16.1.1 Protocol or Protocol Amendments

The final global protocol (Protocol Amendment 2) incorporating all amendments is provided on the following pages. Also provided is the original protocol as well as Amendment 01.

- Protocol Amendment 02, dated 10 Sep 2020
- Protocol Amendment 01, dated 09 Mar 2020
- Original Protocol, dated 08 Oct 2019

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-G000-230
Study Protocol Title:	A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 JP
Sponsor's Investigational Product Name:	E7080/Lenvatinib
Indication:	Osteosarcoma
Phase:	2
Approval Date(s):	Original Protocol 08 Oct 2019 Amendment 01 09 Mar 2020 Amendment 02 10 Sep 2020
IND Number:	146642
EudraCT Number:	2019-003696-19
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 02

Date: 10 Sep 2020

Change New text is in **bold** and deleted text is in strikethrough font.	**Rationale**	**Affected Protocol Sections**
Age of consent: clarified that the age at which a subject is required to sign the informed consent and/or assent form will follow local country requirements. Additionally, biomarker analysis for subjects who are not/cannot be consented, at the appropriate age per local country requirements, will not be performed.	Added for clarity as different countries have different age requirements for providing consent.	Synopsis, Study Design Section 5.3 Section 9.7.1.7.2
This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately **80**~~70~~ investigational sites worldwide.	Revised the number of sites.	Synopsis, Sites Section 6
Revised primary objective and endpoint to progression-free survival (PFS), and revised PFS rate at 4 months (PFS-4m) to be a secondary objective and endpoint.	Updated based on Health Authority feedback.	Synopsis, Objectives Section 7.4 Section 8.1 Section 8.2 Section 9.2 Section 9.7.1.1.1 Section 9.7.1.1.2 Section 9.7.1.6 Section 9.7.1.6.1 Section 9.7.2
Added objective response rate (ORR) as a secondary objective and endpoint.	ORR was added to supplement the secondary endpoint of ORR at 4 months	Synopsis, Secondary Objectives Section 8.2 Section 9.2 Section 9.7.1.1.2 Section 9.7.1.6.1
Compare the proportion of subjects who achieve complete removal of baseline lesion(s) ~~following completion of chemotherapy~~ between the 2 arms.	Update made for clarification	Synopsis, Statistical Methods Section 8.3
The Sponsor~~Eisai~~ will closely monitor enrollment, to ensure that **a minimum of 36 subjects are <17** ~~at least 32 subjects are <18~~ years of age at the time of informed consent.	Updated per health authority feedback.	Synopsis, Study Design Section 9.1 Section 9.3

The Randomization Phase will begin at the time of randomization of the first subject and will end on the data cutoff date for the primary analysis (ie, when approximately 38 PFS events, as determined by IIR, are observed) ~~for the PFS-1y and OS-1y analysis~~. After the data cutoff date for the primary analysis ~~for the PFS-1y and OS-1y analysis~~ has occurred, all subjects who are still on study treatment will enter the Extension Phase. ~~Data cutoff (for PFS-1y and OS-1y analysis) will occur when the last subject has completed 18 cycles of treatment or discontinues before the end of Cycle 18, whichever occurs first.~~	Change made in-line with updates to the primary endpoint.	Synopsis, Study Design Section 9.1.2 Section 9.1.2.2 Section 9.1.3.1 Section 9.3.3 Section 9.5.1.2.1 Section 9.7.1.6
All AEs, **including SAEs** will be captured up to 30 days after last dose of study drug.	To clarify SAE collection period.	Synopsis, Section 9.1.2.2 Section 9.1.3.1 Table 5, z Table 6, t Table 7. t
The *Follow-up Period* will begin the day after the Off-Treatment Visit and will last **for up to** ~~until death or for~~ 2 years after end of treatment for a subject, unless the study is terminated by the sponsor, or the subject discontinues due to withdrawal of consent, or is lost to follow-up.	Clarified that the survival follow-up period may last for up to 2 years.	Synopsis, Section 9.1.2.2 Section 9.1.3.2 Section 9.3.3 Section 9.5.1.2.1
Off-Treatment: Tumor assessments at the Off-Treatment Visit (within 1 week of the Off-treatment Visit) are only necessary for subjects who discontinue study treatment without disease progression, if more than 4 weeks have passed since the previous assessment and if the subject will not continue with follow-up scans. **Follow-up:** ~~After treatment discontinuation, tumor assessment~~**For subjects who discontinue study treatment without disease progression, tumor assessments** should continue to be performed according to the schedule: every 6±1 weeks until Week 18±1 week, then every 9±1 weeks until Week 54±1 week, thereafter, to be performed every 12±2 weeks, until documentation of progression or start of a new anticancer agent.	Clarified tumor assessment requirements at the Off-Treatment visit and during Follow-up.	Table 5, q
Added Optional Lenvatinib Crossover Treatment for Subjects in Arm B who experience progressive disease.	Considering the high unmet medical need in this population, the option to crossover to lenvatinib was added.	Synopsis, Study Design Section 9.1.4 Section 9.5.1.2.1 Section Figure 1 Table 7, footnotes a and l

In case the study is discontinued by the sponsor, the sponsor will ~~continue to~~ provide study drug (outside the study) for subjects **who have not met the criteria for study drug discontinuation** ~~requiring continuation of treatment.~~	Clarified study drug provision in the event of study discontinuation by Sponsor.	Synopsis, Study Design Section 9.1.3.1 Section 9.1.3.2 Section 9.1.4 Table 7, footnote l
Inclusion Criterion 2: Refractory or relapsed osteosarcoma after 1 to 2 prior **lines of** systemic treatments.	Clarified that subjects are eligible after 1 or 2 prior lines of systemic treatment.	Synopsis, Inclusion Criteria Section 9.3.1
Inclusion Criterion 3: **Measurable disease is defined as a lesion** ~~A lesion Must be accurately measurable~~ with a minimum size (by long axis) of 10 mm using computed tomography/magnetic resonance imaging (CT/MRI) (lymph nodes must be accurately measurable with a minimum size [by short axis] of 15 mm)… **Any other non-measurable lesions will be considered evaluable disease.**	Clarified the definitions of measurable and evaluable disease.	Synopsis, Inclusion Criteria Section 9.3.1
Inclusion Criterion 8: Adequate blood coagulation function defined by International Normalized Ratio **or prothrombin time (INR/PT) and activated partial thromboplastin time or partial thromboplastin time (aPTT/PTT)** ≤1.5 unless participant is receiving anticoagulant therapy, as long as INR**/PT and aPTT/PTT are** within therapeutic range of intended use of anticoagulants.	Update INR assessment to INR/PT and aPTT/PTT.	Synopsis, Inclusion Criteria Section 9.3.1 Table 4, c
Inclusion Criterion 11: Adequate cardiac function as evidenced by left ventricular ejection fraction ≥50% at baseline as determined by echocardiography **or multigated acquisition (MUGA) scan.**	Clarification that cardiac function can be evaluated by ECHO or MUGA scan.	Synopsis, Inclusion Criteria Section 9.3.1 Section 9.5.1.4 Section 9.5.1.4.7 Table 5, k Table 6, g
Inclusion Criterion 13: Washout before Cycle 1 Day 1 of 3 weeks in case of prior chemotherapy, 6 weeks if treatment included nitrosoureas; 4 weeks for definitive radiotherapy, 2 weeks for palliative radiotherapy; and 3 months from high-dose chemotherapy and stem cell rescue. **For all other anti-cancer therapies, washout before Cycle 1 Day 1 of at least 5 half-lives (or at least 28 days, whichever is shorter).** Subjects must have recovered (to Grade ≤1, except for alopecia, ototoxicity, and Grade ≤2 peripheral neuropathy, per Common Terminology Criteria for Adverse Events [CTCAE] v5.0) from the acute toxic effects of all prior anticancer therapy before Cycle 1 Day 1.	Clarified the washout period for other prior anti-cancer therapies not otherwise specified in Inclusion Criterion 13	Synopsis, Inclusion Criteria Section 9.3.1

Added Inclusion Criterion 14: **Must have no prior history of lenvatinib treatment.**	Added to clarify that prior treatment with lenvatinib is not permitted.	Synopsis, Inclusion Criteria Section 9.3.1
Exclusion Criterion 9: **Has clinically significant cardiovascular disease within 6 months from first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability. Note: Medically controlled arrhythmia would be permitted.**	Added additional exclusion criterion to account for risk of cardiotoxicity with vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs).	Synopsis, Exclusion Criteria Section 9.3.2
Exclusion Criterion 17: ~~Active viral hepatitis (B or C) as demonstrated by positive serology~~ **Known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected)**. Note: Testing for Hepatitis B or Hepatitis C is required at screening only when mandated by local health authority.	Clarified definition of known active hepatitis B and C.	Synopsis, Exclusion Criteria Section 9.3.2
Exclusion Criterion 19: Females of childbearing potential* who: - Do not agree to use a highly effective method of contraception for the entire study period and for 28 days after lenvatinib discontinuation or 12 months after etoposide and ifosfamide discontinuation, ie: ◦ total abstinence (if it is their preferred and usual lifestyle) ◦ an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) ◦ a contraceptive implant ◦ an oral contraceptive. ****(with additional barrier method)** ~~Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing with study drug and throughout the study and for 28 days after lenvatinib discontinuation or 12 months after etoposide and ifosfamide discontinuation~~ 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, ~~or the subject has changed oral hormonal contraceptive product/dose within 4 weeks prior to study drug administration~~, 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. * All post pubertal females will be considered	Updated to align with lenvatinib standard contraceptive language.	Synopsis, Exclusion Criteria Section 9.3.2

to be of childbearing potential unless they have early menopause (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 stable dose of the same oral hormonal contraceptive product for at least 4 weeks before dosing with study drug(s) and for the duration of the study.**		
Bisphosphonates and denosumab for the treatment of osteosarcoma are not permitted.	Due to their potential antitumor activity, denosumab and bisphosphonates are prohibited (unless indicated for the management of an AE, eg, hypercalcemia).	Synopsis, Concomitant Drug/Therapy Section 9.4.7.2
The concomitant use of live vaccines (e.g., measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid [oral] vaccines) are not permitted. Seasonal influenza vaccines for injection are generally killed virus vaccines and therefore, are permitted. However intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and therefore, are not permitted. Additionally, the concomitant use of live vaccines with chemotherapy is contraindicated in immunosuppressed patients.	Per health authority feedback, the prohibited concomitant treatments have been updated to exclude yellow fever or other live vaccines.	Synopsis, Concomitant Drug/Therapy Section 9.4.7.2
~~Granulocyte colony stimulating factor (G-CSF) may be used to mitigate the toxicity of ifosfamide and etoposide.~~	Clarification: G-CSF is already stated as permitted within Section 8.4.1.2 (Management of Ifosfamide-Etoposide Associated Toxicity) and Section 8.4.7 (Prior and Concomitant Therapy).	Synopsis, Concomitant Drug/Therapy
Subjects ~~in Arm A in the presence of clinical benefit,~~ may continue **study** treatment ~~with lenvatinib~~ after protocol permissible surgery, **in the presence of clinical benefit, with Sponsor approval.**	Clarification: option to continue treatment after protocol permissible surgery (i.e. after Week 18) applies to both treatment arms.	Synopsis, Concomitant Drug/Therapy Section 9.4.7.3
PK Assessments: Blood samples for plasma concentrations of lenvatinib will be collected from all subjects from Arm A only as described in the Schedule of Assessments. **Pharmacokinetic sampling should not be performed for any subject with a body weight <13 kg (please see Section 8.5.1.3.1).**	Updated per health authority feedback and standard guidelines for pediatric blood draw volumes in order to ensure that the maximum is not exceeded.	Synopsis, Pharmacokinetic Assessments Table 5, n Section 9.5.1.3.1

Pharmacodynamic Assessments: **Optional** ~~P~~pharmacodynamic serum and archived fixed tumor tissue samples for biomarker analysis **may**~~will~~ be collected from subjects randomized to Arm A only, as described in the Schedule of Assessments. **Pharmacodynamic sampling should not be performed for any subject with a body weight <16 kg (please see Section 8.5.1.3.2).** Pharmacodynamic serum and tumor biomarkers assessed in this study will be based on those identified in other lenvatinib clinical studies. Pharmacodynamic biomarker analysis will be performed as described in a separate analysis plan. **Note: Providing blood samples for pharmacodynamic biomarker assessment is optional and will not impact subject eligibility.**	Updated per health authority feedback and standard guidelines for pediatric blood draw volumes in order to ensure that the maximum is not exceeded, Text was also revised to clarify that blood samples for pharmacodynamic assessments are optional and do not impact study eligibility.	Synopsis, Pharmacodynamic and Other Biomarker Assessments Table 5, v Section 9.5.1.3.2 Section 9.7.1.7.2 Appendix Table 11-1
Other Assessments: **Every effort should be made to administer the PedsQL questionnaires as soon as possible after the decision to discontinue study treatment is made.**	Clarification added per health authority feedback.	Section 9.5.1.5 Table 5, u Table 6, o
Objectives and Endpoints updated to specify review based on independent and investigator assessment.	Clarified the evaluation of efficacy endpoints based on independent and investigator review.	Synopsis, Objectives Section 8.2 Section 8.3 Section 9.7.1.1 Section 9.7.1.1.2 Section 9.7.1.1.3
Tumor assessments will then be performed every 6 weeks ±1 week following **the date of randomization**~~start of treatment on Cycle 1 Day 1 during the chemotherapy treatment period~~ until Week 18.	Clarified that tumor assessments will occur following the date of randomization.	Synopsis, Efficacy Assessments Section 9.5.1.2.1 Table 5 Appendix Table 11-1
Efficacy analyses: **All primary statistical analyses will be conducted at the data cutoff date for the primary analysis (ie, when approximately 38 PFS events, as determined by IIR, are observed).** ~~Additional follow-up analysis will be based on the date of data cutoff for the additional follow-up analysis for OS or at the time of last subject last visit, whichever occurs later.All the statistical analysis will be conducted at the PFS-1y/OS-1y analysis data cutoff date (ie, when the last subject has completed 18 cycles of treatment or discontinues before the end of Cycle 18, whichever occurs first), including the analysis of PFS 4m rate. Additional follow-up analysis will be based on the date of data cutoff for the additional follow-up analysis for OS or at the~~	Revised based on the change in primary objective and endpoint.	Synopsis, Randomization Phase, Efficacy Analysis Section 9.1.2 Section 9.7.1.6

~~time of last subject last visit, whichever occurs later.~~		
Primary analysis: **Progression-free survival (PFS) will be analyzed and compared between the treatment arm and control arm using the stratified log-rank test with time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years) as strata. PFS censoring rules will follow FDA guidance of 2007 and will be detailed in the statistical analysis plan. Median PFS will be calculated using the K-M [Kaplan-Meier (1958)] product-limit estimates for each treatment arm along with 2-sided 95% CIs (estimated with a generalized Brookmeyer and Crowley method [Brookmeyer and Crowley (1982)]. The K-M estimates of PFS will be plotted over time. The Cox regression model will be used to estimate the hazard ratio and its 95% CIs stratified by the stratification factors.** ~~The primary analysis of PFS-4m rate will be based upon data provided by IIR of tumor assessments. PFS-4m rate and their Greenwood standard errors will be evaluated using the K-M estimates from both treatment groups. The statistical significance of the difference in the 2 K-M PFS-4m rates comparing lenvatinib + chemotherapy agent (Test Arm) vs. chemotherapy agent alone (Control Arm) will be tested using a 2-sided 80% CI. This 2-sided 80% CI and a p-value will be constructed using the difference of these 2 K-M PFS-4m rates and the 2 corresponding Greenwood standard errors. Statistical significance of the difference is declared if the CI is entirely above 0. This is equivalent to a test using a 1-sided test at alpha=0.1. The 2-sided 95% CIs will also be provided for descriptive purposes. PFS-4m rate will also be analyzed using a binomial approach as a sensitivity analysis by excluding subjects whose PFS are censored prior to 18 weeks.~~	Revised based on the change in primary objective and endpoint.	Synopsis, Primary Analysis Section 9.7.1.6.1

Secondary analyses: ~~PFS-4m and PFS-1y rate will be analyzed using the same methods as the primary efficacy analysis. PFS censoring rules will follow FDA guidance of 2007, however, removal of baseline lesions after completion of Week 18 without progression is not a trigger for PFS censoring after 18 weeks (refer to Concomitant Drug/Therapy – allowed concomitant treatment/procedures).~~ **The PFS-4m rate and PFS-1y rate will be estimated on the Full Analysis Set using the K-M method for the primary efficacy PFS analysis. PFS-4m/PFS-1y rate and their Greenwood standard errors will be evaluated using the K-M estimates from both treatment groups. The statistical significance of the difference in the 2 K-M PFS-4m rates will base on its 2-sided 95% CI. This 2-sided 95% CI and a p-value will be constructed using the difference of these 2 K-M PFS-4m/PFS-1y rates and the 2 corresponding Greenwood standard errors.** Overall survival (OS) will be compared between treatment arm and control arm **following the same statistical method for the primary efficacy PFS endpoint.**~~using the stratified logrank test with time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years) as strata. Median OS with 2-sided 80% and 95% CIs will be calculated using K-M product-limit estimates for each treatment arm, and the K-M estimates of OS will be plotted over time. The Cox regression model will be used to estimate the hazard ratio and its 80% and 95% CIs stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years).~~ Kaplan-Meier (K-M) estimates will also be presented for 4, 6, 9, and 12 months with 2-sided ~~80% and~~ 95% CIs.	Revised based on the change in secondary objectives and endpoints.	Synopsis, Secondary Analysis Section 9.7.1.6.1

Sample size rationale: ~~A binomial based comparison of 2 proportions using correction for continuity was used for sample size estimation. A total sample size of 72 subjects is estimated to achieve 80% statistical power at 1 sided alpha of 0.1 to detect a difference of 30% based on the assumption that PFS 4m for Arm A (lenvatinib arm) is 55% and for Arm B is 25%. Alpha is the type 1 error probability of declaring lenvatinib arm being effective when the true lenvatinib arm PFS 4m rate is only 25%.~~ **A total sample size of 72 subjects is estimated for the primary efficacy endpoint of PFS. Assuming a hazard ratio of 0.4 (median PFS of 3.5 and 8.75 months for the control and investigational arms, respectively), a one-sided type 1 error rate of 0.025, and power of 80%, 38 PFS events are required for the primary analysis.**	Statistical assumptions updated based on revised primary endpoint.	Synopsis, Sample Size Rationale Section 9.7.2
Discussion of Study Design: The endpoint was determined as appropriate for the study, given the unique biology of the osteosarcoma**.** ~~(bone lesions do not shrink) and the vital role of surgical resection of metastatic lesions, where possible, in the management of patients with this tumor. Pulmonary metastases are most common in osteosarcoma, and the ability to achieve a second surgical remission has consistently been shown essential for long-term survival following relapse (Kempf Bielack, et al., 2005; Leary, et al., 2013; Bacci, et al., 2005; Chou, et al., 2005; Hawkins and Arndt, 2003). The protocol allows for surgical resection of baseline lesions after completion of the Week 18 tumor assessment. This timepoint allows for surgical resection after completion of chemotherapy without confounding data due to subjects undergoing surgery.~~	Justification has been revised to align with the updated primary endpoint.	Section 9.2
Blood Pressure: BP that is consistently above the 95th percentile based on sex, age, and height/length **for subjects <18 years old; or BP ≥140/90 mmHg for subjects ≥18 to 25 years old** requires further evaluation... **BP values for the management of hypertension for participants 18 to 25 years old are included in parentheses in Section 8.4.1.1.2.**	Clarified that guidelines also specify BP values for subjects >18 years old.	Section 9.4.1.1.1 Table 5, h Table 6, e Table 7, e Figure 2
New section added: **Management of Fistula Formation and Gastrointestinal Perforation**	Added to align with current lenvatinib toxicity management guidelines	Section 9.4.1.1.10

New section added: **Management Guidelines for QT Prolongation**	Added to align with current lenvatinib QT prolongation management guidelines.	Section 9.4.1.1.11
The chemotherapy regimen schedule will consist of ifosfamide 3000 mg/m2/day IV infusion over **at least** 30 minutes for 3 consecutive days (Day 1 to Day 3 of each cycle) and etoposide 100 mg/m2/day IV infusion for 3 consecutive days (Day 1 to Day 3 of each cycle).	Clarified the minimum infusion time for chemotherapy administration.	Section 9.4.2.2
It is recommended that mesna uroprotection be administered at a dose equivalent to that administered for ifosfamide.	Clarified the administration of mesna along with ifosfamide.	Section 9.4.2.2
The safety, tolerability and activity of single-agent lenvatinib, and lenvatinib in combination with chemotherapy (ifosfamide and etoposide), have been assessed in E7080-G000-207 (Study 207), a phase 1/2, multicenter, open-label study in children, adolescents and young adults with solid tumors, including relapsed or refractory osteosarcoma, and radioiodine- refractory differentiated thyroid carcinoma. The recommended phase 2 dose (RP2D) of lenvatinib was determined in the phase 1b portion as 14 mg/m2 orally once daily when given as single-agent as well as in combination with etoposide (100 mg/m2 IV once daily for 3 days) + ifosfamide (3000 mg/m2 IV once daily for 3 days), administered on days 1 to 3 of each 21-day cycle, for 5 cycles. The dose of lenvatinib is the same as the RP2D for lenvatinib monotherapy, also established in Study 207. **BSA will be used to determine the dose of lenvatinib for each subject. After adjustment for BSA, the daily dose of lenvatinib cannot exceed 24 mg. Please see section 6.3.1 for further details on the results of Study 207.**	Additional details of Study 207 have been provided to justify the dose selection in study 230.	Section 9.4.4
Added dental examinations to the study assessments	Added per health authority feedback in order to monitor tooth formation.	Section 9.5.1.1.2 Section 9.5.1.4 Section 9.5.1.4.7 Table 5, s Table 6, q Section 9.7.1.8 Section 9.7.1.8.6

Clarification of tumor assessment requirements.	Revised to specify frequency and methodology for tumor assessments.	Synopsis, Efficacy Assessments Section 9.5.1.2.1
CT scans: Screening CT scans should be performed with ~~oral and~~ iodinated intravenous contrast and MRI scans should be performed with intravenous gadolinium chelate.	Clarified that only iodinated IV contrast is required for CT scans, and not both oral and iodinated IV contrast.	Section 9.5.1.2.1 Table 5, q
Changed description of palatability questionnaire to 'facial hedonic scale' from a 'visual analog scale.'	Revised to correct the description of the scale used in the palatability questionnaire.	Section 9.5.1.2.2 Section 9.7.1.9.2
Changed criteria for completing the palatability questionnaire: All subjects who receive suspension formulation with the exception of subjects using a nasogastric or gastrostomy tube, must complete the questionnaire ~~according to the Schedule of Assessments~~ **on C1D1 (or the subsequent visit)**.	Clarified that the palatability questionnaire must be completed on C1D1 or the subsequent visit.	Section 9.5.1.2.2 Table 5, p Table 7, m
For this study, the study drug ~~is~~ **are** lenvatinib**, ifosfamide, and etoposide.**	Clarified that there are 3 study drugs in study 230.	Section 9.5.1.4.1
An echocardiogram or MUGA scan to assess LVEF will be performed during the screening phase, every 16~~±~~**2** weeks following the first dose of study drug while the subject is on treatment or sooner, if clinically indicated, and at (or within 1 week following) the off-treatment assessment.	Clarified the time window permitted for ECHO during study.	Section 9.5.1.4.7
Vital Signs Assessment On Cycle 1 Day 8, subjects will **have a telephone or clinic visit** ~~be contacted by telephone~~ to assess for the development of early toxicity. Subjects will be provided with a BP cuff to monitor BP at home or can have the measurement done by a local healthcare provider, and will report the C1D8 measurement at telephone contact. An unscheduled visit can occur prior to C1D15 if deemed necessary by the investigator.	Clarified that C1D8 contact can be via telephone call or clinic visit.	Table 5, i Section 9.5.1.4.4
Archival Tumor Samples An archival tumor sample from the most recent surgery or biopsy for identification of predictive biomarkers and pathology review may be collected from subjects in Arm A at any time during the study, unless no such material is available. **Providing archival tumor samples is optional and does not impact subject eligibility.**	Clarified that providing archival tumor samples is optional and does not impact eligibility.	Table 5, w

Height will be assessed at the Baseline Visit, Day 1 of every 4 cycles during the Treatment Phase, at the Off-treatment Visit and every 3 months during the Post-treatment Follow-up. **Assessment of height in Post-treatment Follow-up is not required once pubertal development is complete. Proximal tibial growth plate x-rays should be conducted for subjects aged <18 years** at baseline and at the Off-treatment visit**.**	Clarified the required age for proximal tibial growth plate x-rays, and the requirement for height assessment in post-treatment follow-up.	Table 5, s Table 6, m
Tanner Staging is only required for female subjects ≥8 years old, and male subjects ≥9 years old. Tanner Stage will be assessed at the Baseline Visit, at the Off-treatment Visit, and annually thereafter during the Post-treatment Follow-up. **Tanner Staging is not required once pubertal development is complete (i.e. Tanner Stage 5).**	Clarified the required ages for Tanner Staging, and the requirement for Tanner Staging in post-treatment follow-up.	Table 5, t Table 6, n
Extension Phase: **HRQoL will be collected at week 18 and the Off-Treatment visit.**	Revised to include PROs during the Extension Phase.	Table 6, o
Exploratory analyses: **The difference in the proportion of subjects who achieve complete removal of baseline lesion(s) and the proportion of subjects with unresectable baseline lesions(s) that are converted to resectable between the 2 treatment arms and corresponding 2-sided 95% CIs will be calculated.**	Added text to detail exploratory analysis of the difference in lesions removal between the 2 study arms.	Synopsis, Exploratory Objectives Section 8.3 Section 9.7.1.6.2
Extent of exposure: The number of cycles/days on treatment, quantity of study drug administered, **dose intensity**, and the number of subjects requiring dose reductions, treatment interruption, and treatment discontinuation due to adverse events will be summarized.	Revised to specify that dose intensity will be summarized.	Section 9.7.1.8.1
Other safety analyses: **Tooth formation abnormalities will be listed and analyzed if appropriate.**	Added in line with the inclusion of dental examination.	Section 9.7.1.8.6
Added a new sub-section describing the benefit-risk assessment for this study.	Added based on HA feedback.	Section 7.4.1
Removed Appendix 4: Preparation of Lenvatinib Suspension	The preparation instructions have been removed from the protocol appendix and are now included in the Pharmacy Manual.	~~Appendix 4~~ Section 9.4.1 Section 9.4.2
Appendix ~~5~~**4**: Palatability Questionnaire	The free text field has been removed from the taste and appearance sections of the questionnaire, as subject/guardian response will	Appendix 4

	be based on the selection of the faces.	
Appendix 11 (new)	Included to reflect country-specific changes incorporated into the study protocol for Sweden and Germany.	Appendix 11
France amendment (current FRA-2)	The changes noted in the country specific amendments for France, are included in this global amendment; therefore this global amendment will now be used as the protocol for France.	Appendix 11
Administrative changes	Minor editorial and formatting changes.	Throughout the protocol

Amendment 01

Date: 09 March 2020

Change New text is in bold and deleted text is in strikethrough font.	**Rationale**	**Affected Protocol Sections**
Inclusion Criterion 7 is updated as follows: 7. Adequate bone marrow function as evidenced by: a. absolute neutrophil count (ANC) ≥~~1.0~~ **1.5**×10^9/L. (subjects with bone marrow involvement should have ANC ≥0.8×10^9/L and leucocyte count ≥1×10^9/L). b. hemoglobin ≥8.0 g/dL (a hemoglobin of <8.0 g/dL is acceptable if it is corrected by growth factor or transfusion before Cycle 1 Day 1). c. platelet count ≥~~75~~ **100**×10^9/L.	The minimum neutrophil and platelet counts required to establish eligibility have been revised for consistency with the etoposide Summary of Product Characteristics per health authority request.	Synopsis, Section 8.3.1
Exclusion Criterion 20 is added: A contraindication to any of the study drugs (lenvatinib, ifosfamide, and etoposide) per local prescribing information.	An exclusion criterion due to contraindications to any of the study drugs has been added per health authority request.	Synopsis, Section 8.3.2
Prior and Concomitant Therapy	Per health authority request, subjects who receive other anticancer therapy, except as	Synopsis, Section 8.4.7.2

Subjects should not receive other antitumor therapies while on study. If a subject receives additional antitumor therapies other than the study drug(s), such as chemotherapy, targeted therapies, immunotherapy, or antitumor interventions - such as surgery or palliative radiotherapy (other than as described below), this will be judged to represent evidence of disease progression, and ~~continuation of the~~study medication **should be discontinued** ~~and further participation in the study must be discussed and agreed upon with the sponsor .~~	specified in the protocol, should be discontinued from study treatment.	
For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least ~~1 week~~**2 weeks** after, once there is evidence of adequate healing and no risk of bleeding.	Revised to align with the updated lenvatinib label	Synopsis, 8.4.7.3
Vital Signs Assessment **On Cycle 1 Day 8, subjects will be contacted by telephone to assess for the development of early toxicity. Subjects will be provided with a BP cuff to monitor BP at home or can have the measurement done by a local healthcare provider, and will report the C1D8 measurement at telephone contact. An unscheduled visit can occur prior to C1D15 if deemed necessary by the investigator.**	Per health authority request, a Cycle 1 Day 8 telephone contact has been added to monitor for early toxicity (including increase in blood pressure).	Section 8.5.2 (Schedule of Procedures/Assessments, Table 5 footnote j – new footnote, subsequent footnotes renumbered)
Pharmacodynamic Biomarkers The Schedule of Procedures/Assessments (Table 5) has been updated as follows: Blood samples will be collected only from subjects in Arm A at the Baseline Visit, C1D15 ~~C1D8~~, Day 1 of Cycles 2, 4, and 6, for assessment of blood serum sample to measure factors implicated in angiogenesis.	To lessen patient burden, the protocol has been updated to move the optional pharmacodynamic blood sample collection from C1D8 to C1D15. This eliminates the potential need for a study site visit for the sole purpose of collecting this optional pharmacodynamic blood sample on C1D8.	Section 8.5.2 (Schedule of Procedures/Assessments, Table 5, footnote v)
Administrative changes.	Minor editorial and formatting changes.	Throughout the protocol.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No. E7080
Name of Active Ingredient: Lenvatinib
Study Protocol Title

A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)

Investigator

Principal Investigator: Dr Nathalie Gaspar

Sites

Approximately 80 sites worldwide

Study Period and Phase of Development

Approximately 36 months

Phase 2

Objectives

Primary Objective

To evaluate whether lenvatinib in combination with ifosfamide and etoposide (Arm A) is superior to ifosfamide and etoposide (Arm B) in improving progression-free survival (PFS) by independent imaging review (IIR) using Response Evaluation Criteria In Solid Tumors (RECIST 1.1), in children, adolescents, and young adults with relapsed or refractory osteosarcoma.

Secondary Objectives

The secondary objectives of the study are to:

1. Compare difference in PFS rate at 4 months (PFS-4m) between the 2 treatment arms per IIR
2. Compare difference in PFS rate at 1 year (PFS-1y) between the 2 treatment arms per IIR
3. Compare difference in overall survival (OS) and OS rate at 1 year (OS-1y) between the 2 treatment arms
4. Compare difference in objective response rate at 4 months (ORR-4m) between the 2 treatment arms per IIR
5. Compare difference in objective response rate (ORR) between the 2 treatment arms per IIR
6. Compare difference in safety and tolerability between the 2 treatment arms
7. Characterize the pharmacokinetics (PK) of lenvatinib, when administered in combination with ifosfamide and etoposide
8. Compare difference in health-related quality of life (HRQoL) as assessed by using the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales and Cancer Module between the 2 treatment arms
9. Assess the palatability and acceptability of the suspension formulation of lenvatinib in subjects receiving the suspension formulation in the study

Exploratory Objectives

The exploratory objectives of the study are to:

1. Explore difference in duration of response (DOR), disease control rate (DCR), and clinical benefit rate (CBR) between the 2 treatment arms per IIR and investigator assessment
2. Explore difference in PFS, PFS-4m, PFS-1y, ORR-4m, and ORR between the 2 treatment arms per investigator assessment
3. Compare between the 2 treatment arms:
   - the proportion of subjects who achieve complete removal of baseline lesion(s)
   - the proportion of subjects with unresectable baseline lesion(s) that are converted to resectable

4. Investigate the relationship between tumor biomarkers and clinical response and toxicity of lenvatinib in combination with ifosfamide and etoposide
Study Design E7080-G000-230 is a multicenter, randomized, open-label, parallel-group, Phase 2 study to compare the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide in children, adolescents, and young adults with relapsed or refractory osteosarcoma. Approximately 72 eligible subjects will be randomized to 1 of the following 2 treatment arms in a 1:1 ratio within the strata: • Arm A: lenvatinib 14 mg/m^2 (orally, once daily) plus ifosfamide 3000 mg/m^2/day (intravenously [IV], Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) • Arm B: ifosfamide 3000 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) Randomization will follow a predefined randomization scheme based on the following stratification factors: time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 and ≥18 years). The Sponsor will closely monitor enrollment, to ensure that a minimum of 36 subjects are <17 years of age at the time of informed consent. The study will be conducted in 3 Phases: a Prerandomization Phase, a Randomization Phase, and an Extension Phase. The **Prerandomization Phase** will consist of 2 periods: Screening and Baseline. The Prerandomization Phase will last no longer than 28 days. The Screening Period will establish protocol eligibility and the Baseline Period will confirm eligibility. The **Randomization Phase** will consist of 2 periods: Treatment Period and Follow-up Period. The Randomization Phase will begin at the time of randomization of the first subject and will end on the data cutoff date for the primary analysis (ie, when approximately 38 PFS events, as determined by IIR, are observed). After the data cutoff date for the primary analysis has occurred, all subjects who are still on study treatment will enter the Extension Phase. The ***Treatment Period*** for each subject will begin at the time of randomization and will end at the completion of the Off-Treatment Visit, which will occur within 30 days after the final dose of study treatment. Subjects will receive study treatment as continuous 21-day cycles in both treatment arms. Treatment cycles will be counted continuously regardless of dose interruptions. If chemotherapy administration is precluded on Day 1 of a treatment cycle, the subject may resume treatment once recovered at the discretion of investigator. Subsequent chemotherapy will be administered every 21 (±1) days starting from the timepoint it was resumed. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments. Subjects randomized to Arm A will continue to receive lenvatinib until disease progression (PD) confirmed by IIR, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor, whichever occurs first. Disease progression (PD) must be confirmed by IIR prior to the investigator discontinuing study treatment for a subject. In situations where the investigator judges that alternative treatments must be instituted immediately for a subject's safety, study drugs may be discontinued without waiting

for IIR confirmation of radiographic evidence of PD. If possible, before discontinuation of the subject from the study, the investigator should consult with the sponsor.

The ***Follow-up Period*** begins the day after the Off-Treatment Visit and will continue for up to 2 years after end of treatment for a subject, unless the subject withdraws consent, or is lost to follow up, or the sponsor terminates the study.

Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn, however, an investigator may consult public records to establish survival status if permitted by local regulations.

All adverse events (AEs), including serious adverse events (SAEs), will be captured for 30 days after the last dose of study drug.

All subjects who end study treatment without IIR confirmed PD, will continue to undergo tumor assessments every 6 weeks until Week 18, then every 9 weeks until Week 54, thereafter, every 12 weeks until confirmation of disease progression by IIR as described in the tumor assessments in the assessment schedule, or until another anticancer therapy is initiated.

Subjects in both Arm A and Arm B will be followed for survival every 12 weeks (±1 week) and all subsequent anticancer treatments received will be recorded. Subjects who are being followed for survival at the time of data cutoff for the primary analysis (ie, at the end of the Randomization Phase) will continue to be followed for survival during the Follow-up Period of the Extension Phase.

Extension Phase: The Extension Phase will consist of 2 periods: Treatment Period and Follow-up Period.

In the ***Treatment Period***, subjects still on study treatment following the completion of the Randomization Phase will continue study treatment as outlined in Section 9.4.1 until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor. Tumor assessments will be performed according to the local standard of care. Independent imaging review (IIR) review and confirmation of radiographic evidence of PD will not be required, and scans will no longer be required to be sent to the imaging core laboratory (ICL). The Off-Treatment Visit will occur within 30 days after the final dose of study treatment. All AEs, including SAEs will be captured up to 30 days after last dose of study drug. In case the study is discontinued by the sponsor, the sponsor will provide study drug (outside the study) for subjects who have not met the criteria for study drug discontinuation.

The ***Follow-up Period*** will begin the day after the Off-Treatment Visit and will last for up to 2 years after end of treatment for a subject, unless the study is terminated by the sponsor, or the subject discontinues due to withdrawal of consent, or is lost to follow-up. Subjects will be treated by the investigator according to the prevailing local standard of care. Subjects will be followed every 12 weeks (±1week) for survival and all subsequent anticancer treatments received will be recorded.

The definition of end of the study, as required by certain regulatory agencies, will be the date of data cutoff for the final analysis or the time of last subject last visit, whichever occurs later.

Optional Lenvatinib Crossover (for Subjects in Arm B Only):
Subjects in Arm B with disease progression per RECIST 1.1 may be eligible for optional treatment with lenvatinib±chemotherapy. **Note:** subjects may only receive a maximum of 5 cycles of chemotherapy for the duration of the study. Optional crossover treatment must be initiated within 30 days of documented disease progression.

Optional lenvatinib crossover is only available if the following conditions are met:

- Subject experiences disease progression per RECIST 1.1 (as confirmed by IIR for all subjects who crossover prior to the start of the Extension Phase); and
- No new systemic anti-cancer medication was administered after the last dose of study drugs; and
- The subject meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria; and
- The study is ongoing.

Treatment with lenvatinib±chemotherapy will continue until the next disease progression (per RECIST 1.1 as assessed by investigator), development of unacceptable toxicity, subject request, or withdrawal of consent, whichever occurs first. If the sponsor terminates the study, the sponsor will continue to provide study drug(s) (outside of the study) for subjects requiring continuation of treatment.

Prior to optional lenvatinib crossover, baseline tumor assessment must be re-established (i.e., new tumor assessment scans performed), unless the last tumor assessment scans were performed within 4 weeks prior to Cycle 1 Day 1 of the crossover treatment.

Subjects who qualify to receive Optional Lenvatinib Crossover Treatment will be followed according to the schedule of procedures/assessments in Table 7.

Number of Subjects

Approximately 72 subjects will be randomized (36 subjects in each arm).

For the primary endpoint (intent–to-treat analysis), a minimum of 36 patients <17 years old (at the time of informed consent) will be randomized.

Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of high grade osteosarcoma.
2. Refractory or relapsed osteosarcoma after 1 to 2 prior lines of systemic treatments.
3. Measurable or evaluable disease per RECIST 1.1 that meets the following criteria:
   - Measurable disease is defined as a lesion with a minimum size (by long axis) of 10 mm using computed tomography/magnetic resonance imaging (CT/MRI) (lymph nodes must be accurately measurable with a minimum size [by short axis] of 15 mm).
   - Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must have subsequently grown unequivocally to be deemed a target lesion.
   - Any other non-measurable lesions will be considered evaluable disease.
4. Aged 2 years to ≤25 years at the time of informed consent.
5. Life expectancy of 12 weeks or more.
6. Lansky play score ≥50% or Karnofsky Performance Status score ≥50%. Use Karnofsky for subjects ≥16 years of age and Lansky for subjects <16 years of age. Subjects who are unable to walk because of paralysis, but who are able to perform ADL while wheelchair bound, will be considered ambulatory for the purpose of assessing the performance score.
7. Adequate bone marrow function as evidenced by:
   a. absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L.

      (subjects with bone marrow involvement should have ANC $\geq 0.8\times10^9$/L and leucocyte count $\geq 1\times10^9$/L).

b. hemoglobin ≥8.0 g/dL (a hemoglobin of <8.0 g/dL is acceptable if it is corrected by growth factor or transfusion before Cycle 1 Day 1).

c. platelet count ≥100×10^9/L.

8. Adequate blood coagulation function defined by International Normalized ratio or prothrombin time (INR/PT) and activated partial thromboplastin time or partial thromboplastin time (aPTT/PTT) ≤1.5 unless participant is receiving anticoagulant therapy, as long as INR/PT and aPTT/PTT are within therapeutic range of intended use of anticoagulants.
9. Adequate liver function as evidenced by:
   a. Bilirubin ≤1.5 times the upper limit of normal (ULN).
   b. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3×ULN (in the case of liver metastases ≤5×ULN).
10. Adequate renal function as evidenced by:
    a. Serum creatinine based on age/gender as below. If serum creatinine is greater than maximum serum creatinine for age/gender as shown in the table below, then creatinine clearance (or radioisotope glomerular filtration rate [GFR]) must be >70 mL/min/1.73 m^2.

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

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

    b. Urine dipstick <2+ for proteinuria. Subjects who have ≥2+ proteinuria on dipstick urinalysis should undergo a spot protein-creatinine (P/C) ratio test that should be Grade <2 per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and if possible perform a 24-hour urine collection (children and adolescents ≤12 years of age must have ≤500 mg of protein/24 hours and subjects >12 years of age must have ≤1 g of protein/24 hours).
    c. No clinical evidence of nephrotic syndrome.
11. Adequate cardiac function as evidenced by left ventricular ejection fraction ≥50% at baseline as determined by echocardiography or multigated acquisition (MUGA) scan.
12. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as:
    a. BP <95th percentile for sex, age, and height/length at screening (as per National Heart Lung and Blood Institute guidelines) and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1. Subjects >18 years of age should have BP ≤150/90 mm Hg at screening and no change in antihypertensive therapy within 1 week prior to Cycle 1 Day 1.
13. Washout before Cycle 1 Day 1 of 3 weeks in case of prior chemotherapy, 6 weeks if treatment included nitrosoureas; 4 weeks for definitive radiotherapy, 2 weeks for palliative radiotherapy;

and 3 months from high-dose chemotherapy and stem cell rescue. For all other anti-cancer therapies, washout before Cycle 1 Day 1 of at least 5 half-lives (or at least 28 days, whichever is shorter). Subjects must have recovered (to Grade ≤1, except for alopecia, ototoxicity, and Grade ≤2 peripheral neuropathy, per CTCAE v5.0) from the acute toxic effects of all prior anticancer therapy before Cycle 1 Day 1.

