinations are being performed to evaluate subjects for potential anomalies in tooth formation and eruption schedule.

A dental examination by a qualified healthcare professional should be conducted per local institutional guidelines at baseline (C1D1±4 weeks), and thereafter per local standard of care (but no less than annually), and as part of the Off-treatment assessment. If the most recent dental exam is within 6 months prior to the Off-treatment Visit, the dental examination is not required. Postbaseline dental examinations are not required for subjects for whom permanent teeth (excluding third molars) are evaluated to be fully erupted at Baseline.

An echocardiogram to assess left ventricular shortening fraction or echocardiogram/MUGA scan to assess left ventricular ejection fraction (LVEF) will be performed during screening, Cycle 2 Day 1 (predose), Cycle 5 Day 1 (predose) and every 6th Cycle thereafter (Cycle 11 Day 1, Cycle 17 Day 1, etc predose each) and at the Off-treatment Visit or sooner if clinically indicated.

9.5.1.6 Other Assessments

Pregnancy Test

A serum β-hCG test will be performed for females of childbearing potential (see definition included in the Inclusion/Exclusion criteria). A serum or urine pregnancy test will be performed at Screening and Baseline (or within 72 hours prior to the first dose of study treatment), prior to Day 1 of each subsequent cycle and at the Off-treatment Visit in females of childbearing potential. The results must be reviewed prior to administration of study drug on Cycle 1 Day 1 and within 48 hours prior to dispensing study drug for all subsequent cycles. Blood and urine samples will be taken at designated time points as specified in the Schedule of Assessments (Table 7 and Table 8).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 7 and Table 8 present the Schedule of Procedures/Assessments for the study.

Table 7 Schedule of Assessments – Phase 1

Phase	**Pretreatment**		**Treatment[a] (All cycles are 28 days in duration)**										**Post-Treatment**
Period	**Screening**[b]	**Baseline**[c]	**Treatment Phase**[d]					**Extension Phase**[d]				**Off-Treatment Visit**	**Follow-up**[e]
Visit	1	2	3	4	5	6	7	8	9	10	11	99[x]	
Cycle			**Cycle 1**					**Cycle 2 - Last**					
Day	-28 to -2	-1	1	2	8	15	22	1	8	15	22		
Procedures/Assessments													
Informed consent	X												
Inclusion/exclusion	X	X											
Demographic data	X												
Medical/surgical history	X	X											
Prior anticancer medication/ procedures	X	X											
Pregnancy test[f]	X	X						X				X	
Lansky play score/ Karnofsky PS[g]	X	X						X				X	
Physical examination[h]	X	X				X		X				X	
Vital signs[i]	X	X	X		X	X	X	X	X[i]	X	X[i]	X	
12-lead ECG[j]	X							X				X	
Echocardiogram/MUGA scan[k]	X							X				X	
Clinical chemistry and hematology[l]	X	X				X		X		X		X	
INR	X												
Urine dipstick testing[m]	X		X		X	X	X	X	X[m]	X	X[m]	X	
PK blood samples[n]			X	X		X	X	X[n]					
Study treatment			Combination of lenvatinib (QD) and everolimus (QD) based on BSA calculations at Day 1 of each cycle										
Tumor assessments: RECIST 1.1[o]	X		Scans will be performed at Week 4 ±1 week					Scans will be performed at Week 12 ±1 week, Week 24 ±1 week, and then every 12 weeks ±1 week thereafter, or as clinically indicated					
Brain CT/MRI (RECIST 1.1)[p]	X		Brain scans will be performed at screening, and if clinically indicated.										
Brain MRI (RANO)[q]	X		Scans will be performed at Week 4 ±1 week					Scans will be performed at Week 12 ±1 week, Week 24 ±1 week, and then every 12 weeks ±1 week thereafter, or as clinically indicated					

Table 7 Schedule of Assessments – Phase 1

Phase	**Pretreatment**		**Treatment[a] (All cycles are 28 days in duration)**										**Post-Treatment**
Period	**Screening**[b]	**Baseline**[c]	**Treatment Phase**[d]					**Extension Phase**[d]				**Off-Treatment Visit**	**Follow-up**[e]
Visit	1	2	3	4	5	6	7	8	9	10	11	99[x]	
Cycle			**Cycle 1**					**Cycle 2 - Last**					
Day	-28 to -2	-1	1	2	8	15	22	1	8	15	22		
Procedures/Assessments													
Proximal tibial growth plates x-ray[r]		X										X	
Dental examination[r]	X							X				X	
Pharmacodynamic biomarkers[s]		X				X		X				X	
Blood sample for cf-nucleic acid[s]		X				X		X				X	
Archival tumor block or slides[t]		X											
Blood genomic DNA [u]		X											
Concomitant medications[v]	Throughout												
AEs/SAEs[w]	Throughout												

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, MUGA = multigated acquisition, PK = pharmacokinetics, PR = partial response, PS = performance score, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1, RANO = Response Assessment in Neuro-Oncology, RR = respiratory rate, SAE = serious adverse event, TNM = tumor-node-metastasis, Tx = treatment.

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. Duration of Treatment Phase: 1 Cycle (Visit 3-7); Duration of Extension Phase Cycle 2 – Last (Visit 8 – Last). Subjects benefiting from study treatment in the opinion of the investigator will continue treatment until disease progression, development of unacceptable toxicity, or protocol off study criteria are met, 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), prior to Day 1 of each subsequent cycle and at the off-treatment visit in females of childbearing potential. The results must be reviewed prior to administration of study drug on Cycle 1 Day 1 and within 48 hours prior to dispensing study drug for all subsequent cycles.
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 and at the Off-treatment Visit.
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. Height measurement will be obtained at Baseline Visit, at C4D1 and thereafter at D1 of every third cycle. 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 in the protocol. Blood pressure (BP) monitoring will occur at least weekly during the first 2 cycles.
j. Single 12-lead ECG. If possible, the subject should be in the recumbent position for a period of 5 minutes prior to the ECG. It should be performed at screening, Cycle 2 Day 1 (predose), Cycle 5 Day 1 (predose) and every 6th Cycle thereafter (C11D1, C17D1, etc. predose each) and at the off-treatment visit.
k. An echocardiogram/MUGA scan will be performed during screening, Cycle 2 Day 1 (predose), Cycle 5 Day 1 (predose) and every 6th Cycle thereafter (C11D1, C17D1, etc predose each) and at the Off-treatment Visit or sooner if clinically indicated. The assessments may be performed within 1 week prior to Day 1 of each scheduled cycle.
l. Clinical chemistry and hematology results must be reviewed prior to administration of study drug on C1D1 and within 48 hours prior to 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).
m. Urine dipstick testing should be performed at screening and on Day 1, 8, 15 and 22 for Cycle 1 (Treatment Phase) and on Day 1, 8, 15 and 22 for Cycle 2 (Extension Phase), bi-weekly thereafter in the Extension Phase or more frequently as clinically indicated and at the Off-treatment Visit. For subjects with history of proteinuria ≥2+, and management of proteinuria please refer to the protocol. 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 part of urine dipstick.
n. PK blood samples (2 mL per time point) will be drawn for lenvatinib during the Treatment Phase on Cycle 1 Day 1 and Cycle 1 Day 15 at predose and at 30 min, 1h, 2h, 3h, 4h and 8 h postdose, and predose on Cycle 1 Day 2 and Cycle 1 Day 22, and during the Extension Phase on Cycle 2 Day 1 and Cycle 3 Day 1 samples will be collected at predose and at 2-8 hours postdose from Phase 1 subjects remaining on study. PK blood samples (2 mL per time point) will be drawn for everolimus during the Treatment Phase on Cycle 1 Day 1 at predose and 1h postdose, Cycle 1 Day 2 at predose, Cycle 1 Day 15 at predose and at 1 hour postdose, and on Cycle 1 Day 22 at predose and at 1 hour postdose. With the exception of the predose samples on Cycle 1 Day 1, all other predose samples are to be drawn at 24 hour post dose administered on the previous day. If dose interruption is necessary at these time points, please contact the sponsor.
o. For all tumor types except HGG, **Screening:** Tumor assessments using CT chest and CT/MRI of the 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. During the **Treatment Phase** tumor assessments using CT chest and CT/MRI of the abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed at Week 4 ±1 week, and in the **Extension Phase** at Week 12 ±1 week, Week 24 ±1 week and every 12 weeks ±1 week thereafter or as clinically indicated. For subjects with primary CNS tumors and no other known areas of disease only target and non-target lesions plus any areas of newly suspected disease must be scanned. All responses are to be confirmed at a follow-up examination after ≥28 days following the initial indication of response. Scans should be performed using 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. All responses should be confirmed at a follow-up examination after ≥28 days.
p. Brain CT with contrast or MRI pre- and post- gadolinium contrast will be performed at Screening, and if clinically indicated.
q. For HGG, RANO criteria will be followed, **Screening**: Tumor assessments using MRI of the brain that will be followed as target lesions and non-target lesions should be performed within 28 days prior to the C1D1. During the **Treatment Phase** tumor assessments of the same brain lesions as at Screening, should be performed at Week 4 ±1 week, and in the **Extension Phase** at Week 12 ±1 week, Week 24 ±1 week and every 12 weeks ±1 week thereafter, or as clinically indicated. All responses should be confirmed at a follow-up examination after ≥28 days following the initial indication of response. The same methodology (MRI) and scan acquisition techniques (including use or nonuse of IV contrast) should be used as was used for the screening assessments.
r. Proximal tibial growth plates x-rays should be conducted at Baseline and at the Off-treatment visit (for subjects with open plates at the baseline visit). A dental examination by a qualified healthcare professional should be conducted per local institutional guidelines at baseline (C1D1±4 weeks), and thereafter per local standard of care (but no less than annually) and as part of the Off-treatment assessment. If the most recent dental examination is within 6 months prior to the Off-treatment Visit, the dental exam is not required. Post-baseline dental exams are not required for subjects for whom permanent teeth (excluding third molars) are evaluated to be fully erupted at baseline.
s. Blood samples will be collected from consenting subjects (optional) for plasma and serum at Baseline, and predose on Cycle 1 Day15, Cycle 2 Day 1, and then matched with tumor assessments, and at the Off-treatment Visit. Only subjects with BSA >0.68 m^2 are eligible to consent (optional) to blood samples for plasma and serum studies. Serum sample will be used for evaluating biomarkers of response and plasma sample for cf-nucleic acid to explore proteins and genetic alterations in genes implicated in angiogenesis.

t. An archival tumor sample from the most recent surgery or biopsy for identification of predictive biomarkers will be collected (if available) from all enrolled subjects at any time during the study.
u. 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.
v. Concomitant medications will be recorded throughout the study and for 28 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 28 days after last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 hours.
x. The off-treatment assessments should occur within 28 days of the final dose of study treatment.

Table 8 Schedule of Assessments – Phase 2

Phase	**Pretreatment**		**Treatment[a] (All cycles are 28 days in duration)**															**Post-Treatment**
Period	**Screening[b]**	**Baseline[c]**	**Treatment Phase[d]**													**Extension Phase**		**Off-Treatment Visit**	**Follow-up[e]**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	99[x]	
Cycle			**Cycle 1**					**Cycle 2**				**Cycle 3**		**Cycle 4**		**Cycle 5 - Last**			
Day	-28 to -2	-1	1	2	8	15	22	1	8	15	22	1	15	1	15	1	15		
Procedures/Assessments																			
Informed consent	X																		
Inclusion/exclusion	X	X																	
Demographic data	X																		
Medical/surgical history	X	X																	
Prior anticancer medication/ procedures	X	X																	
Pregnancy test[f]	X	X						X				X		X		X		X	
Lansky play score/ Karnofsky PS[g]	X	X						X				X		X		X		X	
Physical examination[h]	X	X				X		X				X		X		X		X	
Vital signs[i]	X	X	X		X	X	X	X	X[i]	X	X[i]	X		X		X	X	X	
12-lead ECG[j]	X							X								X		X	
Echocardiogram/MUGA scan[k]	X							X								X		X	
Clinical chemistry and hematology[l]	X	X				X		X		X		X	X	X	X	X	X	X	
INR	X																		
Urine dipstick testing[m]	X		X		X	X	X	X	X[m]	X	X[m]	X	X	X	X	X	X	X	
PK blood samples[n]			X			X		X[n]				X[n]							
Study treatment			Combination of lenvatinib (QD) and everolimus (QD) based on BSA calculations at Day 1 of each cycle																

Table 8 Schedule of Assessments – Phase 2

Phase	**Pretreatment**		**Treatment[a] (All cycles are 28 days in duration)**																**Post-Treatment**
Period	**Screening[b]**	**Baseline[c]**	**Treatment Phase[d]**													**Extension Phase**		**Off-Treatment Visit**	**Follow-up[e]**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	99[x]	
Cycle			**Cycle 1**					**Cycle 2**				**Cycle 3**		**Cycle 4**		**Cycle 5 - Last**			
Day	-28 to -2	-1	1	2	8	15	22	1	8	15	22	1	15	1	15	1	15		
Procedures/Assessments																			
Tumor assessments: RECIST 1.1[o]	X		Scans will be performed at Week 8 ±1 week and Week 16 ±1 week													Scans will be performed at Week 24 ±1 week and every 12 weeks ±1 week thereafter, or as clinically indicated			
Brain CT/MRI (RECIST 1.1)[p]	X		Brain scans will be performed at screening, and if clinically indicated.																
Brain MRI (RANO)[q]	X		Scans will be performed at Week 8 ±1 week and Week 16 ±1 week													Scans will be performed at Week 24 ±1 week and every 12 weeks ±1 week thereafter, or as clinically indicated			
Proximal tibial growth plates x-ray[r]		X																X	
Dental examination[r]	X		X															X	
Pharmacodynamic biomarkers[s]		X				X		X										X	
Blood sample for cf-nucleic acid[s]		X				X		X										X	
Archival tumor block or slides[t]		X																	
Blood genomic DNA [u]		X																	
Concomitant medications[v]	Throughout																		
AEs/SAEs[w]	Throughout																		

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, MUGA = multigated acquisition, PK = pharmacokinetics, PR = partial response, PS = performance score, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1, RR = respiratory rate, RANO = Response Assessment in Neuro-Oncology, SAE = serious adverse event, TNM = tumor-node-metastasis, Tx = treatment.