14. Must have no prior history of lenvatinib treatment.
15. Written and signed informed consent from the parent(s) or legal guardian and assent from the minor subject. Written informed consent from subjects ≥18 years.
16. Willing and able to comply with the protocol, scheduled follow-up, and management of toxicity as judged by the investigator.

Exclusion Criteria

1. Any active infection or infectious illness unless fully recovered prior to Cycle 1 Day 1 (ie, no longer requiring systemic treatment).
2. Subjects with central nervous system metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy, surgery, or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 2 weeks before Cycle 1 Day 1.
3. Active second malignancy within 2 years prior to enrollment ([in addition to osteosarcoma], but not including definitively treated superficial melanoma, carcinoma-in-situ, basal or squamous cell carcinoma of the skin).
4. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
5. Has had major surgery within 3 weeks prior to Cycle 1 Day 1.

   Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
6. Known hypersensitivity to any component(s) of the study drugs (lenvatinib, ifosfamide, and etoposide, or their ingredients).
7. Currently receiving any investigational drug or device in another clinical study or within 28 days prior to Cycle 1 Day 1.
8. A clinically significant ECG abnormality, including a marked baseline prolonged QT or QTc interval (eg, a repeated demonstration of a QTc interval >480 msec).
9. Has clinically significant cardiovascular disease within 6 months from first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability. **Note:** Medically controlled arrhythmia would be permitted.
10. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that in the opinion of the investigator might affect the absorption of lenvatinib.
11. Pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula.
12. Gastrointestinal bleeding or active hemoptysis (bright red blood of at least ½ teaspoon) within 3 weeks prior to Cycle 1 Day 1.
13. Radiographic evidence of intratumoral cavitation, encasement, or invasion of a major blood vessel. Additionally, the degree of proximity to major blood vessels should be considered for exclusion because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.

14. History of ifosfamide-related Grade ≥3 nephrotoxicity or encephalopathy.
15. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
16. Known to be human immunodeficiency virus (HIV) positive. Note: HIV testing is required at screening only when mandated by local health authority.
17. Known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected). Note: Testing for Hepatitis B or Hepatitis C is required at screening only when mandated by local health authority.
18. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG]) (human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG / hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
19. Females of childbearing potential* who:
    - Do not agree to use a highly effective method of contraception for the entire study period and for 28 days after lenvatinib discontinuation or 12 months after etoposide and ifosfamide discontinuation, ie:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device (IUD) or intrauterine 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.

    * All post pubertal females will be considered to be of childbearing potential unless they have early menopause (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 stable dose of the same oral hormonal contraceptive product for at least 4 weeks before dosing with study drug(s) and for the duration of the study.
20. 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 28 days after lenvatinib discontinuation or 6 months after discontinuation of etoposide and ifosfamide). No sperm donation is allowed during the study period and for 28 days after lenvatinib discontinuation or 6 months after discontinuation of etoposide and ifosfamide.
21. A contraindication to any of the study drugs (lenvatinib, ifosfamide, and etoposide) per local prescribing information.

Study Treatments

Body surface area (BSA) will be used to determine the amount of study drugs administered, and must be calculated on Day 1 of each cycle based on the subject's current height and body weight. The dose should be rounded to the nearest whole number.

Test Arm (Arm A): Lenvatinib + Ifosfamide + Etoposide

Lenvatinib 14 mg/m^2, orally administered once daily in each 21-day cycle.

Lenvatinib is provided as hard capsules containing 1 mg, 4 mg, or 10 mg lenvatinib. An extemporaneous suspension of lenvatinib capsules should be used for subjects unable to swallow capsules. After adjustment for BSA, the daily dose cannot exceed 24 mg QD.

Ifosfamide 3000 mg/m^2/day, IV, for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Etoposide 100 mg/m^2/day, IV, for 3 consecutive days (Day 1 to 3) , every 21 days, for a maximum of 5 cycles.

Treatment with lenvatinib will continue in 21-day cycles after chemotherapy is discontinued, until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor.

In case the study is discontinued by the sponsor, the sponsor will provide study drug (outside the study) for subjects who have not met the criteria for study drug discontinuation.

Control Arm (Arm B): Ifosfamide + Etoposide

Ifosfamide 3000 mg/m^2/day, IV, daily for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Etoposide 100 mg/m^2/day, IV, daily for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Optional Lenvatinib Crossover (for Subjects in Arm B Only):
Subjects in Arm B with disease progression per RECIST 1.1 may be eligible for optional treatment with lenvatinib±chemotherapy. Please see Section 9.1.4 for further details.

Duration of Treatment

A subject will remain on study treatment until 1 or more of the following events occur(s):

- Progressive disease (as confirmed by IIR*)
- Unacceptable toxicity
- Subject request
- Withdrawal of consent
- Termination of the study by the Sponsor

*Confirmation of disease progression by IIR is only required during the Randomization Phase.

Concomitant Drug/Therapy

Prohibited Concomitant Therapies and Drugs

Subjects should not receive other antitumor therapies while on study. If a subject receives additional antitumor therapies other than the study drug(s), such as chemotherapy, targeted therapies, immunotherapy, or antitumor interventions - such as surgery or palliative radiotherapy (other than as described below), this will be judged to represent evidence of disease progression, and the study medication should be discontinued.

Bisphosphonates and denosumab for the treatment of osteosarcoma are not permitted.

The concomitant use of live vaccines (e.g., measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid [oral] vaccines) are not permitted. Seasonal influenza vaccines for

injection are generally killed virus vaccines and therefore, are permitted. However intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and therefore, are not permitted. Additionally, the concomitant use of live vaccines with chemotherapy is contraindicated in immunosuppressed patients.

For further information on the prohibited concomitant therapies for ifosfamide and etoposide, please refer to the respective prescribing information.

The following concomitant treatments/procedures are allowed:

a. Removal of existing (not new) osteosarcoma lesion (eg, surgical, radiofrequency ablation, cryotherapy, thermoablation, stereotactic radiotherapy, etc.) after completion of the Week 18 tumor assessment. Subjects may continue study treatment after protocol permissible surgery, in the presence of clinical benefit, with Sponsor approval.

b. Palliative radiotherapy is allowed for ≤2 significantly symptomatic nontarget lesions.

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 2 weeks after, once there is evidence of adequate healing and no risk of bleeding.

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

Assessments

Efficacy Assessments

Tumor assessment will be performed based on RECIST 1.1. Investigator–determined response assessments will be performed at each assessment time point and entered onto the case report form (CRF). Copies of all tumor assessment scans will be sent to an imaging core laboratory (ICL) designated by the sponsor for efficacy assessment and for confirmation of PD. Tumor assessments will be carried out following the guidelines provided by the ICL.

During the Screening Period, tumor assessments of the chest, abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed within 28 days prior to Cycle 1 Day 1. A brain scan (CT scan with contrast or MRI pre- and post-gadolinium) will be performed at screening as clinically indicated, and thereafter during the study as clinically indicated. Historical CT or MRI scans performed within 28 days prior to Cycle 1 Day 1 may be used as screening scans (baseline scans) to demonstrate eligibility, as long as they meet minimum standards as separately defined by the ICL.

If available, bone imaging obtained within 8 weeks prior to Cycle 1 Day 1 should be sent to the ICL. Bone lesions noted on the screening/baseline images should be followed as non-target lesions with modalities other than nuclear medicine scans.

Tumor assessments will then be performed every 6 weeks ±1 week following the date of randomization until Week 18. Following completion of the chemotherapy treatment period (ie, after Week 18), the frequency of tumor assessments will be every 9 weeks ±1 week until Week 54 ±1 week. Thereafter, they will be performed every 12 weeks ±2 weeks until documentation of PD (please see schedule of assessments for details). At any point, the CT/MRI scan should be performed earlier than the scheduled time point, if clinically indicated. After data cutoff for the primary analysis, tumor assessments should be performed following the prevailing local standard of care.

Disease progression per RECIST 1.1 during the randomization phase must be confirmed by IIR prior to the investigator discontinuing study treatment.

In the event that the investigator considers alternative treatments must be instituted immediately for management of urgent medical complications of PD, study drugs may be discontinued without waiting for independent confirmation of radiographic evidence of PD. Subjects who discontinue study treatment without PD will continue to undergo tumor assessments according to the schedule until PD is documented or another anticancer therapy is initiated.

Prior to optional lenvatinib crossover, baseline tumor assessment must be re-established (i.e., new tumor assessment scans performed), unless the last tumor assessment scans were performed within 4 weeks prior to Cycle 1 Day 1 of the crossover treatment.

During the Optional Lenvatinib Crossover Treatment Phase, tumor assessments will be performed as clinically indicated per the institutional guidelines (but no less frequently than every 12 weeks), following the prevailing local standard of care. Scans are not required to be submitted to the independent imaging core laboratory during the Optional Lenvatinib Crossover Treatment Phase.

Pharmacokinetic Assessments

Blood samples for plasma concentrations of lenvatinib will be collected from all subjects from Arm A only as described in the Schedule of Assessments. Pharmacokinetic sampling should not be performed for any subject with a body weight <13 kg (please see Section 9.5.1.3.1).

Pharmacodynamic and Other Biomarker Assessments

Optional pharmacodynamic serum and archived fixed tumor tissue samples for biomarker analysis may be collected from subjects randomized to Arm A only, as described in the Schedule of Assessments. Pharmacodynamic sampling should not be performed for any subject with a body weight <16 kg (please see Section9.5.1.3.2). Pharmacodynamic serum and tumor biomarkers assessed in this study will be based on those identified in other lenvatinib clinical studies. Pharmacodynamic biomarker analysis will be performed as described in a separate analysis plan.

Note: Providing blood samples for pharmacodynamic biomarker assessment is optional and will not impact subject eligibility.

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs), including all grades per National Cancer Institute (NCI) CTCAE v5.0 (for both increasing and decreasing severity), and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and physical examinations.

Progression of osteosarcoma and signs and symptoms clearly related to the progression of the osteosarcoma should not be captured as an AE. Disease progression is a study endpoint and should be captured in the CRF as per the guidelines for reporting disease progression.

Other Assessments

HRQoL assessment will be performed per the Schedule of Assessments. Impact of treatment on HRQoL will be assessed using the PedsQL (including the Generic Core Scales and Cancer Module).

Bioanalytical Methods

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

Statistical Methods

Study Endpoints

Efficacy endpoints related to tumor assessments will be evaluated by independent imaging review (IIR) and investigator assessment.

Primary Endpoint

PFS (progression-free survival) by IIR is defined as the time from the date of randomization to the date of the first documentation of PD or death (whichever occurs first) as determined by IIR using RECIST 1.1.

Secondary Endpoints

- **PFS-4m rate (progression-free survival rate at 4 months) by IIR** is defined as the percentage of subjects who are alive and without PD at 4 months from the randomization date as determined by IIR of radiological imaging using RECIST 1.1. The PFS-4m rate is estimated using the Kaplan-Meier (K-M) method.
- **PFS-1y rate (progression-free survival rate at 1 year) by IIR** is defined as the percentage of subjects who are alive and without PD at 1 year from the randomization date as determined by IIR of radiological imaging using RECIST 1.1. The PFS-1y rate is estimated using the K-M method.
- **Overall survival (OS)** is defined as the time from the date of randomization to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cutoff for the primary analysis, will be censored at the date the subject was last known to be alive, or date of data cutoff for the primary analysis, whichever occurs first. Overall survival rate at 1 year (OS-1y) will be estimated using the K-M method.
- **Objective response rate by IIR at 4 months (ORR-4m)** is defined as the proportion of subjects who have best overall response of complete response (CR) or partial response (PR) as determined by IIR using RECIST 1.1 within the first 4 months.
- **Objective response rate (ORR) by IIR** is defined as the proportion of subjects who have best overall response of complete response (CR) or partial response (PR) as determined by IIR using RECIST 1.1.
- **Safety** will be assessed summarizing the incidence of treatment-emergent adverse events (TEAEs) and SAEs together with all other safety parameters.
- Assessment of population-based PK parameters of lenvatinib.
- Score changes from baseline for all PedsQL scales including Generic Core Scales and Cancer Module. Scores will be calculated for total generic score, total cancer score, each physical function subscale including physical health, psychosocial health, emotional function, social function, school/work function in the Generic Core Scales, and each subscales in the cancer module.
- Palatability and acceptability of the suspension formulation of lenvatinib in subjects receiving the suspension formulation in the study will be assessed using the Palatability Questionnaire (see Appendix 4).

Exploratory Endpoints

- **Duration of response (DOR) by IIR and investigator assessment** is defined as the time from the date a response was first documented until the date of the first documentation of PD or date of death from any case.
- **Disease control rate (DCR) by IIR and investigator assessment** is the proportion of subjects who have a best overall response of CR or PR or stable disease (SD). In this context, stable

disease is defined as stable disease at ≥7 weeks after randomization to be considered best overall response.

- **Clinical benefit rate (CBR) by IIR and investigator assessment** is the proportion of subjects who have best overall response of CR or PR or durable SD (duration of SD ≥23 weeks after randomization).
- Efficacy endpoints (PFS, PFS-4m, PFS-1y, ORR-4m, and ORR) evaluated based on investigator assessment
- Proportion of subjects who achieve complete removal of baseline lesions.
- **Blood and tumor biomarkers** will be assessed for identifying potential correlation with clinical outcomes-related endpoints.

Analysis Sets

The Full Analysis Set (Intent-to-Treat Analysis [ITT]) includes all randomized subjects regardless of the treatment actually received. This is the primary analysis population used for the efficacy analyses which will be based on the ITT principle.

The Per Protocol Analysis Set includes those subjects from the ITT set who received at least 1 dose of any study drug, had no major protocol deviations and had both baseline and at least one postbaseline tumor assessment. Subjects for whom death occurred prior to the first postbaseline tumor assessment will also be included. The per protocol analysis set will be the secondary analysis set for efficacy endpoints.

The Safety Analysis Set includes subjects who received at least 1 dose of any study drug. This is the analysis population used for all safety analyses which will be based on as-treated principle.

Population Pharmacokinetic (PK) Analysis Set includes the subjects who have received at least 1 dose of lenvatinib with documented dosing history and have measurable plasma levels of lenvatinib.

The Pharmacodynamic Analysis Set includes subjects who received at least 1 dose of study drug and had sufficient pharmacodynamic data (eg, at least 1 evaluable/measurable pharmacodynamic parameter).

The HRQoL Analysis Set will consist of all randomized subjects who have received at least 1 dose of study medication, and have at least 1 patient-reported outcome (PRO) assessment completed beyond baseline. For PRO analysis, subjects will be analyzed as randomized and not according to treatment actually received.

Efficacy Analyses

Efficacy analyses will be based primarily on the Full Analysis Set.

All primary statistical analyses will be conducted at the data cutoff date for the primary analysis (ie, when approximately 38 PFS events, as determined by IIR, are observed).

Primary Analysis

Progression-free survival (PFS) will be analyzed and compared between the 2 treatment arms using the stratified log-rank test with time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years) as strata. PFS censoring rules will follow FDA guidance of 2007 and will be detailed in the statistical analysis plan. Median PFS will be calculated using the Kaplan-Meier (K-M) product-limit estimates for each treatment arm along with 2-sided 95% confidence intervals (CIs) . The K-M estimates of PFS will be plotted over time. The Cox regression model will be used to estimate the hazard ratio and its 95% CIs stratified by the stratification factors.

Secondary Analyses

The PFS-4m rate and PFS-1y rate will be estimated on the Full Analysis Set using the K-M method for the primary efficacy PFS analysis. PFS-4m/PFS-1y rate and their Greenwood standard errors will be evaluated using the K-M estimates from both treatment groups. The statistical significance of the difference in the 2 K-M PFS-4m rates will be based on its 2-sided 95% CI. This 2-sided 95% CI and a p-value will be constructed using the difference of these 2 K-M PFS-4m/PFS-1y rates and the 2 corresponding Greenwood standard errors.

Overall survival (OS) will be compared between treatment arm and control arm following the same statistical method for the primary efficacy PFS endpoint. Kaplan-Meier (K-M) estimates of OS rate will also be presented for 4, 6, 9, and 12 months with 2-sided 95% CIs.

The ORR will be summarized and compared between the two treatment arms using stratified Miettinen and Nurminen's method. The difference in ORR and its 2-sided 95% confidence interval from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported. The stratification factors used for randomization will be applied to the analysis. The ORR-4m will be summarized and compared between arms using the same approach as for ORR.

Exploratory Analyses

Median DOR among responders for each arm will be presented along with its corresponding 2-sided 95% CIs. Disease Control Rate (DCR) and CBR will be summarized and compared between arms using the same approach as for ORR.

Pharmacodynamic and Other Biomarker Analyses

Pharmacodynamic, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.

Blood serum samples may be analyzed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, or other assays/methods and new technology in an effort to identify biomarkers.

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

Data obtained from the pharmacodynamic samples will be used for research. The pharmacodynamic samples will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib and for potential diagnostic development. If the subject reaches the age of 18 years (or at the appropriate age per local country requirements) while on the study, and becomes competent to give informed consent, his/her consent will be obtained using separate informed consent forms (ICFs) to continue on the study. Further analyses will not be performed on samples collected from subjects who do not reconsent at the age of 18 years (or at the appropriate age per local country requirements).

Pharmacokinetic Analyses

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

Lenvatinib data from Arm A of the study will be pooled with available data from other studies and subjected to population PK analysis. 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.

Other Analyses

Health-Related Quality of Life (HRQoL):

The PedsQL for all subjects(self- and proxy-rating) will be collected at baseline, at C2D1, C3D1, Week 18, C8D1, C18 D1, and at the Off-Treatment visit.

Interim Analyses

No interim analysis is planned for this study.

The safety monitoring will be conducted by the 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 recommendation whether to stop the study for safety will be reached by the IDMC based on their review of safety data with treatment information. The function and membership of the IDMC will be described in the IDMC charter.

Sample Size Rationale

A total sample size of 72 subjects is estimated for the primary efficacy endpoint of PFS. Assuming a hazard ratio of 0.4 (median PFS of 3.5 and 8.75 months for the control arm and the test arm, respectively), a one-sided type 1 error rate of 0.025, and power of 80%, 38 PFS events are required for the primary analysis. The total sample size of 72 subjects is estimated to achieve 38 PFS events assuming the analysis occurs approximately 32 months after the first subject is randomized (assuming a 20-month enrollment period), and accounts for a dropout rate of up to 40%.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADL	Activities of daily living
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ANC	absolute neutrophil count
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
BSA	body surface area
C1, C5, CX	Cycle 1, Cycle 5, Cycle X
CA	Competent Authorities
CBR	clinical benefit rate
CFR	Code of Federal Regulations
C_{max}	maximum drug or metabolite concentration
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP/CYP3A4	Cytochrome P450/cytochrome P4503A4
DCR	disease control rate
DOR	duration of response
DTC	differentiated thyroid cancer
ESMO	European Society for Medical Oncology
ETO	Etoposide
FGFR	fibroblast growth factor receptor
FGF	fibroblast growth factor

GFR	glomerular filtration rate
G-CSF	granulocyte-colony stimulating factor
HRQoL	health-related quality of life
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICL	imaging core laboratory
ID	identification
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IFO	Ifosfamide
INR	International Normalized Ratio
IIR	independent imaging review
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenously
IVRS	interactive voice response system
KDR	kinase insert domain receptor
K-M	Kaplan-Meier
LEN	Lenvatinib
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
OS-1y	overall survival rate at 1 year
PD	progressive disease/disease progression
PDGFR	platelet-derived growth factor receptor

PedsQL	Pediatric Quality of Life Inventory
PFS	progression-free survival
PFS-4m	progression-free survival rate at 4 months
PFS-1y	progression-free survival rate at 1 year
PK	pharmacokinetic(s)
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PT	preferred term
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
RP2D	recommended Phase 2 dose
RPLS	reversible posterior leukoencephalopathy syndrome
RTK	receptor tyrosine kinase
RTKI	receptor tyrosine kinase inhibitor
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SmPC	summary of product characteristics
SOC	system organ class
SOP	standard operating procedure
SUSARs	suspected unexpected serious adverse reactions
TEAEs	treatment-emergent adverse events
TKI	tyrosine kinase inhibitors
TNM	tumor-node metastasis
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
VEGF	vascular endothelial growth factor

VEGFR	vascular endothelial growth factor receptor
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF) /assent, and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice), Section 3, and any local regulations (eg, European Union [EU] Clinical Trials Directive 2001/20/EC or Code of Federal Regulations, Title 21 CFR Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate(s) [CRAs], 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.

Documented study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) 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 (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

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

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The definition of the end of the study is the date of the data cutoff for the final analysis or last subject/last visit, including discontinuation from the study for any reason, whichever occurs later.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA 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 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
- An IRB waiver request will be submitted before study initiation for non-US sites conducted under an Investigational New Drug (IND) application.
- 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.
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

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

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable 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 legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. In countries where specific laws for children are established for informed consent, those local laws will be applied. After the ICF and/or assent form and any other written information to be provided to subjects is read and explained to the subject or the subject's 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 and/or assent form, 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 ICF and/or assent form before any study-

specific procedures are performed. The subject is required to sign an ICF and/or assent at 18 years of age (or at the appropriate age per local country requirements). No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (eg, EU Clinical Trials Directive 2001/20/EC or Code of Federal Regulations, Title 21, CFR Part 50). Each subject and the subject's parent(s) or legally acceptable representative must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

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

When the subject reaches the age of 18 years (or at the appropriate age per local country requirements) while on study, and becomes competent to give informed consent, his/her consent will be obtained using separate ICF to continue on the study.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 80 investigational sites worldwide.

The name, telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Osteosarcoma

Cancer is a relatively uncommon diagnosis in the pediatric population, and the overall incidence is low (18.6 cases per 100,000 children [Howlader, et al., 2019]). Solid tumors constitute approximately 60% of childhood malignancies (Howlader, et al., 2019). Malignant bone tumors are the fifth most common solid tumor type accounting for about 5% of childhood tumors (Howlader, et al., 2019; Kaatsch, 2010).

Osteosarcoma is the most commonly diagnosed primary malignancy of the bone in children and young adults, and accounts for approximately 5% of childhood tumors, with an estimated annual incidence of 4.4 cases per 1 million in people younger than 24 years (Mirabello, et al., 2009). Osteosarcoma occurs predominantly in adolescents and young adults. The median age at diagnosis is 20 years, with the incidence peaking at 15 to 19 years of age (ESMO, guidelines, 2014). According to the American Cancer Society, osteosarcoma in this age group is 8 per 1 million (Ward, et al., 2014).

There are both intrinsic and extrinsic factors that have been shown to contribute to the development of osteosarcoma. Studies have demonstrated that several genetic abnormalities, including the overexpression of vascular endothelial growth factor (VEGF) receptor (VEGFR), platelet-derived growth factor (PDGF) receptor (PDGFR), and c-fos, are associated with the development of osteosarcoma in laboratory models as well as humans (Gorlick and Khanna, 2010). However, osteosarcoma is not characterized by a single oncogenic driver. The vast majority of abnormal oncogenes and tumor-suppressor genes associated with osteosarcoma are also common in the most prevalent cancers (Gorlick and Khanna, 2010). Extrinsic factors such as ionizing radiation, which is used for the treatment of childhood solid tumors, have been well implicated in the development of a second malignancy, with osteosarcoma being the most likely to develop within the first 2 decades following treatment (Le Vu, et al., 1988).

The management of osteosarcoma is multimodal; patients not amenable to surgery or patients at second or third relapse have a poor prognosis. Metastatic osteosarcoma is common (10% to 20%) (NCCN, Bone cancer guidelines, 2020; Casali, et al., 2018), with the most frequent site being the lung (>85%). In the case of isolated lung metastases, more than a third of patients with a second surgical remission survive for >5 years (Casali, et al., 2018). Approximately 25% of all patients with primary metastatic osteosarcoma and >40% of those who achieve a complete surgical remission may become long-term survivors (Casali, et al., 2018) as compared with 65% to 70% of patients with localized disease (Meazza and Scanagatta, 2016).

About 30% to 40% of patients with localized disease and 80% of those with metastatic disease experience relapse (NCCN Bone Cancer Guidelines, 2020; Casali, et al., 2018; Ferrari, 2003). The presence of solitary metastasis, time to first relapse, and complete resectability of disease at first recurrence are the most significant prognostic indicators for improved survival. Patients whose tumor is not amenable to surgery, or with second or third recurrence, or who have metastases to the bone, have a poor prognosis. In general, despite second-line treatment, the prognosis of recurrent disease in osteosarcoma has remained poor, with long-term postrelapse survival of <20% (NCCN Bone Cancer Guidelines, 2020; Casali, et al., 2018).

7.2 Current Therapeutic Options

There has been no substantial progress in the treatment of osteosarcoma since the 1980s. Current treatment utilizes multi-agent chemotherapy and surgical resection of all clinically detectable disease.

Treatment of Newly Diagnosed Disease

Newly diagnosed osteosarcoma is typically managed with neoadjuvant chemotherapy followed by surgical removal of the primary tumor and all clinically evident metastatic disease, followed by adjuvant chemotherapy. Surgical resection of all clinically detectable sites of disease is vital, regardless of number and site, as complete resection is predictive of

survival (Meazza and Scanagatta, 2016). For patients with unresectable disease at multiple sites, experimental therapy is also considered, due to the poor prognosis for these patients.

The most effective chemotherapy regimens include the combination of high-dose methotrexate, doxorubicin, and cisplatin and has become the standard treatment for high-grade osteosarcoma (NCCN Bone Cancer Guidelines, 2020; Ferrari and Serra, 2015; Isakoff, et al., 2015).

Treatment of Relapsed, Refractory, and Progressive Disease

Second-line treatment for relapsed disease consists of chemotherapy and/or surgical resection (NCCN Bone Cancer Guidelines, 2020; Casali, et al., 2018). The role of second-line chemotherapy for recurrent osteosarcoma is much less well defined than that of surgery, and there is no accepted standard regimen (Casali, et al., 2018). For patients with resectable solitary metastasis to the lung, surgical resection only may be adequate. For those with recurrent pulmonary metastases that are resectable, surgery is advised in addition to neoadjuvant or adjuvant chemotherapy, regardless of the number of previous lung relapses and the number of secondary pulmonary lesions (Briccoli, et al., 2005). Aggressive surgical resection of metastases and the ability to achieve a second surgical remission have consistently been shown essential for long-term survival following relapse (Leary, et al., 2013; Kempf-Bielack, et al., 2005; Bacci, et al., 2005; Chou, et al., 2005; Hawkins and Arndt, 2003).

As per the European Society for Medical Oncology (ESMO) guidelines for bone sarcoma, treatment options for recurrent osteosarcoma include ifosfamide ± etoposide ± carboplatin, and other active drugs (Casali, et al., 2018). Preferred regimens for second-line therapy per the National Comprehensive Cancer Network (NCCN) bone sarcoma guidelines include ifosfamide (high dose) with or without etoposide, regorafenib, sorafenib, and sorafenib plus everolimus (NCCN Bone Cancer Guidelines, 2020).

In the event of subsequent relapse, the NCCN guidelines (NCCN Bone Cancer Guidelines, 2020) and ESMO guidelines (Casali, et al., 2018) strongly encourage participation in clinical studies. Otherwise, patients with disease progression or relapse after second-line therapy are managed with surgical resection, palliative radiotherapy, or best supportive care.

7.3 Lenvatinib

E7080 (lenvatinib) is a potent multiple receptor tyrosine kinase (RTK) inhibitor (RTKI) that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other pro-angiogenic and oncogenic pathway-related RTKs, including fibroblast growth factor (FGF) receptor (FGFR) 1-4, PDGF receptor alpha (PDGFRα), KIT, and RET. Therefore, lenvatinib exerts its in vivo antitumoural activity based on multiple mechanisms involved in and through effects related to angiogenesis (including reversion of resistance) and the tumor microenvironment, as well as direct inhibitory action on the tumour cells. Recent studies have also demonstrated lenvatinib's immunomodulatory activity in the tumor microenvironment. This includes decreases in immunosuppressive tumor-associated

macrophages, activated cytotoxic T cell increases, and activation of interferon-gamma signaling. These all contribute to lenvatinib's antitumor activity in immunocompetent mice (Kato, et al., 2019; Kimura, et al., 2018).

7.3.1 Clinical Data on Lenvatinib in Combination with Ifosfamide and Etoposide for Treatment of Relapsed or Refractory Osteosarcoma

The safety, tolerability and activity of single-agent lenvatinib, and lenvatinib in combination with chemotherapy (ifosfamide and etoposide), have been assessed in E7080-G000-207 (hereafter referred to as Study 207), an ongoing Phase 1/2, multicenter, open-label study in children, adolescents and young adults with solid tumors, including relapsed or refractory osteosarcoma, and radioiodine- refractory differentiated thyroid carcinoma. The recommended Phase 2 dose (RP2D) of lenvatinib was determined in the Phase 1b portion as 14 mg/m^2 orally once daily when given as single-agent as well as in combination with etoposide (100 mg/m^2 IV once daily for 3 days) + ifosfamide (3000 mg/m^2 IV once daily for 3 days), administered on days 1 to 3 of each 21-day cycle, for 5 cycles. Safety and efficacy is being assessed in the Phase 2 portion of the study.

Data from Study 207 have shown that patients with osteosarcoma may benefit from treatment with lenvatinib. In the single agent expansion cohort in relapsed/refractory osteosarcoma, (n=31; Cohort 2B), 9 of 28 evaluable patients (32.1%) achieved progression-free survival (PFS) at 4 months (PFS-4m), median PFS was 3.0 months (95% CI: 1.8, 5.5). Two out of 29 subjects (6.9%) with measurable disease had a partial response (PR) (Gaspar, et al., 2018).

Among the 31 subjects included in the safety analysis set for the single-agent lenvatinib expansion cohort, the most common adverse events were: headache (48%), vomiting (45%), decreased appetite, diarrhea, and hypothyroidism (42% each), proteinuria (39%), increased blood TSH, hypertension, nausea, pyrexia, and weight decreased (36% each). Five subjects (16.1%) discontinued treatment due to TEAEs, and 8 subjects (25.8%) reported TEAEs leading to study drug dose reduction. There were no treatment-related fatal TEAEs (Gaspar, et al., 2018).

In a pooled analysis of subjects from Phase 1b and 2 receiving lenvatinib 14 mg/m^2 in combination with ifosfamide plus etoposide (N=35; full analysis set), the primary efficacy endpoint, PFS-4 rate based on RECIST 1.1 by investigator assessment, was 67.9% (95% CI: 47.6, 84.1). As of the data cutoff date of 23 Jul 2019, the objective response rate (ORR) was 12.5%, including 4 subjects with PR. Median PFS was 11.1 months (95% CI: 4.5, 12.6), and median overall survival (OS) was 16.3 months (95% CI: 12.6, NE) (Gaspar, et al., 2019).

Overall treatment with lenvatinib in combination with ifosfamide and etoposide in this patient population was associated with a manageable safety profile, and no unexpected toxicities were observed. Among the 31 subjects included in the safety analysis set, the most frequent treatment-emergent adverse events (TEAEs) were anemia (71%), nausea and vomiting (61% each), diarrhea (52%), neutropenia, platelet count decreased, and white blood cell count decreased (48% each). The most common treatment-related grade ≥3 TEAEs were anemia (52%), neutropenia (48%), platelet count decreased and white blood cell count

decreased (42% each), neutrophil count decreased (32%), and thrombocytopenia (29%). Eight subjects (25.8%) discontinued treatment due to TEAEs, and 15 subjects (48.4%) reported TEAEs leading to study drug dose reduction. There were no treatment-related fatal TEAEs (Gaspar, et al., 2019).

7.4 Study Rationale

Study 230, a randomized, controlled Phase 2 study, will evaluate the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide in children, adolescents, and young adults with relapsed or refractory osteosarcoma. Eligible patients aged 2 to 25 years old will receive ifosfamide and etoposide with or without lenvatinib (14 mg/m^2; RP2D from Study 207). Subjects randomized to Arm A can continue to receive lenvatinib until disease progression, intolerable toxicity, or withdrawal of consent. Approximately 72 subjects will be treated in the study. The primary objective of the study is to demonstrate that lenvatinib in combination with ifosfamide and etoposide has superior efficacy compared to ifosfamide and etoposide based on PFS in children, adolescents and young adults with relapsed or refractory osteosarcoma.

Pediatric solid tumors are highly vascularized. Angiogenesis and vasculogenesis are the fundamental processes by which new blood vessels are formed. As with normal tissue, the growing tumor requires an extensive network of capillaries to provide the necessary nutrients and oxygen. Moreover, the new intratumor blood vessels offer a way for tumor cells to enter the circulation and metastasize to distant organs and thus play an indispensable role in solid tumor growth and metastasis. Thus, inhibition of angiogenesis is a viable target for anticancer therapy. Moreover, vascular normalization allows reoxygenation, hence the addition of an anti-VEGF to chemotherapy may result in increased uptake of drugs into tumor tissue (Tuettenberg, et al., 2006).

7.4.1 Benefit-Risk Assessment

As discussed in Section 7.3.1, the safety, tolerability and activity of single-agent lenvatinib, and lenvatinib in combination with chemotherapy (ifosfamide and etoposide), have been assessed in Study 207. A pooled analysis of patients enrolled in Phase 1b and Phase 2, who received lenvatinib at the RP2D in combination with chemotherapy was conducted (N=35; data cutoff date 23 Jul 2019). In this heavily pretreated population, PFS-4m was 67.9% (95% CI: 47.6, 84.1), median PFS was 11.1 months (95% CI: 4.5, 12.6), and median overall survival was 16.3 months (95% CI: 12.6, NE). The activity of lenvatinib in combination with ifosfamide plus etoposide, as assessed by PFS-4m is clinically meaningful, displaying encouraging results when compared to other agents recommended in the ESMO guidelines for relapsed or refractory osteosarcoma (PFS-4m from 42% to 46%) (Casali, et al., 2018; Grignani et al., 2012; Berger et al., 2009).

In Study 207, no treatment-related fatal TEAEs were observed and safety data indicate that the toxicity of the combination is manageable and consistent with the known toxicities of each study drug and the disease under study.

Based on these data, the benefit-risk profile is considered favorable and further study of the combination within a randomized controlled trial is warranted.

8 STUDY OBJECTIVES

8.1 Primary Objective

To evaluate whether lenvatinib in combination with ifosfamide and etoposide (Arm A) is superior to ifosfamide and etoposide (Arm B) in improving PFS by independent imaging review (IIR) using Response Evaluation Criteria In Solid Tumors (RECIST 1.1), in children, adolescents, and young adults with relapsed or refractory osteosarcoma.

8.2 Secondary Objectives

The secondary objectives of the study are to:

1. Compare difference in PFS rate at 4 months (PFS-4m) between the 2 treatment arms per IIR
2. Compare difference in PFS rate at 1 year (PFS-1y) between the 2 treatment arms per IIR
3. Compare difference in OS and OS rate at 1 year (OS-1y) between the 2 treatment arms
4. Compare difference in objective response rate at 4 months (ORR-4m) between the 2 treatment arms per IIR
5. Compare difference in objective response rate (ORR) between the 2 treatment arms per IIR
6. Compare difference in safety and tolerability between the 2 treatment arms
7. Characterize the pharmacokinetics (PK) of lenvatinib, when administered in combination with ifosfamide and etoposide
8. Compare difference in health-related quality of life (HRQoL) as assessed by using the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales and Cancer Module between the 2 treatment arms
9. Assess the palatability and acceptability of the suspension formulation of lenvatinib in subjects receiving the suspension formulation in the study

8.3 Exploratory Objective(s)

The exploratory objectives of the study are to:

1. Explore difference in duration of response (DOR), disease control rate (DCR), and clinical benefit rate (CBR) between the 2 treatment arms per IIR and investigator assessment
2. Explore difference in PFS, PFS-4m, PFS-1y, ORR-4m, and ORR between the 2 treatment arms based on investigator assessment
3. Compare between the 2 treatment arms:
   - the proportion of subjects who achieve complete removal of baseline lesion(s)
   - the proportion of subjects with unresectable baseline lesion(s) that are converted to resectable

4. Investigate the relationship between subject tumor biomarkers and clinical response and toxicity of lenvatinib in combination with ifosfamide and etoposide

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, open-label, parallel-group, Phase 2 study to compare the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide in children, adolescents, and young adults with relapsed or refractory osteosarcoma.

Approximately 72 eligible subjects will be randomized to 1 of the following 2 treatment arms in a 1:1 ratio within the strata:

- Arm A: lenvatinib 14 mg/m^2 (orally, once daily) plus ifosfamide 3000 mg/m^2/day (intravenously [IV], Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)
- Arm B: ifosfamide 3000 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)

Randomization will follow a predefined randomization scheme based on the following stratification factors: time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 and ≥18 years).

The Sponsor will closely monitor enrollment, to ensure that a minimum of 36 subjects are <17 years of age at the time of informed consent.

The study will be conducted in 3 Phases: a Pre-randomization Phase, a Randomization Phase, and an Extension Phase.

The end of the study will be the date of data cutoff for the final analysis or the time of last subject last visit, whichever occurs later.

An overview of the overall study design is presented in Figure 1.

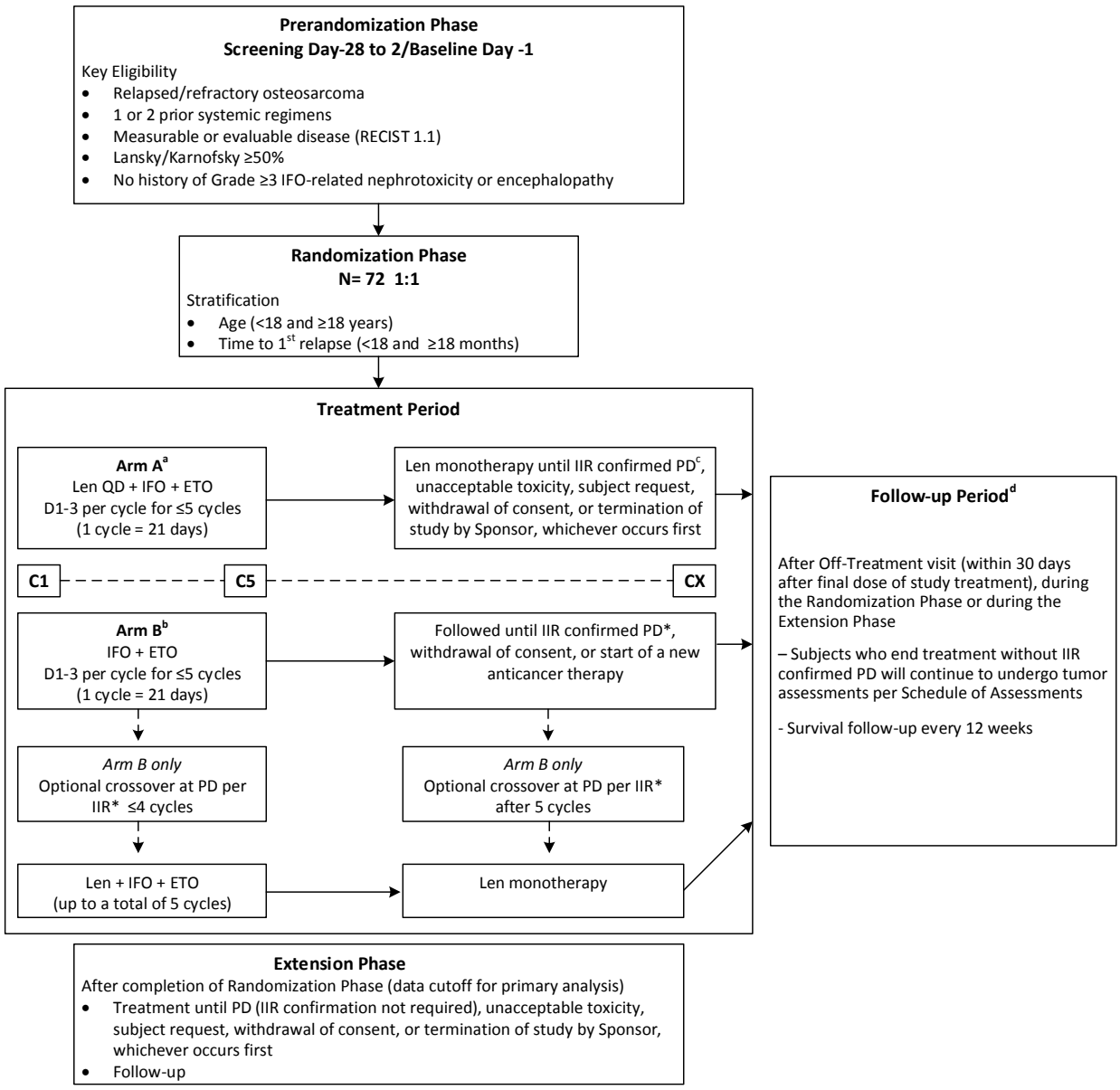

Figure 1 Overall Study Design

[a] **Arm A** = lenvatinib+ifosfamide+ etoposide (ifosfamide+etoposide for maximum of 5 cycles); lenvatinib to be continued until disease progression, intolerable toxicity, subject request, withdrawal of consent , or study termination by the sponsor, whichever occurs first.

[b] **Arm B =** ifosfamide+ etoposide (maximum of 5 cycles). *Subjects in Arm B with disease progression per RECIST 1.1 may be eligible for optional treatment with lenvatinib±chemotherapy. Please see Section 9.1.4 for further details.

[c] IIR confirmation of disease progression is only required prior to the start of the Extension Phase.

[d] Follow-up can occur during the Randomization Phase (if the subject discontinued treatment during the Randomization Phase), or during the Extension Phase, after the termination of study treatment.

C1 = Cycle 1; C2 = Cycle 2; CX = Cycle X; ETO = etoposide; IFO = ifosfamide; IIR = independent imaging review; Len = lenvatinib; PD = progressive disease/disease progression; QD = once daily; RECIST = Response Evaluation for Solid Tumors

9.1.1 Prerandomization Phase

The Prerandomization Phase will consist of 2 periods: Screening and Baseline. The Prerandomization Phase will last no longer than 28 days. The Screening Period will establish protocol eligibility and the Baseline Period will confirm eligibility.

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.

Subjects must have a histologically or cytologically confirmed diagnosis of high grade refractory or relapsed osteosarcoma as detailed in the Inclusion Criteria (Section 9.3.1).

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

9.1.1.2 Baseline 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 drug (Cycle 1 Day 1). Baseline assessments may be performed on Day -1 or on Cycle 1 Day 1 prior to dosing. Clinical laboratory tests (Table 4), including a pregnancy test (where applicable), should be performed within 72 hours prior to the first dose of study drug.