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. Duration of Treatment Phase: 4 Cycles (Visit 3-15); Duration of Extension Phase Cycle 5 – Last (Visit 16 – Last). Subjects benefiting from study treatment in the opinion of the investigator will continue treatment until disease progression, development of unacceptable toxicity, or protocol off study criteria are met, 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), prior to Day 1 of each subsequent cycle and at the off-treatment visit in females of childbearing potential. The results must be reviewed prior to administration of study drug on Cycle 1 Day 1 and within 48 hours prior to dispensing study drug for all subsequent cycles.
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 in the Treatment Phase and Extension Phase thereafter and at the Off-treatment Visit.
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 in the Treatment Phase and Extension Phase, 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). Height measurement will be obtained at Baseline Visit, at C4D1 and thereafter at D1 of every third cycle. 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 in the protocol. Blood pressure (BP) monitoring will occur at least weekly during the first 2 cycles.
j. Single 12-lead ECG. If possible, the subject should be in the recumbent position for a period of 5 minutes prior to the ECG. It should be performed at screening, Cycle 2 Day 1 (predose) in the Treatment Phase, and at Cycle 5 Day 1 (predose) and every 6th Cycle thereafter (C11D1, C17D1, etc predose each) in the Extension Phase, and at the Off-treatment visit.
k. An echocardiogram/MUGA scan will be performed during screening, Cycle 2 Day 1 (predose) in the Treatment Phase, and at Cycle 5 Day 1 (predose) and every 6th Cycle thereafter (C11D1, C17D1, etc predose each) in the Extension Phase, and at the Off-treatment Visit or sooner if clinically indicated. The assessments may be performed within 1 week prior to Day 1 of each scheduled cycle.
l. Clinical chemistry and hematology results must be reviewed prior to administration of study drug on C1D1 and within 48 hours prior to dispensing study drug for all subsequent cycles in the Treatment Phase and Extension Phase. 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).
m. Urine dipstick testing should be performed at screening and on Day 1, 8, 15 and 22 for Cycles 1-2 in the Treatment Phase, bi-weekly thereafter or more frequently in the Treatment Phase and Extension Phase as clinically indicated and at the Off-treatment Visit. For subjects with history of proteinuria ≥2+, and management of proteinuria please refer to the protocol. 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 part of urine dipstick.
n. Sparse sampling (two 2 mL samples [total 4 mL blood] per time point) for PK analysis of lenvatinib and everolimus will be performed in the Treatment Phase during Cycle 1 Day 1 at 0.5-4 hours and 6-10 hours postdose and on Cycle 1 Day15 at predose and 0.5-4 hours and 6-10 hours postdose and on Cycles 2 and 3 predose. With the exception of the predose samples on Cycle 1 Day 1, all other predose samples are to be drawn at 24 hour post dose administered on the previous day. If dose interruption is necessary at these time points, please contact the sponsor.
o. For all tumor types except HGG, **Screening:** Tumor assessments using CT chest and CT/MRI of the 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. In the **Treatment Phase** tumor assessments using CT chest and CT/MRI of the abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed at Week 8 ±1 week and Week 16 ±1 week, and in the **Extension Phase** at Week 24 ±1 week, and then every 12 weeks ± 1 week thereafter or as clinically indicated. All responses are to be confirmed at a follow-up examination after ≥28 days following the initial indication of response. Scans should be performed using 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. All responses should be confirmed at a follow-up examination after ≥28 days.
p. Brain CT with contrast or MRI pre- and post-gadolinium contrast will be performed at Screening, and if clinically indicated.

q. For HGG, RANO criteria will be followed, **Screening**: Tumor assessments using MRI of the brain that will be followed as target lesions and non-target lesions should be performed within 28 days prior to the C1D1. In the **Treatment Phase** tumor assessments of the same brain lesions as at Screening, should be performed at Week 8 ±1 week and Week 16 ±1 week, and in the **Extension Phase** at Week 24 ±1 week and every 12 weeks ±1 week thereafter, or as clinically indicated. All responses should be confirmed at a follow-up examination after ≥28 days following the initial indication of response. The same methodology (MRI) and scan acquisition techniques (including use or nonuse of IV contrast) should be used as was used for the screening assessments.
r. Proximal tibial growth plates x-rays should be conducted at Baseline and at the Off-treatment visit (for subjects with open plates at the Baseline Visit). A dental examination by a qualified healthcare professional should be conducted per local institutional guidelines at baseline (C1D1±4 weeks), and thereafter per local standard of care (but no less than annually), and as part of the Off-treatment assessment. If the most recent dental examination is within 6 months prior to the Off-treatment Visit, the dental exam is not required. Post-baseline dental exams are not required for subjects for whom permanent teeth (excluding third molars) are evaluated to be fully erupted at baseline.
s. Blood samples will be collected from consenting subjects (optional) for plasma and serum at Baseline, and predose on Cycle 1 Day15, Cycle 2 Day 1, and then matched with tumor assessments, and at the Off-treatment Visit. Only subjects with BSA >0.68 m^2 are eligible to consent (optional) to blood samples for plasma and serum studies. Serum sample will be used for evaluating biomarkers of response and plasma sample for cf-nucleic acid to explore proteins and genetic alterations in genes implicated in angiogenesis.
t. An archival tumor sample from the most recent surgery or biopsy for identification of predictive biomarkers will be collected (if available) from all enrolled subjects at any time during the study.
u. 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.
v. Concomitant medications will be recorded throughout the study and for 28 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 28 days after last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 hours.
x. The off-treatment assessments should occur within 28 days of the final dose of study treatment.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to the Schedule of Procedures/Assessments (Table 7 and Table 8).

9.5.3 Appropriateness of Measurements

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

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, ECGs/echocardiograms, 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 1 business day (or 24 hours for EU sites) from the date the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected through the last visit. 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 Study 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 1 business day 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 must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's 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 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, 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 1 business day from the date 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 1 business day from the date 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

9.5.4.3.1 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.

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 the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 7 and Table 8).

The investigator will promptly explain to the subject 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 other.

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 (or guardian/legally authorized representative) to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject (or guardian/legally authorized representative) whether the subject 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 (or guardian/legally authorized representative), 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, 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 as identified on Form FDA 1572 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 is completed 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

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, Q1, Q3, and range (minimum and maximum), unless otherwise specified.

Efficacy data will be analyzed using the Evaluable Analysis Set, safety data will be analyzed using the Safety Analysis Set, PK data will be analyzed using the PK Analysis Set, and PD data will be analyzed using the PD Analysis Set. All analyses will be performed by dose level in Phase 1 (if appropriate) and for each study cohort in Phase 2, unless otherwise specified.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINTS

Primary Endpoints for Phase 1

- MTD and RP2D of lenvatinib in combination with everolimus
- Safety and toxicity of lenvatinib in combination with everolimus

Primary Endpoint for Phase 2

- ORR, defined as the proportion of subjects who have the best overall response (BOR) of complete response (CR) or partial response (PR), at Week 16

9.7.1.1.2 SECONDARY ENDPOINTS

Secondary Endpoints for Phase 1 and Phase 2

- ORR at the time of data cutoff
- DCR, defined as the proportion of subjects who have the BOR of CR or PR or stable disease (SD) (SD duration ≥7 weeks since the first dose of the study treatment)
- CBR, defined as the proportion of subjects who have the BOR of CR or PR or durable SD (SD duration ≥23 weeks since the first dose of the study treatment)
- DOR, defined as the time from the date of the first documented CR or PR to the date of the disease progression objectively documented or death (whichever occurs first)

- Plasma PK of lenvatinib and trough concentrations of everolimus when administered in combination
- Safety and toxicity of lenvatinib in combination with everolimus in Phase 2

9.7.1.1.3 EXPLORATORY ENDPOINTS

- Assess candidate alterations in genes and/or proteins that may contribute to tumor development and predictive marker of response in archival tumor tissue
- Correlative blood and tumor biomarkers of treatment effects and outcomes

9.7.1.2 Definitions of Analysis Sets

- **Evaluable Analysis Set**, defined as all subjects, who have measurable disease present at baseline and at least 1 post-baseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease. This will be the analysis set for efficacy.
- **Safety Analysis Set**, defined as all subjects who received at least 1 dose of study drug (lenvatinib or everolimus).
- **Pharmacokinetic (PK) Analysis Set**, defined as subjects in Safety Analysis Set who had at least 1 measurable postdose plasma concentration with an adequately documented dosing history.
- **Pharmacodynamic (PD) Analysis Set**, defined as all subjects in Safety Analysis Set who had evaluable PD data.