Subjects who complete the Baseline Period and continue to meet the criteria for inclusion/exclusion (as detailed in Section 9.3.1 and Section 9.3.2) will begin the Randomization Phase of this study.

9.1.2 Randomization Phase

The Randomization Phase will consist of 2 periods: Treatment Period and Follow-up Period. The Randomization Phase will begin at the time of randomization of the first subject and will end on the data cutoff date for the primary analysis (ie, when approximately 38 PFS events, as determined by IIR, are observed).

After the data cutoff date for the primary analysis has occurred, all subjects who are still on study treatment will enter the Extension Phase.

9.1.2.1 Treatment Period

The Treatment Period for each subject will begin at the time of randomization and will end at the completion of the Off-Treatment Visit which will occur within 30 days after the final dose of study treatment.

Subjects will receive study treatment as continuous 21-day cycles in both treatment arms. Treatment cycles will be counted continuously regardless of dose interruptions. If chemotherapy administration is precluded on Day 1 of a treatment cycle, the subject may resume treatment once recovered at the discretion of investigator. Subsequent chemotherapy will be administered every 21 (±1) days starting from the timepoint it was resumed. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments (Table 5). Subjects randomized to Arm A will continue to receive lenvatinib until disease progression (PD) confirmed by IIR, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor, whichever occurs first.

Disease progression (PD) must be confirmed by IIR prior to the investigator discontinuing study treatment for a subject. In situations where the investigator judges that alternative treatments must be instituted immediately for a subject's safety, study drugs may be discontinued without waiting for IIR confirmation of radiographic evidence of PD. If possible, before discontinuation of the subject from the study, the investigator should consult with the sponsor.

9.1.2.2 Follow-Up Period

The Follow-up Period begins the day after the Off-Treatment Visit and will continue for up to 2 years after end of treatment for a subject, unless the subject withdraws consent or the sponsor terminates the study.

Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn, however, an investigator may consult public records to establish survival status if permitted by local regulations.

All adverse events (AEs), including serious adverse events (SAEs), will be captured for 30 days after the last dose of study drug.

All subjects who end study treatment without IIR confirmed PD, will continue to undergo tumor assessments every 6 weeks until Week 18, then every 9 weeks until Week 54, thereafter, every 12 weeks until IIR confirmation of radiographic evidence of PD as described in the tumor assessments in the assessment schedule, or until another anticancer therapy is initiated.

Subjects in both Arm A and Arm B will be followed for survival every 12 weeks (±1 week) and all subsequent anticancer treatments received will be recorded. Subjects who are being followed for survival at the time of data cutoff for the primary analysis (ie, at the end of the

Randomization Phase) will continue to be followed for survival during the Follow-up Period of the Extension Phase.

9.1.3 Extension Phase

The Extension Phase will consist of 2 periods: Treatment Period and Follow-up Period.

9.1.3.1 Treatment Period

In the Treatment Period, subjects still on study treatment following the completion of the Randomization Phase will continue to receive study treatment as outlined in Section 9.1.2.1 until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor. Tumor assessments will be performed according to the local standard of care. Independent imaging review (IIR) review and confirmation of radiographic evidence of PD will not be required, and scans will no longer be required to be sent to the imaging core laboratory (ICL). The Off-Treatment Visit will occur within 30 days after the final dose of study treatment. All AEs, including SAEs will be captured up to 30 days after last dose of study drug. In case the study is discontinued by the sponsor, the sponsor will provide study drug (outside the study) for subjects who have not met the criteria for study drug discontinuation.

9.1.3.2 Follow-Up Period

The Follow-up Period will begin the day after the Off-Treatment Visit and will last for up to 2 years after end of treatment for a subject, unless the study is terminated by the sponsor, or the subject discontinues due to withdrawal of consent, or is lost to follow-up. Subjects will be treated by the investigator according to the prevailing local standard of care. Subjects will be followed every 12 weeks (±1week) for survival and all subsequent anticancer treatments received will be recorded.

9.1.4 Optional Lenvatinib Crossover (for Subjects in Arm B Only):

Subjects in Arm B with disease progression per RECIST 1.1 may be eligible for optional treatment with lenvatinib±chemotherapy. **Note:** subjects may only receive a maximum of 5 cycles of chemotherapy for the duration of the study. Optional crossover treatment must be initiated within 30 days of documented disease progression.

Optional lenvatinib crossover is only available if the following conditions are met:

- Subject experiences disease progression per RECIST 1.1 (as confirmed by IIR for all subjects who crossover prior to the start of the Extension Phase); and
- No new systemic anti-cancer medication was administered after the last dose of study drugs; and
- The subject meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria; and
- The study is ongoing.

Treatment with lenvatinib±chemotherapy will continue until the next disease progression (per RECIST 1.1 as assessed by investigator), development of unacceptable toxicity, subject request, or withdrawal of consent, whichever occurs first. If the sponsor terminates the study, the sponsor will continue to provide study drug(s) (outside of the study) for subjects requiring continuation of treatment.

Prior to optional lenvatinib crossover, baseline tumor assessment must be re-established (i.e., new tumor assessment scans performed), unless the last tumor assessment scans were performed within 4 weeks prior to Cycle 1 Day 1 of the crossover treatment.

Subjects who qualify to receive Optional Lenvatinib Crossover Treatment will be followed according to the schedule of procedures/assessments in Table 7.

9.2 Discussion of Study Design, Including Choice of Control Groups

The study has been designed as an open-label, randomized study to compare the safety and efficacy of lenvatinib in combination with the ifosfamide and etoposide with ifosfamide and etoposide alone in children, adolescents, and young adults with relapsed or refractory osteosarcoma. Ifosfamide and etoposide will be used as the control group since it is a recognized treatment option for patients with relapsed osteosarcoma.

Progression-free survival (PFS) as compared to control, with blinded IIR of radiological imaging using RECIST 1.1 criteria will be evaluated as the primary endpoint. The endpoint was determined as appropriate for the study, given the unique biology of the osteosarcoma. To avoid bias in efficacy assessment, the analysis for primary endpoint is based on tumor assessment by IIR, a central independent blinded assessment. Progression-free survival at 4 months (PFS-4m), at 1 year (PFS-1y), ORR at 4 months, ORR, OS at 1 year (OS-1y), and OS will also be evaluated in the study as secondary endpoints.

Pharmacodynamic serum and tumor biomarkers identified in other lenvatinib clinical studies may be assessed in samples collected from subjects enrolled in this study in the test arm only (Arm A: lenvatinib + ifosfamide + etoposide) and may be used for exploratory analysis for evaluation of response-related and/or safety-related outcomes.

The study will also assess health related quality of life (HRQoL) using validated questionnaires.

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups.

9.3 Selection of Study Population

Approximately 72 subjects between 2 and ≤25 years of age will be randomized (36 subjects in each arm). Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

For evaluation of the primary endpoint (intent–to-treat analysis), a minimum of 36 subjects <17 years old (at the time of informed consent) will be randomized.

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 high grade osteosarcoma.
2. Refractory or relapsed osteosarcoma after 1 to 2 prior lines of systemic treatments.
3. Measurable or evaluable disease per RECIST 1.1 that meets the following criteria:
   - Measurable disease is defined as a lesion with a minimum size (by long axis) of 10 mm using computed tomography/magnetic resonance imaging (CT/MRI) (lymph nodes must be accurately measurable with a minimum size [by short axis] of 15 mm).
   - Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must have subsequently grown unequivocally to be deemed a target lesion.
   - Any other non-measurable lesions will be considered evaluable disease.
4. Aged 2 years to ≤25 years at the time of informed consent.
5. Life expectancy of 12 weeks or more.
6. Lansky play score ≥50% or Karnofsky Performance Status score ≥50%. Use Karnofsky for subjects ≥16 years of age and Lansky for subjects <16 years of age. Subjects who are unable to walk because of paralysis, but who are able to perform ADL while wheelchair bound, will be considered ambulatory for the purpose of assessing the performance score.
7. Adequate bone marrow function as evidenced by:
   a. absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L.

      (subjects with bone marrow involvement should have ANC $\geq 0.8\times10^9$/L and leucocyte count $\geq 1\times10^9$/L).
   b. hemoglobin ≥8.0 g/dL (a hemoglobin of <8.0 g/dL is acceptable if it is corrected by growth factor or transfusion before Cycle 1 Day 1).
   c. platelet count $\geq 100\times10^9$/L.
8. Adequate blood coagulation function defined by International Normalized ratio or prothrombin time (INR/PT) and activated partial thromboplastin time or partial thromboplastin time (aPTT/PTT) ≤1.5 unless participant is receiving anticoagulant therapy, as long as INR/PT and aPTT/PTT are within therapeutic range of intended use of anticoagulants.
9. Adequate liver function as evidenced by:
   a. Bilirubin ≤1.5 times the upper limit of normal (ULN).
   b. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3×ULN (in the case of liver metastases ≤5×ULN).
10. Adequate renal function as evidenced by:
    a. Serum creatinine based on age/gender as below. If serum creatinine is greater than maximum serum creatinine for age/gender as shown in the table below, then

creatinine clearance (or radioisotope glomerular filtration rate [GFR]) must be >70 mL/min/1.73 m^2.

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

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

b. Urine dipstick <2+ for proteinuria. Subjects who have ≥2+ proteinuria on dipstick urinalysis should undergo a spot protein-creatinine (P/C) ratio test that should be Grade <2 per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and if possible perform a 24-hour urine collection (children and adolescents ≤12 years of age must have ≤500 mg of protein/24 hours and subjects >12 years of age must have ≤1 g of protein/24 hours).

c. No clinical evidence of nephrotic syndrome.

11. Adequate cardiac function as evidenced by left ventricular ejection fraction (LVEF) ≥50% at baseline as determined by echocardiography or multigated acquisition (MUGA) scan.
12. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as:
    a. BP <95th percentile for sex, age, and height/length at screening (as per National Heart Lung and Blood Institute guidelines) and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1. Subjects >18 years of age should have BP ≤150/90 mm Hg at screening and no change in antihypertensive therapy within 1 week prior to Cycle 1 Day 1.
13. Washout before Cycle 1 Day 1 of 3 weeks in case of prior chemotherapy, 6 weeks if treatment included nitrosoureas; 4 weeks for definitive radiotherapy, 2 weeks for palliative radiotherapy; and 3 months from high-dose chemotherapy and stem cell rescue. For all other anti-cancer therapies, washout before Cycle 1 Day 1 of at least 5 half-lives (or at least 28 days, whichever is shorter). Subjects must have recovered (to Grade ≤1, except for alopecia, ototoxicity, and Grade ≤2 peripheral neuropathy, per CTCAE v5.0) from the acute toxic effects of all prior anticancer therapy before Cycle 1 Day 1.
14. Must have no prior history of lenvatinib treatment.
15. Written and signed informed consent from the parent(s) or legal guardian and assent from the minor subject. Written informed consent from subjects ≥18 years.
16. Willing and able to comply with the protocol, scheduled follow-up, and management of toxicity as judged by the investigator.

9.3.2 Exclusion Criteria

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

1. Any active infection or infectious illness unless fully recovered prior to Cycle 1 Day 1 (ie, no longer requiring systemic treatment).
2. Subjects with central nervous system metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy, surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 2 weeks before Cycle 1 Day 1.
3. Active second malignancy within 2 years prior to enrollment ([in addition to osteosarcoma], but not including definitively treated superficial melanoma, carcinoma-in-situ, basal or squamous cell carcinoma of the skin).
4. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
5. Has had major surgery within 3 weeks prior to Cycle 1 Day 1.
   - Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
6. Known hypersensitivity to any component(s) of the study drugs (lenvatinib, ifosfamide, and etoposide, or their ingredients).
7. Currently receiving any investigational drug or device in another clinical study or within 28 days prior to Cycle 1 Day 1.
8. A clinically significant ECG abnormality, including a marked baseline prolonged QT or QTc interval (eg, a repeated demonstration of a QTc interval >480 msec).
9. Has clinically significant cardiovascular disease within 6 months from first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability. **Note:** Medically controlled arrhythmia would be permitted.
10. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that in the opinion of the investigator might affect the absorption of lenvatinib.
11. Pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula.
12. Gastrointestinal bleeding or active hemoptysis (bright red blood of at least ½ teaspoon) within 3 weeks prior to Cycle 1 Day 1.
13. Radiographic evidence of intratumoral cavitation, encasement, or invasion of a major blood vessel. Additionally, the degree of proximity to major blood vessels should be considered for exclusion because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.
14. History of ifosfamide-related Grade ≥3 nephrotoxicity or encephalopathy.
15. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.

16. Known to be human immunodeficiency virus (HIV) positive. Note: HIV testing is required at screening only when mandated by local health authority.
17. Known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected). Note: Testing for Hepatitis B or Hepatitis C is required at screening only when mandated by local health authority.
18. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG]) (human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG /hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of any study drug.
19. Females of childbearing potential* who:
    - Do not agree to use a highly effective method of contraception for the entire study period and for 28 days after lenvatinib discontinuation or 12 months after etoposide and ifosfamide discontinuation, ie:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device (IUD) or intrauterine 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.

    * All post pubertal females will be considered to be of childbearing potential unless they have early menopause (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 stable dose of the **same oral hormonal contraceptive product for at least 4 weeks before dosing with study drug(s) and for the duration of the study.
20. 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 28 days after lenvatinib discontinuation or 6 months after discontinuation of etoposide and ifosfamide). No sperm donation is allowed during the study period and for 28 days after lenvatinib discontinuation or 6 months after discontinuation of etoposide and ifosfamide.

21. A contraindication to any of the study drugs (lenvatinib, ifosfamide, and etoposide) per local prescribing information.

9.3.3 Removal of Subjects From Therapy or Assessment

Subjects will continue to receive study treatment until any of the following occur:

- Progressive disease (as confirmed by IIR*)
- Unacceptable toxicity
- Subject request
- Withdrawal of consent
- Termination of the study by the Sponsor

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 protocol-specified off-treatment visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents.

During the Follow-Up Period, subjects who have discontinued study treatment without progression should have disease assessments as per the appropriate tumor assessment schedule in Table 5 and Table 6 from the date of the last assessment until PD is documented or another anticancer therapy is initiated. After data cutoff for the primary analysis, tumor assessments may be performed as clinically indicated per institutional guidelines (but no less frequently than every 12 weeks), following the prevailing local standard of care, and IIR confirmation of radiographic evidence of PD will not be required.

All subjects will be followed for survival for up to 2 years after end of treatment for a subject, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up after completion of the primary study analysis.

*Confirmation of disease progression by IIR is only required during the Randomization Phase.

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

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

Test Arm (Arm A): Lenvatinib + Ifosfamide + Etoposide

Lenvatinib 14 mg/m^2, orally administered once daily in each 21-day cycle.

Lenvatinib is provided as hard capsules containing 1 mg, 4 mg, or 10 mg lenvatinib. An extemporaneous suspension of lenvatinib capsules should be used for subjects unable to swallow capsules. After adjustment for body surface area (BSA), the daily dose cannot exceed 24 mg QD.

Ifosfamide 3000 mg/m^2/day, IV, for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Etoposide 100 mg/m^2/day, IV, for 3 consecutive days (Day 1 to 3) , every 21 days, for a maximum of 5 cycles.

Treatment with lenvatinib will continue in 21-day cycles after chemotherapy is discontinued, until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor. In case the study is discontinued by the sponsor, the sponsor will provide study drug (outside the study) for subjects who have not met the criteria for study drug discontinuation.

Control Arm (Arm B): Ifosfamide + Etoposide

Ifosfamide 3000 mg/m^2/day, IV, daily for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Etoposide 100 mg/m^2/day, IV, daily for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

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

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

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

Subjects will receive study treatment as continuous 21-day cycles in both treatment arms. Treatment cycles will be counted continuously regardless of dose interruptions. If chemotherapy administration is precluded on Day 1 of a treatment cycle, the subject may resume treatment once recovered at the discretion of investigator. Subsequent chemotherapy will be administered every 21 (±1) days starting from the timepoint it was resumed.

Optional Lenvatinib Crossover (for Subjects in Arm B Only):

Subjects in Arm B with disease progression per RECIST 1.1 may be eligible for optional treatment with lenvatinib±chemotherapy. Please see Section 9.1.4 for further details.

9.4.1.1 Lenvatinib Dose Reduction and Interruption Instructions

Adverse events will be graded using CTCAE version 5.0.

Dose reduction and interruptions for subjects who experience lenvatinib related toxicity will be managed as described in Table 1.

The starting dose of lenvatinib is 14 mg/m^2. Dose reductions occur in succession based on the previous dose level. Each dose level reduction is a 20% reduction from the previous dose.

Once the study drug dose level 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.

Refer to the subsections below for management of hypertension, posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (PRES/RPLS), proteinuria, hepatotoxicity, thromboembolic events, hypocalcemia, gastrointestinal symptoms and acute abdominal pain, and hemorrhage, as appropriate, before consulting the dose modification table below.

Table 1 Criteria for Temporary Discontinuation of Study Drug, Dose Reduction, and Resumption of Treatment

Dose Modification Guidelines for Lenvatinib 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] or Grade 3[e]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	11.2 mg/m^2 (or 20% reduction of the starting dose) orally QD (one-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	9.0 mg/m^2 (or 20% reduction of the previous dose) orally QD (one-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	7.2 mg/m^2 (or 20% reduction of the previous dose) orally QD (one-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with sponsor
Grade 4[f]: Discontinue Study Treatment		

Note: For grading see CTCAE version 5.0. Collect all CTC grades of adverse events, decreasing and increasing grade.

BMI = body mass index, CTCAE = Common Terminology Criteria for Adverse Events

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, hypertension, 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 1 weight 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 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. Obesity is defined as body mass index (BMI) percentiles corresponding to 30 kg/m², related to the age of the children (Cole, et al., 2000) or BMI ≥ the 95th percentile for children and teens of the same age and sex (Ogden, et al., 2002) (Appendix 7 and Appendix 8).

e: 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.

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

9.4.1.1.1 BLOOD PRESSURE

For children, blood pressure varies by the sex and age of the child and it is closely related to height and weight. Blood pressure will be assessed in terms of percentile for sex, age and height/length. Guidelines to sex, age, and height-specific percentiles of blood pressure are provided in Appendix 5 and Appendix 6. BP that is consistently above the 95th percentile based on sex, age, and height/length for subjects <18 years old; or BP ≥140/90 mmHg for

subjects ≥18 to 25 years old requires further evaluation. A referral to a cardiologist is recommended for patients who develop hypertension during the study. Ideally, cardiovascular assessments and the management of hypertension should be supervised by a cardiologist. Exercise, excitement, coughing, crying, and struggling may raise the systolic pressure of children as much as 40 to 50 mmHg greater than their usual level. Variability in blood pressure in children of approximately the same age and body build should be expected and serial measurements should always be obtained when evaluating a patient with hypertension. BP values for the management of hypertension for participants 18 to 25 years old are included in parentheses in Section 9.4.1.1.1 .

9.4.1.1.2 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 mm Hg] for sex, age, and height/length at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1 Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be conducted as detailed in the Schedule of Procedures/ Assessments (Table 5 and Table 6). Hypertension will be graded using CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

If the subject's initial BP measurement is elevated (systolic BP ≥95th percentile [BP ≥140 mm Hg] or diastolic BP ≥95th percentile [BP ≥90 mm Hg]), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥95th percentile [BP ≥140 mm Hg] or diastolic BP ≥95th percentile [BP ≥90 mm Hg]) is confirmed on 2 assessments obtained 30 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when systolic BP ≥95th percentile [BP ≥140 mm Hg] or diastolic BP ≥95th percentile [BP ≥90 mm Hg] is first observed on 2 assessments obtained 30 minutes apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instances where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled

hypertension (eg, BP ≥99th percentile [BP ≥160/100 mm Hg], significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant comorbidities). Once the subject has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

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

The following guidelines should be followed for the management of systolic BP ≥99th percentile (BP ≥160 mm Hg) or diastolic BP ≥99th percentile (BP ≥100 mm Hg) confirmed on repeat measurements after at least 30 minutes:

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

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

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

    - If systolic BP ≥99th percentile (BP ≥160 mm Hg) or diastolic BP ≥99th percentile (BP ≥100 mm Hg) recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP <95th percentile (BP ≤150 mm Hg) and diastolic BP <95th percentile (BP ≤95 mm Hg) and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥99th percentile (BP ≥160 mm Hg) or diastolic BP ≥99th percentile (BP ≥100 mm Hg) recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction only when systolic BP <95th percentile (BP ≤150 mm Hg and diastolic BP <95th

percentile (BP ≤95 mm Hg) and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

- Additional dose reduction should be discussed with the Sponsor.

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

- Institute appropriate medical management
- Discontinue lenvatinib

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

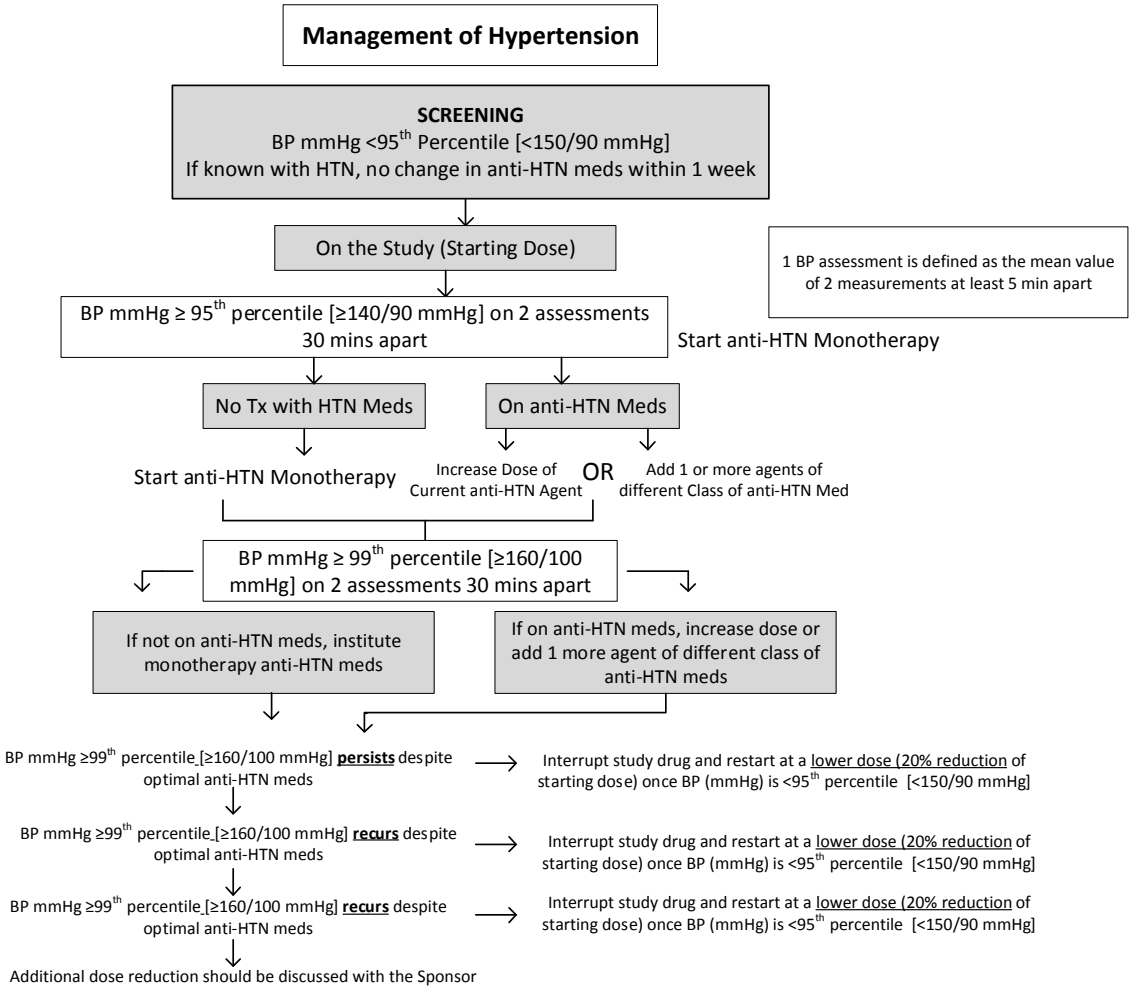

Figure 2 Management of Hypertension

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

9.4.1.1.3 MANAGEMENT OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME/REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME

Posterior Reversible encephalopathy Syndrome (PRES)/Reversible Posterior Leukoencephalopathy Syndrome (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. An MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP (see Section 9.4.1.1.1 and 9.4.1.1.2), and neurologic consultation is advised. In subjects with signs or symptoms of PRES/RPLS, dose modification guidelines as per Table 1 should be followed.

9.4.1.1.4 MANAGEMENT OF PROTEINURIA

Regular assessment for proteinuria should be conducted as detailed in the Schedule of Assessments (Table 5 and Table 6). Guidelines for assessment and management of proteinuria are summarized as follows:

Grading of Proteinuria

- Grading according to CTCAE 5.0 (Cancer Therapy Evaluation Program, 2017) will be based on the protein-creatinine ratio or 24-hour urinary protein result, if available. For subjects ≥18 years of age, if the subject has 4+ proteinuria by dipstick, a 24-hour urinary protein result is required to confirm Grade 3 proteinuria.

Management of Proteinuria

- Management of lenvatinib administration will be based on the grade of proteinuria according to Table 1.
- In the event of nephrotic syndrome, lenvatinib must be discontinued.

Detection and Confirmation

- Perform urine dipstick testing per the Schedule of Assessments (Table 5 and Table 6)
- For subjects ≥18 years of age, a 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot urine protein-to-creatinine ratio [UPCR] test) AND for subjects <18 years of age, an immediate spot UPCR test, and if possible, a 24-hour urine collection (initiated as soon as possible and at least within 72 hours) is required in the following situations:
  - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on lenvatinib
  - A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
  - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+
- For subjects ≥18 years of age, a 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Monitoring

- Urine dipstick testing for subjects with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.
- Proteinuria monitoring can be performed at the local laboratory or investigator site, but must be managed by the site physician.

9.4.1.1.5 MANAGEMENT OF HEPATOTOXICITY

Regular monitoring of liver function tests (ALT, AST, bilirubin levels) should be conducted as detailed in the Schedule of Assessments (Table 5 and Table 6) 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 1). Appropriate supportive care should be provided together with close monitoring. If hepatic (any grade per CTCAE v5) failure occurs the study drug must be discontinued.

9.4.1.1.6 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 1). Appropriate supportive care should be provided together with close monitoring. If a subject experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, study drug must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study drug discontinuation.

9.4.1.1.7 MANAGEMENT OF HYPOCALCEMIA

Serum calcium should be monitored monthly per the Schedule of Assessments (Table 5 and Table 6). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

Corrected calcium = ([4 – serum albumin in g/dL] ×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.

9.4.1.1.8 MANAGEMENT OF GASTROINTESTINAL SYMPTOMS AND ACUTE ABDOMINAL PAIN

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

For adverse events of abdominal pain believed related to lenvatinib or more specific adverse events believed related to lenvatinib that result in the symptom of abdominal pain, follow instructions contained in Table 1 regarding study treatment dose reduction and interruption. For Grade 4 adverse events that result in abdominal pain, study drug 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), dose modification guidelines should be followed as per Table 1. 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.

9.4.1.1.9 MANAGEMENT OF HEMORRHAGE

Dose modification guidelines as per Table 1 for lenvatinib related adverse events should be followed for the management of hemorrhage. Either resume lenvatinib at a reduced dose or discontinue lenvatinib, depending on the severity and persistence of hemorrhage.

9.4.1.1.10 MANAGEMENT OF FISTULA FORMATION AND GASTROINTESTINAL PERFORATION

Lenvatinib should be discontinued in any participants who develop grade ≥4 fistula (gastrointestinal or non-gastrointestinal), or gastrointestinal perforation of any grade.

9.4.1.1.11 MANAGEMENT GUIDELINES FOR 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.

9.4.1.2 Management of Ifosfamide-Etoposide Associated Toxicity

Blood counts should be closely monitored during and prior to the next cycle of chemotherapy. Chemotherapy-associated myelosuppression should be managed by granulocyte-colony stimulating factor (G-CSF). It is recommended that pegylated G-CSF or G-CSF be administered at least 24 to 72 hours after completion of ifosfamide-etoposide chemotherapy; use of G-CSF is recommended until white blood cell (WBC) counts are $\geq 1 \times 10^9$/L. Guidelines for dose modification for ifosfamide and etoposide associated toxicities are provided in the Table 2 below.

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

Table 2 Criteria for Dose Modification of Chemotherapy Dose

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

ANC = absolute neutrophil count, RBC = red blood cell, ULN = upper limit normal.

9.4.2 Identity of Investigational Product(s)

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. Instructions for the preparation of the lenvatinib suspension are provided in the Pharmacy Manual.

9.4.2.1 Chemical Name of E7080

- Test drug code: E7080
- Generic name: lenvatinib

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

9.4.2.2 Comparator Drug

Cytotoxic Chemotherapy: Ifosfamide and Etoposide

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

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

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

Anti-emetic or any other prophylaxis should be administered in accordance with institutional guidelines.

9.4.2.3 Labeling for Study Drug

Lenvatinib and the combination chemotherapy drugs, ifosfamide and etoposide, where supplied by the sponsor 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.

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

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

9.4.2.4 Storage Conditions

Lenvatinib will be stored in accordance with the labeled storage conditions. The expiry date for lenvatinib will be established based on manufacturing date and is based on formulation testing. The expiry date of the lenvatinib will either be on the label and in the interactive voice response system (IVRS) system.

Ifosfamide and etoposide will be stored in accordance with the labeled storage conditions. The expiry date of the ifosfamide and etoposide will be the same as the commercial products provided.

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

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study. All subjects who provide signed informed consent and/or assent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

After the Baseline Period, subjects will be randomized to 1 of the following 2 treatment arms in a 1:1 ratio:

- Arm A: lenvatinib 14 mg/m^2 (orally, once daily) plus ifosfamide 3000 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)
- Arm B: ifosfamide 3000 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)

Randomization will be performed centrally by an IVRS. Randomization will follow a predefined randomization scheme based on the following stratification factors: time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 and ≥18 years). Time to first relapse/refractory disease will be calculated starting from date of initial diagnosis.

9.4.4 Selection of Doses in the Study

The dose of lenvatinib, ifosfamide and etoposide in this study is the RP2D (14 mg/m^2 + ifosfamide 3000 mg/m^2 + etoposide 100 mg/m^2) established in Study 207. The safety, tolerability and activity of single-agent lenvatinib, and lenvatinib in combination with chemotherapy (ifosfamide and etoposide), have been assessed in Study 207, a phase 1/2, multicenter, open-label study in children, adolescents and young adults with solid tumors, including relapsed or refractory osteosarcoma, and radioiodine- refractory differentiated thyroid carcinoma. The recommended phase 2 dose (RP2D) of lenvatinib was determined in the phase 1b portion as 14 mg/m^2 orally once daily when given as single-agent as well as in combination with etoposide (100 mg/m^2 IV once daily for 3 days) + ifosfamide (3000 mg/m^2 IV once daily for 3 days), administered on days 1 to 3 of each 21-day cycle, for 5 cycles.. BSA will be used to determine the daily dose of lenvatinib for each subject. After adjustment for BSA, the daily dose of lenvatinib cannot exceed 24 mg. Please see Section 7.3.1 for further details on the results of Study 207.

9.4.5 Selection and Timing of Dose for Each Subject

Lenvatinib capsules are to be taken orally once a day at approximately the same time in the morning without regard to food intake for 21 days from Cycle 1 onward. If a subject misses a dose, it may be taken within the 12 hours following the usual time of the morning dose. If more than 12 hours have elapsed from the time of the usual daily dose, lenvatinib should be taken the next day at the usual time in the morning. In the event a subject vomits after study drug administration, the subject should not take another dose until the next scheduled dose.

Study drugs should be administered at the clinic on PK sampling days. All scheduled visits must be conducted as per protocol, irrespective of treatment interruption.

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

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

Aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and low-molecular-weight heparin (LMWH) are permissible but should be used with caution. Granulocyte colony-stimulating factor (g-CSF) or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell (RBC) counts.

9.4.7.1 Drug-Drug Interactions

The weak inhibitory effect on CYP enzymes (in vitro) exhibited by lenvatinib suggests a low risk of lenvatinib interference with the PK of other drugs co-administered in usual clinical practice. There is no clinically meaningful drug-drug interaction (DDI) risk when lenvatinib is co-administered with CYP3A substrates such as midazolam. Simultaneous CYP3A4/P-gp inhibitions by ketoconazole slightly (15% to 19%) increased systemic exposure to lenvatinib after oral administration as measured by AUC and C_{max} in humans. Since no change was observed in half-life, t_{max}, or t_{lag}, the slight increase in systemic exposure is probably related to a decrease in first pass metabolism. However, since the magnitude of the change is small, coadministration of lenvatinib with CYP3A4/P-gp inhibitors is not of clinical concern. Similarly, PK data did not suggest any major effects of rifampin on the exposure or disposition of lenvatinib. Following administration of a single dose of lenvatinib with a single dose of rifampin, lenvatinib exposure increased about 31%. In contrast, following administration of multiple doses of rifampin, free lenvatinib exposure was reduced about 9% and about 18% for total lenvatinib. These findings suggest that there is no clinically meaningful influence of either P-gp inhibition (single dose of rifampin) or simultaneous P-gp and CYP3A4 induction (multiple doses of rifampin) on lenvatinib PK.

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

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Subjects should not receive other antitumor therapies while on study. If a subject receives additional antitumor therapies other than the study drug(s), such as chemotherapy, targeted therapies, immunotherapy, or antitumor interventions - such as surgery or palliative radiotherapy (other than as described below), this will be judged to represent evidence of disease progression, and the study medication should be discontinued.

Bisphosphonates and denosumab for the treatment of osteosarcoma are not permitted.

The concomitant use of live vaccines (e.g., measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid [oral] vaccines) are not permitted. Seasonal influenza vaccines for injection are generally killed virus vaccines and therefore are permitted. However intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and therefore are not permitted. Additionally, the concomitant use of live vaccines with chemotherapy is contraindicated in immunosuppressed patients.

For further information on the prohibited concomitant therapies for ifosfamide and etoposide, please refer to the respective prescribing information.

9.4.7.3 Permitted Concomitant Treatment/Procedures

The following concomitant treatments/procedures are allowed:

a. Removal of existing (not new) osteosarcoma lesion (eg, surgical, radiofrequency ablation, cryotherapy, thermoablation, stereotactic radiotherapy, etc.) after completion of the Week 18 tumor assessment. Subjects may continue study treatment after protocol permissible surgery in the presence of clinical benefit, with Sponsor approval.

b. Palliative radiotherapy is allowed for ≤2 significantly symptomatic nontarget lesions.

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 2 weeks after, once there is evidence of adequate healing and no risk of bleeding.

Any additional procedural or subject specific particularities should be discussed with the investigator and the sponsor.

9.4.8 Treatment Compliance

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

9.4.9 Drug Supplies and Accountability

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

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

- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, or a completed Investigator and Site Information Form
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572 or Investigator and Site Information Form
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

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

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

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

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Products Regulatory Agency [MHRA]). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator or the designated pharmacist by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's

personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

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

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Screening/Baseline Assessments

9.5.1.1.1 DEMOGRAPHY

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

9.5.1.1.2 BASELINE ASSESSMENTS

Baseline assessments will be performed at Day -1 or at Cycle 1 Day 1 prior to treatment. Assessments will include confirmation of subject eligibility with the inclusion and exclusion criteria, medical and surgical history, prior medications and procedures, pregnancy test (serum or urine) within 72 hours of the first dose of study medication), Lansky play score (see Appendix 2) or Karnofsky performance status score (see Appendix 3), tumor-node metastasis (TNM) Staging (at initial diagnosis of the disease), vital signs, clinical chemistry and hematology, urine dipstick testing, height, Tanner's staging (see Appendix 9), dental examinations, proximal tibial growth plates, and pharmacodynamic biomarkers (for Arm A only).

9.5.1.1.3 MEDICAL HISTORY

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 5, and Table 6). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the

Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.2 Efficacy Assessments

9.5.1.2.1 TUMOR RESPONSE ASSESSMENTS

Tumor assessment will be performed based on RECIST 1.1 (Appendix 1). Investigator-determined response assessments will be performed at each assessment time point and entered onto the appropriate CRF. Copies of all tumor assessment scans will be sent to an ICL designated by the sponsor for efficacy assessment and for confirmation of PD. Tumor assessments will be carried out following the guidelines provided by the ICL. Subjects must have evaluable disease or measurable disease based on RECIST 1.1.

At Screening

During the Screening Period, tumor assessments of the chest, abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed within 28 days prior to Cycle 1 Day 1. 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.

Brain scans by MRI with and without contrast enhancement or CT with contrast enhancement will be performed at screening as clinically indicated.

Historical scans (within 28 days prior to the Cycle 1 Day 1) may be used to demonstrate eligibility as long as they meet minimum standards as separately defined by the ICL. For subjects with rapidly progressive disease, it is advised that imaging be repeated prior to Cycle 1 Day 1.

If available, bone imaging obtained within 8 weeks prior to Cycle 1 Day 1 should be sent to the ICL. Bone lesions noted on the screening/baseline images should be followed as non-target lesions with modalities other than nuclear medicine scans.

During Treatment Phase

CT scans of the chest and CT/MRI of other known sites of disease, plus any areas of newly suspected disease will be performed using the same methodology as at screening every 6 weeks ±1 week, following the date of randomization until Week 18. Following completion of the chemotherapy treatment period (ie, after Week 18), the frequency of tumor assessments will be every 9 weeks ±1 week until Week 54 ±1 week. Thereafter, they will be performed every 12 weeks ±2 weeks until documentation of PD. At any point, scans should be performed earlier than the scheduled time point, if clinically indicated. Any bone imaging obtained during the treatment phase should be sent to the ICL. Any non-target bone lesions should be followed with modalities other than nuclear medicine scans; if a non-target bone lesion is not evaluable (NE) for a timepoint, the lesion should be considered as NE, but timepoint response does not need to be evaluated as NE.

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

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

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

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

Brain scans by MRI with and without contrast enhancement or CT with contrast enhancement will be performed as clinically indicated. If protocol eligible brain metastases are present at screening, a CT/MRI of the brain must be performed at all tumor assessment time points (eg, every 6, 9, or 12 weeks).

Disease progression per RECIST 1.1 during the randomization phase must be confirmed by IIR prior to the investigator discontinuing study treatment for a subject. In the event that the investigator considers alternative treatments must be instituted immediately for management of urgent medical complications of PD, study drugs may be discontinued without waiting for independent confirmation of radiographic evidence of PD. Subjects who discontinue study

treatment without PD will continue to undergo tumor assessments according to the schedule until PD is documented or another anticancer therapy is initiated. If possible, before discontinuation of the subject from the study, the investigator should consult with the sponsor.

During Post-treatment Follow-up

Subjects who discontinue treatment without PD will have tumor assessments performed as per the appropriate tumor assessment schedule) or sooner if clinically indicated, for documented PD or until another anticancer therapy is initiated, whichever occurs first.

After data cutoff for the primary analysis, tumor assessments may be performed as clinically indicated as per the institutional guidelines (but no less frequently than every 12 weeks), following the prevailing local standard of care. All subjects will be followed for survival for up to 2 years after end of treatment, unless the study is terminated by the sponsor, or the subject discontinues due to withdrawal of consent, or is lost to follow-up.

During the Optional Lenvatinib Crossover Treatment Phase

Prior to optional lenvatinib crossover, baseline tumor assessment must be re-established (i.e., new tumor assessment scans performed), unless the last tumor assessment scans were performed within 4 weeks prior to Cycle 1 Day 1 of the crossover treatment.

During the Optional Lenvatinib Crossover Treatment Phase, tumor assessments will be performed as clinically indicated per the institutional guidelines (but no less frequently than every 12 weeks), following the prevailing local standard of care. Scans are not required to be submitted to the independent imaging core laboratory during the Optional Lenvatinib Crossover Treatment Phase.

9.5.1.2.2 PALATABILITY AND ACCEPTABILITY OF LENVATINIB SUSPENSION FORMULATION

The palatability and acceptability of lenvatinib suspension formulation will be assessed using the Palatability Questionnaire (see Appendix 4). All subjects who receive suspension formulation with the exception of subjects using a nasogastric or gastrostomy tube, must complete the questionnaire on C1D1 (or the subsequent visit). If the subject is unable to complete the questionnaire, this must be done by a parent or legal guardian. Measurement of palatability will be assessed using a facial Hedonic scale (Guinard, 2001).

9.5.1.3 Pharmacokinetic, Pharmacodynamic, and Other Biomarker Assessments

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

In order to ensure patient safety and not exceed the maximum allowable volume for blood collections, pharmacokinetic sampling should not be performed for any subject with a body weight <13 kg. Blood samples (2 mL each) will be collected from all subjects from Arm A only at the time points shown in Table 3. Pharmacokinetic blood samples will also be drawn pretreatment on the day of tumor assessment as described in the Table 3. Actual time and

date of PK blood collection as well as time of drug administration will be recorded on the appropriate page of the CRF. Exposure parameters such as area under the concentration × time curve (AUC) will be derived from posterior estimates of the PK parameters from the final population PK model. For the time points shown in Table 3, subjects or their parents will be instructed not to take the dose of lenvatinib prior to arriving at the study site. Lenvatinib capsule administration will be recorded in the eCRF. The Cycle 1 Day 1 and Day 15 doses of lenvatinib will be administered at the study site at approximately the same time of day in order to accommodate PK sample collection timing. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in a separate Laboratory Manual.

Table 3 Lenvatinib Pharmacokinetic Sampling Time Points

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

Note: All predose samples are to be drawn approximately 24 hours following the dose administered on the previous day.
h = hour(s).
a. If dose interruption is necessary in these time points, please contact the sponsor.

Only samples from all subjects randomized to Arm A will be collected. Lenvatinib will be quantified using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method.

9.5.1.3.2 PHARMACODYNAMIC AND OTHER BIOMARKER ASSESSMENTS

In order to ensure patient safety and not exceed the maximum allowable volume for blood collections, pharmacodynamic sampling should not be performed for any subject with a body weight <16 kg. Optional pharmacodynamic serum and archived fixed tumor tissue samples for biomarker analysis may be collected from study subjects randomized to Arm A (ie, lenvatinib + ifosfamide + etoposide), as specified in the Schedule of Procedures/Assessments.

Note: Providing blood samples for pharmacodynamic biomarker assessment is optional and will not impact subject eligibility.

Pharmacodynamic serum and tumor biomarkers identified in other lenvatinib clinical studies may be assessed in samples collected from subjects enrolled in this study. Pharmacodynamic biomarker analysis will be performed as described in an analysis plan provided separately.

Blood biomarker samples may be used for exploratory analysis for evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development (see Appendix 10).

9.5.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all grades per National Cancer Institute (NCI) CTCAE v5.0 (for both increasing and decreasing severity), and serious adverse events (SAEs); regular laboratory evaluation of hematology, blood chemistry, and urine values; periodic measurement of vital signs and 12-lead ECGs; and echocardiograms or MUGA scans, Lansky play score or Karnofsky performance status score, physical examinations, dental examinations, and height assessments as detailed in the Schedule of Assessments (Table 5 and Table 6).

Clinical and laboratory toxicities/symptomatology will be graded according to CTCAE v5.0 (Cancer Therapy Evaluation Program, 2017).

9.5.1.4.1 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, ifosfamide, and etoposide.

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 PD.
- 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, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit and for 30 days after the subject's last dose. Refer to Section 9.5.4.1 for the time period after the end of treatment for SAE collection.

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 (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed for 30 days after the subject's last study drug dose, or until resolution, whichever comes first. Subjects with onset of an AE or deterioration of a preexisting AE during the AE collection period will be followed until resolution to baseline, start of a new anticancer treatment, or death. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

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

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v5.0 (Cancer Therapy Evaluation Program, 2017). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

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.

9.5.1.4.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

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

Other important medical events 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

9.5.1.4.3 Laboratory Measurements

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 4. Subjects should be in a seated or supine position during blood

collection. The Schedule of Procedures/Assessments (Table 5 and Table 6) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 4 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes[a]	Bicarbonate, chloride, potassium, sodium, calcium, magnesium, phosphorus
Liver function tests	ALT, alkaline phosphatase, AST, conjugated (direct) bilirubin[b], total bilirubin, INR/PT, aPTT/PTT[c]
Renal function tests	BUN or urea, creatinine
Other chemistries	Albumin, amylase, glucose, LDH, lipase, total protein
Thyroid function tests[d]	Thyroid stimulating hormone, free T4 level
Urinalysis for microscopy[e]	RBCs
Urine dipstick testing[e,f]	Blood, protein, glucose
Other[g]	Pregnancy test (serum or urine β–hCG)

ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN = blood urea nitrogen, β hCG = beta-human chorionic gonadotropin, INR = International Normalized ratio, LDH = lactate dehydrogenase, aPTT = activated partial thromboplastin time, RBC = red blood cells, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cells.

a. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting treatment.
b. Direct bilirubin should be assessed if total bilirubin is elevated.
c. INR/PT and aPTT/PTT should only be performed as part of the screening assessment. During the study, INR/PT and aPTT/PTT should be performed if clinically indicated.
d. Thyroid function will be assessed every 2 cycles for all subjects.
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
f. 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.
g. For sites in Germany: HIV and Hepatitis B/C tests are required during Screening.

All clinical laboratory tests during the study will be performed at qualified local laboratories. All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and sent to the local laboratory on the day of collection unless otherwise instructed.

Clinical chemistry and hematology results must be reviewed prior to administration of study drug on Cycle 1 Day 1 and within 48 hours after dispensing study drug for all subsequent cycles. Electrolytes such as potassium, calcium, and magnesium should be monitored and

abnormalities, when considered clinically significant, should be corrected in all participants before starting treatment. Scheduled assessments may be performed within 72 hours prior to the visit. If ≥ Grade 3 hematologic or clinical chemistry toxicity, repeat laboratory test and AEs assessment at least every 3 days (until improvement to < Grade 3). Refer to Table 1 (study drug dose reduction and interruption instructions) for the management of clinically significant laboratory abnormalities. Every effort should be made to collect samples for analysis at the local laboratory at the same time.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF (see Section 9.5.4.3.2).

9.5.1.4.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute]), body temperature (in centigrade), weight (kg), and height (cm) will be obtained at the visits designated in the Schedule of Assessments (Table 5 and Table 6) by a validated method. Blood pressure and pulse will be measured after the subject has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person. On Cycle 1 Day 8, subjects will have a telephone or clinic visit to assess for the development of early toxicity. Subjects will be provided with a BP cuff to monitor BP at home or can have the measurement done by a local healthcare provider, and will report the C1D8 measurement at telephone contact. An unscheduled visit can occur prior to C1D15 if deemed necessary by the investigator.

Only 1 BP measurement is needed for subjects with systolic BP <95th percentile (BP <140 mm Hg) and diastolic BP <95th percentile (BP <90 mmHg). If the subject's initial BP measurement is elevated (systolic BP ≥95th percentile [≥140 mmHg] or diastolic BP ≥95th percentile [≥90 mmHg]), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥95th percentile [≥140 mm Hg] or diastolic BP ≥95th percentile [≥90 mm Hg]), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

9.5.1.4.5 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 5 and Table 6). 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.

9.5.1.4.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Assessments (Table 5 and Table 6). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3×4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. If possible, subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

QTc prolongation has been seen in some lenvatinib studies. Monitor ECGs every cycle (as specified in the Schedule of Assessments) in participants with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Drugs known to prolong the QTc interval (including Class Ia and III antiarrhythmics) must be used cautiously. Please refer to the lenvatinib IB or lenvatinib prescribing information.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

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

9.5.1.4.7 OTHER SAFETY ASSESSMENTS

Pregnancy Test

A serum β-hCG test will be performed for females of childbearing potential (see definition included in the Inclusion/Exclusion criteria, Sections 9.3.1 and 9.3.2). A serum or urine pregnancy test will be performed at Screening, Baseline (or within 72 hours prior to the first dose of study medication), on Day 1 of each cycle from Cycle 2 onwards, and at the Off-treatment Visit in women of childbearing potential. Blood and urine samples will be taken at designated time points as specified in the Schedule of Assessments (Table 5 and Table 6).

Echocardiogram or Multigated Acquisition (MUGA) Scan

An echocardiogram or MUGA scan to assess LVEF will be performed during the screening phase, every 16±2 weeks following the first dose of study drug while the subject is on treatment or sooner, if clinically indicated, and at (or within 1 week following) the off-treatment assessment. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

Dental Examination

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

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 examination is not required. Post-baseline dental examinations are not required for subjects for whom permanent teeth (excluding third molars) are evaluated to be fully erupted at baseline.

9.5.1.5 Other Assessments

Health-related quality of life (HRQoL) assessment will be performed per the Schedule of Assessments (Table 5 and Table 6). Impact of treatment on HRQoL will be assessed using the PedsQL (including the Generic Core Scales and Cancer Module). Data will be collected as parent-report for toddlers (ages 2 to years) and children (ages 5 to 7), and as self-report for subjects aged ≥8 years . Self-report is the preferred data collection method for all subjects aged ≥8, however to improve adherence and reduce missing data, parents or caregivers will be required to report on QoL when self-report is not available; patient's proxy report is still very relevant especially when child self -report is not possible

The PedsQL is a modular instrument designed to measure HRQoL in pediatric and adults population. The PedsQL 4.0 Generic Core Scales are multidimensional child self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL disease specific modules. The PedsQL 3.0 Cancer Module was designed to measure pediatric cancer specific HRQOL.

It is best practice and strongly recommended that the PedsQL measurement modules are administered to randomized subjects prior to drug administration or any other interaction with site staff. Every effort should be made to administer the PedsQL questionnaires as soon as possible after the decision to discontinue study treatment is made.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 5 presents the schedule of procedures/assessments for the Randomization Phase of the study.

Table 6 presents the schedule of procedures/assessments for the Extension Phase of the study.

Table 7 presents the schedule of procedures/assessments for the Optional Lenvatinib Crossover Treatment Phase of the study.

Table 5 Schedule of Assessments in Study E7080-G000-230 – Randomization Phase

Phase	**Prerandomization**		**Randomization [a] (All cycles are 21 days in duration)**																	
Period	**Screening[b]**	**Baseline[c]**	**Treatment[d]**																**Off-Tx**	**Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18+**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6-X**		
Day	**-28 to -2**	**-1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Procedures/Assessments																				
Informed consent	X																			
Inclusion/exclusion	X	X																		
Randomization (IVRS)			X																	
Demographic data	X																			
Medical/surgical history	X	X																		
Prior medication/ procedures	X	X																		
Pregnancy test[e]	X	X				X			X			X			X			X	X	
Lansky play score/ Karnofsky PS[f]	X	X	X			X			X			X			X			X		
TNM Staging	X																			
Physical examination[g]	X	X	X		X	X		X	X			X			X			X	X	
Vital signs[h]	X	X	X	X[i]	X	X		X	X			X			X			X	X	
12-lead ECG[j]	X		X			X												X	X	
Echocardiogram or MUGA scan[k]	X	Performed every 16±2 weeks following the first dose of study drug or sooner, if clinically indicated																	X	
Clinical chemistry and hematology[l]	X	X			X	X		X	X			X			X			X	X	
Urine dipstick testing[m]	X	X			X	X		X	X			X			X			X	X	
PK blood samples[n]			X		X	X														

Table 5 Schedule of Assessments in Study E7080-G000-230 – Randomization Phase

Phase	**Prerandomization**		**Randomization [a] (All cycles are 21 days in duration)**																	
Period	**Screening[b]**	**Baseline[c]**	**Treatment[d]**																**Off-Tx**	**Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18+**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6-X**		
Day	**-28 to -2**	**-1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Procedures/Assessments																				
Study treatment[o]			Arm A: Combination of lenvatinib (QD) + ifosfamide + etoposide (Days 1-3 of Cycles 1-5 only) [based on BSA calculations at Day 1 of each Cycle]; after Cycle 5 subjects will receive lenvatinib alone. Arm B: Ifosfamide + etoposide (Days 1-3 of Cycles 1-5 only) [based on BSA calculations at Day 1 of each Cycle]																
Palatability Questionnaire[p]			X																	
Tumor assessments: CT/MRI[q]	X		CT chest and CT/MRI of other areas of known disease at Screening plus any areas of newly suspected disease should be performed every 6±1 week after the date of randomization or sooner if clinically indicated until Week 18±1 week, then every 9±1 weeks until Week 54±1 week. Thereafter, to be performed every 12±2 weeks until documentation of PD.																X[q]	
Brain CT/MRI[r]	X		Brain scans will be performed at screening as clinically indicated, and thereafter during treatment if clinically indicated. For subjects with protocol-eligible, treated brain metastases at Screening, brain scans should be performed at all tumor assessment time points.																	
Height[s]		X	X									X						X	X	X
Tanner Stage[t]		X																	X	X
Proximal tibial growth plate x-ray[s]		X																	X	
Dental examination[s]		X	X as per standard of care or at least annually																X	
HRQoL[u]		X	HRQoL will be collected on C2D1, C3D1, Week 18, C8D1, and C18D1.																X[u]	
Pharmacodynamic biomarkers[v]		X			X	X						X						X		
Archival tumor block or slides[w]		X																		X
Survival[x]				X																X

Table 5 Schedule of Assessments in Study E7080-G000-230 – Randomization Phase

Phase	**Prerandomization**		**Randomization [a] (All cycles are 21 days in duration)**																	
Period	**Screening[b]**	**Baseline[c]**	**Treatment[d]**																**Off-Tx**	**Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18+**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6-X**		
Day	**-28 to -2**	**-1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Procedures/Assessments																				
Concomitant medications[y]	Throughout																			X
AEs/SAEs[z]	Throughout																			X

AE = adverse event, BP = blood pressure, C1D1 = Cycle 1 Day 1, C1D2 = Cycle 1 Day 2, C1D8 = Cycle 1/Day 8, C1D15 = Cycle 1 Day 15, CR = complete response, CT = computerized tomography, h = hour, HR = heart rate, HRQoL = Health-Related Quality of Life, IV = intravenous, IVRS = Interactive Voice Response System, MRI = magnetic resonance imaging, MUGA = multiple-gated acquisition, PD = progressive disease/disease progression, PK = pharmacokinetics, PR = partial response, PS = performance score, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1, RR = respiratory rate, SAE = serious adverse event, TNM = tumor-node-metastasis, Tx = treatment.

a. During Cycle 1, efforts should be made to conduct study visits on the day scheduled (±1 day); from Cycle 2 onwards, efforts should be made to conduct study visits on the day scheduled (±3 days).
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. For subjects randomized to Arm A, subjects benefiting from study treatment in the opinion of the investigator will continue lenvatinib treatment until PD, intolerable toxicity, noncompliance with safety or efficacy assessments, voluntary discontinuation by the subject at any time, or study termination by the sponsor, whichever occurs first.
e. 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), on Day 1 of each cycle from Cycle 2 onwards, and at the Off-treatment Visit in women of childbearing potential.
f. A Lansky play score or Karnofsky performance status score will be obtained at the Screening, Baseline, and C1D1 Visit, and Day 1 of every subsequent cycle visit thereafter.
g. 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, C2D1, C2D15, and Day 1 visit of each subsequent cycle, and at the Off-treatment Visit. A symptom-directed physical examination will be performed on C1D1 and at any time during the study, as clinically indicated.

Table 5 Schedule of Assessments in Study E7080-G000-230 – Randomization Phase

Phase	Prerandomization		Randomization [a] (All cycles are 21 days in duration)																	
Period	Screening[b]	Baseline[c]	Treatment[d]																Off-Tx	Follow-up
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+		
Cycle			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6-X		
Day	-28 to -2	-1	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1		
Procedures/Assessments																				

h. Assessments will include vital signs (resting BP, HR, RR, and body temperature) and weight. Blood pressure that is consistently above the 95th percentile for sex, age, and height/length for subjects <18 years old; or BP ≥140/90 mmHg for subjects ≥18 to 25 years old requires further evaluation. Refer to hypertension management guidelines in Section 9.4.1.1.2.

i. On Cycle 1 Day 8, subjects will have a telephone or clinic visit to assess for the development of early toxicity. Subjects will be provided with a BP cuff to monitor BP at home or can have the measurement done by a local healthcare provider, and will report the C1D8 measurement at telephone contact. An unscheduled visit can occur prior to C1D15 if deemed necessary by the investigator.

j. Single 12-lead ECG. If possible, subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. ECG should be conducted at Screening, C1D1, C2D1, D1 of every 4th cycle (ie, C6, C10, C14, etc.). ECG at C1D1 and C2D1 should be conducted approximately 2 hours after lenvatinib dose. For high risk subjects (as defined in lenvatinib product label), conduct ECG in every cycle.

k. An echocardiogram or MUGA scan is to be performed during screening, every 16±2 weeks, and at the Off-Treatment visit, or sooner if clinically indicated.

l. Clinical chemistry and hematology results must be reviewed by the investigator prior to administration of study drug on C1D1 and within 48 hours after administering any study drug for all subsequent cycles. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting treatment. 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). TSH should be assessed for all subjects. For sites in Germany: HIV and Hepatitis B/C tests are required during Screening.

m. Urine dipstick testing should be performed at Screening, Baseline, C1D15, C2D1, C2D15, and Day 1 of every subsequent cycle, or more frequently as clinically indicated, and at the Off-treatment Visit. For subjects with a history of proteinuria ≥2+, urine dipstick testing should be performed until the results have been 1+ or negative for 2 treatment cycles. If a new event of proteinuria ≥2+ occurs, refer to Section 9.4.1.1.4 for further management guidelines. Urine glucose should be performed as part of the urine dipstick.

n. Sampling (one 2 mL sample per time point) for PK analysis of lenvatinib will be performed (in subjects in Arm A only) on Cycle 1 Day 1 at 0.5 to 4 hours and 6 to 10 hours postdose, on Cycle 1 Day 15 at predose, 0.5 to 4 hours and 6 to 10 hours postdose, and on Cycle 2 Day 1 at predose. All predose samples are to be drawn approximately 24 hours following the dose administered on the previous day. If dose interruption is necessary at these time points, please contact the sponsor. Pharmacokinetic sampling should not be performed for any subject with a body weight <13 kg (please see Section 9.5.1.3.1).

Table 5 Schedule of Assessments in Study E7080-G000-230 – Randomization Phase

Phase	Prerandomization		Randomization [a] (All cycles are 21 days in duration)																	
Period	Screening[b]	Baseline[c]	Treatment[d]																Off-Tx	Follow-up
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+		
Cycle			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6-X		
Day	-28 to -2	-1	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1		
Procedures/Assessments																				

o. Subjects randomized to Arm A will continue to receive lenvatinib only after completion of 5 cycles with lenvatinib+ifosfamide+etoposide until progressive disease, unacceptable toxicity, subject request, study termination by the sponsor, subject noncompliance with safety or efficacy assessments, or withdrawal of consent. Subjects randomized to Arm B will be off-treatment after 5 cycles of ifosfamide+etoposide.

p. All subjects who receive suspension formulation, with the exception of subjects using a nasogastric or gastrostomy tube, must complete the Palatability Questionnaire on C1D1 (or the subsequent visit). If the subject is unable to complete the questionnaire this must be done by their parents or their legal guardian.

q. **Screening**: Tumor assessments of the chest, abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1. Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with iodinated IV contrast and MRI scans should be performed with IV gadolinium chelate.
Treatment Phase: Tumor assessments of the chest, and other areas of known disease at Screening or newly suspected disease should be performed every 6±1 weeks from the date of randomization until Week 18±1 week, then every 9±1 weeks until Week 54±1 week, and thereafter, every 12±2 weeks until documentation of PD during the Treatment Phase (or sooner if there is evidence of progressive disease) and should utilize the same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as was used for the screening assessments. Tumor response will be assessed according to RECIST 1.1. Any CR or PR must be confirmed not less than 4 weeks following the initial achievement of the response. **Off-Treatment:** Tumor assessments at the Off-Treatment Visit (within 1 week of the Off-treatment Visit) are only necessary for subjects who discontinue study treatment without disease progression, if more than 4 weeks have passed since the previous assessment and if the subject will not continue with follow-up scans.
Follow-up: For subjects who discontinue study treatment without disease progression, tumor assessments should continue to be performed according to the schedule: every 6±1 weeks until Week 18±1 week, then every 9±1 weeks until Week 54±1 week, thereafter, to be performed every 12±2 weeks, until documentation of progression or start of a new anticancer agent.

r. Brain CT with contrast or MRI pre- and post- gadolinium contrast will be performed at the Screening Visit as clinically indicated, and thereafter during treatment as clinically indicated. For subjects with protocol-eligible treated brain metastases, brain CT/MRI will be performed at all tumor assessment time points.

s. Height will be assessed at the Baseline Visit, Day 1 of every 4 cycles during the Treatment Phase, at the Off-treatment Visit and every 3 months during the Post-treatment Follow-up. Assessment of height in Post-treatment Follow-up is not required once pubertal development is complete. Proximal tibial growth plate x-rays should be conducted for subjects aged <18 years at baseline and at the Off-treatment Visit. If the growth plates are closed at baseline

Table 5 Schedule of Assessments in Study E7080-G000-230 – Randomization Phase

Phase	Prerandomization		Randomization [a] (All cycles are 21 days in duration)																	
Period	Screening[b]	Baseline[c]	Treatment[d]																Off-Tx	Follow-up
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+		
Cycle			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6-X		
Day	-28 to -2	-1	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1		
Procedures/Assessments																				

then the subject does not need a reassessment at the Off-treatment Visit. X-ray of only 1 leg is required, and if reassessment is needed at the Off-treatment Visit, the x-ray must be performed on the same leg as at Screening. Tibial growth plate x-rays will be optional for Germany. 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.

t. Tanner Staging is only required for female subjects ≥8 years old, and male subjects ≥9 years old. Tanner Stage will be assessed at the Baseline Visit, at the Off-treatment Visit, and annually thereafter during the Post-treatment Follow-up. Tanner Staging is not required once pubertal development is complete (ie, Tanner Stage 5).

u. Every effort should be made to administer the PedsQL questionnaires as soon as possible after the decision to discontinue study treatment is made.

v. Optional blood samples may be collected only from subjects in Arm A at the Baseline Visit, C1D15, Day 1 of Cycles 2, 4, and 6, for assessment for blood serum sample to measure factors implicated in angiogenesis. Pharmacodynamic sampling should not be performed for any subject with a body weight <16 kg (please see Section 9.5.1.3.1).

w. An archival tumor sample from the most recent surgery or biopsy for identification of predictive biomarkers and pathology review may be collected from subjects in Arm A at any time during the study, unless no such material is available. Providing archival tumor samples is optional and does not impact subject eligibility.

x. Survival data will be collected every 3 months for up to 2 years as per the protocol. All anticancer therapies will be collected.

y. Concomitant medications will be recorded throughout the study and for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of Survival Follow-up.

z. All AEs, including SAEs will be recorded from the date of signed informed consent, throughout the study, and for 30 days after last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 hours.

Table 6 presents the Schedule of Procedures/Assessments for the Extension Phase of the study.

Table 6 Schedule of Assessments in Study E7080-G000-230 – Extension Phase

Phase	**Extension[a]**		
Period	**Treatment Period [a]**		**Follow-up Period**
Visit	**98**	**99**	
Cycle	**Cycle X +1 and beyond**	**Off-Tx Visit**	
Day	**1**		
Procedures/Assessments			
Pregnancy test[b]	X	X	
Lansky play score/ Karnofsky PS[c]	X	X	
Physical examination[d]	X	X	
Vital signs[e]	X	X	
12-lead ECG[f]	As clinically indicated		
Echocardiogram or MUGA scan[g]	As clinically indicated		
Clinical chemistry and hematology[h]	X	X	
Urine dipstick testing[i]	X	X	
Study treatment[j]	Arm A: Lenvatinib+ifosfamide+etoposide[a] Arm B: Ifosfamide + etoposide[a]		
Tumor assessments: CT/MRI[k]	After data cutoff for the primary analysis, tumor assessments may be performed as clinically indicated as per the institutional guidelines (but no less frequently than every 12 weeks), following the prevailing local standard of care.		
Brain CT/MRI[l]	After data cutoff for the primary analysis, tumor assessments may be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care.		
Height[m]	To be checked every 4 cycles	X	X
Tanner Stage[n]		X	X
HRQoL[o]	X	X	
Proximal Tibial growth plate x-ray[p]		X	
Dental examinations[q]	X	X	
Survival[r]	X		X
Concomitant medications[s]	Throughout		X
AEs/SAEs[t]	Throughout		X

AE = adverse event, CT = computerized tomography, ECG = electrocardiogram, HRQoL = Health-Related Quality of Life, ICL = imaging core laboratory, MRI = magnetic resonance imaging, MUGA = multiple-gated acquisition, PD = disease progression, PS = performance status, SAE = serious adverse event.

a. In the Treatment Period, subjects still on study treatment following the completion of the Randomization Phase will continue to receive study treatment as outlined in Section 9.1.2.1 until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor, whichever occurs first.
b. A serum or urine pregnancy test will be performed on Day 1 of each cycle and at the Off-treatment Visit in women of childbearing potential.
c. A Lansky play score or Karnofsky performance status score will be obtained at Day 1 of every cycle visit.
d. A physical examination will be performed at Day 1 visit of each cycle, and at the Off-treatment Visit. A

Table 6 Schedule of Assessments in Study E7080-G000-230 – Extension Phase

Phase	Extension[a]		
Period	Treatment Period [a]		Follow-up Period
Visit	98	99	
Cycle	Cycle X +1 and beyond	Off-Tx Visit	
Day	1		

symptom-directed physical examination will be performed at any time as clinically indicated.

e. Assessments will include vital signs (resting BP, HR, RR, and body temperature), and weight. Blood pressure that is consistently above the 95th percentile for sex, age, and height/length for subjects <18 years old; or BP ≥140/90 mmHg for subjects ≥18 to 25 years old requires further evaluation. Refer to hypertension management guidelines in Section 9.4.1.1.2.
f. Single 12-lead ECG. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.
g. An echocardiogram or MUGA scan is to be performed as clinically indicated.
h. Clinical chemistry and hematology results must be reviewed within 48 hours after administering any study drug for all subsequent cycles. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting treatment. 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). TSH should be assessed for all subjects.
i. Urine dipstick testing should be performed on Day 1 of every cycle, or more frequently as clinically indicated, and at the Off-treatment Visit. For subjects with a history of proteinuria ≥2+, urine dipstick testing should be performed until the results have been 1+ or negative for 2 consecutive cycles. If a new event of proteinuria ≥2+ occurs, refer to Section 9.4.1.1.4 for further management guidelines. Urine glucose should be performed as part of the urine dipstick.
j. Subjects randomized to Arm A will continue to receive lenvatinib only until progressive disease, unacceptable toxicity, or withdrawal of consent.
k. After data cutoff for the primary analysis, tumor assessments may be performed as clinically indicated as per the institutional guidelines (but no less frequently than every 12 weeks), following the prevailing local standard of care. The scans will no longer be required to be sent to the ICL.
l. Brain CT with contrast or MRI pre- and post- gadolinium contrast will be performed as per the institutional guidelines, following the prevailing local standard of care.
m. Height will be assessed at the Baseline Visit, Day 1 of every 4 cycles during the Treatment Phase, at the Off-treatment Visit and every 3 months during the Post-treatment Follow-up. Assessment of height in Post-treatment Follow-up is not required once pubertal development is complete.
n. Tanner Staging is only required for female subjects ≥8 years old and male subjects ≥9 years old. Tanner Stage will be assessed at the Baseline Visit, at the Off-treatment Visit, and annually thereafter during the Post-treatment Follow-up. Tanner Staging is not required once pubertal development is complete (i.e., Tanner Stage 5).
o. HRQoL will be collected at week 18 and the Off-Treatment visit. Every effort should be made to administer the PedsQL questionnaires as soon as possible after the decision to discontinue study treatment is made.
p. Proximal tibial growth plate x-rays should be conducted for subjects aged <18 years at baseline and at the Off-treatment Visit. If the growth plates are closed at baseline then the subject does not need a reassessment at the Off-treatment Visit. X-ray of only 1 leg is required, and if reassessment is needed at the Off-treatment Visit, the x-ray must be performed on the same leg as at Screening. Tibial growth plate x-rays will be optional for Germany.
q. 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.

Table 6 Schedule of Assessments in Study E7080-G000-230 – Extension Phase

Phase	Extension[a]		
Period	Treatment Period [a]		Follow-up Period
Visit	98	99	
Cycle	Cycle X +1 and beyond	Off-Tx Visit	
Day	1		

r. Survival data will be collected every 3 months for up to 2 years as per the protocol. All anticancer therapies will be collected.

s. Concomitant medications will be recorded throughout the study and for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of Survival Follow-up.

t. All AEs, including SAEs will be recorded from the date of signed informed consent, throughout the study, and for 30 days after last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 hours.

Table 7 presents the schedule of procedures/assessments for the Optional Lenvatinib Crossover Treatment Phase of the study.

Table 7 Schedule of Assessments in Study E7080-G000-230 – Optional Lenvatinib Crossover Treatment Phase

Phase	**Baseline[a]**	**Optional Lenvatinib Crossover[a]**							
Period		**Treatment Period**							**Follow-up Period**
Visit	**1**	**2+**							
Cycle		**1**			**2**		**3 and beyond**	**Off-Tx Visit**	
Day	**-1**	**1**	**8**	**15**	**1**	**15**	**1**		
Procedures/Assessments									
Review eligibility[b]	X								
Lansky Play/Karnofsky PS Score[c]	X	X			X		X	X	
Physical Examination[d]	X	X		X	X	X	X	X	
Vital Signs[e]	X	X	X[f]	X	X	X	X	X	
12-lead ECG[g]	X	X			X			X	
ECHO or MUGA scan[h]	X	Performed every 16±2 weeks following first dose of study drug, or sooner if clinically indicated						X	
Clinical chemistry and hematology[i]	X			X	X	X	X	X	
Urine dipstick test[j]	X			X	X	X	X	X	
Pregnancy test[k]	X				X		X	X	
Study treatment[l]		Lenvatinib±chemotherapy							
Palatability Questionnaire[m]		X							
HRQoL	X	HRQoL will be collected at Baseline, C2D1, C3D1, and Week 18							
Tumor assessment: CT/MRI[n]	X	Tumor assessments may be performed as clinically indicated per the institutional guidelines (but no less frequently than every 12 weeks), following the prevailing local standard of care.							
Brain CT/MRI[o]	Brain CT/MRI scans may be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care.								
Height[p]	X	X					X	X	X
Tanner Stage[q]	X							X	X
Survival[r]		X							X
Concomitant medications[s]	X	Throughout							X
AEs/SAEs[t]	X	Throughout							X

AE = adverse event, CT = computerized tomography, ECG = electrocardiogram, HRQoL = Health-Related Quality of Life, ICL = imaging core laboratory, MRI = magnetic resonance imaging, MUGA = multiple-gated acquisition, PD = disease progression, PS = performance status, SAE = serious adverse event.

a. Baseline assessments (except ECG, MUGA, and Tumor scans) may occur within 72 hours prior to C1D1. For subjects in Arm B only: subjects may be eligible for additional treatment with lenvatinib ± chemotherapy following disease progression. Note: subjects may only receive a maximum of 5 cycles of chemotherapy for the duration of the study.

Optional crossover treatment must be initiated within 30 days of documented disease progression. Please see Section 9.1.4 of the protocol for further details.

b. Subjects should meet all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria. If required locally, written informed consent will be obtained prior to assessment for Optional Lenvatinib Crossover treatment.
c. A Lansky play score or Karnofsky performance status score will be obtained at Baseline, Day 1 of every cycle, and at the Off-treatment visit.
d. A comprehensive physical examination (including a neurological examination) will be performed at Baseline, C1D15, C2D1, C2D15, Day 1 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.
e. Assessments will include vital signs (resting BP, HR, RR, and body temperature) and weight. Blood pressure that is consistently above the 95th percentile for sex, age, and height/length for subjects <18 years old; or BP ≥140/90 mmHg for subjects ≥18 to 25 years old requires further evaluation. Refer to hypertension management guidelines in Section 9.4.1.1.2.
f. On Cycle 1 Day 8, subjects will have a telephone or clinic visit to assess for the development of early toxicity. Subjects will be provided with a BP cuff to monitor BP at home or can have the measurement done by a local healthcare provider, and will report the C1D8 measurement at telephone contact. An unscheduled visit can occur prior to C1D15 if deemed necessary by the investigator.
g. Single 12-lead ECG. Baseline ECG may be performed within 28 days prior to C1D1. If possible, subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. ECG should be conducted at C1D1, C2D1, D1 of every 4th cycle (i.e., C6, C10, C14, etc.), and at the Off-treatment visit. For high risk subjects (as defined in lenvatinib product label), conduct ECG in every cycle.
h. An echocardiogram or MUGA scan is to be performed at Baseline, every 16±2 weeks following first dose of study drug, and at the Off-Treatment visit, or sooner if clinically indicated. The Baseline ECHO/MUGA may be performed within 28 days prior to C1D1.
i. Clinical chemistry and hematology results must be reviewed by the investigator prior to administration of study drug on C1D1 and within 48 hours after administering any study drug for all subsequent cycles. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting treatment. 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). TSH should be assessed for all subjects.
j. Urine dipstick testing should be performed at Baseline, C1D15, C2D1, C2D15, and Day 1 of every subsequent cycle, or more frequently as clinically indicated, and at the Off-treatment Visit. For subjects with a history of proteinuria ≥2+, urine dipstick testing should be performed until the results have been 1+ or negative for 2 treatment cycles. If a new event of proteinuria ≥2+ occurs, refer to Section 9.4.1.1.4 for further management guidelines. Urine glucose should be performed as part of the urine dipstick.
k. A serum or urine pregnancy test will be performed at the Baseline Visit (or within 72 hours prior to the first dose of study medication), on Day 1 of each cycle from Cycle 2 onwards, and at the Off-treatment Visit in women of childbearing potential.
l. Subjects on optional lenvatinib crossover treatment will continue to receive lenvatinib until disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent, whichever occurs first. If the sponsor terminates the study, the sponsor will provide study drug(s) (outside of the study) for subjects who have not met the criteria for study drug discontinuation.
m. All subjects who receive suspension formulation, with the exception of subjects using a nasogastric or gastrostomy tube, must complete the Palatability Questionnaire on C1D1 (or the subsequent visit). If the subject is unable to complete the questionnaire this must be done by their parents or their legal guardian.
n. Prior to optional lenvatinib crossover, baseline tumor assessment must be re-established (i.e., new tumor assessment scans performed), unless the last assessment was performed within 4 weeks prior to Cycle 1 Day 1 of the crossover treatment. Tumor assessments may be performed as clinically indicated as per the institutional guidelines (but no less frequently than every 12 weeks), following the prevailing local standard of care. The scans will no longer be required to be sent to the ICL.
o. Brain CT with contrast or MRI pre- and post- gadolinium contrast will be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care.

p. Height will be assessed at the Baseline Visit, Day 1 of every 4 cycles during treatment, at the Off-treatment Visit and every 3 months during the Post-treatment Follow-up. Assessment of height in Post-treatment Follow-up is not required once pubertal development is complete.
q. Tanner Staging is only required for female subjects ≥8 years old, and male subjects ≥9 years old. Tanner Stage will be assessed at the Baseline Visit, at the Off-treatment Visit, and annually thereafter during the Post-treatment Follow-up. Tanner Staging is not required once pubertal development is complete (i.e. Tanner Stage 5).
r. Survival data will be collected every 3 months for up to 2 years as per the protocol. All anticancer therapies will be collected.
s. Concomitant medications will be recorded throughout the study and for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of Survival Follow-up.
t. All AEs, including SAEs will be recorded from the date of signed informed consent, throughout the study, and for 30 days after last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 hours.

9.5.2.2 Description of Procedures/Assessments Schedule

Refer to Table 5 for schedule and description of procedures in the Randomization Phase and Table 6 for the Extension Phase.

9.5.3 Appropriateness of Measurements

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

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

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

9.5.4.1 Reporting of Serious Adverse Events

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

Serious adverse events, regardless of causality assessment, must be collected for 30 days after the subject's last dose. 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 relevant follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the relevant 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 and/or the designated CRO monitor 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 a female subject in which the estimated date of conception is either before the last visit or within 30 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug 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, a spontaneous abortion or an induced abortion done due to safety concerns for either mother or fetus are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the 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 24 hours 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 and Intentional Overdose, even if asymptomatic, are 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.

9.5.4.3.2 Reporting of Abnormal Hepatic Tests of Clinical Interest

The following combination of abnormal laboratory tests*, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing and whether nonserious or serious, should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1). If the event does not meet serious criteria, the seriousness criteria on the SAE form should be indicated as "nonserious."

- Elevated AST or ALT lab value that is greater than or equal to 3× the upper limit of normal

  AND

- Elevated total bilirubin lab value that is greater than or equal to 2× the upper limit of normal

  AND AT THE SAME TIME

- Alkaline phosphatase lab value that is less than 2× the upper limit of normal

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology. In addition to reporting the abnormal hepatic laboratory tests on a SAE form, the site should also consult the medical monitor for guidance on assessment and follow-up. At a minimum, laboratory testing should be repeated at least once weekly until improvement or identification of a cause unrelated to study drug use that is unlikely to improve.

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 SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject (or subject's parent or guardian) may elect to discontinue study drug at any time for safety, medical, or personal reasons. Subjects who choose to discontinue study drug prior to PD will be followed in the post-study treatment follow-up period and continue to undergo regularly scheduled disease assessment until documentation of PD or start of an alternative anticancer treatment. All subjects who discontinue study drug will be followed for OS and all post progression cancer treatments administered will be recorded. Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Assessments (Table 5 and Table 6).

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

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, progression of disease, withdrawal of consent, pregnancy, study terminated by sponsor, or administrative/other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

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

9.6 Data Quality Assurance

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

9.6.1 Data Collection

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

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

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

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the end of the Randomization Phase after database lock and randomization codes have been released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

Efficacy endpoints related to tumor assessments will be evaluated by independent imaging review (IIR) and investigator assessment.

9.7.1.1.1 PRIMARY ENDPOINT

Progression-free survival (PFS) by IIR is defined as the time from the date of randomization to the date of the first documentation of PD or death (whichever occurs first) as determined by IIR using RECIST 1.1.

9.7.1.1.2 SECONDARY ENDPOINTS

- Progression-free survival rate at 4 months (PFS-4m) by IIR is defined as the percentage of subjects who are alive and without PD at 4 months from the randomization date as determined by IIR of radiological imaging using RECIST 1.1. The PFS-4m rate is estimated using the Kaplan-Meier (K-M) method.
- Progression-free survival rate at 1 year (PFS-1y rate) by IIR is defined as the percentage of subjects who are alive and without PD at 1 year from the randomization date as determined by IIR of radiological imaging using RECIST 1.1. The PFS-1y rate is estimated using the K-M method.
- Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cutoff for the primary analysis, will be censored at the date the subject was last known to be alive, or date of data cutoff for the primary analysis, whichever occurs first. Overall survival rate at 1 year will be estimated using the K-M method.
- Objective response rate by IIR at 4 months (ORR-4m) is defined as the proportion of subjects who have best overall response of complete response (CR) or partial response (PR) as determined by IIR using RECIST 1.1 within the first 4 months.
- Objective response rate (ORR) by IIR is defined as the proportion of subjects who have best overall response of complete response (CR) or partial response (PR) as determined by IIR using RECIST 1.1.
- Safety will be assessed summarising the incidence of TEAEs and SAEs together with all other safety parameters.
- Assessment of population-based PK parameters of lenvatinib.
- Score changes from baseline for all PedsQL scales including Generic Core Scales and Cancer Module. Scores will be calculated for total generic score, total cancer score, each physical function subscale including physical health, psychosocial health, emotional function, social function, school/work function in the Generic Core Scales, and each subscales in the cancer module.

- Palatability and acceptability of the suspension formulation of lenvatinib in subjects receiving the suspension formulation in the study will be assessed using the Palatability Questionnaire (see Appendix 4).

9.7.1.1.3 EXPLORATORY ENDPOINTS

- Duration of response (DOR) by IIR and investigator assessment is defined as the time from the date a response was first documented until the date of the first documentation of PD or date of death from any case.
- Disease control rate (DCR) by IIR and investigator assessment is the proportion of subjects who have a best overall response of CR or PR or stable disease (SD). In this context, stable disease is defined as stable disease at ≥ 7 weeks after randomization to be considered best overall response.
- Clinical benefit rate (CBR) by IIR and investigator assessment is the proportion of subjects who have best overall response of CR or PR or durable SD (duration of SD ≥ 23 weeks after randomization).
- Efficacy endpoints (PFS, PFS-4m, PFS-1y, ORR-4m, and ORR) evaluated based on investigator assessment
- Proportion of subjects who achieve complete removal of baseline lesions and the proportion of subjects with unresectable baseline lesions(s) that are converted to resectable between the 2 treatment arms.
- Blood and tumor biomarkers will be assessed for identifying potential correlation with clinical outcomes-related endpoints.

9.7.1.2 Definitions of Analysis Sets

The Full Analysis Set (Intent-to-Treat Analysis [ITT]) includes all randomized subjects regardless of the treatment actually received. This is the primary analysis population used for the efficacy analyses which will be based on the ITT principle.

The Per Protocol Analysis Set includes those subjects from the ITT set who received at least 1 dose of any study drug, had no major protocol deviations, and had both baseline and at least one postbaseline tumor assessment. Subjects for whom death occurred prior to the first postbaseline tumor assessment will also be included. The per protocol analysis set will be the secondary analysis set for efficacy endpoints.

The Safety Analysis Set includes subjects who received at least 1 dose of any study drug. This is the analysis population used for all safety analyses which will be based on as-treated principle.

Population Pharmacokinetic (PK) Analysis Set includes the subjects who have received at least 1 dose of lenvatinib with documented dosing history and have measurable plasma levels of lenvatinib.

The Pharmacodynamic Analysis Set includes subjects who received at least 1 dose of study drug and had sufficient pharmacodynamic data (eg, at least 1 evaluable/measurable pharmacodynamic parameter).

The HRQoL Analysis Set will consist of all randomized subjects who have received at least 1 dose of study medication, and have at least 1 patient-reported outcome (PRO) assessment completed beyond baseline. For PRO analysis, subjects will be analyzed as randomized and not according to treatment actually received.

9.7.1.3 Subject Disposition

Reasons for screening failure will be summarized.

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

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Full Analysis Set will be summarized using descriptive statistics. Continuous demographic and baseline variables (including age, sex, race, height, and weight) will be summarized using n (number of subjects with available data), mean, standard deviation, median, quartiles 1 and 3, and range (minimum and maximum) unless otherwise specified. Categorical variables will be summarized by number and percentage.

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). Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) class indicating therapeutic classification. Prior medications will be defined as medications that started prior to the first dose of study drug and were either continued during the study or stopped prior to the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. All medications will be will be summarized and listed by drug and drug class and by treatment arm.

9.7.1.6 Efficacy Analyses

Efficacy analyses will be based primarily on the Full Analysis Set.

All primary statistical analyses will be conducted at the data cutoff date for the primary analysis (ie, when approximately 38 PFS events, as determined by IIR, are observed).

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary efficacy endpoint of progression-free survival (PFS) per IIR will be analyzed and compared between the 2 treatment armsusing the stratified log-rank test with time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years) as strata. PFS censoring rules will follow FDA guidance of 2007 and will be detailed in the statistical analysis plan. Median PFS will be calculated using the K-M product-limit estimates for each treatment arm along with 2-sided 95% CIs (estimated with a generalized Brookmeyer and Crowley method [Brookmeyer and Crowley (1982)]. The K-M estimates of PFS will be plotted over time. The Cox regression model will be used to estimate the hazard ratio and its 95% CIs stratified by the stratification factors.

Secondary Efficacy Analyses

The PFS-4m rate and PFS-1y rate per IIR will be estimated using the K-M method for the primary efficacy endpoint PFS per IIR. PFS-4m/PFS-1y rate and their Greenwood standard errors will be evaluated using the K-M estimates from both treatment groups. The statistical significance of the difference in the 2 K-M PFS-4m rates will base on its 2-sided 95% CI. This 2-sided 95% CI and a p-value will be constructed using the difference of these 2 K-M PFS-4m/PFS-1y rates and the 2 corresponding Greenwood standard errors.