9.7.1.3 Subject Disposition

The number (percentage) of subjects who completed the study treatment/study and discontinued from the study treatment/study and reasons for discontinuation will be provided.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for each cohort in Phase 2 as well as by dose level in Phase 1 if appropriate. Demographic and baseline variables include, but are not limited to age, sex, race, Lansky score, and Karnofsky score.

9.7.1.5 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). The number (percentage) of subjects who took prior and concomitant medications will be summarized, using Anatomical Therapeutic Chemical (ATC) class and WHO DD preferred term. Prior medications will be defined as medications that started 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 or started up to 28 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

Data cutoff for the primary study analysis in Phase 2 will occur when all evaluable subjects have completed at least 4 treatment cycles and, if applicable, a confirmatory scan has been performed (in case of a PR or CR at Week 16), or have discontinued study treatment early.

The following are evaluability criteria for objective response and non-target disease response analysis:

- **Evaluable for objective response**: Only those subjects who have measurable disease present at baseline and have their disease re-evaluated at post-baseline visits will be considered evaluable for objective response. These subjects will have their response classified according to RECIST 1.1 (for Ewing sarcoma/pPNET and rhabdomyosarcoma) or RANO (for HGG).
- **Evaluable for non-target disease response**: Subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease and have had their disease re-evaluated at post-baseline visits will be considered evaluable for non-target disease. Subjects with only non-target disease will be summarized by their best overall response. The response will be classified according to RECIST 1.1 defined categories for subjects with non-target disease only.

9.7.1.6.1 Primary Efficacy Analysis

Phase 1

The study will utilize the rolling 6 design. The primary objective of Phase 1 is to determine the MTD and to establish the RP2D.

Phase 2

The primary efficacy endpoint in Phase 2 is ORR at 16 weeks. Objective responses will count only confirmed CR and PR. Estimated ORR and its exact 95% CI using the Clopper-Pearson method will be presented.

9.7.1.6.2 Secondary Efficacy Analyses for phase 1 and phase 2

The secondary efficacy endpoints will be ORR at the time of data cutoff, DCR, CBR and DOR. These endpoints in Phase 1 will be summarized if appropriate and listed by dose level, and ORR will be based on only subjects with measureable disease at screening/baseline. For Phase 2, the ORR, DCR and CBR will be provided with exact 95% CIs using the Clopper-Pearson method. The DOR will be analyzed using Kaplan-Meier approach among the responders (CR or PR). If a subject had no record of disease progression or did not die before the data cutoff date, or before early discontinuation (including discontinuations due to toxicity, undocumented clinical progression, change of cancer treatment, or decreasing performance status), then the subject will be censored at the last available tumor assessment.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSIS

Lenvatinib and everolimus concentration versus time data will be tabulated and summarized and graphically presented.

Plasma concentrations of lenvatinib from the intense sampling in Phase 1 will be used to determine the following PK parameters: area under the plasma concentration time course profile (AUC), maximum observed concentration (C_{max}), and time from dosing to the maximum observed concentration (T_{max}). Other PK parameters may be determined as data permit.

For both lenvatinib and everolimus, data from Phase 1 and 2 of the study will be pooled with available data from other studies and subjected to population PK analysis. For each drug, the PK model will be parameterized in terms of clearance and volume of distribution.

Details of the population PK analysis will be provided in a separate analysis plan.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOKINETIC/PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Correlation between clinical response to treatment associated with a combination of lenvatinib and everolimus and blood or tumor biomarkers will be examined using descriptive statistics and graphic displays as appropriate. Details will be provided in a separate analysis plan.

Pharmacokinetic/PD exposure-safety relationships will be explored. Safety endpoints will be most frequent AEs of special interest and dose reductions. Exploratory/graphical analyses will be conducted for PK/PD evaluations, and may be followed by model-based analyses. A detailed analysis plan will be provided separately.

9.7.1.8 Safety Analyses

Safety variables include study drug exposure, treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, 12-lead ECGs, cardiac function by echocardiography/MUGA scan, urine dipstick, and Lansky play scores or Karnofsky performance scores.

All toxicities will be summarized. The following are evaluability criteria for toxicity analysis:

- **Evaluable for toxicity:** All subjects who received at least one dose of study treatment are evaluable for toxicity. For Phase 1, toxicities during Cycle 1 will be used for the purpose of dose escalations according to the rolling 6 design. Subjects who developed a DLT or received at least 75% of the prescribed dose during cycle 1 are considered fully evaluable for toxicity for the purpose of dose escalation.

The incidence of treatment-emergent adverse events (TEAEs) and SAEs will be summarized by system organ class and preferred term. Laboratory test data, vital signs, 12-lead ECGs, cardiac function by echocardiography/MUGA scan, urine dipstick, Lansky play scores or Karnofsky performance scores, and their changes or shifts from baseline will be summarized using descriptive statistics, as appropriate. Summary of study drug exposure will be provided. Prior and concomitant medications, medical/surgical history and subject demographics will be summarized.

9.7.1.8.1 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 AEs will be summarized.

9.7.1.8.2 Adverse Events

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

A TEAE is defined as an AE that emerges during 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.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by CTCAE grade if appropriate.

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

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug or leading to study drug dose changes will be summarized by MedDRA SOC and PT. A

subject data listing of all AEs leading to discontinuation from study drug or leading to study drug dose changes will be provided.

9.7.1.8.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each post-baseline visit will be summarized by visit using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and shifts from baseline to worst postbaseline will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and at least 1 post-baseline results.

Laboratory parameters will be categorized according to CTCAE grades, and shift tables from baseline CTCAE grades to the worst post-baseline grades will be provided.

9.7.1.8.4 Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit. A shift table of hypertension from baseline to worst post-baseline grades will be provided.

9.7.1.8.5 Electrocardiograms

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit. Shift tables will present shifts from baseline in ECG interpretation (categorized as normal, abnormal, not clinically significant, and abnormal clinically significant) to the worst post-baseline assessment.

9.7.1.8.6 Other Safety Analyses

Shift tables of Lansky play scores and Karnofsky performance scores from baseline will be provided.

Descriptive statistics and changes from baseline for left ventricular shortening fraction assessed on echocardiogram and LVEF assessed on echocardiogram or MUGA scans will be presented. Percent reduction from baseline will also be summarized.

9.7.2 Determination of Sample Size

Phase 1 – Determination of the Maximum Tolerated Dose: The total number of subjects required for the Phase 1 portion of this study will depend upon the toxicities observed as the study progresses. The minimum number of evaluable subjects required for this study is 4. The projected maximum number of evaluable subjects required is 48. Once the MTD or RP2D has been defined, up to 6 additional subjects with recurrent or refractory solid tumors may be enrolled to acquire PK data in a representative number of young subjects. Therefore, a maximum of 54 subjects are expected to be enrolled in the 4 dose escalation levels, and PK expansion. The Phase 1 part of the study is expected to be completed within 18 months. In

the event that each of Dose Levels -1, 1, 2, and 3 are expanded to 12 subjects, an absolute maximum of 54 subjects would be required allowing for 20% to be non-evaluable and including up to 6 additional subjects for PK analysis.

Phase 2: Phase 2 will require a minimum of 10 evaluable subjects per disease cohort and a maximum of 20 (10 evaluable subjects in each stage of Simon's optimal 2-stage design). Therefore, a maximum of 22 subjects per cohort will be enrolled to allow for a 10% non-evaluable rate. This design has 88% power to detect a 20% increase in the response rate at the significance level of one-sided alpha = 0.07 assuming a null response rate of 5% and alternative response rate ≥25%.

9.7.3 Interim Analysis

For each disease cohort (Ewing sarcoma/pPNET, rhabdomyosarcoma and HGG) in Phase 2, there will be 1 futility analysis: this is planned for after the first 10 evaluable subjects have completed at least 4 treatment cycles and, if applicable, a confirmatory scan has been performed (in case of a PR or CR at week 16), or have discontinued study drug early (before Week 16). At the futility analysis, if there are no responders (CR/PR), then the enrollment for that cohort will be discontinued for lack of efficacy. If 1 or more responses are observed, the accrual will continue.

Independent data monitoring committee (IDMC)

Safety monitoring will be conducted by an independent data monitoring committee (IDMC). The frequency of safety reviews will be defined in the IDMC charter. Minutes from the open meetings of the IDMC will be provided if requested by regulatory agencies. The function and membership of the IDMC will be described in the IDMC charter.

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.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

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 (or appropriate study team member) and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

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 (or if regionally required, the head of the medical institution) 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 (or, if regionally required, the head of the medical institution) 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 (or if regionally required, the head of the medical institution) 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, electroencephalograms, 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 where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following items, the data recorded directly on the CRF are to be considered source data:

- Study drug compliance (eg, the reason for any change of dosage)
- Indication for prior/concomitant medication (drug/therapy)
- Discontinuation information (eg, in the case of lost to follow-up due to the subject choice)
- Sampling date and time for the drug concentration
- Sampling date for the clinical laboratory tests

- Comments and other information on AEs (eg, severity, relationship to study drug, outcome)

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) 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 15 years following the completion of the study.

For sites in Canada, the Sponsor should retain all study documents to maintain complete and accurate records, including those specified above, for a period of 25 years.

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

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. 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 designated contractor) 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.

The Eisenhauer article published in the European Journal of Cancer, is available online at: http://linkinghub.elsevier.com/retrieve/pii/S0959804908008733.

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: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf]

Appendix 3 Monoclonal Antibodies Half-lives

Table of Antibody Half-lives for protocol eligibility purposes (12/18/15)

Antibody	Half-Life	Washout Period	COG Protocol/Reference
Alemtuzumab (Campath®; anti CD52)	11 hours	33 hours	Pediatr Blood Cancer 2009;53(6):978-983 (ADVL0222)
Bevacizumab (Avastin®; anti-VEGF)	12 days	36 days	J Clin Oncol 2008;26(3):399-405 (ADVL 0314)
Brentuximab vedotin (Adcetris; anti CD30)	5 days	15 days	FDA label
Ch 14.18 (anti-GD2)	3 days	9 days	ANBL0931, ANBL1221
Cetuximab (Erbitux®; anti-EGFR)	5 days	15 days	J Clin Oncol 2009;27(30):5102-5108
Cixutumumab (IMC-A12; anti-IGFR-I)	7 days	21 days	J Clin Oncol 27:15s, 2009
Epratuzumab (anti-CD22)	23 days	69 days	J Clin Oncol 2005;23(22):5044-5051
Gemtuzumab (Mylotarg®; anti-CD33)	3 days	9 days	J Clin Pharmacol 2004;44:873; PDR 2009; AAML03P1
I-3F8	3 days	9 days	Health Phys. 2007 Jan;92(1):33-9
Ipilimumab	15 days	45 days	ADVL1412
Lorvotuzumab (IMGN901)	24 hr	3 days	ADVL1522
Nimotuzumab	13 days	39 days	J Cancer Res Ther. 2015 Aug;11 Suppl 1:C32-7
Nivolumab	25 days	75 days	ADVL1412
Ontuxizumab (MORAb-004)	93 hr	12 days	ADVL1213
Pembrolizumab (MK-3475)	26 days	78 days	Onco Targets Ther. 2015; 8: 2535–2543
Ramucirumab	15 days	45 days	ADVL1416
Rituximab (Rituxan®; anti CD20)	22 days	66 days	PDR, 63rd edition, 2009
SGN-30 (anti-CD30)	25 days	75 days	Blood 2008;111(4):1848-1854
Other Agents	**Half-Life**	**Washout Period**	**COG Protocol/Reference**
GDC-0449 (HH antagonist)	14 days	42 days	NEJM 2009;361(12):1173-1178

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 as follows:

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

Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, et al for The American Thyroid Association Guidelines Task. Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015;25(7):716-59.

Kumagai A, Reiners C, Drozd V, Yamashita S. Childhood thyroid cancers and radioactive iodine therapy: necessity of precautious radiation health risk management. Endocr J. 2007;54(6):839-47.

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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;23:989-96.

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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)	↓	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)	↓	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/

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

	BP	Systolic BP (mmHg)							Diastolic BP (mmHg)						
AGE	Percentile	Percentile of Height							Percentile of Height						
(Year)	↓	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
I	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)	↓	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