Overall survival (OS) will be compared between treatment arm and control arm following the same statistical method for the primary efficacy PFS endpoint. The K-M estimates will also be presented for 4, 6, 9, and 12 months (ie OS-1y) with 2-sided 95% CIs. OS-1y will be analyzed using the same approach as for the PFS-4m.

The ORR by IIR will be summarized and compared between the two treatment arms using stratified Miettinen and Nurminen's method. The difference in ORR and its 2-sided 95% confidence interval from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported. The stratification factors used for randomization will be applied to the analysis. The ORR-4m by IIR will be summarized and compared between arms using the same approach as for ORR.

9.7.1.6.2 EXPLORATORY EFFICACY ANALYSES

Median DOR by IIR among responders for each arm will be presented along with its corresponding 2-sided 95% CIs. Disease Control Rate (DCR) and CBR by IIR will be summarized and compared between arms using the same approach as for ORR. Efficacy endpoints PFS, PFS-4m, PFS-1y, ORR-4m, ORR, DOR, DCR, and CBR evaluated based on investigator assessment will be analyzed using the same approach as for the endpoints assessed by IIR.

The difference in the proportion of subjects who achieve complete removal of baseline lesion(s) and the proportion of subjects with unresectable baseline lesions(s) that are

converted to resectable between the 2 treatment arms and corresponding two-sided 95% CIs will be calculated.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

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

Lenvatinib data from Arm A of the study will be pooled with available data from other studies and subjected to population PK analysis. 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 AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.

Optional pharmacodynamic serum and archived, fixed tumor tissue biomarkers may be collected from subjects in Arm A only as described in the Schedule of Assessments. Pharmacodynamic serum and tumor biomarkers in this study will be identified as in other lenvatinib clinical studies.

Blood serum samples may be analyzed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, or other assays/methods and new technology in an effort to identify biomarkers.

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

Data obtained from the pharmacodynamic samples will be used for research. The pharmacodynamic samples will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib and for potential diagnostic development. If the subject reaches the age of 18 years (or at the appropriate age per local country requirements) while on the study, and becomes competent to give informed consent, his/her consent will be obtained using separate ICFs to continue on the study. Further analyses will not be performed on samples collected from subjects who do not reconsent at the age of 18 years (or at the appropriate age per local country requirements).

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment group, will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables), as appropriate. Safety variables include TEAEs, clinical laboratory parameters, vital signs, 12-lead ECG results, Lansky play scores or Karnofsky performance scores, physical examination, height, tooth formation abnormalities, closure of proximal tibial plates, and LVEF. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

The number of cycles/days on treatment, quantity of study drug administered, dose intensity, and the number of subjects requiring dose reductions, treatment interruption, and treatment discontinuation due to adverse events 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 (Version 20.1 or higher) 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 (and within 30 days of the last study treatment), having been absent at pretreatment (Baseline) or

- Re-emerges 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 TEAEs will be summarized by treatment group. 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 highest CTCAE grade.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

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-related TEAEs will also be summarized by highest CTCAE grade.

Adverse events will be summarized using the Safety Analysis Set. The number of AEs and number and incidence (%) of subjects with AEs will be summarized by treatment group and overall. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by SOC and by PT will be calculated. Incidence (%) by causal relationship with study drug and by severity (CTCAE v5.0) will also be calculated. For clinically significant events, time of onset, and recovery will be reported.

Adverse events will be summarized for descriptive purposes by age (2 to <6, 6 to <18, and ≥18), and sex.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. All deaths will also be summarized.

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

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug 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 9.5.1.4.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.4.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on shift tables that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

9.7.1.8.4 VITAL SIGNS

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

Percentiles for BP values (only for subjects <18 years old) will also be summarized using a shift table of worst postbaseline from Baseline measurement by categories (<90th percentile, 90th to 95th percentile, 95th to ≤99th percentile, systolic BP or diastolic BP >99th percentile). See Appendix 5 and Appendix 6 for detail on percentiles.

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for electrocardiogram parameters (HR, PR, QRS, QT, QTcB, QTcF and RR) and changes from Baseline will be presented by visit. Electrocardiogram (ECG) findings will be summarized. A shift table of worst postbaseline values from Baseline for ECG findings will be provided.

QTc Bazett and QTc Fridericia will be summarized. QTc Bazett and QTc Fridericia will be categorized as both maximum increases from Baseline and maximum postbaseline values.

9.7.1.8.6 OTHER SAFETY ANALYSES

Descriptive summary statistics for LVEF changes from baseline will be calculated and summarized.

The shift of worst postbaseline proteinuria from Baseline will be summarized.

Thyroid-stimulating hormone values will be summarized in 2 categories (≤ULN and >ULN).

Lansky play scores or Karnofsky Performance Status score scores will be summarized by shifts from Baseline to worst postbaseline visit.

Radiographic findings of proximal tibial growth plates will be listed and analyzed if appropriate.

Tooth formation abnormalities will be listed and analyzed if appropriate.

9.7.1.9 Other Analyses

9.7.1.9.1 HEALTH-RELATED QUALITY OF LIFE

Descriptive statistics will be presented for all PedsQL endpoints at each analysis time period by treatment arm. Baseline is defined as the later value of Day -1 or at Cycle 1 Day 1 prior to treatment.

This will be collected at baseline, at C2D1, C3D1, Week 18, C8D1, C18 D1 and at the Off-Treatment Visit. Score change from baseline in PedsQL at each analysis timepoint will be analyzed. Primary timepoint for assessment is at week 18 for all PedsQL endpoints.

Detailed HRQoL analysis plan will be provided in a separate analysis plan and the results will be provided in a stand-alone report.

9.7.1.9.2 PALATABILITY AND ACCEPTABILITY QUESTIONNAIRE

Measurement of palatability will be assessed using a facial Hedonic scale (Guinard, 2001), in subjects receiving the suspension formulation in the study.

9.7.2 Determination of Sample Size

A total sample size of 72 subjects is estimated for the primary efficacy endpoint of PFS. A median PFS of 3.5 months for Arm B (control arm) has been estimated by comparing available PFS data from clinically active agents in this patient population (Davis, et al., 2019; Palmerini, et al, 2016; Grignani, et al., 2012). With respect to Arm A (lenvatinib plus chemotherapy arm), a median PFS of 8.75 months is estimated based on the results from Study 207.

Therefore, assuming a hazard ratio of 0.4, a 1-sided type 1 error rate of 0.025, and power of 80%, the required number of PFS events for the study is 38. The primary PFS analysis is estimated to occur at approximately 32 months after the first subject is randomized (assuming a 20-month enrollment period), and accounts for a dropout rate of up to 40%.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

The safety monitoring will be conducted by the independent data monitoring committee (IDMC). The frequency of the 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 recommendation of whether to stop the study for safety will be reached by the IDMC based on their review of safety data with treatment information. 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 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 IVRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source
- Electronic Patient-Reported Outcome by self-reported measures

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.

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 for US sites), Investigator and Site Information Form (for non-US sites), 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.

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

Appendix 2 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.

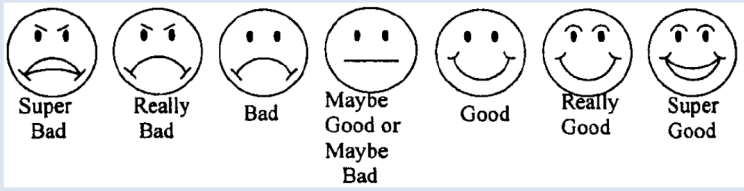
Appendix 3 Karnofsky Performance Status Scale Definitions Rating (%) Criteria

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 4 Palatability Questionnaire

Study E7080-G000-230- Palatability Questionnaire

Subject ID: 1 0 0 1	**Treatment Dose:** **Visit Cycle:** **Date:**
Taste	 *(Please circle according to your experience)*
Appearance	 *(Please circle according to your experience)*
Smell	 *(Please circle according to your experience)*
Mouth Feel (how does it feel in your mouth?)	 *(Please circle according to your experience)*

Overall Acceptability	 *(Please circle according to your experience)*

Appendix 5 Blood Pressure Levels for Boys by Age and Height Percentile

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

	BP	Systolic BP (mmHg)							Diastolic BP (mmHg)						
AGE	Percentile	Percentile of Height							Percentile of Height						
(Year)	Ð	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	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 6 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)	Ð	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
l	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
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63

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

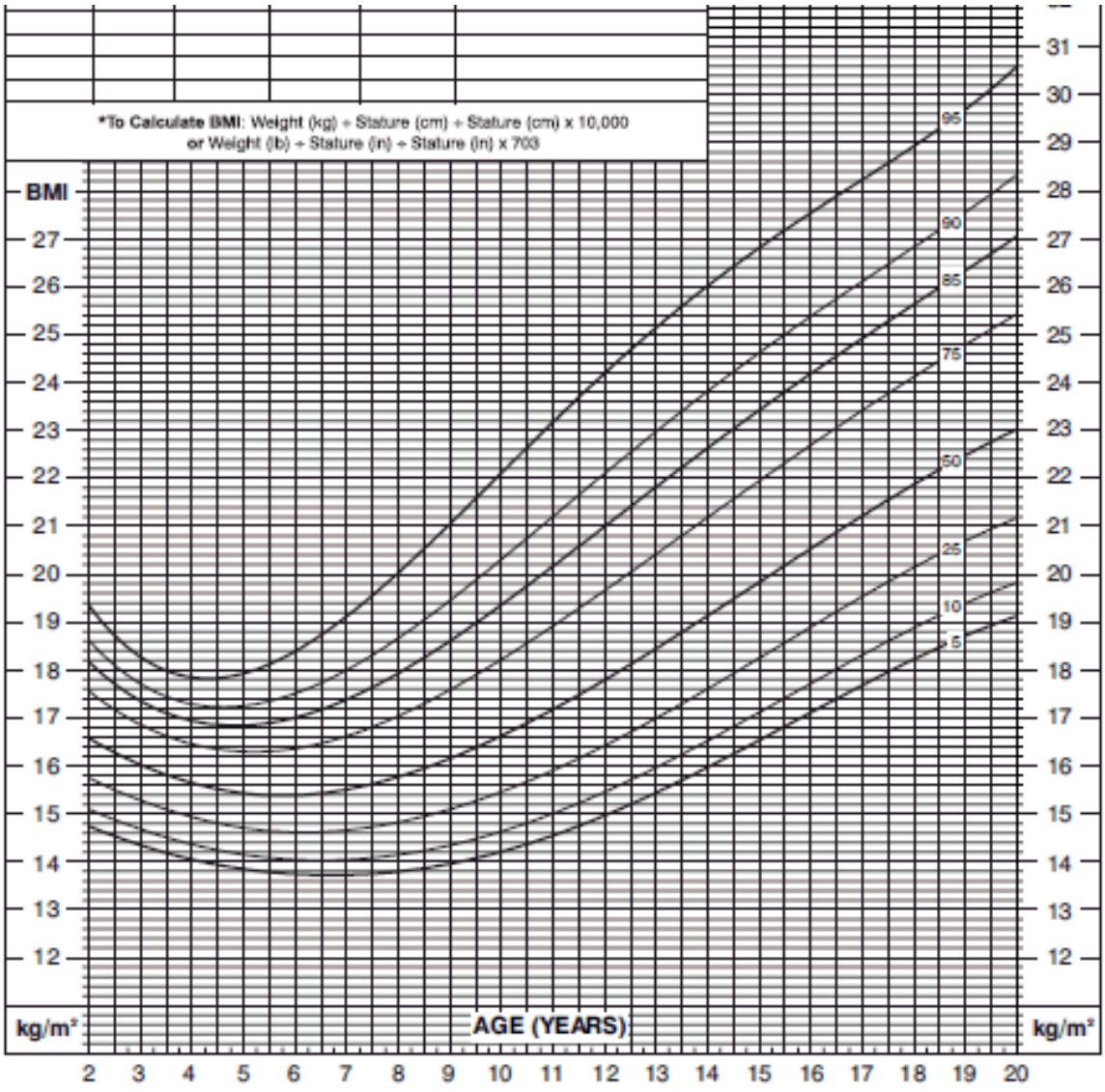
BP, blood pressure

* 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 7 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).

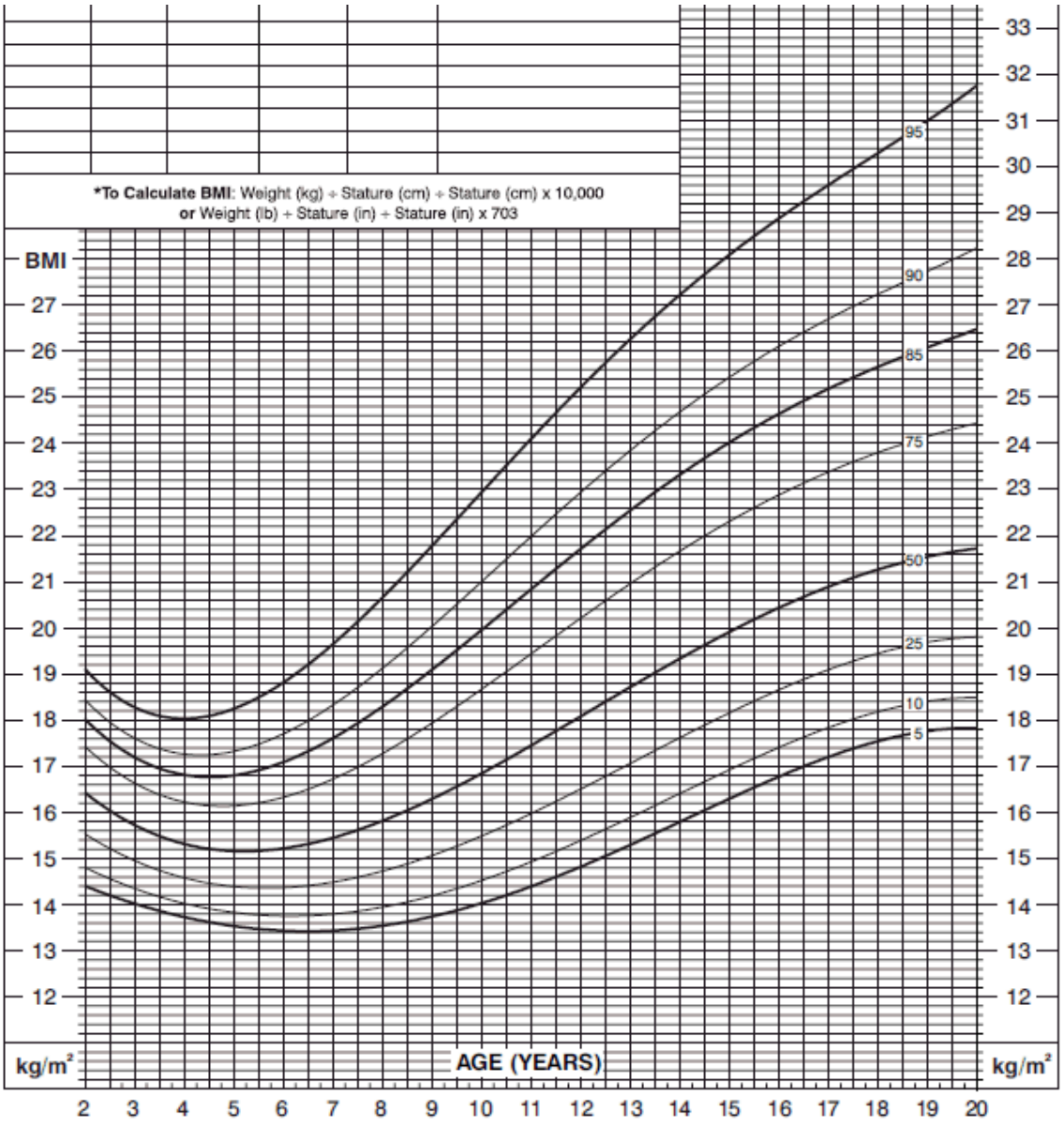
http://www.cdc.gov/growthcharts

Link for the charts is provided below

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

Appendix 8 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.ht

Appendix 9 Tanner's Staging

Boys Tanner Stage progression scale*

Genitalia:

1= The testes, scrotum and penis are about the same size and shape as they were when you were a child

2= The testes and scrotum are bigger. The skin of the scrotum has changed. The scrotum, the sack holding the testes, has gotten lower. The penis has gotten only a little bigger.

3= The penis has grown in length. The testes and scrotum have grown and dropped lower.

4= The penis has gotten even bigger. It is wider. The glans (the head of the penis) is bigger. The scrotum is darker than before. It is bigger because the testes are bigger.

5= The penis, scrotum, and testes are the size and shape of an adult man.

Pubic Hair:

1= There is no pubic hair at all.

2= There is a little soft, long, lightly-colored hair. Most of the hair is at the base of the penis.

This hair may be straight or a little curly.

3= The hair is darker in this stage. It is more curled. It has spread out and thinly covers a bigger area.

4= the hair is now as dark, curly, and course as that of an adult man. The area that the hair covers is not as big as that of an adult man. The hair has NOT spread out to the legs.

5= The hair has spread out to the legs. The hair is now like that of an adult man. It covers the same area as that of an adult man.

Girls Tanner Stage progression scale

Breast:

1= The nipple is raised a little. The rest of the breast is still flat.

2= This is the breast bud stage. In this stage, the nipple is raised more than in stage 1. The breast is a small mound. The areola is larger than stage 1.

3= The breast and areola are both larger than in stage 2. The areola does not stick out away from the breast.

4= The areola and the nipple make up a mound that sticks up above the shape of the breast. NOTE: This stage may not happen at all for some girls. Some girls develop from stage 3 to stage 5 with no stage 4

5= This is the mature adult stage. The breasts are fully developed. Only the nipple sticks out in this stage. The areola has moved back in the general shape of the breast.

Pubic Hair:

1= There is no pubic hair at all.

2= There is a little soft, long lightly-colored hair. This hair may be straight or a little curly.

3= The hair is darker in this stage. It is coarser more curled. It has spread out and thinly covers a bigger area.

4= the hair is now as dark, curly, and course as that of an adult female. The area that the hair covers is not as big as that of an adult female. The hair has NOT spread out to the legs.

5= The hair is now like that of an adult female. It covers the same area as that of an adult female. The hair usually forms a triangular (V) pattern as it spreads out to the legs.

*Adapted from: Morris, N.M., and Udry, J.R., (1980). Validation of a Self-Administered Instrument to Assess Stage of Adolescent Development. Journal of Youth and Adolescence, Vol. 9, No. 3: 271-80.

Appendix 10 Pharmacodynamic, and Other Biomarker Research

Subjects enrolled in this clinical study may have biologic samples collected for pharmacodynamic, 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.

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

Sample Collection and Handling

Sample collection for pharmacodynamic analysis is optional. 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 pharmacodynamic 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 study 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 pharmacodynamic, 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, pharmacodynamic, 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 11 Country-Specific Requirements

Sweden

As requested by the Swedish health authority, the calculation of serum creatinine is revised to include the 2009 Schwartz equation for subjects < 18 years of age and the maxumun serum creatinine values are provided in µmol/L because Standard International Units are used for reporting plasma creatinine in Sweden.

8.3.1 Inclusion Criteria

10. Adequate renal function as evidenced by:
    a. Serum creatinine based on age/gender as below. If serum creatinine is greater than maximum serum creatinine for age/gender as shown in the table below, then creatinine clearance (or radioisotope glomerular filtration rate [GFR]) must be >70 mL/min/1.73 m^2. If applicable, the 2009 Schwartz equation must be used to estimate GFR for subjects aged <18 years (ie, eGFR = 36.5 x height [cm]/plasma creatinine [µmol/L]) (Schwartz, et al., 2009).

Age	Maximum Serum Creatinine (mg/dL)		Maximum Serum Creatinine (µmol/L)	
	Male	Female	Male	Female
2 to <6 years	0.8	0.8	70.72	70.72
6 to <10 years	1	1	88.4	88.4
10 to <13 years	1.2	1.2	106.08	106.08
13 to <16 years	1.5	1.4	132.6	123.76
≥16 years	1.7	1.4	150.28	123.76

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

b. Urine dipstick <2+ for proteinuria. Subjects who have ≥2+ proteinuria on dipstick urinalysis should undergo a spot protein-creatinine (P/C) ratio test that should be Grade <2 per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and if possible perform a 24-hour urine collection (children and adolescents ≤12 years of age must have ≤500 mg of protein/24 hours and subjects >12 years of age must have ≤1 g of protein/24 hours).

c. No clinical evidence of nephrotic syndrome.

References

Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20(3):629-37.

Germany

New section added to outline the measures taken within the protocol to reduce risk and burden as per the German health authority request.

8.2.1 Participant Risk and Burden

The clinical study protocol will be conducted in accordance with 'Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population' in order to reduce the risk and burden to the participants. The degree of burden and risk is continuously monitored and assessed by the Investigator through the various study assessments outlined in the Section 9.5.2 – Schedule of Procedures/Assessments, and the threshold for discontinuation is clearly defined in Section 9.3.3 – Removal of Subjects From Therapy or Assessment. Thus, should the benefit/risk assessment adversely change during the study for a subject, he/she will be discontinued.

Safety assessments will be conducted per Section 9.5.1.4 of the protocol to ensure participant safety and reduce risks. Both safety and efficacy assessments have been outlined to allow for adequate assessment of clinical benefit, and when possible, have been gradually reduced in frequency with consideration of minimizing patient burden. The summary of measures taken to mitigate risk and burden within the protocol are outlined in Appendix Table 11-1.

Appendix Table 11-1 Measures to Reduce Participant Risk and Burden:

Protocol Section	Considerations and Measures Taken
Section 9.1.2, Tumor Assessments:	During the randomization phase the frequency in which tumor assessments are performed reduces gradually; initially performed, every 6 weeks ±1 week, following the date of randomization. Following Week 18, tumor assessments occur every 9 weeks ±1 week until week 54 ±1 week. Thereafter, they will be performed every 12 weeks ±2 weeks until documentation of PD. The initial schedule of scans allows for the detection of early progression in order to ensure the subjects is deriving treatment benefit, and then reduces gradually to reduce risk and burden.
Section 9.3, Selection of Study Population	To ensure appropriate monitoring of subject risk, inclusion and exclusion criteria have taken consideration of age and gender where clinically relevant, eg, serum creatinine and blood pressure thresholds, performance status scoring, and proteinuria determination.

Section 9.5.1.4, Safety assessment	The protocol requires continuous monitoring of patient safety and recording of all adverse events (AE)s and serious adverse events (SAEs), including laboratory data, graded per National Cancer Institute (NCI), CTCAE v5.0 beginning from the time the subject signs the study ICF through the last visit and for 30 days after the subject's last dose.
Section 8.5.2, Table 6, Schedule of Assessments (Randomization Phase)	Urinalysis by urine dipstick, and cardiac monitoring by ECG reduce in frequency. This allows for detection of early toxicity, and then reduces gradually to reduce patient burden. Furthermore, safety monitoring measures have been taken with consideration of age and gender to ensure appropriate monitoring of subject risk. This includes age-specific performance status scoring systems, and the inclusion of age-specific thresholds in the toxicity management guidelines for proteinuria (Section 9.4.1.1.4) and hypertension (Section 9.4.1.1.2).
Section 9.5.2, Table 7, Schedule of Assessments (Extension Phase)	Extension phase: Study assessments are reduced in number and frequency following the completion of the PFS-1y and OS-1y analysis (ie, at the end of the Randomization phase) to reduce patient burden and risk; tumor assessments are performed in accordance with local standard of care, while ECG, echocardiograms, sampling for PK and PD analysis, and HRQoL assessments will not be required.
Section 9.5.1.4.3 Laboratory Measurements: Maximum Puncture Attempts. Maximum Blood Volume Sampling.	For children requiring venipuncture, if the practitioner is unsuccessful after two attempts, it is recommended that another suitably trained professional perform venipuncture while assessing the child's coping skills. A maximum of 3 attempts may be considered; however, clinical need and risk/benefit of further attempts should be assessed at the discretion of the investigator The maximum volume of blood to be collected is 5% of the total blood volume over a 30-day period (Howie, et al 2010, Children's Memorial Research Center (CMRC), 2006).
Section 9.5.1.3.1: Pharmacokinetic	In order to ensure subject safety and not exceed the maximum allowable volume for blood collections,

Assessments; Table 6, Schedule of Assessments	pharmacokinetic (PK) sampling should not be performed for any subject with a body weight less than 13 kg
Section 9.5.1.3.2: Pharmacodynamic and other Biomarker Assessments; Table 5, Schedule of Assessments	In order to ensure subject safety and not exceed the maximum allowable volume for blood collections, pharmacodynamic sampling should not be performed for any subject with a body weight less than 16 kg Furthermore, to reduce subject burden, blood sampling for pharmacodynamic biomarker assessment is optional for all subjects and will not impact eligibility.
Section 9.5.2, Table 5, Schedule of Assessments (Randomization Phase): Footnote w	Providing archival tumor samples is optional to minimize subject burden and does not impact eligibility.
Section 9.7.3 Interim Analysis	Periodic safety monitoring will be conducted by the independent data monitoring committee (IDMC) to further mitigate subject risk.

Additional changes for sites in Germany:

- Section 9.5.1.4.3, Section 9.5.2.1, Table 6 (footnote h), Table 7 (footnote i): Clinical chemistry and hematology results must be reviewed by the investigator prior to administration of study drug ~~on C1D1 and within 48 hours after dispensing study drug for all subsequent cycles.~~
- **Section 9.5.1.4.3: Laboratory Measurements**

  Maximum Number of Puncture Attempts

  Central venous access is recommended for subjects in this study and thus, if possible, blood draws should be obtained using the central line or port. For children requiring venipuncture, if the practitioner is unsuccessful after two attempts, it is recommended that another suitably trained professional perform venipuncture while assessing the child's coping skills. A maximum of 3 attempts may be considered; however, clinical need and risk/benefit of further attempts should be assessed at the discretion of the investigator. Utilization of procedures to minimize any pain, reduce distress associated with blood sampling, and increase successful venous access should be considered including topical anaesthesia, application of warmth/cooling, alternative puncture site sampling and ultrasound guidance where applicable and in accordance with local institutional guidelines.

  Maximum Blood Volume Sampling

  The maximum volume of blood to be collected is 5% of the total blood volume over a 30-day period (Howie, et al 2010, Children's Memorial Research Center (CMRC), 2006). In order to

ensure the maximum allowable blood volume is not exceeded, please refer to Section 9.5.1.3.1 and Section 9.5.1.3.2 of the protocol which details weight limits for pharmacokinetic and pharmacodynamic blood sampling. The estimated total volume of blood is not expected to exceed:

The scheduled blood volume collections are outlined in the table below.

Blood Sample Collection Schedule

Period	**Screening**	**Baseline**	**Treatment**																**Off-Tx**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18+**	
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6-X**	
Day	**-28 to -2**	**-1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Procedures/ Assessments																			
Clinical chemistry and hematology[a]	10	10			10	10		10	10			10			10			10	10
PK blood samples (Arm A)[b]			4		6	2													
Pharmacodynamic biomarker (Arm A)[c]		4			4	4						4						4	
Total volume (mL)[d]	**10**	**14**	**4**		**20**	**16**		**10**	**10**			**14**			**10**			**14**	**10**

a. Clinical chemistry and hematology blood samples (approximately 10mL per time point) will be taken at Screening, Baseline, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, Day 1 of each subsequent cycle, and at the Off-treatment visit.

b. For Arm A subjects only: Six (6) pharmacokinetic analysis blood samples (one 2 mL sample per time point) will be taken at Cycle 1 Day 1 at 0.5 to 4 hours and 6 to 10 hours postdose, on Cycle 1 Day 15 at predose, 0.5 to 4 hours and 6 to 10 hours postdose, and Cycle 2 Day 1 at predose. (Total 12 mL). Please see Section 9.5.1.3.1 for further details on PK blood sampling weight limits.

c. For Group A subjects only: Five (5) Pharmacodynamic biomarker blood samples (one 4 mL sample per time point) will be taken at the Baseline Visit, C1D15, Day 1 of Cycles 2, 4, and 6. (Total 20 mL). Please see Section 9.5.1.3.2 for further details on pharmacodynamic blood sampling weight limits.

d. Total maximum volume of blood taken at each visit (mL)

Section 9.3.2 Exclusion Criteria

- Exclusion Criterion 15: Known to be human immunodeficiency virus (HIV) positive. Note: **HIV testing is a required evaluation for study entry and needs to be performed in order to evaluate eligibility. This testing can be performed at any time during the Screening period**

  Exclusion Criterion 16: Active viral hepatitis (B or C) as demonstrated by positive serology. Note: **Hepatitis B/C tests are required evaluations for study entry and need to be**

performed in order to evaluate eligibility. This testing can be performed at any time during the Screening period

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E7080-G000-230

Study Protocol Title: A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)

Investigational Product Name: E7080/Lenvatinib

IND Number: 146642

EudraCT Number: 2019-003696-19

SIGNATURES

Authors:

PPD

15 Sep 2020
Date

Oncology Business Group, Eisai Ltd.

PPD

15 SEP 2020
Date

Oncology Business Group, Eisai Ltd.

PPD

15 Sept 2020
Date

Oncology Business Group, Eisai Ltd.

PPD

15 Sep 2020
Date

Oncology Business Group, Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7080-G000-230
Study Protocol Title:	A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)
Investigational Product Name:	E7080/Lenvatinib
IND Number:	146642
EudraCT Number:	2019-003696-19

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

Medical Institution

Investigator	Signature	Date

TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-G000-230
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Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 JP
Sponsor's Investigational Product Name:	E7080/Lenvatinib
Indication:	Osteosarcoma
Phase:	2
Approval Date(s):	Original Protocol 08 Oct 2019 Amendment 01 09 Mar 2020
IND Number:	146642
EudraCT Number:	2019-003696-19
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 01

Date: 09 March 2020

Change New text is in bold and deleted text is in strikethrough font.	**Rationale**	**Affected Protocol Sections**
Inclusion Criterion 7 is updated as follows: 7. Adequate bone marrow function as evidenced by: a. absolute neutrophil count (ANC) ≥~~1.0~~ **1.5**×10^9/L. (subjects with bone marrow involvement should have ANC ≥0.8×10^9/L and leucocyte count ≥1×10^9/L). b. hemoglobin ≥8.0 g/dL (a hemoglobin of <8.0 g/dL is acceptable if it is corrected by growth factor or transfusion before Cycle 1 Day 1). c. platelet count ≥~~75~~ **100**×10^9/L.	The minimum neutrophil and platelet counts required to establish eligibility have been revised for consistency with the etoposide Summary of Product Characteristics per health authority request.	Synopsis, Section 8.3.1
Exclusion Criterion 20 is added: A contraindication to any of the study drugs (lenvatinib, ifosfamide, and etoposide) per local prescribing information.	An exclusion criterion due to contraindications to any of the study drugs has been added per health authority request.	Synopsis, Section 8.3.2
Prior and Concomitant Therapy Subjects should not receive other antitumor therapies while on study. If a subject receives additional antitumor therapies other than the study drug(s), such as chemotherapy, targeted therapies, immunotherapy, or antitumor interventions - such as surgery or palliative radiotherapy (other than as described below), this will be judged to represent evidence of disease progression, and ~~continuation of the~~study medication **should be discontinued** ~~and further participation in the study must be discussed and agreed upon with the sponsor .~~	Per health authority request, subjects who receive other anticancer therapy, except as specified in the protocol, should be discontinued from study treatment.	Synopsis, Section 8.4.7.2
Vital Signs Assessment **On Cycle 1 Day 8, subjects will be contacted by telephone to assess for the development of early toxicity. Subjects will be provided with a BP cuff to monitor BP at home or can have the measurement done by a local healthcare**	Per health authority request, a Cycle 1 Day 8 telephone contact has been added to monitor for early toxicity (including increase in blood pressure).	Section 8.5.2 (Schedule of Procedures/Assessments, Table 5 footnote j – new footnote, subsequent footnotes renumbered)

provider, and will report the C1D8 measurement at telephone contact. An unscheduled visit can occur prior to C1D15 if deemed necessary by the investigator.		
Pharmacodynamic Biomarkers The Schedule of Procedures/Assessments (Table 5) has been updated as follows: Blood samples will be collected only from subjects in Arm A at the Baseline Visit, C1D15 ~~C1D8~~, Day 1 of Cycles 2, 4, and 6, for assessment of blood serum sample to measure factors implicated in angiogenesis.	To lessen patient burden, the protocol has been updated to move the optional pharmacodynamic blood sample collection from C1D8 to C1D15. This eliminates the potential need for a study site visit for the sole purpose of collecting this optional PD blood sample on C1D8.	Section 8.5.2 (Schedule of Procedures/Assessments, Table 5, footnote v)
Administrative changes.	Minor editorial and formatting changes.	Throughout the protocol.

1 CLINICAL PROTOCOL SYNOPSIS

Compound No. E7080

Name of Active Ingredient: Lenvatinib

Study Protocol Title

A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)

Investigator

Principal Investigator: Dr Nathalie Gaspar

Sites

Approximately 70 sites worldwide

Study Period and Phase of Development

Approximately 36 months

Phase 2

Objectives

Primary Objective

To evaluate whether lenvatinib in combination with ifosfamide and etoposide (Arm A) is superior to ifosfamide and etoposide (Arm B) in improving progression-free survival (PFS) rate at 4 months (PFS-4m) (by independent imaging review [IIR] using Response Evaluation Criteria In Solid Tumors [RECIST 1.1]), in children, adolescents, and young adults with relapsed or refractory osteosarcoma.

Secondary Objectives

The secondary objectives of the study are to:

1. Compare differences in PFS rate at 1 year (PFS-1y) between the 2 treatment arms
2. Compare differences in PFS Kaplan-Meier (K-M) survival curves and median PFS between the 2 treatment arms
3. Compare differences in overall survival (OS) and OS rate at 1 year (OS-1y) between the 2 treatment arms
4. Compare differences in objective response rate (ORR) at 4 months between the 2 treatment arms
5. Compare differences in safety and tolerability between the 2 treatment arms
6. Characterize the pharmacokinetics (PK) of lenvatinib, when administered in combination with ifosfamide and etoposide
7. Compare differences in health-related quality of life (HRQoL) as assessed by using the the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales and Cancer Module between the 2 treatment arms
8. Assess the palatability and acceptability of the suspension formulation of lenvatinib in pediatric subjects receiving the suspension formulation in the study

Exploratory Objectives

The exploratory objectives of the study are to:

1. Explore differences in duration of response (DOR), disease control rate (DCR), and clinical benefit rate (CBR) between the 2 treatment arms

2. Compare the proportion of subjects who achieve complete removal of baseline lesion(s) following completion of chemotherapy between the 2 treatment arms
3. Investigate the relationship between subject tumor biomarkers and clinical response and toxicity of lenvatinib in combination with ifosfamide and etoposide

Study Design

E7080-G000-230 is a multicenter, randomized, open-label, parallel-group, Phase 2 study to compare the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide in children, adolescents, and young adults with relapsed or refractory osteosarcoma.

Approximately 72 eligible subjects will be randomized to 1 of the following 2 treatment arms in a 1:1 ratio within the strata:

- Arm A: lenvatinib 14 mg/m^2 (orally, once daily) plus ifosfamide 3000 mg/m^2/day (intravenously [IV], Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)
- Arm B: ifosfamide 3000 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)

Randomization will follow a predefined randomization scheme based on the following stratification factors: time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 and ≥18 years).

Eisai will closely monitor enrolment, to ensure that at least 32 subjects <18 years of age at the time of informed consent are randomized.

The study will be conducted in 3 Phases: a Prerandomization Phase, a Randomization Phase, and an Extension Phase.

The **Prerandomization Phase** will consist of 2 periods: Screening and Baseline. The Prerandomization Phase will last no longer than 28 days. The Screening Period will establish protocol eligibility and the Baseline Period will confirm eligibility.

The **Randomization Phase** will consist of 2 periods: Treatment Period and Follow-up Period. The Randomization Phase will begin at the time of randomization of the first subject and will end on the data cutoff date for the PFS-1y and OS-1y analysis. After the data cutoff date for the PFS-1y and OS-1y has occurred, all subjects who are still on study treatment will enter the Extension Phase. Data cutoff (for PFS-1y and OS-1y analysis) will occur when the last subject has completed 18 cycles of treatment or discontinues before the end of Cycle 18, whichever occurs first.

The ***Treatment Period*** for each subject will begin at the time of randomization and will end at the completion of the Off-Treatment Visit which will occur within 30 days after the final dose of study treatment

Subjects will receive study treatment as continuous 21-day cycles in both treatment arms. Treatment cycles will be counted continuously regardless of dose interruptions. If chemotherapy administration is precluded on Day 1 of a treatment cycle, the subject may resume treatment once recovered at the discretion of investigator. Subsequent chemotherapy will be administered every 21 (±1) days starting from the timepoint it was resumed.

Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments. Subjects randomized to Arm A will continue to receive lenvatinib until disease progression (PD) confirmed by IIR, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor, whichever occurs first.

Disease progression (PD) must be confirmed by IIR prior to the investigator discontinuing study treatment for a subject. In situations where the investigator judges that alternative treatments must be

instituted immediately for a subject's safety, study drugs may be discontinued without waiting for IIR confirmation of radiographic evidence of PD. If possible, before discontinuation of the subject from the study, the investigator should consult with the sponsor.

The ***Follow-up Period*** begins the day after the Off-Treatment Visit and will continue as long as the subject is alive, unless the subject withdraws consent, or the sponsor terminates the study.

Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn, however, an investigator may consult public records to establish survival status if permitted by local regulations.

All adverse events (AEs) will be captured for 30 days after the last dose of study drug.

All subjects who discontinue study treatment early for reasons other than PD, will continue to undergo tumor assessments every 6 weeks until Week 18, then every 9 weeks until Week 54, thereafter, every 12 weeks until confirmation of disease progression by IIR as described in the tumor assessments in the assessment schedule, or until another anticancer therapy is initiated.

Subjects in both Arm A and Arm B will be followed for survival every 12 weeks (±1 week) and all subsequent anticancer treatments received will be recorded. Subjects who are being followed for survival at the time of data cutoff for the for PFS-1y and OS-1y analysis (ie, at the end of the Randomization Phase) will continue to be followed for survival during the Follow-up Period of the Extension Phase.

Extension Phase: The Extension Phase will consist of 2 periods: Treatment Period and Follow-up Period.

In the ***Treatment Period***, subjects still on lenvatinib in Arm A following the completion of the PFS-1y and OS-1y analysis (ie, at the end of the Randomization Phase) will continue to receive lenvatinib in 21-day cycles until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor. Tumor assessments will be performed according to the local standard of care. Independent imaging review (IIR) review and confirmation of radiographic evidence of PD will not be required, and scans will no longer be required to be sent to the imaging core laboratory (ICL). The Off-Treatment Visit will occur within 30 days after the final dose of study treatment. All AEs will be captured up to 30 days after last dose of study drug. In case the study is discontinued by the sponsor, the sponsor will continue to provide study drug (outside the study) for subjects requiring continuation of treatment.

The ***Follow-up Period*** will begin the day after the Off-Treatment Visit and will last until death or for 2 years after end of treatment for a subject, unless the study is terminated by the sponsor, or the subject discontinues due to withdrawal of consent, or is lost to follow-up. Subjects will be treated by the investigator according to the prevailing local standard of care. Subjects will be followed every 12 weeks (±1week) for survival and all subsequent anticancer treatments received will be recorded.

The definition of end of the study, as required by certain regulatory agencies, will be the date of data cutoff for the final analysis or the time of last subject last visit, whichever occurs later.

Number of Subjects

Approximately 72 subjects will be randomised (36 subjects in each arm).

For the primary endpoint (intent–to-treat analysis), at least 32 subjects <18 years old (at the time of informed consent) will be randomized.

Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of high grade osteosarcoma.
2. Refractory or relapsed osteosarcoma after 1 to 2 prior systemic treatments.
3. Measurable or evaluable disease per RECIST 1.1 that meets the following criteria:

- Must be accurately measurable with a minimum size (by long axis) of 10 mm using computed tomography/magnetic resonance imaging (CT/MRI) (lymph nodes must be accurately measurable with a minimum size [by short axis] of 15 mm).
- Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must have subsequently grown unequivocally to be deemed a target lesion.

4. Aged 2 years to ≤25 years at the time of informed consent.
5. Life expectancy of 12 weeks or more.
6. Lansky play score ≥50% or Karnofsky Performance Status score ≥50%. Use Karnofsky for subjects ≥16 years of age and Lansky for subjects <16 years of age. Subjects who are unable to walk because of paralysis, but who are up in wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
7. Adequate bone marrow function as evidenced by:
   a. absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L.

      (subjects with bone marrow involvement should have ANC $\geq 0.8\times10^9$/L and leucocyte count $\geq 1\times10^9$/L).
   b. hemoglobin ≥8.0 g/dL (a hemoglobin of <8.0 g/dL is acceptable if it is corrected by growth factor or transfusion before Cycle 1 Day 1).
   c. platelet count $\geq 100\times10^9$/L.
8. Adequate blood coagulation function defined by International Normalized ratio (INR) ≤1.5 unless participant is receiving anticoagulant therapy, as long as INR is within therapeutic range of intended use of anticoagulants.
9. Adequate liver function as evidenced by:
   a. Bilirubin ≤1.5 times the upper limit of normal (ULN).
   b. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3×ULN (in the case of liver metastases ≤5×ULN).
10. Adequate renal function as evidenced by:
    a. Serum creatinine based on age/gender as below. If serum creatinine is greater than maximum serum creatinine for age/gender as shown in the table below, then creatinine clearance (or radioisotope glomerular filtration rate [GFR]) must be >70 mL/min/1.73 m^2.

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

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

    b. Urine dipstick <2+ for proteinuria. Subjects who have ≥2+ proteinuria on dipstick urinalysis should undergo a spot protein-creatinine (P/C) ratio test that should be Grade <2 per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and if possible perform a

24-hour urine collection (children and adolescents ≤12 years of age must have ≤500 mg of protein/24 hours and subjects >12 years of age must have ≤1 g of protein/24 hours).

c. No clinical evidence of nephrotic syndrome.

11. Adequate cardiac function as evidenced by left ventricular ejection fraction ≥50% at baseline as determined by echocardiography.
12. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as:
    a. BP <95th percentile for sex, age, and height/length at screening (as per National Heart Lung and Blood Institute guidelines) and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1. Subjects >18 years of age should have BP ≤150/90 mm Hg at screening and no change in antihypertensive therapy within 1 week prior to Cycle 1 Day 1.
13. Washout before Cycle 1 Day 1 of 3 weeks in case of prior chemotherapy, 6 weeks if treatment included nitrosoureas; 4 weeks for definitive radiotherapy, 2 weeks for palliative radiotherapy; and 3 months from high-dose chemotherapy and stem cell rescue. Subjects must have recovered (to Grade ≤1, except for alopecia, ototoxicity, and Grade ≤2 peripheral neuropathy, per CTCAE v5.0) from the acute toxic effects of all prior anticancer therapy before Cycle 1 Day 1.
14. Written and signed informed consent from the parent(s) or legal guardian and assent from the minor subject. Written informed consent from subjects ≥18 years.
15. Willing and able to comply with the protocol, scheduled follow-up, and management of toxicity as judged by the investigator.

Exclusion Criteria

1. Any active infection or infectious illness unless fully recovered prior to Cycle 1 Day 1 (ie, no longer requiring systemic treatment).
2. Subjects with central nervous system metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy, surgery, or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 2 weeks before Cycle 1 Day 1.
3. Active second malignancy within 2 years prior to enrollment ([in addition to osteosarcoma], but not including definitively treated superficial melanoma, carcinoma-in-situ, basal or squamous cell carcinoma of the skin).
4. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
5. Has had major surgery within 3 weeks prior to Cycle 1 Day 1. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
6. Known hypersensitivity to any component(s) of the study drugs (lenvatinib, ifosfamide, and etoposide, or their ingredients).
7. Currently receiving any investigational drug or device in another clinical study or within 28 days prior to Cycle 1 Day 1.
8. A clinically significant ECG abnormality, including a marked baseline prolonged QT or QTc interval (eg, a repeated demonstration of a QTc interval >480 msec).
9. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that in the opinion of the investigator might affect the absorption of lenvatinib.
10. Pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula.
11. Gastrointestinal bleeding or active hemoptysis (bright red blood of at least ½ teaspoon) within 3 weeks prior to Cycle 1 Day 1.
12. Radiographic evidence of intratumoral cavitation, encasement, or invasion of a major blood

vessel. Additionally, the degree of proximity to major blood vessels should be considered for exclusion because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.

13. History of ifosfamide-related Grade ≥3 nephrotoxicity or encephalopathy.
14. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
15. Known to be human immunodeficiency virus (HIV) positive. Note: HIV testing is required at screening only when mandated by local health authority.
16. Active viral hepatitis (B or C) as demonstrated by positive serology. Note: Testing for Hepatitis B or Hepatitis C is required at screening only when mandated by local health authority.
17. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG]) (human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG / hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
18. Females of childbearing potential* who:
    - Do not agree to use a highly effective method of contraception for the entire study period and for 28 days after lenvatinib discontinuation or 12 months after etoposide and ifosfamide discontinuation, ie:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
        - a contraceptive implant
        - an oral contraceptive. Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing with study drug and throughout the study and for 28 days after lenvatinib discontinuation or 12 months after etoposide and ifosfamide discontinuation

          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, or the subject has changed oral hormonal contraceptive product/dose within 4 weeks prior to study drug administration, 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.

    * All post pubertal females will be considered to be of childbearing potential unless they have early menopause (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).
19. 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 28 days after lenvatinib discontinuation or 6 months after discontinuation of etoposide and ifosfamide). No sperm donation is allowed during the study period and for 28 days after lenvatinib discontinuation or 6 months after discontinuation of etoposide and ifsofamide.

20. A contraindication to any of the study drugs (lenvatinib, ifosfamide, and etoposide) per local prescribing information.

Study Treatments

Body surface area (BSA) will be used to determine the amount of study drugs administered, and must be calculated on Day 1 of each cycle based on the subject's current height and body weight. The dose should be rounded to the nearest whole number.

Test Arm (Arm A): Lenvatinib + Ifosfamide + Etoposide

Lenvatinib 14 mg/m^2, orally administered once daily in each 21-day cycle.

Lenvatinib is provided as hard capsules containing 1 mg, 4 mg, or 10 mg lenvatinib. An extemporaneous suspension of lenvatinib capsules should be used for subjects unable to swallow capsules. After adjustment for BSA, the daily dose cannot exceed 24 mg QD.

Ifosfamide 3000 mg/m^2/day, IV, for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Etoposide 100 mg/m^2/day, IV, for 3 consecutive days (Day 1 to 3) , every 21 days, for a maximum of 5 cycles.

Treatment with lenvatinib will continue in 21-day cycles after chemotherapy is discontinued, until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor.

In case the study is discontinued by the sponsor, the sponsor will continue to provide study drug (outside the study) for subjects requiring continuation of treatment.

Control Arm (Arm B): Ifosfamide + Etoposide

Ifosfamide 3000 mg/m^2/day, IV, daily for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Etoposide 100 mg/m^2/day, IV, daily for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Duration of Treatment

A subject will remain on study treatment until 1 or more of the following events occur(s):

- Progressive disease (as confirmed by IIR)
- Unacceptable toxicity
- Subject request
- Withdrawal of consent
- Termination of the study by the Sponsor

Concomitant Drug/Therapy

Prohibited Concomitant Therapies and Drugs

Subjects should not receive other antitumor therapies while on study. If a subject receives additional antitumor therapies other than the study drug(s), such as chemotherapy, targeted therapies, immunotherapy, or antitumor interventions - such as surgery or palliative radiotherapy (other than as described below), this will be judged to represent evidence of disease progression, and the study medication should be discontinued.

For further information on the prohibited concomitant therapies for ifosfamide and etoposide, please refer to the respective prescribing information.

Granulocyte-colony stimulating factor (G-CSF) may be used to mitigate the toxicity of ifosfamide and etoposide.

The following concomitant treatments/procedures are allowed:

a. Removal of existing (not new) osteosarcoma lesion (eg, surgical, radiofrequency ablation, cryotherapy, thermoablation, stereotaxic ratiotherapy, etc.) after completion of the Week 18 tumor assessment. Subjects in Arm A in the presence of clinical benefit, may continue treatment with lenvatinib after protocol permissible surgery.

b. Palliative radiotherapy is allowed for ≤2 significantly symptomatic nontarget lesions.

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

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

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

Assessments

Efficacy Assessments

Tumor assessment will be performed based on RECIST 1.1. Investigator–determined response assessments will be performed at each assessment time point and entered onto the case report form (CRF). Copies of all tumor assessment scans will be sent to an imaging core laboratory (ICL) designated by the sponsor for efficacy assessment and for confirmation of PD. Tumor assessments will be carried out following the guidelines provided by the ICL.

During the Screening Period, tumor assessments of the chest, abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed within 28 days prior to Cycle 1 Day 1. A brain scan (CT scan with contrast or MRI pre- and post-gadolinium) will be performed at screening as clinically indicated, and thereafter during the study as clinically indicated. Historical CT or MRI scans performed within 28 days prior to Cycle 1 Day 1 may be used as screening scans (baseline scans) to demonstrate eligibility, as long as they meet minimum standards as separately defined by the ICL.

Tumor assessments will then be performed every 6 weeks ±1 week following the start of treatment on Cycle 1 Day 1 during the chemotherapy treatment period until Week 18. Following completion of the chemotherapy treatment period (ie, after Week 18), the frequency of tumor assessments will be every 9 weeks ±1 week until Week 54 ±1 week. Thereafter, they will be performed every 12 weeks ±2 weeks until documentation of PD (please see schedule of assessments for details). At any point, the CT/MRI scan should be performed earlier than the scheduled time point, if clinically indicated. After data cutoff for PFS-1y and OS-1y analysis, tumor assessments should be performed following the prevailing local standard of care.

Disease progression per RECIST 1.1 during the randomization phase must be confirmed by IIR prior to the investigator discontinuing study treatment.

In the event that the investigator considers alternative treatments must be instituted immediately for management of urgent medical complications of PD, study drugs may be discontinued without waiting for independent confirmation of radiographic evidence of PD. Subjects who discontinue study treatment without PD will continue to undergo tumor assessments according to the schedule until PD is documented or another anticancer therapy is initiated.

Pharmacokinetic Assessments

Blood samples for plasma concentrations of lenvatinib will be collected from all subjects from Arm A only as described in the Schedule of Assessments.

Pharmacodynamic and Other Biomarker Assessments

Pharmacodynamic serum and archived fixed tumor tissue samples for biomarker analysis will be collected from subjects randomized to Arm A only, as described in the Schedule of Assessments. Pharmacodynamic serum and tumor biomarkers assessed in this study will be based on those identified in other lenvatinib clinical studies. Pharmacodynamic biomarker analysis will be performed as described in a separate analysis plan.

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs), including all grades per National Cancer Institute (NCI) CTCAE v5.0 (for both increasing and decreasing severity), and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and physical examinations.

Progression of osteosarcoma and signs and symptoms clearly related to the progression of the osteosarcoma should not be captured as an AE. Disease progression is a study endpoint and should be captured in the CRF as per the guidelines for reporting disease progression.

Other Assessments

HRQoL assessment will be performed per the Schedule of Assessments. Impact of treatment on HRQoL will be assessed using the PedsQL (including the Generic Core Scales and Cancer Module).

Bioanalytical Methods

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

Statistical Methods

Primary Endpoint

- **PFS-4m rate (progression-free survival rate at 4 months) by IIR** is defined as the percentage of subjects who are alive and without PD at 4 months from the randomization date as determined by IIR of radiological imaging using RECIST 1.1. The PFS-4m rate is estimated on the full analysis set for this study using the K-M method.

Secondary Endpoints

- **PFS-1y rate (progression-free survival rate at 1 year) by IIR** is defined as the percentage of subjects who are alive and without PD at 1 year from the randomization date as determined by IIR of radiological imaging using RECIST 1.1. The PFS-1y rate is estimated on the full analysis set for this study using the K-M method.
- **Progression-free survival (PFS) by IIR** is defined as the time from the date of randomization to the date of the first documentation of PD or death (whichever occurs first) as determined by IIR using RECIST 1.1.
- **Overall survival (OS)** is defined as the time from the date of randomization to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cutoff will be censored at the date the subject was last known alive, or date of data cutoff, whichever occurs first. Overall survival rate at 1 year will be estimated.
- **Objective response rate (ORR) by IIR** at 4 months is defined as the proportion of subjects who have best overall response of complete response (CR) or partial response (PR) as determined by IIR using RECIST 1.1 within the first 4 months.
- **Safety** will be assessed summarizing the incidence of treatment-emergent adverse events

(TEAEs) and SAEs together with all other safety parameters.

- Assessment of population-based PK parameters of lenvatinib.
- Score changes from baseline for all PedsQL scales including Generic Core Scales and Cancer Module. Scores will be calculated for total generic score, total cancer score, each physical function subscale including physical health, psychosocial health, emotional function, social function, school/work function in the Generic Core Scales, and each subscales in the cancer module.
- Palatibility and acceptability of the suspension formulation of lenvatinib in subjects receiving the suspension formulation in the study will be assessed using the Palatability Questionnaire (see Appendix 5).

Exploratory Endpoints

- **Duration of response (DOR) by IIR** is defined as the time from the date a response was first documented until the date of the first documentation of PD or date of death from any case.
- **Disease control rate (DCR) by IIR** is the proportion of subjects who have a best overall response of CR or PR or stable disease (SD). In this context, stable disease is defined as stable disease at ≥7 weeks after randomization to be considered best overall response.
- **Clinical benefit rate (CBR) by IIR** is the proportion of subjects who have best overall response of CR or PR or durable SD (duration of SD ≥23 weeks after randomization).
- Proportion of subjects who achieve complete removal of baseline lesions following completion of chemotherapy.
- **Blood and tumor biomarkers** will be assessed for identifying potential correlation with clinical outcomes-related endpoints.
- All efficacy endpoints listed above (except OS) evaluated based on investigator assessment using RECIST 1.1.

Analysis Sets

The Full Analysis Set (Intent-to-Treat Analysis [ITT]) includes all randomized subjects regardless of the treatment actually received. This is the primary analysis population used for the efficacy analyses which will be based on the ITT principle.

The Per Protocol Analysis Set includes those subjects from the ITT set who received at least 1 dose of any study drug, had no major protocol deviations and had both baseline and at least one postbaseline tumor assessment. Subjects for whom death occurred prior to the first postbaseline tumor assessment will also be included. The per protocol analysis set will be the secondary analysis set for efficacy endpoints.

The Safety Analysis Set includes subjects who received at least 1 dose of any study drug. This is the analysis population used for all safety analyses which will be based on as-treated principle.

Population Pharmacokinetic (PK) Analysis Set includes the subjects who have received at least 1 dose of lenvatinib with documented dosing history and have measurable plasma levels of lenvatinib.

The Pharmacodynamic Analysis Set includes subjects who received at least 1 dose of study drug and had sufficient pharmacodynamic data (eg, at least 1 evaluable/measurable pharmacodynamic parameter).

The HRQoL Analysis Set will consist of all randomized subjects who have received at least 1 dose of study medication, and have completed at least 1 patient-reported outcome (PRO) assessment beyond baseline. For PRO analysis, subjects will be analyzed as randomized and not according to treatment actually received.

Efficacy Analyses

Efficacy analyses will be based primarily on the Full Analysis Set.

All the statistical analysis will be conducted at the PFS-1y/OS-1y analysis data cutoff date (ie, when the last subject has completed 18 cycles of treatment or discontinues before the end of Cycle 18, whichever occurs first), including the analysis of PFS-4m rate. Additional follow-up analysis will be based on the date of data cutoff for the additional follow-up analysis for OS or at the time of last subject last visit, whichever occurs later.

Primary Analysis

The primary analysis of PFS-4m rate will be based upon data provided by IIR of tumor assessments. PFS-4m rate and their Greenwood standard errors will be evaluated using the K-M estimates from both treatment groups. The statistical significance of the difference in the 2 K-M PFS-4m rates comparing lenvatinib + chemotherapy agent (Test Arm) vs. chemotherapy agent alone (Control Arm) will be tested using a 2-sided 80% CI. This 2-sided 80% CI and a p-value will be constructed using the difference of these 2 K-M PFS-4m rates and the 2 corresponding Greenwood standard errors. Statistical significance of the difference is declared if the CI is entirely above 0. This is equivalent to a test using a 1-sided test at alpha=0.1. The 2-sided 95% CIs will also be provided for descriptive purposes. PFS-4m rate will also be analyzed using a binomial approach as a sensitivity analysis by excluding subjects whose PFS are censored prior to 18 weeks.

Secondary Analyses

PFS-1y rate will be analyzed using the same methods as the primary efficacy analysis. PFS censoring rules will follow FDA guidance of 2007, however, removal of baseline lesions after completion of Week 18 without progression is not a trigger for PFS censoring after 18 weeks (refer to Concomitant Drug/Therapy – allowed concomitant treatment/procedures).

Overall survival (OS) will be compared between treatment arm and control arm using the stratified logrank test with time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years) as strata. Median OS with 2-sided 80% and 95% CIs will be calculated using K-M product-limit estimates for each treatment arm, and the K-M estimates of OS will be plotted over time. The Cox regression model will be used to estimate the hazard ratio and its 80% and 95% CIs stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years). Kaplan-Meier (K-M) estimates will also be presented for 4, 6, 9, and 12 months with 2-sided 80% and 95% CIs.

Median PFS and 2-sided 80% and 95% (as exploratory) CIs will be presented, and the K-M estimates of PFS will be plotted over time. The Cox regression model will be used to estimate the hazard ratio and its 80% and 95% CIs stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years). Kaplan-Meier (K-M) estimates will also be presented for 4, 6, 9, and 12 months with 2-sided 80% and 95% CIs.

The ORR will be compared between the test and control groups using either a chi-square test or a Cochran-Mantel-Haenszel test stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years), as appropriate. Corresponding odds ratios and their 2-sided 80% and 95% CIs comparing the groups will also be presented. The individual treatment group ORRs will also be calculated along with exact 95% confidence intervals using the Clopper and Pearson method.

Exploratory Analyses

Median DOR among responders for each arm will be presented along with its corresponding 2-sided 95% CIs. Disease Control Rate (DCR) and CBR will be calculated with exact 95% CIs using the Clopper and Pearson method. The differences of the above rates between 2 groups and corresponding two-sided 95% CIs will be calculated respectively.

Pharmacodynamic and Other Biomarker Analyses

Pharmacodynamic, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.

Blood serum samples may be analyzed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, or other assays/methods and new technology in an effort to identify biomarkers.

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

Data obtained from the pharmacodynamic samples will be used for research. The pharmacodynamic samples will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib and for potential diagnostic development. If the subject reaches 18 years of age prior to the date of final sample analyses they will be reconsented. No further analyses will be performed on these collected samples from subjects who either do not reconsent after their 18th birthday or cannot be reached for reconsenting and the sample will be destroyed. When the subject reaches the age of 18 years (or 16 years in the UK) while on the study, and becomes competent to give informed consent, his/her consent will be obtained using separate informed consent forms (ICFs) to continue on the study.

Pharmacokinetic Analyses

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

Lenvatinib data from Arm A of the study will be pooled with available data from other studies and subjected to population PK analysis. 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.

Other Analyses

Health-Related Quality of Life (HRQoL):

The PedsQL for all subjects(self- and proxy-rating) will be collected at baseline, at C2D1, C3D1, Week 18, C8D1, C18 D1, and at the Off-Treatment visit.

Interim Analyses

No interim analysis is planned for this study.

The safety monitoring will be conducted by the 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 recommendation whether to stop the study for safety will be reached by the IDMC based on their review of safety data with treatment information. The function and membership of the IDMC will be described in the IDMC charter.

Sample Size Rationale

A binomial-based comparison of 2 proportions using correction for continuity was used for sample size estimation. A total sample size of 72 subjects is estimated to achieve 80% statistical power at 1-sided alpha of 0.1 to detect a difference of 30% based on the assumption that PFS-4m for Arm A (lenvatinib arm) is 55% and for Arm B is 25%. Alpha is the type 1 error probability of declaring lenvatinib arm being effective when the true lenvatinib arm PFS-4m rate is only 25%.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANC	absolute neutrophil count
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
BSA	body surface area
CA	Competent Authorities
CBR	clinical benefit rate
CFR	Code of Federal Regulations
C_{max}	maximum drug or metabolite concentration
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP/CYP3A4	Cytochrome P450/cytochrome P4503A4
DCR	disease control rate
DOR	duration of response
DTC	differentiated thyroid cancer
ESMO	European Society for Medical Oncology
FGFR	fibroblast growth factor receptor
FGF	fibroblast growth factor
GFR	glomerular filtration rate
G-CSF	granulocyte-colony stimulating factor
HRQoL	health-related quality of life
HR	heart rate
ICF	informed consent form

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICL	imaging core laboratory
ID	identification
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IIR	independent imaging review
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenously
IVRS	interactive voice response system
KDR	kinase insert domain receptor
K-M	Kaplan-Meier
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
OS-1y	overall survival rate at 1 year
PD	progressive disease/disease progression
PDGFR	platelet-derived growth factor receptor
PedsQL	Pediatric Quality of Life Inventory
PFS	progression-free survival
PFS-4m	progression-free survival rate at 4 months
PFS-1y	progression-free survival rate at 1 year
PK	pharmacokinetic(s)
PR	partial response
PRES	posterior reversible leukoencephalopathy syndrome
PT	preferred term
QD	once daily

QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
RP2D	recommended Phase 2 dose
RPLS	reversible posterior leukoencephalopathy syndrome
RTK	receptor tyrosine kinase
RTKI	receptor tyrosine kinase inhibitor
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SmPC	summary of product characteristics
SOC	system organ class
SOP	standard operating procedure
SUSARs	suspected unexpected serious adverse reactions
TEAEs	treatment-emergent adverse events
TKI	tyrosine kinase inhibitors
TNM	tumor-node metastasis
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WHO DD	World Health Organization Drug Dictionary

4 ETHICS

4.1 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 the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice), Section 3, and any local regulations (eg, European Union [EU] Clinical Trials Directive 2001/20/EC or Code of Federal Regulations, Title 21 CFR Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate(s) [CRAs], 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.

Documented study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) 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 (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

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

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The definition of the end of the study is the date of the data cutoff for the final analysis or last subject/last visit, including discontinuation from the study for any reason, whichever occurs later.

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

4.2 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 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
- An IRB waiver request will be submitted before study initiation for non-US sites conducted under an Investigational New Drug (IND) application.
- 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.
- Other applicable regulatory authorities' requirements or directives

4.3 Subject Information and Informed Consent

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

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable 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 legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. In countries where specific laws for children are established for informed consent, those local laws will be applied. After the ICF and/or assent form and any other written information to be provided to subjects is read and explained to the subject or the subject's 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 and/or assent form, 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 ICF and/or assent form before any study-

specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (eg, EU Clinical Trials Directive 2001/20/EC or Code of Federal Regulations, Title 21, CFR Part 50). Each subject and the subject's parent(s) or legally acceptable representative must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

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

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

5 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 70 investigational sites worldwide.

The name, telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Regulatory Binder provided to each site.

6 INTRODUCTION

6.1 Osteosarcoma

Cancer is a relatively uncommon diagnosis in the pediatric population, and the overall incidence is low (18.6 cases per 100,000 children [Howlader, et al., 2019]). Solid tumors constitute approximately 60% of childhood malignancies (Howlader, et al., 2019). Malignant bone tumors are the fifth most common solid tumor type accounting for about 5% of childhood tumors (Howlader, et al., 2019; Kaatsch, 2010).

Osteosarcoma is the most commonly diagnosed primary malignancy of the bone in children and young adults, and accounts for approximately 5% of childhood tumors, with an estimated annual incidence of 4.4 cases per 1 million in people younger than 24 years (Mirabello, et al., 2009). Osteosarcoma occurs predominantly in adolescents and young adults. The median age at diagnosis is 20 years, with the incidence peaking at 15 to 19 years of age (ESMO, guidelines, 2014). According to the American Cancer Society, osteosarcoma in this age group is 8 per 1 million (Ward, et al., 2014).

There are both intrinsic and extrinsic factors that have been shown to contribute to the development of osteosarcoma. Studies have demonstrated that several genetic abnormalities, including the overexpression of vascular endothelial growth factor (VEGF) receptor (VEGFR), platelet-derived growth factor (PDGF) receptor (PDGFR), and c-fos, are associated with the development of osteosarcoma in laboratory models as well as humans (Gorlick and Khanna, 2010). However, osteosarcoma is not characterized by a single oncogenic driver. The vast majority of abnormal oncogenes and tumor-suppressor genes associated with osteosarcoma are also common in the most prevalent cancers (Gorlick and Khanna, 2010). Extrinsic factors such as ionizing radiation, which is used for the treatment of childhood solid tumors, have been well implicated in the development of a second malignancy, with osteosarcoma being the most likely to develop within the first 2 decades following treatment (Le Vu, et al., 1998).

The management of osteosarcoma is multimodal; patients not amenable to surgery or patients at second or third relapse have a poor prognosis. Metastatic osteosarcoma is common (10% to 20%) (NCCN, Bone cancer guidelines, 2020, Casali, et al., 2018), with the most frequent site being the lung (>85%). In the case of isolated lung metastases, more than a third of patients with a second surgical remission survive for >5 years (Casali, et al., 2018). Approximately 25% of all patients with primary metastatic osteosarcoma and >40% of those who achieve a complete surgical remission may become long-term survivors (Casali, et al., 2018) as compared with 65% to 70% of patients with localized disease (Meazza and Scanagatta, 2016).

About 30% to 40% of patients with localized disease and 80% of those with metastatic disease experience relapse (Casali, et al., 2018; NCCN, Bone cancer guidelines, 2020; Ferrari, 2003). The presence of solitary metastasis, time to first relapse, and complete resectability of disease at first recurrence are the most significant prognostic indicators for improved survival. Patients whose tumor is not amenable to surgery, or with second or third recurrence, or who have metastases to the bone, have a poor prognosis. In general, despite second-line treatment, the prognosis of recurrent disease in osteosarcoma has remained poor, with long-term postrelapse survival of <20% (Casali, et al., 2018; NCCN Bone Cancer Guidelines, 2020).

6.2 Current Therapeutic Options

There has been no substantial progress in the treatment of osteosarcoma since the 1980s. Current treatment utilizes multi-agent chemotherapy and surgical resection of all clinically detectable disease.

Treatment of Newly Diagnosed Disease

Newly diagnosed osteosarcoma is typically managed with neoadjuvant chemotherapy followed by surgical removal of the primary tumor and all clinically evident metastatic disease, followed by adjuvant chemotherapy. Surgical resection of all clinically detectable sites of disease is vital, regardless of number and site, as complete resection is predictive of

survival (Meazza and Scanagatta, 2016). For patients with unresectable disease at multiple sites, experimental therapy is also considered, due to the poor prognosis for these patients.

The most effective chemotherapy regimens include the combination of high-dose methotrexate, doxorubicin, and cisplatin and has become the standard treatment for high-grade osteosarcoma (Ferrari and Serra, 2015; Isakoff, et al., 2015; NCCN Bone Cancer Guidelines, 2020).

Treatment of Relapsed, Refractory, and Progressive Disease

Second-line treatment for relapsed disease consists of chemotherapy and/or surgical resection (Casali, et al., 2018; NCCN Bone Cancer Guidelines, 2020). The role of second-line chemotherapy for recurrent osteosarcoma is much less well defined than that of surgery, and there is no accepted standard regimen (Casali, et al., 2018). For patients with resectable solitary metastasis to the lung, surgical resection only may be adequate. For those with recurrent pulmonary metastases that are resectable, surgery is advised in addition to neoadjuvant or adjuvant chemotherapy, regardless of the number of previous lung relapses and the number of secondary pulmonary lesions (Briccoli, et al., 2005). Aggressive surgical resection of metastases and the ability to achieve a second surgical remission have consistently been shown essential for long-term survival following relapse (Kempf-Bielack, et al., 2005; Leary, et al., 2013; Bacci, et al., 2005; Chou, et al., 2005; Hawkins and Arndt, 2003).

As per the European Society for Medical Oncology (ESMO) guidelines for bone sarcoma, treatment options for recurrent osteosarcoma include ifosfamide ± etoposide ± carboplatin, and other active drugs (Casali, et al., 2018). Preferred regimens for second-line therapy per the National Comprehensive Cancer Network (NCCN) bone sarcoma guidelines include ifosfamide (high dose) with or without etoposide, regorafenib, sorafenib, and sorafenib plus everolimus (NCCN Bone Cancer Guidelines, 2020).

In the event of subsequent relapse, the NCCN guidelines (NCCN Bone Cancer Guidelines, 2020) and ESMO guidelines (Casali, et al., 2018) strongly encourage participation in clinical studies. Otherwise, patients with disease progression or relapse after second-line therapy are managed with surgical resection, palliative radiotherapy, or best supportive care.

6.3 Lenvatinib

E7080 (lenvatinib) is a potent multiple receptor tyrosine kinase (RTK) inhibitor (RTKI) that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other pro-angiogenic and oncogenic pathway-related RTKs, including fibroblast growth factor (FGF) receptor (FGFR) 1-4, PDGF receptor alpha (PDGFRα), KIT, and RET. Therefore, lenvatinib exerts it's in vivo antitumoural activity based on multiple mechanisms involved in and through effects related to angiogenesis (including reversion of resistance) and the tumor microenvironment, as well as direct inhibitory action on the tumour cells. Recent studies have also demonstrated lenvatinib's immunomodulatory activity in the tumor microenvironment. This includes decreases in immunosuppressive tumor-associated

macrophages, activated cytotoxic T cell increases, and activation of interferon-gamma signaling. These all contribute to lenvatinib's antitumor activity in immunocompetent mice (Kato, et al., 2019; Kimura, et al., 2018).

6.3.1 Clinical Data on Lenvatinib in Combination with Ifosfamide and Etoposide for Treatment of Relapsed or Refractory Osteosarcoma

The safety, tolerability and activity of single-agent lenvatinib, and lenvatinib in combination with chemotherapy (ifosfamide and etoposide), have been assessed in E7080-G000-207 (Study 207), a phase 1/2, multicenter, open-label study in children, adolescents and young adults with solid tumors, including relapsed or refractory osteosarcoma, and radioiodine- refractory differentiated thyroid carcinoma. The recommended phase 2 dose (RP2D) of lenvatinib was determined in the phase 1b portion as 14 mg/m^2 orally once daily when given as single-agent as well as in combination with etoposide (100 mg/m^2 IV once daily for 3 days) + ifosfamide (3000 mg/m^2 IV once daily for 3 days), administered on days 1 to 3 of each 21-day cycle, for 5 cycles. Safety and efficacy is being assessed in the Phase 2 portion of the study.

Data from Study 207 have shown that patients with osteosarcoma may benefit from treatment with lenvatinib. In the single agent expansion cohort in relapsed/refractory osteosarcoma, (n=31; Cohort 2B), 9 of 28 evaluable patients (32.1%) achieved progression-free survival (PFS) at 4 months (PFS-4m), median PFS was 3.0 months (95% CI: 1.8, 5.5). Two out of 29 subjects (6.9%) with measurable disease had a partial response (PR) (Gaspar, et al., 2018).

Among the 31 subjects included in the safety analysis set for the single-agent lenvatinib expansion cohort, the most common adverse events were: headache (48%), vomiting (45%), decreased appetite, diarrhea, and hypothyroidism (42% each), proteinuria (39%), increased blood TSH, hypertension, nausea, pyrexia, and weight decreased (36% each). Five subjects (16.1%) discontinued treatment due to TEAEs, and 8 subjects (25.8%) reported TEAEs leading to study drug dose reduction. There were no treatment-related fatal TEAEs (Gaspar, et al., 2018).

In a pooled analysis of subjects from Phase 1b and 2 receiving lenvatinib 14 mg/m^2 in combination with ifosfamide plus etoposide (N=35; full analysis set), the primary efficacy endpoint, PFS-4 rate based on RECIST 1.1 by investigator assessment, was 67.9% (95% CI: 47.6, 84.1). As of the data cutoff date of 23 Jul 2019, the objective response rate (ORR) was 12.5%, including 4 subjects with PR. Median PFS was 11.1 months (95% CI: 4.5, 12.6), and median overall survival (OS) was 16.3 months (95% CI: 12.6, NE) (Gaspar, et al., 2019).

Overall treatment with lenvatinib in combination with ifosfamide and etoposide in this patient population was associated with a manageable safety profile, and no unexpected toxicities were observed. Among the 31 subjects included in the safety analysis set, the most frequent treatment-emergent adverse events (TEAEs) were anemia (71%), nausea and vomiting (61% each), diarrhea (52%), neutropenia, platelet count decreased, and white blood cell count decreased (48% each). The most common treatment-related grade ≥3 TEAEs were anemia (52%), neutropenia (48%), platelet count decreased and white blood cell count

decreased (42% each), neutrophil count decreased (32%), and thrombocytopenia (29%). Eight subjects (25.8%) discontinued treatment due to TEAEs, and 15 subjects (48.4%) reported TEAEs leading to study drug dose reduction. There were no treatment-related fatal TEAEs (Gaspar, et al., 2019).

6.4 Study Rationale

Study 230, a randomized, controlled Phase 2 study, will evaluate the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide in children, adolescents, and young adults with relapsed or refractory osteosarcoma. Eligible patients aged 2 to 25 years old will receive ifosfamide and etoposide with or without lenvatinib (14 mg/m^2; RP2D from Study 207). Subjects randomized to Arm A can continue to receive lenvatinib until disease progression, intolerable toxicity, or withdrawal of consent. Approximately 72 subjects will be treated in the study. The primary objective of the study is to demonstrate that lenvatinib in combination with ifosfamide and etoposide has superior efficacy compared to ifosfamide and etoposide based on the PFS-4m rate in children, adolescents and young adults with relapsed or refractory osteosarcoma.

Pediatric solid tumors are highly vascularized. Angiogenesis and vasculogenesis are the fundamental processes by which new blood vessels are formed. As with normal tissue, the growing tumor requires an extensive network of capillaries to provide the necessary nutrients and oxygen. Moreover, the new intratumor blood vessels offer a way for tumor cells to enter the circulation and metastasize to distant organs and thus play an indispensable role in solid tumor growth and metastasis. Thus, inhibition of angiogenesis is a viable target for anticancer therapy. Moreover, vascular normalisation allows reoxygenation, hence the addition of an anti-VEGF to chemotherapy may result in increased uptake of drugs into tumor tissue (Tuettenberg, et al., 2006).

7 STUDY OBJECTIVES

7.1 Primary Objective

To evaluate whether lenvatinib in combination with ifosfamide and etoposide (Arm A) is superior to ifosfamide and etoposide (Arm B) in improving PFS-4m rate (by independent imaging review [IIR] using Response Evaluation Criteria In Solid Tumors [RECIST 1.1]), in children, adolescents, and young adults with relapsed or refractory osteosarcoma.

7.2 Secondary Objectives

The secondary objectives of the study are to:

1. Compare differences in PFS rate at 1 year (PFS-1y) between the 2 treatment arms
2. Compare differences in PFS Kaplan-Meier (K-M) survival curves and median PFS between the 2 treatment arms
3. Compare differences in OS and OS rate at 1 year (OS-1y) between the 2 treatment arms

4. Compare differences in objective response rate (ORR) at 4 months between the 2 treatment arms
5. Compare differences in safety and tolerability between the 2 treatment arms
6. Characterize the pharmacokinetics (PK) of lenvatinib, when administered in combination with ifosfamide and etoposide
7. Compare differences in health-related quality of life (HRQoL) as assessed by using the the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales and Cancer Module between the 2 treatment arms
8. Assess the palatability and acceptability of the suspension formulation of lenvatinib in pediatric subjects receiving the suspension formulation in the study

7.3 Exploratory Objective(s)

The exploratory objectives of the study are to:

1. Explore differences in duration of response (DOR), disease control rate (DCR), and clinical benefit rate (CBR) between the 2 treatment arms
2. Compare the proportion of subjects who achieve complete removal of baseline lesion(s) following completion of chemotherapy between the 2 treatment arms
3. Investigate the relationship between subject tumor biomarkers and clinical response and toxicity of lenvatinib in combination with ifosfamide and etoposide

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This is a multicenter, randomized, open-label, parallel-group, Phase 2 study to compare the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide in children, adolescents, and young adults with relapsed or refractory osteosarcoma.

Approximately 72 eligible subjects will be randomized to 1 of the following 2 treatment arms in a 1:1 ratio within the strata:

- Arm A: lenvatinib 14 mg/m^2 (orally, once daily) plus ifosfamide 3000 mg/m^2/day (intravenously [IV], Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)
- Arm B: ifosfamide 3000 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)

Randomization will follow a predefined randomization scheme based on the following stratification factors: time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 and ≥18 years).

Eisai will closely monitor enrolment, to ensure that at least 32 subjects <18 years of age at the time of informed consent are randomized.

The study will be conducted in 3 Phases: a Pre-randomization Phase, a Randomization Phase, and an Extension Phase.

The end of the study will be the date of data cutoff for the final analysis or the time of last subject last visit, whichever occurs later.

An overview of the study design is presented in Figure 1.

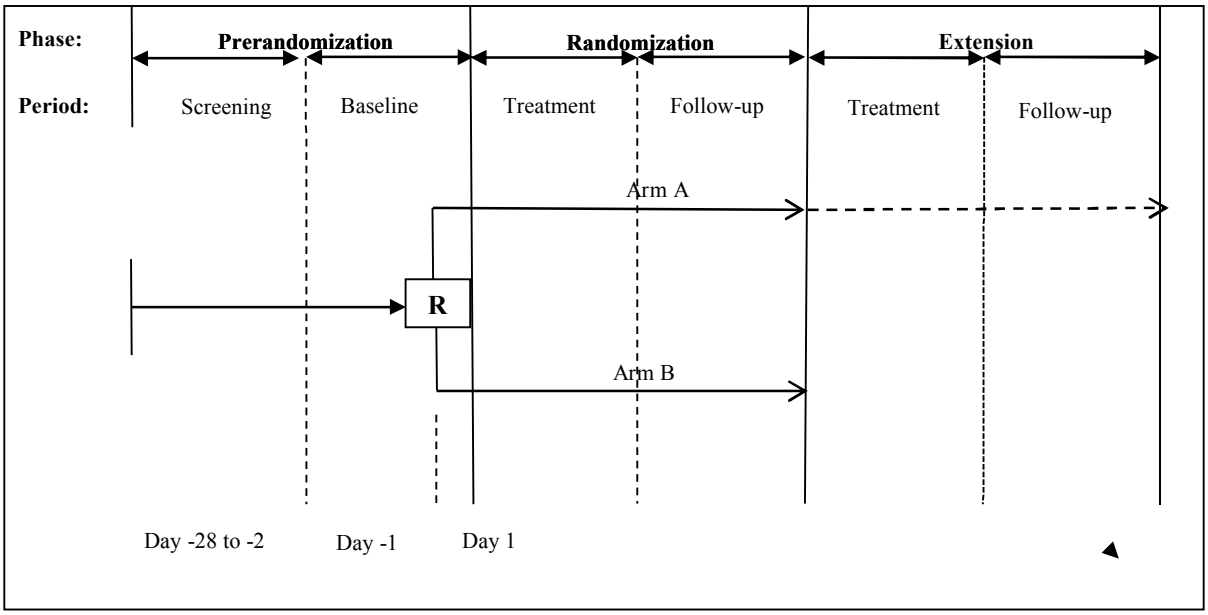

Figure 1 Overall Study Design

Follow-up can occur during the Randomization Phase (if the subject discontinued treatment during the Randomization Phase), or during the Extension Phase, after the termination of study treatment.
Arm A = lenvatinib+ifosfamide+ etoposide (ifosfamide+etoposide for maximum of 5 cycles; lenvatinib to be continued until disease progression, intolerable toxicity, subject request, withdrawal of consent, or study termination by the sponsor, whichever occurs first.
Arm B = ifosfamide+ etoposide (maximum of 5 cycles)
R = randomization

8.1.1 Prerandomization Phase

The Prerandomization Phase will consist of 2 periods: Screening and Baseline. The Prerandomization Phase will last no longer than 28 days. The Screening Period will establish protocol eligibility and the Baseline Period will confirm eligibility.

8.1.1.1 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 4.3.

Subjects must have a histologically or cytologically confirmed diagnosis of high grade refractory or relapsed osteosarcoma as detailed in the Inclusion Criteria (Section 8.3.1).

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

8.1.1.2 Baseline Period

The purpose of the Baseline Period is to confirm protocol eligibility as specified in the inclusion/exclusion criteria (as detailed in Section 8.3.1 and Section 8.3.2). Results of baseline assessments must be obtained prior to the first dose of study drug (Cycle 1 Day 1). Baseline assessments may be performed on Day -1 or on Cycle 1 Day 1 prior to dosing. Clinical laboratory tests (Table 4), including a pregnancy test (where applicable), should be performed within 72 hours prior to the first dose of study drug.

Subjects who complete the Baseline Period and continue to meet the criteria for inclusion/exclusion (as detailed in Section 8.3.1 and Section 8.3.2) will begin the Randomization Phase of this study.

8.1.2 Randomization Phase

The Randomization Phase will consist of 2 periods: Treatment Period and Follow-up Period. The Randomization Phase will begin at the time of randomization of the first subject and will end on the data cutoff date for the PFS-1y and OS-1y analysis. Data cutoff for PFS-1y and OS-1y analysis will occur when the last subject has completed 18 cycles of treatment or discontinues before the end of Cycle 18, whichever occurs first.

After the data cutoff date for the PFS-1y and OS-1y analysis has occurred, all subjects who are still on study treatment will enter the Extension Phase.

8.1.2.1 Treatment Period

The Treatment Period for each subject will begin at the time of randomization and will end at the completion of the Off-Treatment Visit which will occur within 30 days after the final dose of study treatment.

Subjects will receive study treatment as continuous 21-day cycles in both treatment arms. Treatment cycles will be counted continuously regardless of dose interruptions. If chemotherapy administration is precluded on Day 1 of a treatment cycle, the subject may resume treatment once recovered at the discretion of investigator. Subsequent chemotherapy will be administered every 21 (±1) days starting from the timepoint it was resumed. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments (Table 5). Subjects randomized to Arm A will continue to receive lenvatinib until disease progression (PD) confirmed by IIR, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor, whichever occurs first.

Disease progression (PD) must be confirmed by IIR prior to the investigator discontinuing study treatment for a subject. In situations where the investigator judges that alternative treatments must be instituted immediately for a subject's safety, study drugs may be discontinued without waiting for IIR confirmation of radiographic evidence of PD. If possible, before discontinuation of the subject from the study, the investigator should consult with the sponsor.

8.1.2.2 Follow-Up Period

The Follow-up Period begins the day after the Off-Treatment Visit and will continue as long as the subject is alive, unless the subject withdraws consent or the sponsor terminates the study.

Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn, however, an investigator may consult public records to establish survival status if permitted by local regulations.

All adverse events (AEs) will be captured for 30 days after the last dose of study drug.

All subjects who discontinue study treatment early for reasons other than PD, will continue to undergo tumor assessments every 6 weeks until Week 18, then every 9 weeks until Week 54, thereafter, every 12 weeks until IIR confirmation of radiographic evidence of PD as described in the tumor assessments in the assessment schedule, or until another anticancer therapy is initiated.

Subjects in both Arm A and Arm B will be followed for survival every 12 weeks (±1 week) and all subsequent anticancer treatments received will be recorded. Subjects who are being followed for survival at the time of data cutoff for the for PFS-1y and OS-1y analysis (ie, at the end of the Randomization Phase) will continue to be followed for survival during the Follow-up Period of the Extension Phase.

8.1.3 Extension Phase

The Extension Phase will consist of 2 periods: Treatment Period and Follow-up Period.

8.1.3.1 Treatment Period

In the Treatment Period, subjects still on lenvatinib in Arm A following the completion of the PFS-1y and OS-1y analysis (ie, at the end of the Randomization Phase) will continue to receive lenvatinib in 21-day cycles until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor. Tumor assessments will be performed according to the local standard of care. Independent imaging review (IIR) review and confirmation of radiographic evidence of PD will not be required, and scans will no longer be required to sent to the imaging core laboratory (ICL). The Off-Treatment Visit will occur within 30 days after the final dose of study treatment. All AEs will be captured up to 30 days after last dose of study drug. In case the study is

discontinued by the sponsor, the sponsor will continue to provide study drug (outside the study) for subjects requiring continuation of treatment.

8.1.3.2 Follow-Up Period

The Follow-up Period will begin the day after the Off-Treatment Visit and will last until death or for 2 years after end of treatment for a subject, unless the study is terminated by the sponsor, or the subject discontinues due to withdrawal of consent, or is lost to follow-up. Subjects will be treated by the investigator according to the prevailing local standard of care. Subjects will be followed every 12 weeks (±1week) for survival and all subsequent anticancer treatments received will be recorded.