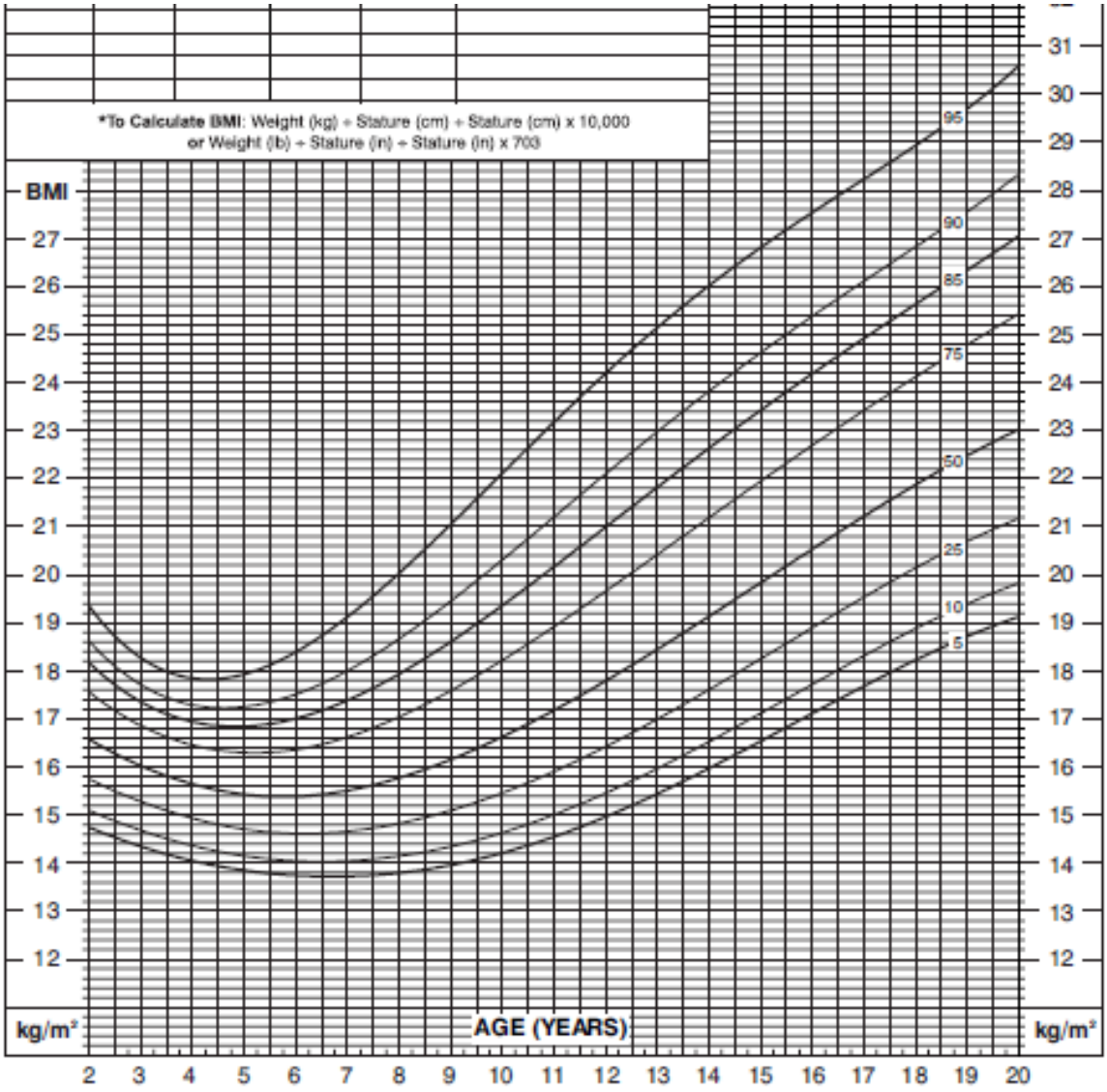
BP = blood pressure

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/

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)

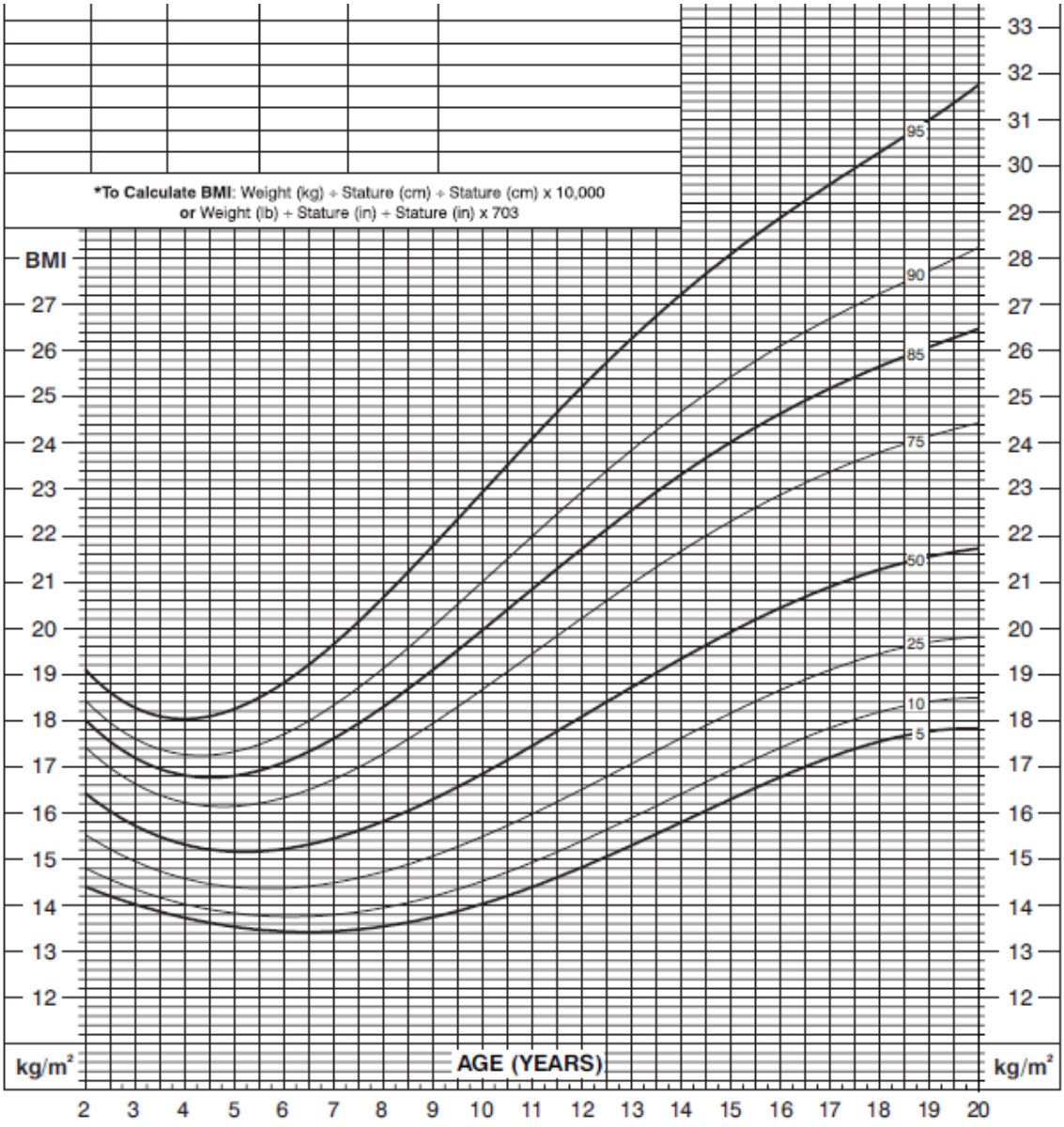
http://www.cdc.gov/growthcharts

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.html

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 (optional) will be bound by the sample principles and processes outlined in the main/separate study protocol.

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 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 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 children or anyone who may handle the trash.

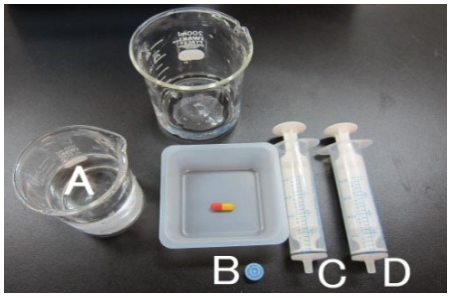
Caregivers should not open the capsule in order to avoid repeated exposure to the contents of the capsule.

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.

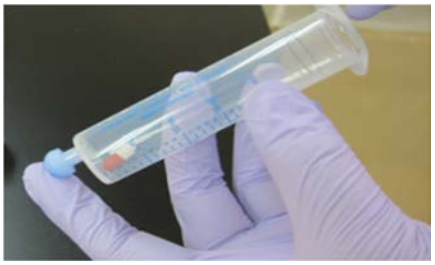
All unused products and packaging from used products should be returned to the site by the patient or caregiver at the next visit. Do not throw away any medicines via wastewater or household waste.

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 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)



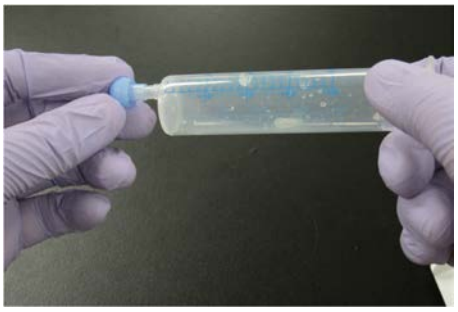
Place 1 capsule* into a syringe. Close the tip port of the syringe with a cap.
* One to 5 capsules are allowed to be placed into a 20 mL syringe.