8.2 Discussion of Study Design, Including Choice of Control Groups

The study has been designed as an open-label, randomized study to compare the safety and efficacy of lenvatinib in combination with the ifosfamide and etoposide with ifosfamide and etoposide alone in children, adolescents, and young adults with relapsed or refractory osteosarcoma. Ifosfamide and etoposide will be used as the control group since it is a recognized treatment option for patients with relapsed osteosarcoma.

Progression-free survival (PFS) rate at 4 months (PFS-4m) as compared to control, with blinded IIR of radiological imaging using RECIST 1.1 criteria will be evaluated as the primary endpoint. The endpoint was determined as appropriate for the study, given the unique biology of the osteosarcoma (bone lesions do not shrink) and the vital role of surgical resection of metastatic lesions, where possible, in the management of patients with this tumor. Pulmonary metastases are most common in osteosarcoma, and the ability to achieve a second surgical remission has consistently been shown essential for long-term survival following relapse (Kempf Bielack, et al., 2005; Leary, et al., 2013; Bacci, et al., 2005; Chou, et al., 2005; Hawkins and Arndt, 2003). The protocol allows for surgical resection of baseline lesions after completion of the Week 18 tumor assessment. This timepoint allows for surgical resection after completion of chemotherapy without confounding data due to subjects undergoing surgery. To avoid bias in efficacy assessment, the analysis for primary endpoint is based on tumor assessment by IIR, a central independent blinded assessment. Progression-free survival at 1 year (PFS-1y), PFS, and OS will also be evaluated in the study as secondary endpoints.

Pharmacodynamic serum and tumor biomarkers identified in other lenvatinib clinical studies will be assessed in samples collected from subjects enrolled in this study in the test arm only (Arm A: lenvatinib + ifosfamide + etoposide) and may be used for exploratory analysis for evaluation of response-related and/or safety-related outcomes.

The study will also assess health related quality of life (HRQoL) using validated questionnaires.

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg,

demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups.

8.3 Selection of Study Population

Approximately 72 subjects between 2 and ≤25 years of age will be randomised (36 subjects in each arm). Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

For evaluation of the primary endpoint (intent–to-treat analysis), at least 32 subjects <18 years old (at the time of informed consent) will be randomized.

8.3.1 Inclusion Criteria

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

1. Histologically or cytologically confirmed diagnosis of high grade osteosarcoma.
2. Refractory or relapsed osteosarcoma after 1 to 2 prior systemic treatments.
3. Measurable or evaluable disease per RECIST 1.1 that meets the following criteria:
   - Must be accurately measurable with a minimum size (by long axis) of 10 mm using computed tomography/magnetic resonance imaging (CT/MRI) (lymph nodes must be accurately measurable with a minimum size [by short axis] of 15 mm).
   - Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must have subsequently grown unequivocally to be deemed a target lesion.
4. Aged 2 years to ≤25 years at the time of informed consent.
5. Life expectancy of 12 weeks or more.
6. Lansky play score ≥50% or Karnofsky Performance Status score ≥50%. Use Karnofsky for subjects ≥16 years of age and Lansky for subjects <16 years of age. 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.
7. Adequate bone marrow function as evidenced by:
   a. absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L.

      (subjects with bone marrow involvement should have ANC $\geq 0.8\times10^9$/L and leucocyte count $\geq 1\times10^9$/L).
   b. hemoglobin ≥8.0 g/dL (a hemoglobin of <8.0 g/dL is acceptable if it is corrected by growth factor or transfusion before Cycle 1 Day 1).
   c. platelet count $\geq 100\times10^9$/L.
8. Adequate blood coagulation function defined by International Normalized Ratio (INR) ≤1.5 unless participant is receiving anticoagulant therapy, as long as INR is within therapeutic range of intended use of anticoagulants.
9. Adequate liver function as evidenced by:
   a. Bilirubin ≤1.5 times the upper limit of normal (ULN).

b. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3×ULN (in the case of liver metastases ≤5×ULN).

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

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

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

    b. Urine dipstick <2+ for proteinuria. Subjects who have ≥2+ proteinuria on dipstick urinalysis should undergo a spot protein-creatinine (P/C) ratio test that should be Grade <2 per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and if possible perform a 24-hour urine collection (children and adolescents ≤12 years of age must have ≤500 mg of protein/24 hours and subjects >12 years of age must have ≤1 g of protein/24 hours).
    c. No clinical evidence of nephrotic syndrome.

11. Adequate cardiac function as evidenced by left ventricular ejection fraction (LVEF) ≥50% at baseline as determined by echocardiography.
12. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as:
    a. BP <95th percentile for sex, age, and height/length at screening (as per National Heart Lung and Blood Institute guidelines) and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1. Subjects >18 years of age should have BP ≤150/90 mm Hg at screening and no change in antihypertensive therapy within 1 week prior to Cycle 1 Day 1.
13. Washout before Cycle 1 Day 1 of 3 weeks in case of prior chemotherapy, 6 weeks if treatment included nitrosoureas; 4 weeks for definitive radiotherapy, 2 weeks for palliative radiotherapy; and 3 months from high-dose chemotherapy and stem cell rescue. Subjects must have recovered (to Grade ≤1, except for alopecia, ototoxicity, and Grade ≤2 peripheral neuropathy, per CTCAE v5.0) from the acute toxic effects of all prior anticancer therapy before Cycle 1 Day 1.
14. Written and signed informed consent from the parent(s) or legal guardian and assent from the minor subject. Written informed consent from subjects ≥18 years.

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

8.3.2 Exclusion Criteria

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

1. Any active infection or infectious illness unless fully recovered prior to Cycle 1 Day 1 (ie, no longer requiring systemic treatment).
2. Subjects with central nervous system metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy, surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 2 weeks before Cycle 1 Day 1.
3. Active second malignancy within 2 years prior to enrollment ([in addition to osteosarcoma], but not including definitively treated superficial melanoma, carcinoma-in-situ, basal or squamous cell carcinoma of the skin).
4. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
5. Has had major surgery within 3 weeks prior to Cycle 1 Day 1. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
6. Known hypersensitivity to any component(s) of the study drugs (lenvatinib, ifosfamide, and etoposide, or their ingredients).
7. Currently receiving any investigational drug or device in another clinical study or within 28 days prior to Cycle 1 Day 1.
8. A clinically significant ECG abnormality, including a marked baseline prolonged QT or QTc interval (eg, a repeated demonstration of a QTc interval >480 msec).
9. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that in the opinion of the investigator might affect the absorption of lenvatinib.
10. Pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula.
11. Gastrointestinal bleeding or active hemoptysis (bright red blood of at least ½ teaspoon) within 3 weeks prior to Cycle 1 Day 1.
12. Radiographic evidence of intratumoral cavitation, encasement, or invasion of a major blood vessel. Additionally, the degree of proximity to major blood vessels should be considered for exclusion because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.
13. History of ifosfamide-related Grade ≥3 nephrotoxicity or encephalopathy.
14. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
15. Known to be human immunodeficiency virus (HIV) positive. Note: HIV testing is required at screening only when mandated by local health authority.

16. Active viral hepatitis (B or C) as demonstrated by positive serology. Note: Testing for Hepatitis B or Hepatitis C is required at screening only when mandated by local health authority.
17. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG]) (human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG /hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of any study drug.
18. Females of childbearing potential* who:
    - Do not agree to use a highly effective method of contraception for the entire study period and for 28 days after lenvatinib discontinuation or 12 months after etoposide and ifosfamide discontinuation, ie:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
        - A contraceptive implant
        - an oral contraceptive. Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing with study drug and throughout the study and for 28 days after lenvatinib discontinuation or 12 months after etoposide and ifosfamide discontinuation .

          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, or the subject has changed oral hormonal contraceptive product/dose within 4 weeks prior to study drug administration, 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.

    * All post pubertal females will be considered to be of childbearing potential unless they have early menopause (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).
19. 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 28 days after lenvatinib discontinuation or 6 months after discontinuation of etoposide and ifosfamide). No sperm donation is allowed during the study period and for 28 days after lenvatinib discontinuation or 6 months after discontinuation of etoposide and ifosfamide.

20. A contraindication to any of the study drugs (lenvatinib, ifosfamide, and etoposide) per local prescribing information.

8.3.3 Removal of Subjects From Therapy or Assessment

Subjects will continue to receive study treatment until any of the following occur:

- Progressive disease (as confirmed by IIR)
- Unacceptable toxicity
- Subject request
- Withdrawal of consent
- Termination of the study by the Sponsor

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 protocol-specified off-treatment visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents.

During the Follow-Up Period, subjects who have discontinued study treatment without progression should have disease assessments as per the appropriate tumor assessment schedule in Table 5 and Table 6 from the date of the last assessment until PD is documented or another anticancer therapy is initiated. After data cutoff of PFS-1y and OS-1y, tumor assessments may be performed as clinically indicated per institutional guidelines, following the prevailing local standard of care, and IIR confirmation of radiographic evidence of PD will not be required.

All subjects will be followed for survival until death or for 2 years after end of treatment for a subject, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up after completion of the primary study analysis.

8.4 Treatment(s)

8.4.1 Treatment(s) Administered

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

Test Arm (Arm A): Lenvatinib + Ifosfamide + Etoposide

Lenvatinib 14 mg/m^2, orally administered once daily in each 21-day cycle.

Lenvatinib is provided as hard capsules containing 1 mg, 4 mg, or 10 mg lenvatinib. An extemporaneous suspension of lenvatinib capsules should be used for subjects unable to

swallow capsules. After adjustment for body surface area (BSA), the daily dose can not exceed 24 mg QD.

Ifosfamide 3000 mg/m^2/day, IV, for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Etoposide 100 mg/m^2/day, IV, for 3 consecutive days (Day 1 to 3) , every 21 days, for a maximum of 5 cycles.

Treatment with lenvatinib will continue in 21-day cycles after chemotherapy is discontinued, until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor. In case the study is discontinued by the sponsor, the sponsor will continue to provide study drug (outside the study) for subjects requiring continuation of treatment.

Control Arm (Arm B): Ifosfamide + Etoposide

Ifosfamide 3000 mg/m^2/day, IV, daily for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Etoposide 100 mg/m^2/day, IV, daily for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

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

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

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

Subjects will receive study treatment as continuous 21-day cycles in both treatment arms. Treatment cycles will be counted continuously regardless of dose interruptions. If chemotherapy administration is precluded on Day 1 of a treatment cycle, the subject may resume treatment once recovered at the discretion of investigator. Subsequent chemotherapy will be administered every 21 (±1) days starting from the timepoint it was resumed.

8.4.1.1 Lenvatinib Dose Reduction and Interruption Instructions

Adverse events will be graded using CTCAE version 5.0.

Dose reduction and interruptions for subjects who experience lenvatinib related toxicity will be managed as described in Table 1.

The starting dose of lenvatinib is 14 mg/m^2. Dose reductions occur in succession based on the previous dose level. Each dose level reduction is a 20% reduction from the previous dose.

Once the study drug dose level 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.

Refer to the subsections below for management of hypertension, posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (PRES/RPLS), proteinuria, hepatotoxicity, thromboembolic events, hypocalcemia, gastrointestinal symptoms and acute abdominal pain, and hemorrhage, as appropriate, before consulting the dose modification table below.

Table 1 Criteria for Temporary Discontinuation of Study Drug, Dose Reduction, and Resumption of Treatment

Dose Modification Guidelines for Lenvatinib 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] or Grade 3[e]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	11.2 mg/m^2 (or 20% reduction of the starting dose) orally QD (one-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	9.0 mg/m^2 (or 20% reduction of the previous dose) orally QD (one-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	7.2 mg/m^2 (or 20% reduction of the previous dose) orally QD (one-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with sponsor
Grade 4[f]: Discontinue Study Treatment		

Note: For grading see CTCAE version 5.0. Collect all CTC grades of adverse events, decreasing and increasing grade.

BMI = body mass index, CTCAE = Common Terminology Criteria for Adverse Events

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, hypertension, 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 1 weight 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 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. Obesity is defined as body mass index (BMI) percentiles corresponding to 30 kg/m², related to the age of the children (Cole, et al., 2000) or BMI ≥ the 95th percentile for children and teens of the same age and sex (Ogden, et al., 2002) (Appendix 8 and Appendix 9).

e: 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.

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

8.4.1.1.1 BLOOD PRESSURE

For children, blood pressure varies by the sex and age of the child and it is closely related to height and weight. Blood pressure will be assessed in terms of percentile for sex, age and height/length. Guidelines to sex, age, and height-specific percentiles of blood pressure are provided in Appendix 6 and Appendix 7. Blood pressure that is consistently above the 95th percentile [for subjects age 18 to 25 years BP ≤140/90 mm Hg] for age and height/length

requires further evaluation. A referral to a cardiologist is recommended for patients who develop hypertension during the study. Ideally, cardiovascular assessments and the management of hypertension should be supervised by a cardiologist. Exercise, excitement, coughing, crying, and struggling may raise the systolic pressure of children as much as 40 to 50 mmHg greater than their usual level. Variability in blood pressure in children of approximately the same age and body build should be expected and serial measurements should always be obtained when evaluating a patient with hypertension.

8.4.1.1.2 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 mm Hg] for sex, age, and height/length at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1 Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be conducted as detailed in the Schedule of Procedures/ Assessments (Table 5 and Table 6). Hypertension will be graded using CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

If the subject's initial BP measurement is elevated (systolic BP ≥95th percentile [BP ≥140 mm Hg] or diastolic BP ≥95th percentile [BP ≥90 mm Hg]), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥95th percentile [BP ≥140 mm Hg] or diastolic BP ≥95th percentile [BP ≥90 mm Hg]) is confirmed on 2 assessments obtained 30 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when systolic BP ≥95th percentile [BP ≥140 mm Hg] or diastolic BP ≥95th percentile [BP ≥90 mm Hg] is first observed on 2 assessments obtained 30 minutes apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instances where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥99th percentile [BP ≥160/100 mm Hg], significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant comorbidities). Once the

subject has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

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

The following guidelines should be followed for the management of systolic BP ≥99th percentile (BP ≥160 mm Hg) or diastolic BP ≥99th percentile (BP ≥100 mm Hg) confirmed on repeat measurements after at least 30 minutes:

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

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

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

    - If systolic BP ≥99th percentile (BP ≥160 mm Hg) or diastolic BP ≥99th percentile (BP ≥100 mm Hg) recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP <95th percentile (BP ≤150 mm Hg) and diastolic BP <95th percentile (BP ≤95 mm Hg) and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥99th percentile (BP ≥160 mm Hg) or diastolic BP ≥99th percentile (BP ≥100 mm Hg) recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction only when systolic BP <95th percentile (BP ≤150 mm Hg and diastolic BP <95th percentile (BP ≤95 mm Hg) and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

- Additional dose reduction should be discussed with the Sponsor.

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

- Institute appropriate medical management
- Discontinue lenvatinib

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

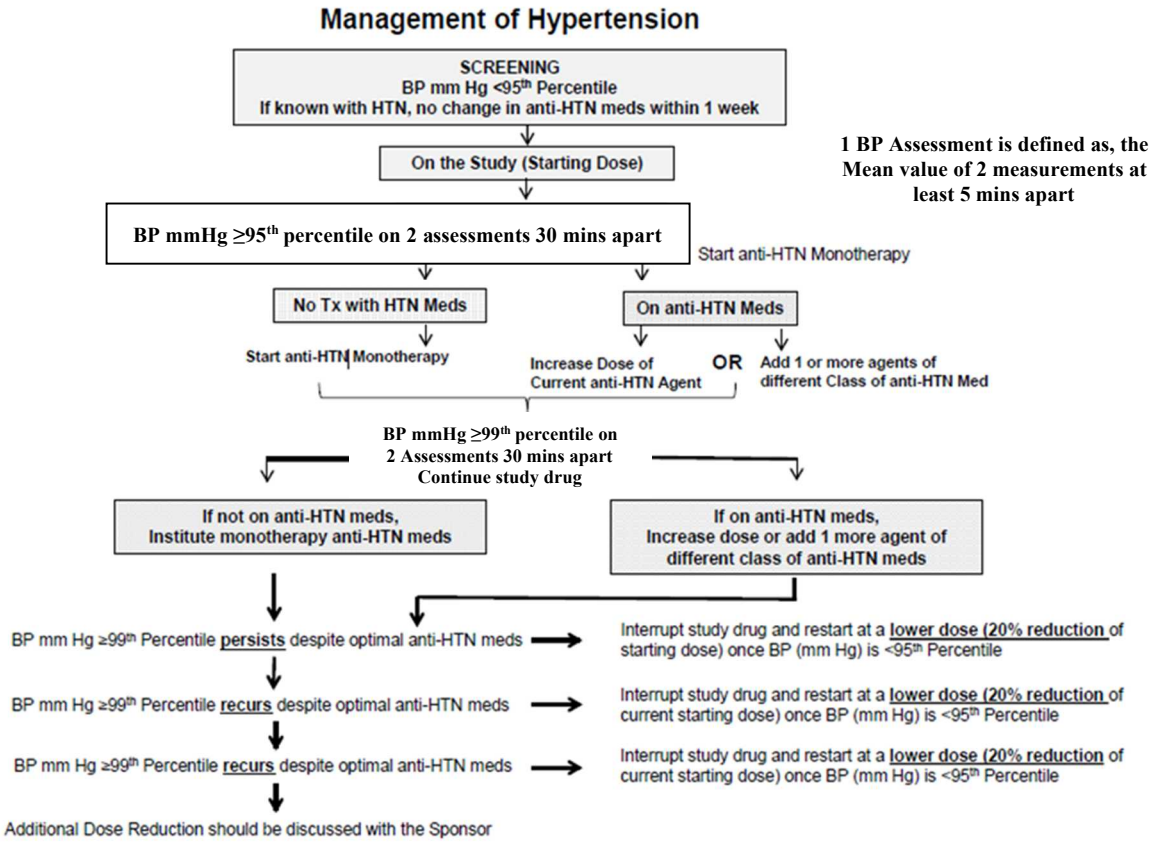

Figure 2 Management of Hypertension

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

8.4.1.1.3 MANAGEMENT OF POSTERIOR REVERSIBLE LEUKOENCEPHALOPATHY SYNDROME/REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME

Posterior Reversible Leukoencephalopathy Syndrome (PRES)/Reversible Posterior Leukoencephalopathy Syndrome (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. An MRI is

necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP (see Section 8.4.1.1.1 and 8.4.1.1.2), and neurologic consultation is advised. In subjects with signs or symptoms of PRES/RPLS, dose modification guidelines as per Table 1 should be followed.

8.4.1.1.4 MANAGEMENT OF PROTEINURIA

Regular assessment for proteinuria should be conducted as detailed in the Schedule of Assessments (Table 5 and Table 6). Guidelines for assessment and management of proteinuria are summarized as follows:

Grading of Proteinuria

- Grading according to CTCAE 5.0 (Cancer Therapy Evaluation Program, 2017) will be based on the protein-creatinine ratio or 24-hour urinary protein result, if available. For subjects ≥18 years of age, if the subject has 4+ proteinuria by dipstick, a 24-hour urinary protein result is required to confirm Grade 3 proteinuria.

Management of Proteinuria

- Management of lenvatinib administration will be based on the grade of proteinuria according to Table 1.
- In the event of nephrotic syndrome, lenvatinib must be discontinued.

Detection and Confirmation

- Perform urine dipstick testing per the Schedule of Assessments (Table 5 and Table 6)
- For subjects ≥18 years of age, a 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot urine protein-to-creatinine ratio [UPCR] test) AND for subjects <18 years of age, an immediate spot UPCR test, and if possible, a 24-hour urine collection (initiated as soon as possible and at least within 72 hours) is required in the following situations:
  - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on lenvatinib
  - A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
  - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+
- For subjects ≥18 years of age, a 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Monitoring

- Urine dipstick testing for subjects with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.

- Proteinuria monitoring can be performed at the local laboratory or investigator site, but must be managed by the site physician.

8.4.1.1.5 MANAGEMENT OF HEPATOTOXICITY

Regular monitoring of liver function tests (ALT, AST, bilirubin levels) should be conducted as detailed in the Schedule of Assessments (Table 5 and Table 6) 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 1). Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study drug must be discontinued.

8.4.1.1.6 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 1). Appropriate supportive care should be provided together with close monitoring. If a subject experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, study drug must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study drug discontinuation.

8.4.1.1.7 MANAGEMENT OF HYPOCALCEMIA

Serum calcium should be monitored monthly per the Schedule of Assessments (Table 5 and Table 6). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

Corrected calcium = ([4 – serum albumin in g/dL] ×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.

8.4.1.1.8 MANAGEMENT OF GASTROINTESTINAL SYMPTOMS AND ACUTE ABDOMINAL PAIN

Initial management of acute abdominal pain in these study subjects should be focused on treating the underlying cause where possible, ensuring appropriate hydration/rehydration, and symptomatic pain improvement consistent with subject's age and in accordance to local and

institutional standards of care. Appropriate supportive care should be provided together with close monitoring.

For adverse events of abdominal pain believed related to lenvatinib or more specific adverse events believed related to lenvatinib that result in the symptom of abdominal pain, follow instructions contained in Table 1 regarding study treatment dose reduction and interruption. For Grade 4 adverse events that result in abdominal pain, study drug 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), dose modification guidelines should be followed as per Table 1. 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.

Lenvatinib should be discontinued in any subject who develops gastrointestinal perforation of any grade or Grade ≥4 fistula.

8.4.1.1.9 MANAGEMENT OF HEMORRHAGE

Dose modification guidelines as per Table 1 for lenvatinib related adverse events should be followed for the management of hemorrhage. Either resume lenvatinib at a reduced dose or discontinue lenvatinib, depending on the severity and persistence of hemorrhage.

8.4.1.2 Management of Ifosfamide-Etoposide Associated Toxicity

Blood counts should be closely monitored during and prior to the next cycle of chemotherapy. Chemotherapy-associated myelosuppression should be managed by granulocyte-colony stimulating factor (G-CSF). It is recommended that pegylated G-CSF or G-CSF be administered at least 24 to 72 hours after completion of ifosfamide-etoposide chemotherapy; use of G-CSF is recommended until white blood cell (WBC) counts are $\geq 1 \times 10^9$/L. Guidelines for dose modification for ifosfamide and etoposide associated toxicities are provided in the Table 2 below.

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

Table 2 Criteria for Dose Modification of Chemotherapy Dose

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

ANC = absolute neutrophil count, RBC = red blood cell, ULN = upper limit normal.

8.4.2 Identity of Investigational Product(s)

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 4 provides instructions for the preparation of the lenvatinib suspension.

8.4.2.1 Chemical Name of E7080

- Test 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

8.4.2.2 Comparator Drug

Cytotoxic Chemotherapy: Ifosfamide and Etoposide

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

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

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

Anti-emetic or any other prophylaxis should be administered in accordance with institutional guidelines.

8.4.2.3 Labeling for Study Drug

Lenvatinib and the combination chemotherapy drugs, ifosfamide and etoposide, where supplied by the sponsor 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.

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

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

8.4.2.4 Storage Conditions

Lenvatinib will be stored in accordance with the labeled storage conditions. The expiry date for lenvatinib will be established based on manufacturing date and is based on formulation testing. The expiry date of of the lenvatinib will either be on the label and in the interactive voice response system (IVRS) system.

Ifosfamide and etoposide will be stored in accordance with the labeled storage conditions. The expiry date of the ifosfamide and etoposide will be the same as the commercial products provided.

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

8.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study. All subjects who provide signed informed consent and/or assent to participate in this study and satisfy all eligibility requirements (see Section 8.3) will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

After the Baseline Period, subjects will be randomized to 1 of the following 2 treatment arms in a 1:1 ratio:

- Arm A: lenvatinib 14 mg/m^2 (orally, once daily) plus ifosfamide 3000 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)
- Arm B: ifosfamide 3000 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)

Randomization will be performed centrally by an IVRS. Randomization will follow a predefined randomization scheme based on the following stratification factors: time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 and ≥18 years). Time to first relapse/refractory disease will be calculated starting from date of initial diagnosis.

8.4.4 Selection of Doses in the Study

The dose of lenvatinib, ifosfamide and etoposide in this study is the RP2D (14 mg/m^2 + ifosfamide 3000 mg/m^2 + etoposide 100 mg/m^2) established in Study 207. The dose of lenvatinib is the same as the RP2D for lenvatinib monotherapy, also established in Study 207.

8.4.5 Selection and Timing of Dose for Each Subject

Lenvatinib capsules are to be taken orally once a day at approximately the same time in the morning without regard to food intake for 21 days from Cycle 1 onward. If a subject misses a dose, it may be taken within the 12 hours following the usual time of the morning dose. If more than 12 hours have elapsed from the time of the usual daily dose, lenvatinib should be taken the next day at the usual time in the morning. In the event a subject vomits after study drug administration, the subject should not take another dose until the next scheduled dose.

Study drugs should be administered at the clinic on PK sampling days. All scheduled visits must be conducted as per protocol, irrespective of treatment interruption.

8.4.6 Blinding

The study will not be blinded.

8.4.7 Prior and Concomitant Therapy

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

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

Aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and low-molecular-weight heparin (LMWH) are permissible but should be used with caution. Granulocyte colony-stimulating factor (g-CSF) or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell (RBC) counts.

8.4.7.1 Drug-Drug Interactions

The weak inhibitory effect on CYP enzymes (in vitro) exhibited by lenvatinib suggests a low risk of lenvatinib interference with the PK of other drugs co-administered in usual clinical practice. There is no clinically meaningful drug-drug interaction (DDI) risk when lenvatinib is co-administered with CYP3A substrates such as midazolam. Simultaneous CYP3A4/P-gp inhibitions by ketoconazole slightly (15% to 19%) increased systemic exposure to lenvatinib after oral administration as measured by AUC and C_{max} in humans. Since no change was observed in half-life, t_{max}, or t_{lag}, the slight increase in systemic exposure is probably related

to a decrease in first pass metabolism. However, since the magnitude of the change is small, coadministration of lenvatinib with CYP3A4/P-gp inhibitors is not of clinical concern. Similarly, PK data did not suggest any major effects of rifampin on the exposure or disposition of lenvatinib. Following administration of a single dose of lenvatinib with a single dose of rifampin, lenvatinib exposure increased about 31%. In contrast, following administration of multiple doses of rifampin, free lenvatinib exposure was reduced about 9% and about 18% for total lenvatinib. These findings suggest that there is no clinically meaningful influence of either P-gp inhibition (single dose of rifampin) or simultaneous P-gp and CYP3A4 induction (multiple doses of rifampin) on lenvatinib PK.

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

8.4.7.2 Prohibited Concomitant Therapies and Drugs

Subjects should not receive other antitumor therapies while on study. If a subject receives additional antitumor therapies other than the study drug(s), such as chemotherapy, targeted therapies, immunotherapy, or antitumor interventions - such as surgery or palliative radiotherapy (other than as described below), this will be judged to represent evidence of disease progression, and the study medication should be discontinued.

For further information on the prohibited concomitant therapies for ifosfamide and etoposide, please refer to the respective prescribing information.

8.4.7.3 Permitted Concomitant Treatment/Procedures

The following concomitant treatments/procedures are allowed:

a. Removal of existing (not new) osteosarcoma lesion (eg, surgical, radiofrequency ablation, cryotherapy, thermoablation, stereotaxic ratiotherapy, etc.) after completion of the Week 18 tumor assessment. Subjects in Arm A in the presence of clinical benefit, may continue treatment with lenvatinib after protocol permissible surgery.

b. Palliative radiotherapy is allowed for ≤2 significantly symptomatic nontarget lesions.

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

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

Any additional procedural or subject specific particularities should be discussed with the investigator and the sponsor.

8.4.8 Treatment Compliance

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

8.4.9 Drug Supplies and Accountability

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

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, or a completed Investigator and Site Information Form
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572 or Investigator and Site Information Form
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

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

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

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to the site but not dispensed to the

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

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Products Regulatory Agency [MHRA]). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator or the designated pharmacist by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

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

8.5 Study Assessments

8.5.1 Assessments

8.5.1.1 Screening/Baseline Assessments

8.5.1.1.1 DEMOGRAPHY

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

8.5.1.1.2 BASELINE ASSESSMENTS

Baseline assessments will be performed at Day -1 or at Cycle 1 Day 1 prior to treatment. Assessments will include confirmation of subject eligibility with the inclusion and exclusion criteria, medical and surgical history, prior medications and procedures, pregnancy test

(serum or urine) within 72 hours of the first dose of study medication), Lansky play score (see Appendix 2) or Karnofsky performance status score (see Appendix 3), tumor-node metastasis (TNM) Staging (at initial diagnosis of the disease), vital signs, clinical chemistry and hematology, urine dipstick testing, height, Tanner's staging (see Appendix 10), proximal tibial growth plates, and pharmacodynamic biomarkers (for Arm A only).

8.5.1.1.3 MEDICAL HISTORY

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 5, and Table 6). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

8.5.1.2 Efficacy Assessments

8.5.1.2.1 TUMOR RESPONSE ASSESSMENTS

Tumor assessment will be performed based on RECIST 1.1 (Appendix 1). Investigator-determined response assessments will be performed at each assessment time point and entered onto the appropriate CRF. Copies of all tumor assessment scans will be sent to an ICL designated by the sponsor for efficacy assessment and for confirmation of PD. Tumor assessments will be carried out following the guidelines provided by the ICL. Subjects must have evaluable disease or measurable disease based on RECIST 1.1.

At Screening

During the Screening Period, tumor assessments of the chest, abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed within 28 days prior to Cycle 1 Day 1. 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.

Brain scans by MRI with and without contrast enhancement or CT with contrast enhancement will be performed at screening as clinically indicated.

Historical scans (within 28 days prior to the Cycle 1 Day 1) may be used to demonstrate eligibility as long as they meet minimum standards as separately defined by the ICL.

During Treatment Phase

CT/MRI scans of, chest, abdomen, pelvis, and other known sites of disease plus any areas of newly suspected disease will be performed using the same methodology as at screening every 6 weeks ±1 week, following the start of treatment on Cycle 1 Day 1 during the chemotherapy treatment period until Week 18. Following completion of the chemotherapy treatment period (ie, after Week 18), the frequency of tumor assessments will be every 9 weeks ±1 week until Week 54 ±1 week. Thereafter, they will be performed every 12 weeks ±2 weeks until documentation of PD. At any point, scans should be performed earlier than the scheduled time point, if clinically indicated.

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

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

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

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

Brain scans by MRI with and without contrast enhancement or CT with contrast enhancement will be performed as clinically indicated. If protocol eligible brain metastases are present at screening, a CT/MRI of the brain must be performed at all tumor assessment time points (eg, every 6, 9, or 12 weeks).

Disease progression per RECIST 1.1 during the randomization phase must be confirmed by IIR prior to the investigator discontinuing study treatment for a subject. In the event that the investigator considers alternative treatments must be instituted immediately for management of urgent medical complications of PD, study drugs may be discontinued without waiting for independent confirmation of radiographic evidence of PD. Subjects who discontinue study treatment without PD will continue to undergo tumor assessments according to the schedule until PD is documented or another anticancer therapy is initiated. If possible, before discontinuation of the subject from the study, the investigator should consult with the sponsor.

During Post-treatment Follow-up

Subjects who discontinue treatment without PD will have tumor assessments performed as per the appropriate tumor assessment schedule) or sooner if clinically indicated, for documented PD or until another anticancer therapy is initiated, whichever occurs first.

After data cutoff for PFS-1y and OS-1y analysis, tumor assessments may be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care. All subjects will be followed for survival for 2 years after end of treatment or until death, unless the study is terminated by the sponsor, or the subject discontinues due to withdrawal of consent, or is lost to follow-up.

8.5.1.2.2 Palatability and Acceptability of Lenvatinib Suspension Formulation

The palatability and acceptability of lenvatinib suspension formulation will be assessed using the Palatability Questionnaire (see Appendix 5). All subjects who receive suspension formulation with the exception of subjects using a nasogastric or gastrostomy tube, must complete the questionnaire according to the Schedule of Assessments. If the subject is unable to complete the questionnaire, this must be done by a parent or legal guardian. Measurement of palatability will be assessed using the Hedonic scale (Guinard, 2001) which is a Visual Analog Scale (VAS).

8.5.1.3 Pharmacokinetic, Pharmacodynamic, and Other Biomarker Assessments

8.5.1.3.1 Pharmacokinetic Assessments

Blood samples (2 mL each) will be collected from all subjects from Arm A only at the time points shown in Table 3. Pharmacokinetic blood samples will also be drawn pretreatment on the day of tumor assessment as described in the Table 3. Actual time and date of PK blood collection as well as time of drug administration will be recorded on the appropriate page of the CRF. Exposure parameters such as area under the concentration × time curve (AUC) will be derived from posterior estimates of the PK parameters from the final population PK

model. For the time points shown in Table 3, subjects or their parents will be instructed not to take the dose of lenvatinib prior to arriving at the study site. Lenvatinib capsule administration will be recorded in the eCRF. The Cycle 1 Day 1 and Day 15 doses of lenvatinib will be administered at the study site at approximately the same time of day in order to accommodate PK sample collection timing. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in a separate Laboratory Manual.

Table 3 Lenvatinib Pharmacokinetic Sampling Time Points

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

Note: All predose samples are to be drawn approximately 24 hours following the dose administered on the previous day.
h = hour(s).
a. If dose interruption is necessary in these time points, please contact the sponsor.

Only samples from all subjects randomized to Arm A will be collected. Lenvatinib will be quantified using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method.

8.5.1.3.2 Pharmacodynamic and Other Biomarker Assessments

Pharmacodynamic serum and archived fixed tumor tissue samples for biomarker analysis will be collected from study subjects randomized to Arm A (ie, lenvatinib + ifosfamide + etoposide), as specified in the Schedule of Procedures/Assessments. Pharmacodynamic serum and tumor biomarkers identified in other lenvatinib clinical studies will be assessed in samples collected from subjects enrolled in this study. Pharmacodynamic biomarker analysis will be performed as described in an analysis plan provided separately.

Blood biomarker samples may be used for exploratory analysis for evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development (see Appendix 11).

8.5.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all grades per National Cancer Institute (NCI) CTCAE v5.0 (for both increasing and decreasing severity), and serious adverse events (SAEs); regular laboratory evaluation of hematology, blood chemistry, and urine values; periodic measurement of vital signs and 12-lead ECGs; and echocardiograms, Lansky play score or Karnofsky performance status score, physical examinations, and height assessments as detailed in the Schedule of Assessments (Table 5 and Table 6).

Clinical and laboratory toxicities/symptomatology will be graded according to CTCAE v5.0 (Cancer Therapy Evaluation Program, 2017).

8.5.1.4.1 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 drug is lenvatinib.

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 PD.
- 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, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit and for 30 days after the subject's last dose. Refer to Section 8.5.4.1 for the time period after the end of treatment for SAE collection.

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 (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed for 30 days after the subject's last study drug dose, or until resolution, whichever comes first. Subjects with onset of an AE or deterioration of a preexisting AE during the AE collection period will be followed until resolution to baseline, start of a new anticancer treatment, or death. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

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

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v5.0 (Cancer Therapy Evaluation Program, 2017). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

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.

8.5.1.4.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

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

- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events 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

8.5.1.4.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 5 and Table 6) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 4 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Bicarbonate, chloride, potassium, sodium, calcium, magnesium, phosphorus
Liver function tests	ALT, alkaline phosphatase, AST, conjugated (direct) bilirubin[a], total bilirubin, INR[b]
Renal function tests	BUN or urea, creatinine
Other chemistries	Albumin, amylase, glucose, LDH, lipase, total protein
Thyroid function tests[c]	Thyroid stimulating hormone, free T4 level
Urinalysis for microscopy[d]	RBCs
Urine dipstick testing[d,e]	Blood, protein, glucose
Other	Pregnancy test (serum or urine β–hCG)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, β hCG = beta-human chorionic gonadotropin, INR = International Normalized ratio, LDH = lactate dehydrogenase, RBC = red blood cells, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cells.

a. Direct bilirubin should be assessed if total bilirubin is elevated.
b. INR should only be performed as part of the screening assessment. During the study, INR should be performed if clinically indicated.
c. Thyroid function will be assessed every 2 cycles for all subjects.
d. 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
e. 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 at qualified local laboratories. All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and sent to the local laboratory on the day of collection unless otherwise instructed.

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

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 8.5.1.4.1 and the CRF Completion Guidelines. In these instances, the

AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF (see Section 8.5.4.3.2).

8.5.1.4.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute]), body temperature (in centigrade), weight (kg), and height (cm) will be obtained at the visits designated in the Schedule of Assessments (Table 5 and Table 6) by a validated method. Blood pressure and pulse will be measured after the subject has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person. On Cycle 1 Day 8, subjects will be contacted by telephone to assess for the development of early toxicity. Subjects will be provided with a BP cuff to monitor BP at home or can have the measurement done by a local healthcare provider, and will report the C1D8 measurement at telephone contact. An unscheduled visit can occur prior to C1D15 if deemed necessary by the investigator.

Only 1 BP measurement is needed for subjects with systolic BP <95th percentile (BP <140 mm Hg) and diastolic BP <95th percentile (BP <90 mmHg). If the subject's initial BP measurement is elevated (systolic BP ≥95th percentile [≥140 mmHg] or diastolic BP ≥95th percentile [≥90 mmHg]), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥95th percentile [≥140 mm Hg] or diastolic BP ≥95th percentile [≥90 mm Hg]), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

8.5.1.4.5 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 5 and Table 6). 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.

8.5.1.4.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Assessments (Table 5 and Table 6). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3×4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. If possible, subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 8.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Serious Adverse Events and Other Events of Interest), the study site must fax the SAE report including the ECG report to the number indicated in the Investigator File using the SAE reporting form (see Section 8.5.4.1).

8.5.1.4.7 OTHER SAFETY ASSESSMENTS

Pregnancy Test

A serum β-hCG test will be performed for females of childbearing potential (see definition included in the Inclusion/Exclusion criteria, Sections 8.3.1 and 8.3.2). A serum or urine pregnancy test will be performed at Screening, Baseline (or within 72 hours prior to the first dose of study medication), on Day 1 of each cycle from Cycle 2 onwards, and at the Off-treatment Visit in women of childbearing potential. Blood and urine samples will be taken at designated time points as specified in the Schedule of Assessments (Table 5 and Table 6).

Echocardiogram

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

8.5.1.5 Other Assessments

Health-related quality of life (HRQoL) assessment will be performed per the Schedule of Assessments (Table 5 and Table 6). Impact of treatment on HRQoL will be assessed using the PedsQL (including the Generic Core Scales and Cancer Module). Data will be collected as parent-report for toddlers (2 to 4 years) and as self-report for subjects aged ≥5 years. Self-report is the preferred data collection for all subjects aged ≥5, however to improve adherence of participation, it is also acceptable to collect the data as proxy report by observers including parents and caregivers.

The PedsQL is a modular instrument designed to measure HRQoL in pediatric and adults population. The PedsQL 4.0 Generic Core Scales are multidimensional child self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL disease specific modules. The PedsQL 3.0 Cancer Module was designed to measure pediatric cancer specific HRQOL.

It is best practice and strongly recommended that the PedsQL measurement modules are administered to randomized subjects prior to drug administration or any other interaction with site staff.

8.5.2 Schedule of Procedures/Assessments

8.5.2.1 Schedule of Procedures/Assessments

Table 5 presents the schedule of procedures/assessments for the Randomization Phase of the study.

Table 6 presents the schedule of procedures/assessments for the Extension Phase of the study.