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

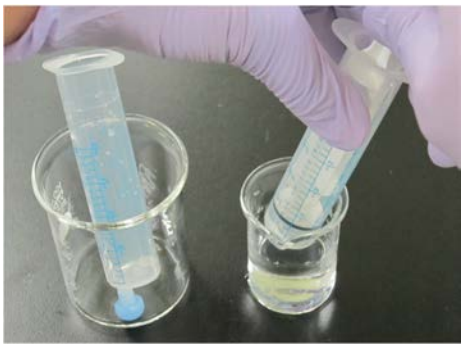
Insert the plunger into the syringe (cylinder) about 2 cm from the end. Leave the syringe upright in a flask for not less than 10 minutes.

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 3 mL of suspension into the mouth of the subject.

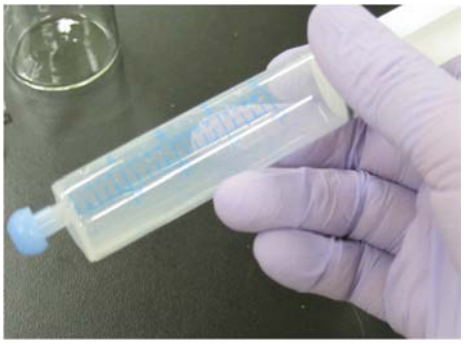


Rinse step
After the administration of the 3 mL suspension from the syringe, recap the syringe for reuse.



Draw up 2 mL of water or apple juice 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).



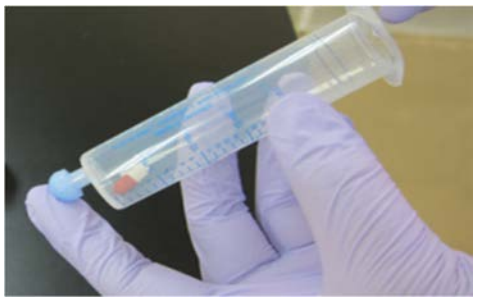
Shake the syringe 10 times to dissolve the remaining granules.

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 (3mL 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)



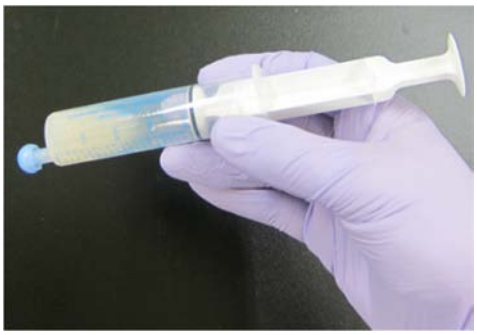
Place 1 capsule* into a syringe with the tip of the port of the syringe closed with a cap and place into a flask.

* 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.

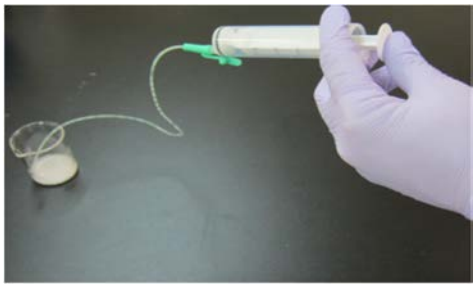
Insert the plunger into the syringe about 2 cm from the end.

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



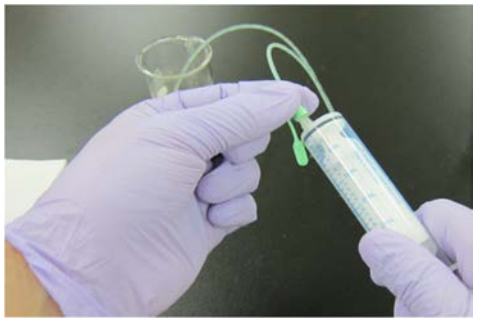
After 10 minutes, shake the syringe for not less than 3 minutes to dissolve the capsule shell completely and to suspend the granules (the capsule shell needs to be dissolved and the granules well suspended).

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

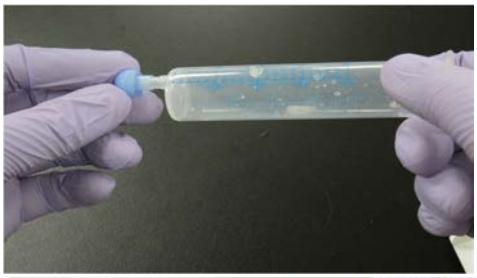


Connect the syringe to an NG tube and administer the 3 mL of suspension through the NG tube. It is recommended where possible, that the syringe is held in the horizontal position while administering the suspension to avoid the possibility of blocking the nasogastric tubing with undissolved granules.

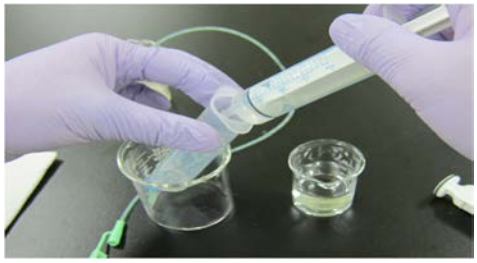
Rinse step



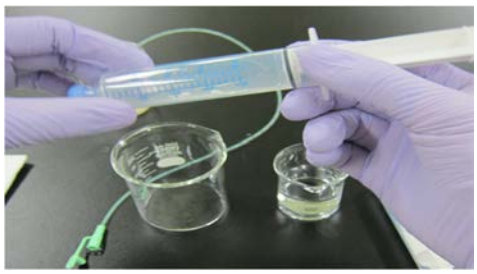
After inserting the suspension, disconnect the NG tube from the syringe.



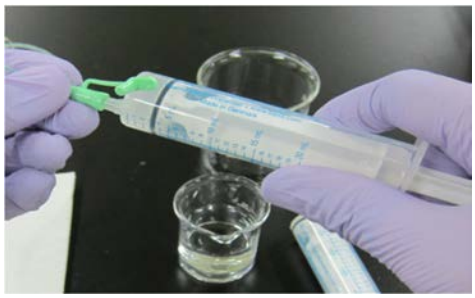
Reconnect the cap (reuse) of the syringe.



Draw up 2 mL of water or apple juice a 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 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 Imaging Scans Methodology for Tumor Assessment

For All Tumor Types Except High Grade Glioma (HGG)

Screening computed tomography (CT) scans should be performed with oral and iodinated intravenous contrast and magnetic resonance imaging (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 of 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 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 assess by both clinical and radiographic techniques, the radiographic (CT/MRI) technique should be used for the assessment of target and non-target lesions.

18-Fluoro-2-deoxyglucose whole-body positron emission tomography (^{18}FDG-PET) scans may be used to assess new lesions if used according to RECIST 1.1 (a new FDG-avid lesion if there is a negative ^{18}FDG-PET scan at baseline; if there was no baseline ^{18}FDG-PET scan, a potential new lesion must be demonstrated with CT or MRI).

For HGG

A standard MRI imaging protocol will be performed for use in the assessment. The brain MRI sequences will include axial T1-weighted spin-echo imaging obtained using a TR of 400 – 600 ms, a TE of 15 ms or less, a field of view of 22 – 24 cm, a matrix of 256 x 256, a slice thickness of 5 mm and intraslice gaps of 1.5 mm or less; axial T2-weighted fast spin echo images using a TR of 2500 – 4500 ms, TE of 100 – 130 ms, echo train length (ETL) of 13 – 25, FOV or 22 – 24 cm, a matrix of 256 x 256, a slice thickness of 5 mm and intraslice gaps of 1.5 mm or less; axial FLAIR images using a TR of 6000 – 9000 ms, TE of 100 – 130

ms, TI of 2000 – 2500 ms, ETL of 13 – 25, a matrix of 256 x 192-256, a slice thickness of 5 mm and intraslice gaps of 1.5 mm or less. After the intravenous injection of 0.1 mmol/kg of gadolinium containing contrast agent, a T1-weighted axial acquisition will be performed using the same parameter ranges as above, followed by a whole brain sagittal or coronal 3D volumetric T1-weighted spoiled gradient echo or fast low angle shot sequence using TR less than 10 ms, TE less than 5 ms, FOV of 25.6 cm or less, and a matrix size appropriate for obtained voxels that are 1.3 mm or less in any direction.

Appendix 14 Response Assessment in Neuro-Oncology (RANO) Criteria

The RANO guidelines are as follows:

Specific lesions are to be evaluated serially with comparative analysis of changes in the area of contrast enhancement, as well as the non-enhancing component will be performed. The product of the maximal cross sectional enhancing diameters will be used to determine the size of the contrast-enhancing lesions as follows:

- **Measurable disease** is defined as bidimensionally contrast-enhancing lesions with clearly defined margins by CT or MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are preferably at most 5 mm apart with 0 mm skip.
- **Non-measurable disease** is defined as either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters <1cm. If there are multiple contrast-enhancing lesions, a maximum of 5 of the largest lesions may be measured and the sum of the products of the perpendicular diameters of these lesions determined.
- For subjects with recurrent disease who have **multiple lesions** of which only 1 or 2 are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response.
- Given the difficulty of differentiating "**pseudoprogression**" from true progression in the first 3 months after irradiation, subjects in this window should only be classified as progressive disease if the progression is outside the radiation field (beyond the high dose region or 80% isodose line) or if there is pathologic confirmation of disease progression.
- **Radiographic response** should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smaller of baseline or the smallest tumor measurement following initiation of therapy (nadir) for determination of progression:
  - Complete Response (CR): Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan at least 4 weeks later, this scan will be considered only stable disease. No new lesions. Stable or improved non-enhancing (T2/FLAIR) lesions. Subjects must be on no corticosteroids and stable or improved clinically.
  - Partial Response (PR): Greater than or equal to 50% decrease, compared to baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease. No progression of non-measurable disease. No new lesions. Stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. Subjects should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically.
  - Stable Disease (SD): This occurs if the subjects did not qualify for CR, PR, or progressive disease (PD) (see below). There should be stable or improved

nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose. The subject should be stable or improved clinically.

- Progressive Disease (PD): Progression is defined as >25% increase in sum of the products of perpendicular diameters of enhancing lesions (over baseline if no decrease) on stable or increasing doses of corticosteroids and/or a significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events. Any new lesion. Clear clinical deterioration not attributable to other causes apart from the tumor. Failure to return for evaluation due to death or deteriorating condition is considered progressive disease as well.

Reference:

Wen P, Macdonald DR, Reardon DA, Cloughesy TF, Sorenson AG, Galanis E, et al. for the Response Assessment in Neuro-Oncology Working Group. Updated Response Assessment Criteria for High-Grade Gliomas. J Clin Oncol. 2010;28:1963-72.

Appendix 15 CYP3A4 Substrates, Inducers and Inhibitors

This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

CYP3A4 Substrates	Strong Inhibitors[1]	Moderate Inhibitors	Weak Inhibitors	Inducers
alfentanil[4,5]	atazanavir	aprepitant	alprazolam	armodafinil
amiodarone[4]	boceprevir	conivaptan	amiodarone	barbiturates
aprepitant[5]	clarithromycin	crizotinib	amlodipine	bosentan
atorvastatin[5]	cobicistat	diltiazem	atorvastatin	carbamazepine
benzodiazepines	darunavir	dronedarone	bicalutamide	deferasirox
bortezomib	delavirdine	erythromycin	cilostazol	echinacea
brentuximab	grapefruit[3]	fluconazole	cimetidine	efavirenz
budesonide[5]	grapefruit juice[3]	fosamprenavir	ciprofloxacin	etravirine
buspirone[5]	indinavir	grapefruit[3]	cyclosporine	fosphenytoin
calcium channel blockers	itraconazole	grapefruit juice[3]	fluvoxamine	glucocorticoids[2]
cisapride	ketoconazole	imatinib	fosaprepitant	modafinil
citalopram/escitalopram	lopinavir/ritonavir	mifepristone	isoniazid	nafcillin
conivaptan[5]	nefazodone	nilotinib	nicardipine	nevirapine
glucocorticoids[2]	nelfinavir	verapamil	propofol	oxcarbazepine
crizotinib	posaconazole		quinidine	phenobarbital
cyclosporine[4]	ritonavir		ranolazine	phenytoin
cyclophosphamide	saquinavir			pioglitazone
dapsone	telaprevir			primidone
darifenacin[5]	telithromycin			rifabutin
darunavir[5]	voriconazole			rifampin
dasatinib[5]				rifapentin
dihydroergotamine				ritonavir
docetaxel				St. John's wort
doxorubicin				topiramate
dronedarone[5]				
eletriptan[5]				
ergotamine[4]				
eplerenone[5]				
erlotinib				
esomeprazole				
estrogens				
etoposide				
everolimus[5]				
felodipine[5]				
fentanyl[4]				
fosaprepitant[5]				
gefitinib				

CYP3A4 Substrates	Strong Inhibitors[1]	Moderate Inhibitors	Weak Inhibitors	Inducers
haloperidol				
HIV antiretrovirals				
HMG Co-A inhibitors[5]				
ifosfamide				
imatinib				
indinavir[5]				
irinotecan				
itraconazole				
ketoconazole				
lansoprazole				
lapatinib				
losartan				
lovastatin[5]				
lurasidone[5]				
macrolide antibiotics				
maraviroc[5]				
medroxyprogesterone				
methadone				
midazolam[5]				
modafinil				
montelukast				
nefazodone				
nilotinib				
nisoldipine[5]				
omeprazole				
ondansetron				
paclitaxel				
pazopanib				
quetiapine[5]				
quinidine[4]				
saquinavir[5]				
sildenafil[5]				
simvastatin[5]				
sirolimus[4,5]				
sunitinib				
tacrolimus[4,5]				
telaprevir				
tamoxifen				
temsirolimus				
teniposide				
tetracycline				
tipranavir[5]				

CYP3A4 Substrates	Strong Inhibitors[1]	Moderate Inhibitors	Weak Inhibitors	Inducers
tolvaptan[5]				
triazolam[5]				
trimethoprim				
vardenafil[5]				
vinca alkaloids				
zolpidem				

[1]Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP3A4 isozyme; however, the degree of that inhibition is unknown.
[2]Dexamethasone is considered a weak CYP3A4 inducer.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates.
[5]Sensitive substrates.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E7080-A001-216
Study Protocol Title:	A Phase 1/2 Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including CNS Tumors
Investigational Product Name:	Lenvatinib (E7080), everolimus
IND Number:	072010

SIGNATURES

Authors:

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Oncology Business Group, Eisai Ltd.

Date

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Oncology Business Group, Eisai Ltd.

Date

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Oncology Business Group, Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7080-A001-216
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Investigational Product Name:	Lenvatinib (E7080), everolimus
IND Number:	072010

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.

<Name of institution>

Medical Institution

<Name, degree>

Investigator	Signature	Date