Table 5 Schedule of Assessments in Study E7080-G000-230 – Randomization Phase

Phase	**Prerandomization**		**Randomization [a] (All cycles are 21 days in duration)**																	
Period	**Screening[b]**	**Baseline[c]**	**Treatment[d]**																**Off-Tx**	**Follow-up[e]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18+**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6-X**		
Day	**-28 to -2**	**-1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Procedures/Assessments																				
Informed consent	X																			
Inclusion/exclusion	X	X																		
Randomization (IVRS)			X																	
Demographic data	X																			
Medical/surgical history	X	X																		
Prior medication/ procedures	X	X																		
Pregnancy test[f]	X	X				X			X			X			X			X	X	
Lansky play score/ Karnofsky PS[g]	X	X	X			X			X			X			X			X		
TNM Staging	X																			
Physical examination[h]	X	X	X		X	X		X	X			X			X			X	X	
Vital signs[i]	X	X	X	X[j]	X	X		X	X			X			X			X	X	
12-lead ECG[k]	X		X			X												X	X	
Echocardiogram[l]	X	Performed every 16±2 weeks following the first dose of study drug or sooner, if clinically indicated																	X	
Clinical chemistry and hematology[m]	X	X			X	X		X	X			X			X			X	X	
Urine dipstick testing[n]	X	X			X	X		X	X			X			X			X	X	
PK blood samples[o]			X		X	X														
Study treatment[p]			Arm A: Combination of lenvatinib (QD) + ifosfamide + etoposide (Days 1-3 of Cycles 1-5 only) [based on BSA calculations at Day 1 of each Cycle]; after Cycle 5 subjects will receive lenvatinib alone. Arm B: Ifosfamide + etoposide (Days 1-3 of Cycles 1-5 only) [based on BSA calculations at Day 1 of each Cycle]																	

Table 5 Schedule of Assessments in Study E7080-G000-230 – Randomization Phase

Phase	**Prerandomization**		**Randomization [a] (All cycles are 21 days in duration)**																	
Period	**Screening[b]**	**Baseline[c]**	**Treatment[d]**																**Off-Tx**	**Follow-up[e]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18+**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6-X**		
Day	**-28 to -2**	**-1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Procedures/Assessments																				
Palatability Questionnaire[q]			X																	
Tumor assessments: CT/MRI[r]	X		CT chest and CT/MRI of other areas of known disease at Screening plus any areas of newly suspected disease should be performed every 6±1 week or sooner if clinically indicated until Week 18±1 week, then every 9±1 weeks until Week 54±1 week. Thereafter, to be performed every 12±2 weeks until documentation of PD.																X	
Brain CT/MRI[s]	X		Brain scans will be performed at screening as clinically indicated, and thereafter during treatment if clinically indicated. For subjects with protocol-eligible, treated brain metastases at Screening, brain scans should be performed at all tumor assessment time points.																	
Height[t]		X	X									X						X	X	X
Tanner Stage[u]		X																	X	X
Proximal Tibial growth plates x-ray[t]		X																	X	
HRQoL		X	HRQoL will be collected on C2D1, C3D1, Week 18, C8D1, and C18D1																X	
Pharmacodynamic biomarkers[v]		X			X	X						X						X		
Archival tumor block or slides[w]		X																		X
Survival[x]				X																X
Concomitant medications[y]	Throughout																			X
AEs/SAEs[z]	Throughout																			X

AE = adverse event, BP = blood pressure, C1D1 = Cycle 1 Day 1, C1D2 = Cycle 1 Day 2, C1D8 = Cycle 1/Day 8, C1D15 = Cycle 1 Day 15, CR = complete response, CT = computerized tomography, h = hour, HR = heart rate, HRQoL = Health-Related Quality of Life, IV = intravenous, IVRS = Interactive Voice Response System, MRI = magnetic resonance imaging, PD = progressive disease/disease progression, PK = pharmacokinetics, PR = partial response, PS =

Table 5 Schedule of Assessments in Study E7080-G000-230 – Randomization Phase

Phase	Prerandomization		Randomization [a] (All cycles are 21 days in duration)																	
Period	Screening[b]	Baseline[c]	Treatment[d]																Off-Tx	Follow-up[e]
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+		
Cycle			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6-X		
Day	-28 to -2	-1	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1		
Procedures/Assessments																				

performance score, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1, RR = respiratory rate, SAE = serious adverse event, TNM = tumor-node-metastasis, Tx = treatment.

a. During Cycle 1, efforts should be made to conduct study visits on the day scheduled (±1 day); from Cycle 2 onwards, efforts should be made to conduct study visits on the day scheduled (±3 days).
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. For subjects randomized to Arm A, subjects benefiting from study treatment in the opinion of the investigator will continue lenvatinib treatment until PD, intolerable toxicity, noncompliance with safety or efficacy assessments, voluntary discontinuation by the subject at any time, or study termination by the sponsor, whichever occurs first.
e. Subjects will be followed every 12 weeks until documentation of PD or until death as per the protocol.
f. A serum or urine pregnancy test will be performed at the Screening and Baseline Visits (or within 72 hours prior to the first dose of study medication), on Day 1 of each cycle from Cycle 2 onwards, if pregnancy is suspected, and at the Off-treatment Visit in women of childbearing potential.
g. A Lansky play score or Karnofsky performance status score will be obtained at the Screening, Baseline, and C1D1 Visit, and Day 1 of every subsequent cycle visit thereafter.
h. A comprehensive physical examination (including a neurological examination) will be performed at the Screening and Baseline Visits (only if screening physical examination was performed >7 days prior to C1D1), C1D15, C2D1, C2D15, and Day 1 visit of each subsequent cycle, and at the Off-treatment Visit. A symptom-directed physical examination will be performed on C1D1 and at any time during the study, as clinically indicated.
i. Assessments will include vital signs (resting BP, HR, RR, and body temperature) and weight. Blood pressure that is consistently above the 95th percentile for sex, age, and height/length requires further evaluation. Refer to hypertension management guidelines in Section 8.4.1.1.2.
j. On Cycle 1 Day 8, subjects will be contacted by telephone to assess for the development of early toxicity. Subjects will be provided with a BP cuff to monitor BP at home or can have the measurement done by a local healthcare provider, and will report the C1D8 measurement at telephone contact. An unscheduled visit can occur prior to C1D15 if deemed necessary by the investigator.
k. Single 12-lead ECG. If possible, subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. ECG should be conducted at

Table 5 Schedule of Assessments in Study E7080-G000-230 – Randomization Phase

Phase	Prerandomization		Randomization [a] (All cycles are 21 days in duration)																	
Period	Screening[b]	Baseline[c]	Treatment[d]																Off-Tx	Follow-up[e]
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+		
Cycle			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6-X		
Day	-28 to -2	-1	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1		
Procedures/Assessments																				

Screening, C1D1, C2D1, D1 of every 4th cycle (ie, C6, C10, C14, etc.). ECG at C1D1 and C2D1 should be conducted approximately 2 hours after lenvatinib dose. For high risk subjects (as defined in lenvatinib product label), conduct ECG monitoring in every cycle.

l. An echocardiogram is performed during screening, every 16±2 weeks, and at the Off-Treatment visit, or sooner if clinically indicated.

m. Clinical chemistry and hematology results must be reviewed by the investigator prior to administration of study drug on C1D1 and within 48 hours after administering any 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). TSH should be assessed for all subjects.

n. Urine dipstick testing should be performed at Screening, Baseline, C1D15, C2D1, C2D15, and Day 1 of every subsequent cycle, or more frequently as clinically indicated, and at the Off-treatment Visit. For subjects with a history of proteinuria ≥2+, urine dipstick testing should be performed until the results have been 1+ or negative for 2 treatment cycles. If a new event of proteinuria ≥2+ occurs, refer to Section 8.4.1.1.4 for further management guidelines. Urine glucose should be performed as part of the urine dipstick.

o. Sampling (one 2 mL sample per time point) for PK analysis of lenvatinib will be performed (in subjects in Arm A only) on Cycle 1 Day 1 at 0.5 to 4 hours and 6 to 10 hours postdose, on Cycle 1 Day 15 at predose, 0.5 to 4 hours and 6 to 10 hours postdose, and on Cycle 2 Day 1 at predose. All predose samples are to be drawn approximately 24 hours following the dose administered on the previous day. If dose interruption is necessary at these time points, please contact the sponsor.

p. Subjects randomized to Arm A will continue to receive lenvatinib only after completion of 5 cycles with lenvatinib+ifosfamide+etoposide until progressive disease, unacceptable toxicity, subject request, study termination by the sponsor, subject noncompliance with safety or efficacy assessments, or withdrawal of consent. Subjects randomized to Arm B will be off-treatment after 5 cycles of ifosfamide+etoposide.

q. All subjects who receive suspension formulation, with the exception of subjects using a nasogastric or gastrostomy tube, must complete the Palatability Questionnaire according to the Schedule of Assessments. If the subject is unable to complete the questionnaire this must be done by their parents or their legal guardian.

r. **Screening**: Tumor assessments of the chest, abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1. Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans should be performed with IV gadolinium chelate.

Table 5 Schedule of Assessments in Study E7080-G000-230 – Randomization Phase

Phase	Prerandomization		Randomization [a] (All cycles are 21 days in duration)																	
Period	Screening[b]	Baseline[c]	Treatment[d]																Off-Tx	Follow-up[e]
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+		
Cycle			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6-X		
Day	-28 to -2	-1	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1		
Procedures/Assessments																				

Treatment Phase: Tumor assessments of the chest, and other areas of known disease at Screening or newly suspected disease should be performed every 6±1 weeks from C1D1 until Week 18±1 week, then every 9±1 weeks until Week 54±1 week, and thereafter, every 12±2 weeks until documentation of PD during the Treatment Phase (or sooner if there is evidence of progressive disease) and should utilize the same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as was used for the screening assessments. Tumor response will be assessed according to RECIST 1.1. Subjects who discontinue must complete the off-treatment tumor assessment. Any CR or PR must be confirmed not less than 4 weeks following the initial achievement of the response. After treatment discontinuation, tumor assessment should continue to be performed according to the schedule: every 6±1 weeks until Week 18±1 week, then every 9±1 weeks until Week 54±1 week, thereafter, to be performed every 12±2 weeks until documentation of progression or start of a new anticancer agent.

s. Brain CT with contrast or MRI pre- and post- gadolinium contrast will be performed at the Screening Visit as clinically indicated, and thereafter during treatment as clinically indicated. For subjects with protocol-eligible treated brain metastases, brain CT/MRI will be performed at all tumor assessment time points.

t. Height will be assessed at the Baseline Visit, Day 1 of every 4 cycles during the Treatment Phase, at the Off-treatment Visit and every 3 months during the Post-treatment Follow-up. Proximal tibial growth plates x-rays should be conducted at baseline and at the Off-treatment Visit. If the growth plates are closed at baseline then the subject does not need a reassessment at the Off-treatment Visit. Tibial growth plate x-rays will be optional for Germany.

u. Tanner Stage will be assessed at the Baseline Visit, at the Off-treatment Visit, and annually thereafter during the Post-treatment Follow-up.

v. Blood samples will be collected only from subjects in Arm A at the Baseline Visit, C1D15, Day 1 of Cycles 2, 4, and 6, for assessment for blood serum sample to measure factors implicated in angiogenesis.

w. An archival tumor sample from the most recent surgery or biopsy for identification of predictive biomarkers and pathology review may be collected from subjects in Arm A at any time during the study, unless no such material is available.

x. Survival data will be collected every 3 months until death as per the protocol. All anticancer therapies will be collected.

y. Concomitant medications will be recorded throughout the study and for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of Survival Follow-up.

z. AEs will be recorded from the date of signed informed consent, throughout the study, and for 30 days after last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 hours.

Table 6 presents the Schedule of Procedures/Assessments for the Extension Phase of the study.

Table 6 Schedule of Assessments in Study E7080-G000-230 – Extension Phase

Phase	**Extension[a]**		
Period	**Treatment Period [a]**		**Follow-up Period**
Visit	**98**	**99**	
Cycle	**Cycle X +1 and beyond**	**Off-Tx Visit**	
Day	**1**		
Procedures/Assessments			
Pregnancy test[b]	X	X	
Lansky play score/ Karnofsky PS[c]	X	X	
Physical examination[d]	X	X	
Vital signs[e]	X	X	
12-lead ECG[f]	As clinically indicated		
Echocardiogram[g]	As clinically indicated		
Clinical chemistry and hematology[h]	X	X	
Urine dipstick testing[i]	X	X	
Study treatment[j]	Arm A: Lenvatinib[a]		
Tumor assessments: CT/MRI[k]	After data cutoff, tumor assessments may be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care.		
Brain CT/MRI[l]	After data cutoff, tumor assessments may be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care.		
Height[m]	To be checked every 4 cycles	X	X
Tanner Stage[n]		X	X
Proximal Tibial growth plates x-ray[o]		X	
Survival[p]	X		X
Concomitant medications[q]	Throughout		X
AEs/SAEs[r]	Throughout		X

AE = adverse event, CT = computerized tomography, ICL = imaging core laboratory, MRI = magnetic resonance imaging, PD = disease progression, PS = performance status, SAE = serious adverse event.

a. Subjects benefiting from study treatment in the opinion of the investigator will continue treatment until PD, intolerable toxicity, subject request, subject noncompliance with safety or efficacy assessments, voluntary discontinuation by the subject at any time, or study termination by the sponsor, whichever occurs first.

Table 6 Schedule of Assessments in Study E7080-G000-230 – Extension Phase

Phase	Extension[a]		
Period	Treatment Period [a]		Follow-up Period
Visit	98	99	
Cycle	Cycle X +1 and beyond	Off-Tx Visit	
Day	1		

b. A serum or urine pregnancy test will be performed on Day 1 of each cycle and at the Off-treatment Visit in women of childbearing potential.
c. A Lansky play score or Karnofsky performance status score will be obtained at Day 1 of every cycle visit.
d. A physical examination will be performed at Day 1 visit of each cycle, and at the Off-treatment Visit. A symptom-directed physical examination will be performed at any time as clinically indicated.
e. Assessments will include vital signs (resting BP, HR, RR, and body temperature), and weight. Blood pressure that is consistently above the 95th percentile for sex, age, and height/length requires further evaluation. Refer to hypertension management guidelines in Section 8.4.1.1.2.
f. Single 12-lead ECG. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.
g. An echocardiogram is performed as clinically indicated.
h. Clinical chemistry and hematology results must be reviewed within 48 hours after administering any 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). TSH should be assessed for all subjects.
i. Urine dipstick testing should be performed on Day 1 of every cycle, or more frequently as clinically indicated, and at the Off-treatment Visit. For subjects with a history of proteinuria ≥2+, urine dipstick testing should be performed until the results have been 1+ or negative for 2 consecutive cycles. If a new event of proteinuria ≥2+ occurs, refer to Section 8.4.1.1.4 for further management guidelines. Urine glucose should be performed as part of the urine dipstick.
j. Subjects randomized to Arm A will continue to receive lenvatinib only until progressive disease, unacceptable toxicity, or withdrawal of consent.
k. After data cutoff, tumor assessments may be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care. The scans will no longer be required to be sent to the ICL.
l. Brain CT with contrast or MRI pre- and post- gadolinium contrast will be performed as per the institutional guidelines, following the prevailing local standard of care.
m. Height will be assessed at the Baseline Visit, Day 1 of every 4 cycles during the Treatment Phase, at the Off-treatment Visit and every 3 months during the Post-treatment Follow-up.
n. Tanner Stage will be assessed at the Baseline Visit, at the Off-treatment Visit, and annually thereafter during the Post-treatment Follow-up.
o. Proximal tibial growth plates x-rays should be conducted at baseline and at the Off-treatment Visit. If the growth plates are closed at baseline then the subject does not need a reassessment at the Off-treatment Visit. Tibial growth plate x-rays will be optional for Germany.
p. Survival data will be collected every 3 months until death as per the protocol. All anticancer therapies will be collected.
q. Concomitant medications will be recorded throughout the study and for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of Survival Follow-up.
r. AEs will be recorded from the date of signed informed consent, throughout the study, and for 30 days after last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 hours.

8.5.2.2 Description of Procedures/Assessments Schedule

Refer to Table 5 for schedule and description of procedures in the Randomization Phase and Table 6 for the Extension Phase.

8.5.3 Appropriateness of Measurements

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

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

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

8.5.4.1 Reporting of Serious Adverse Events

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

Serious adverse events, regardless of causality assessment, must be collected for 30 days after the subject's last dose. 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 relevant follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the relevant 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 and/or the designated CRO monitor to be filed in the sponsor's Trial Master File.

8.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

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

If an adverse outcome of a pregnancy is suspected to be related to study drug 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, a spontaneous abortion or an induced abortion done due to safety concerns for either mother or fetus 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 8.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the 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 24 hours from the date the investigator becomes aware of the outcome.

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

8.5.4.3 Reporting of Events Associated with Special Situations

8.5.4.3.1 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 8.5.4.1) even if the AEs do not meet serious criteria. Abuse and Intentional Overdose, even if asymptomatic, are 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.

8.5.4.3.2 Reporting of Abnormal Hepatic Tests of Clinical Interest

The following combination of abnormal laboratory tests*, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing and whether nonserious or serious, should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 8.5.4.1). If the event does not meet serious criteria, the seriousness criteria on the SAE form should be indicated as "nonserious."

- Elevated AST or ALT lab value that is greater than or equal to 3× the upper limit of normal

  AND

- Elevated total bilirubin lab value that is greater than or equal to 2× the upper limit of normal

  AND AT THE SAME TIME

- Alkaline phosphatase lab value that is less than 2× the upper limit of normal

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology. In addition to reporting the abnormal hepatic laboratory tests on a SAE form, the site should also consult the medical monitor for guidance on assessment and follow-up. At a minimum, laboratory testing should be repeated at least once weekly until improvement or identification of a cause unrelated to study drug use that is unlikely to improve.

8.5.4.4 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.

8.5.4.5 Breaking the Blind

Not applicable

8.5.4.6 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 SUSARs will be reported, as required, to the competent authorities of all involved European member states.

8.5.5 Completion/Discontinuation of Subjects

A subject (or subject's parent or guardian) may elect to discontinue study drug at any time for safety, medical, or personal reasons. Subjects who choose to discontinue study drug prior to PD will be followed in the post-study treatment follow-up period and continue to undergo regularly scheduled disease assessment until documentation of PD or start of an alternative anticancer treatment. All subjects who discontinue study drug will be followed for OS and all post progression cancer treatments administered will be recorded. Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Assessments (Table 5 and Table 6).

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

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, progression of disease, withdrawal of consent, pregnancy, study terminated by sponsor, or administrative/other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

8.5.6 Abuse or Diversion of Study Drug

Not applicable.

8.5.7 Confirmation of Medical Care by Another Physician

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

8.6 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.

8.6.1 Data Collection

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

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

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

8.6.2 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.

8.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed, the database is locked and released, a snapshot of the database is obtained and released, and randomization codes have been released and applied. 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).

8.7.1 Statistical and Analytical Plans

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

8.7.1.1 Study Endpoints

8.7.1.1.1 PRIMARY ENDPOINT

- Progression-free survival rate at 4 months (PFS-4m rate) by IIR is defined as the percentage of subjects who are alive and without PD at 4 months from the randomization date as determined by IIR of radiological imaging using RECIST 1.1. The PFS-4m rate is estimated on the full analysis set for this study using the K-M method.

8.7.1.1.2 SECONDARY ENDPOINTS

- Progression-free survival rate at 1 year (PFS-1y rate) by IIR is defined as the percentage of subjects who are alive and without PD at 1 year from the randomization date as determined by IIR of radiological imaging using RECIST 1.1. The PFS-1y rate is estimated on the full analysis set for this study using the K-M method.
- Progression-free survival (PFS) by IIR is defined as the time from the date of randomization to the date of the first documentation of PD or death (whichever occurs first) as determined by IIR using RECIST 1.1.
- Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cutoff will be censored at the date the subject was last known alive, or date of data cutoff, whichever occurs first. Overall survival rate at 1 year will be estimated.
- Objective response rate (ORR) by IIR at 4 months is defined as the proportion of subjects who have best overall response of complete response (CR) or partial response (PR) as determined by IIR using RECIST 1.1 within the first 4 months.
- Safety will be assessed summarising the incidence of TEAEs and SAEs together with all other safety parameters.
- Assessment of population-based PK parameters of lenvatinib.
- Score changes from baseline for all PedsQL scales including Generic Core Scales and Cancer Module. Scores will be calculated for total generic score, total cancer score, each physical function subscale including physical health, psychosocial health, emotional function, social function, school/work function in the Generic Core Scales, and each subscales in the cancer module.
- Palatibility and acceptability of the suspension formulation of lenvatinib in subjects receiving the suspension formulation in the study will be assessed using the Palatability Questionnaire (see Appendix 5).

8.7.1.1.3 EXPLORATORY ENDPOINTS

- Duration of response (DOR) by IIR is defined as the time from the date a response was first documented until the date of the first documentation of PD or date of death from any case.
- Disease control rate (DCR) by IIR is the proportion of subjects who have a best overall response of CR or PR or stable disease (SD). In this context, stable disease is defined as stable disease at ≥7 weeks after randomization to be considered best overall response.
- Clinical benefit rate (CBR) by IIR is the proportion of subjects who have best overall response of CR or PR or durable SD (duration of SD ≥23 weeks after randomization).
- Proportion of subjects who achieve complete removal of baseline lesions following completion of chemotherapy.
- Blood and tumor biomarkers will be assessed for identifying potential correlation with clinical outcomes-related endpoints.
- All efficacy endpoints above (except OS) will be evaluated by both IIR and investigator assessment using RECIST 1.1.

8.7.1.2 Definitions of Analysis Sets

The Full Analysis Set (Intent-to-Treat Analysis [ITT]) includes all randomized subjects regardless of the treatment actually received. This is the primary analysis population used for the efficacy analyses which will be based on the ITT principle.

The Per Protocol Analysis Set includes those subjects from the ITT set who received at least 1 dose of any study drug, had no major protocol deviations, and had both baseline and at least one postbaseline tumor assessment. Subjects for whom death occurred prior to the first postbaseline tumor assessment will also be included. The per protocol analysis set will be the secondary analysis set for efficacy endpoints.

The Safety Analysis Set includes subjects who received at least 1 dose of any study drug. This is the analysis population used for all safety analyses which will be based on as-treated principle.

Population Pharmacokinetic (PK) Analysis Set includes the subjects who have received at least 1 dose of lenvatinib with documented dosing history and have measurable plasma levels of lenvatinib.

The Pharmacodynamic Analysis Set includes subjects who received at least 1 dose of study drug and had sufficient pharmacodynamic data (eg, at least 1 evaluable/measurable pharmacodynamic parameter).

The HRQoL Analysis Set will consist of all randomized subjects who have received at least 1 dose of study medication, and have completed at least 1 patient-reported outcome (PRO) assessment beyond baseline. For PRO analysis, subjects will be analyzed as randomized and not according to treatment actually received.

8.7.1.3 Subject Disposition

Reasons for screening failure will be summarized.

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

8.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Full Analysis Set will be summarized using descriptive statistics. Continuous demographic and baseline variables (including age, sex, race, height, and weight) will be summarized using n (number of subjects with available data), mean, standard deviation, median, quartiles 1 and 3, and range (minimum and maximum) unless otherwise specified. Categorical variables will be summarized by number and percentage.

8.7.1.5 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). Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) class indicating therapeutic classification. Prior medications will be defined as medications that started prior to the first dose of study drug and were either continued during the study or stopped prior to the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. All medications will be will be summarized and listed by drug and drug class and by treatment arm.

8.7.1.6 Efficacy Analyses

Efficacy analyses will be based primarily on the Full Analysis Set.

All the statistical analysis will be conducted at the PFS-1y/OS-1y analysis data cutoff date (ie, when the last subject has completed 18 cycles of treatment or discontinues before the end of Cycle 18, whichever occurs first), including the analysis of PFS-4m rate. Additional follow-up analysis will based on the date of data cutoff for the additional follow-up analysis for OS or at the time of last subject last visit, whichever occurs later.

8.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis of PFS-4m rate will be based upon data provided by IIR of tumor assessments. PFS-4m rate and their Greenwood standard errors will be evaluated using the K-M estimates from both treatment groups. The statistical significance of the difference in the 2 K-M PFS-4m rates comparing lenvatinib + chemotherapy agent (Test Arm) vs. chemotherapy agent alone (Control Arm) will be tested using a 2-sided 80% CI. This 2-sided

80% CI and a p-value will be constructed using the difference of these 2 K-M PFS-4m rates and the 2 corresponding Greenwood standard errors. Statistical significance of the difference is declared if the CI is entirely above 0. This is equivalent to a test using a 1-sided test at alpha=0.1. The 2-sided 95% CIs will also be provided for descriptive purposes. PFS-4m rate will also be analyzed using a binomial approach as a sensitivity analysis by excluding subjects whose PFS are censored prior to 18 weeks.

8.7.1.6.2 SECONDARY EFFICACY ANALYSES

PFS-1y rate will be analyzed using the same methods as the primary efficacy analysis. PFS censoring rules will follow FDA guidance of 2007, however, removal of baseline lesions after completion of Week 18 without progression is not a trigger for PFS censoring after 18 weeks. (refer to Section 8.4.7.3 for allowed concomitant treatments/procedure in the study).

Overall survival (OS) will be compared between treatment arm and control arm using the stratified logrank test with time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years) as strata. Median OS with 2-sided 80% and 95% CIs will be calculated using K-M product-limit estimates for each treatment arm, and the K-M estimates of OS will be plotted over time. The Cox regression model will be used to estimate the hazard ratio and its 80% and 95% CIs stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years). Kaplan-Meier (K-M) estimates will also be presented for 4, 6, 9 and 12 months with 2-sided 80% and 95% CIs.

Overall PFS will be analyzed similarly to OS. Median PFS and 2-sided 80% and 95% (as exploratory) CIs will be presented, and the K-M estimates of PFS will be plotted over time. The Cox regression model will be used to estimate the hazard ratio and its 80% and 95% CIs stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years). K-M estimates will also be presented for 4, 6, 9, and 12 months with 2-sided 80% and 95% CIs.

The ORR will be compared between the test and control groups using either a chi-square test or a Cochran-Mantel-Haenszel test stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years), as appropriate. Corresponding odds ratios and their 2-sided 80% and 95% CIs comparing the groups will also be presented. The individual treatment group ORRs will also be calculated along with exact 95% confidence intervals using the Clopper and Pearson method.

8.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Median DOR among responders for each arm will be presented along with its corresponding 2-sided 95% CIs. Disease Control Rate (DCR) and CBR will be calculated with exact 95% CIs using the Clopper and Pearson method. The differences of the above rates between 2 groups and corresponding two-sided 95% CIs will be calculated respectively.

8.7.1.7 Pharmacokinetic, Pharmacodynamic, and Other Biomarker Analyses

8.7.1.7.1 PHARMACOKINETIC ANALYSES

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

Lenvatinib data from Arm A of the study will be pooled with available data from other studies and subjected to population PK analysis. 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.

8.7.1.7.2 PHARMACODYNAMIC AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.

Pharmacodynamic serum and archived, fixed tumor tissue biomarkers will be collected from subjects in Arm A only as described in the Schedule of Assessments. Pharmacodynamic serum and tumor biomarkers in this study will be identified as in other lenvatinib clinical studies.

Blood serum samples may be analyzed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, or other assays/methods and new technology in an effort to identify biomarkers.

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

Data obtained from the pharmacodynamic samples will be used for research. The pharmacodynamic samples will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib and for potential diagnostic development. If the subject reaches 18 years of age prior to the date of final sample analyses they will be reconsented. No further analyses will be performed on these collected samples from subjects who either do not reconsent after their 18th birthday or cannot be reached for reconsenting and the sample will be destroyed. When the subject reaches the age of 18 years (or 16 years in the UK) while on the study, and becomes competent to give informed consent, his/her consent will be obtained using separate ICFs to continue on the study.

8.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment group, will be summarized on an “as treated” basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%]

for categorical variables), as appropriate. Safety variables include TEAEs, clinical laboratory parameters, vital signs, 12-lead ECG results, Lansky play scores or Karnofsky performance scores, physical examination, height, closure of proximal tibial plates, and LVEF. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

8.7.1.8.1 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 adverse events will be summarized.

8.7.1.8.2 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 (Version 20.1 or higher) 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 (and within 30 days of the last study treatment), having been absent at pretreatment (Baseline) or

- Re-emerges 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 TEAEs will be summarized by treatment group. 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 highest CTCAE grade.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

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-related TEAEs will also be summarized by highest CTCAE grade.

Adverse events will be summarized using the Safety Analysis Set. The number of AEs and number and incidence (%) of subjects with AEs will be summarized by treatment group and

overall. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by SOC and by PT will be calculated. Incidence (%) by causal relationship with study drug and by severity (CTCAE v5.0) will also be calculated. For clinically significant events, time of onset, and recovery will be reported.

Adverse events will be summarized for descriptive purposes by age (2 to <6, 6 to <18, and ≥18), and sex.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. All deaths will also be summarized.

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

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

8.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 8.5.1.4.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 8.5.1.4.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on shift tables that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

8.7.1.8.4 VITAL SIGNS

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

Percentiles for BP values (only for subjects <18 years old) will also be summarized using a shift table of worst postbaseline from Baseline measurement by categories (<90th percentile,

90th to 95th percentile, 95th to ≤99th percentile, systolic BP or diastolic BP >99th percentile). See Appendix 6 and Appendix 7 for detail on percentiles.

8.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for electrocardiogram parameters (HR, PR, QRS, QT, QTcB, QTcF and RR) and changes from Baseline will be presented by visit. Electrocardiogram (ECG) findings will be summarized. A shift table of worst postbaseline values from Baseline for ECG findings will be provided.

QTc Bazett and QTc Fridericia will be summarized. QTc Bazett and QTc Fridericia will be categorized as both maximum increases from Baseline and maximum postbaseline values.

8.7.1.8.6 OTHER SAFETY ANALYSES

Descriptive summary statistics for LVEF changes from baseline will be calculated and summarized.

The shift of worst postbaseline proteinuria from Baseline will be summarized.

Thyroid-stimulating hormone values will be summarized in 2 categories (≤ULN and >ULN).

Lansky play scores or Karnofsky Performance Status score scores will be summarized by shifts from Baseline to worst postbaseline visit.

Radiographic findings of proximal tibial growth plates will be listed and analyzed if appropriate.

8.7.1.9 Other Analyses

8.7.1.9.1 HEALTH-RELATED QUALITY OF LIFE

Descriptive statistics will be presented for all PedsQL endpoints at each analysis time period by treatment arm. Baseline is defined as the later value of Day -1 or at Cycle 1 Day 1 prior to treatment.

This will be collected at baseline, at C2D1, C3D1, Week 18, C8D1, C18 D1 and at the Off-Treatment Visit. Score change from baseline in PedsQL at each analysis timepoint will be analyzed. Primary timepoint for assessment is at week 18 for all PedsQL endpoints.

Detailed HRQoL analysis plan will be provided in a separate analysis plan and the results will be provided in a stand-alone report.

8.7.1.9.2 PALATABILITY AND ACCEPTABILITY QUESTIONNAIRE

Measurement of palatability will be assessed using the Hedonic scale (Guinard, 2001) which is a Visual Analog Scale (VAS) in subjects receiving the suspension formulation in the study.

8.7.2 Determination of Sample Size

A binomial-based comparison of 2 proportions using correction for continuity was used for sample size estimation. A total sample size of 72 subjects is estimated to achieve 80% statistical power at 1-sided alpha of 0.1 to detect a difference of 30% based on the assumption that PFS-4m for Arm A (lenvatinib arm) is 55% and for Arm B is 25%. Alpha is the type 1 error probability of declaring lenvatinib arm being effective when the true lenvatinib arm PFS-4m rate is only 25%.

8.7.3 Interim Analysis

No interim analysis is planned for this study.

The safety monitoring will be conducted by the independent data monitoring committee (IDMC). The frequency of the 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 recommendation of whether to stop the study for safety will be reached by the IDMC based on their review of safety data with treatment information. The function and membership of the IDMC will be described in the IDMC charter.

8.7.4 Other Statistical/Analytical Issues

Not applicable.

8.7.5 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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10 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

10.1 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 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.

10.2 Adherence to the Protocol

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

10.3 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 IVRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source
- Electronic Patient-Reported Outcome by self-reported measures

10.4 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.

10.5 Identification of Source Data

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

10.6 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 for US sites), Investigator and Site Information Form (for non-US sites), 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.

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.

10.7 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.

10.8 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.

10.9 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.

10.10 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.

10.11 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.

10.12 Subject Insurance and Indemnity

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

11 APPENDICES

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

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

Appendix 2 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 3 Karnofsky Performance Status Scale Definitions Rating (%) Criteria

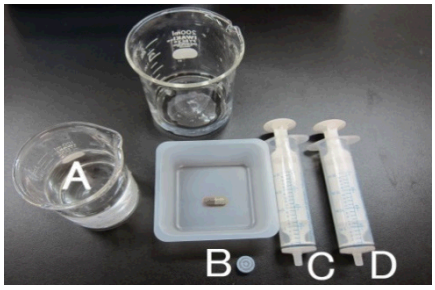
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and 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.

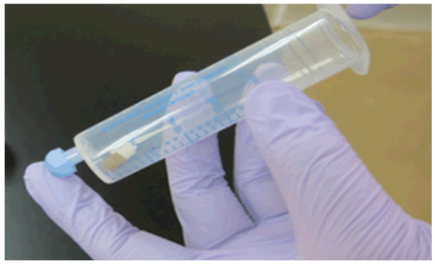
Appendix 4 Preparation of Lenvatinib suspension

Preparation of suspension Prepare the suspension as illustrated by either method. Prepare the suspension with water or apple juice. The suspension should be directly injected into the mouth of the subjects and should not be washed down with additional fluid. The suspension should be taken immediately after preparation.

a. Procedure for suspension administration by syringe

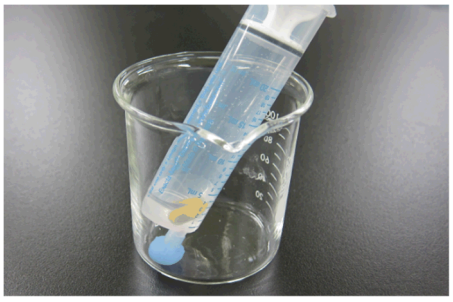


A: Water or apple juice
B: Cap
C: Syringe (20 mL, Baxa preferred)
D: Syringe for rinse (20 mL, Baxa preferred)

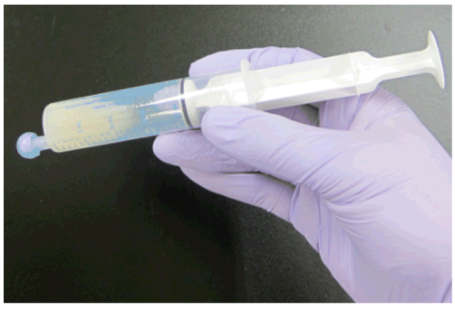


Place one capsule* into a syringe. The tip port of the syringe needs to be closed with a cap.
* One to five capsules are allowed to be placed in a syringe.

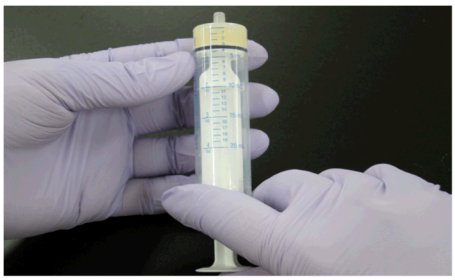
Three (3) mL of water or apple juice is added into the syringe using another (new) syringe.



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

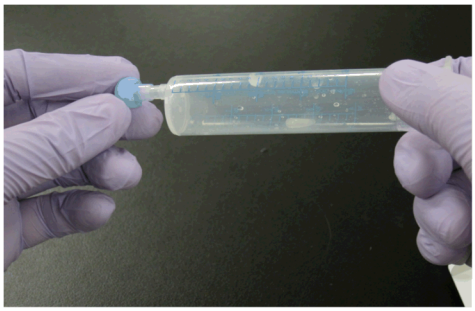


After 10 minutes leaving, shake the syringe for not less than 3 minutes to dissolve the capsule shell completely and to suspend granules (capsule shell needs to be dissolved. It is fine as long as granules are well suspended).

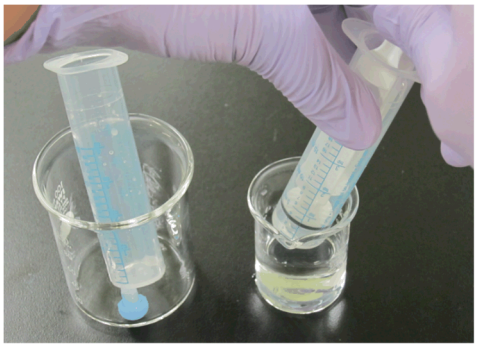


Remove the cap from the syringe.
By sliding the piston, push air out from the syringe, and then administer the 3mL of suspension from the syringe.

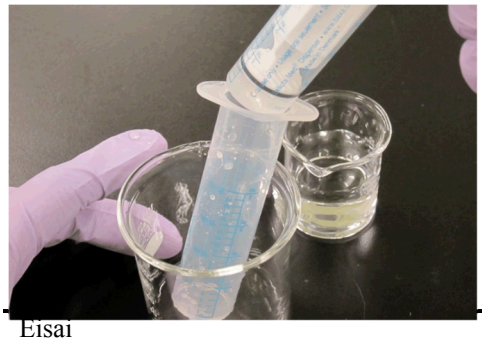
Rinse step



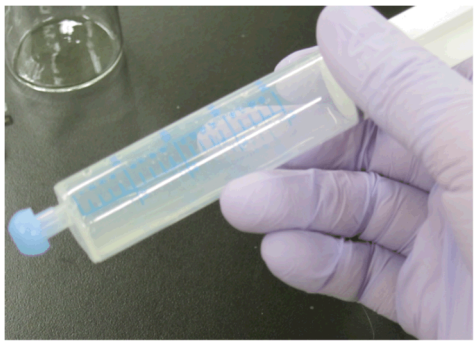
After the administration of 3mL suspension from the syringe, the cap (reuse) is to be connected with the syringe.



2 mL of water or apple juice is to be taken by another (new) syringe.



2 mL of water or apple juice is to be poured into the syringe (which was used for the 3mL suspension).

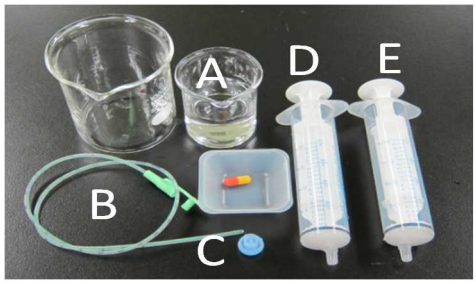


After connecting the cap (reuse), the syringe is to be shaken for 10 times.

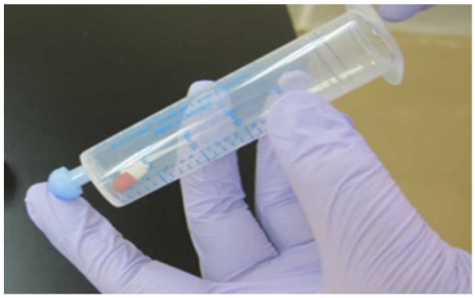
After removing the cap from the syringe, push air out from the syringe, and then 2 mL of rinse liquid is to be administered.

Total volume of suspension to be administrated is 5 ml (=3mL for suspension + 2mL for rinse) for one to five capsules.

b. Procedure of suspension administering by syringe with NG tube



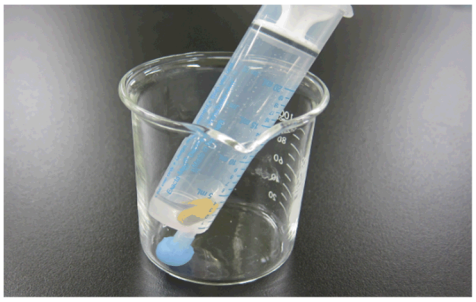
A: Water or apple juice
B: NG tube (Vygon, 6FR)
C: Cap
D: Syringe (20 mL, Baxa, preferred)
E: Syringe for rinse (20 mL, Baxa preferred)



Place one capsule* into a syringe. The tip port of the syringe needs to be closed with a cap.

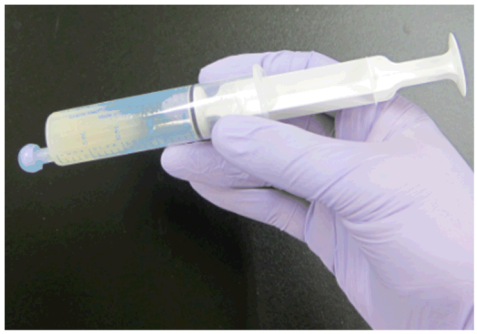
* One to five capsules are allowed to be placed in a syringe.

The 3 mL of water or apple juice is to be poured into the syringe using another (new) syringe.

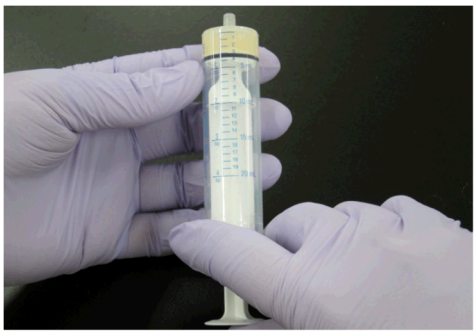


Insert a piston into the syringe (cylinder) about 2 cm from the end.

Leave the syringe for is not less than 10 minutes.

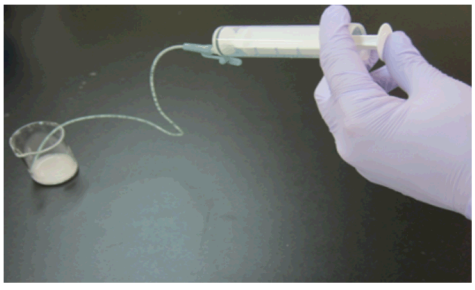


After 10 minutes leaving, shake the syringe for not less than 3 minutes to dissolve the capsule shell completely and to suspend granules (capsule shell needs to be dissolved, but it is fine as long as granules are well suspended).



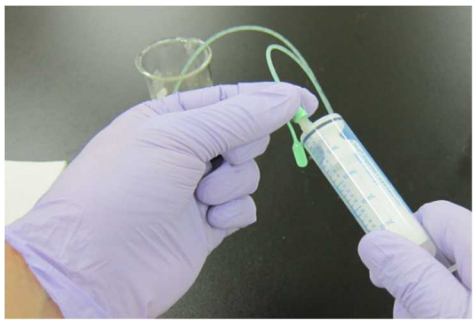
Remove the cap from the syringe.

By sliding the piston, push air out from the syringe.

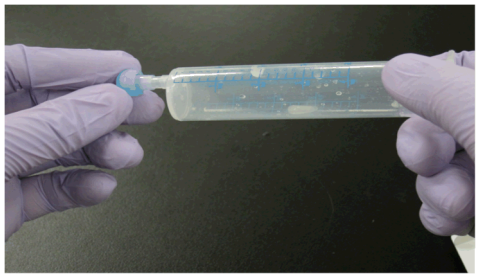


After connecting a NG tube with the syringe, administrate the 3 mL of suspension through the NG tube.

Rinse step



After pouring the suspension, the NG tube is to be taken off from the syringe.



The cap (reuse) is connected with the syringe

Two 2 mL of water or apple juice is to be poured into the syringe by using another (new) syringe.

After inserting the piston to the syringe (about 2cm from the end), shake the syringe for 10 times.

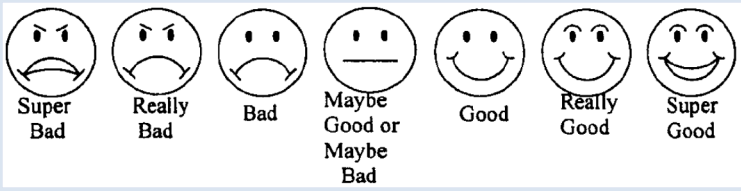
By sliding the piston, push out air from the syringe.

After connecting a NG tube, the 2 mL of rinse liquid is to be administered from the syringe through the NG tube.

Total volume of suspension to be administrated is 5 ml (=3mL for suspension + 2mL for rinse) for one to five capsules.

Appendix 5 Palatability Questionnaire

Study E7080-G000-230- Palatability Questionnaire

Subject ID: 1 0 0 1	**Treatment Dose:** **Visit Cycle:** **Date:**
Taste	 *(Please circle according to your experience)* **Please provide reasons for your rating:** ……
Appearance	 *(Please circle according to your experience)* **Please provide reasons for your rating:** ……
Smell	 *(Please circle according to your experience)*

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

Appendix 6 Blood Pressure Levels for Boys by Age and Height Percentile

		Systolic BP (mmHg)							Diastolic BP (mmHg)						
AGE	BP Percentile	Percentile of Height							Percentile of Height						
(Year)	Ð	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	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
	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

	BP	Systolic BP (mmHg)							Diastolic BP (mmHg)						
AGE	Percentile	Percentile of Height							Percentile of Height						
(Year)	Ð	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	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 7 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)	Ð	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63

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

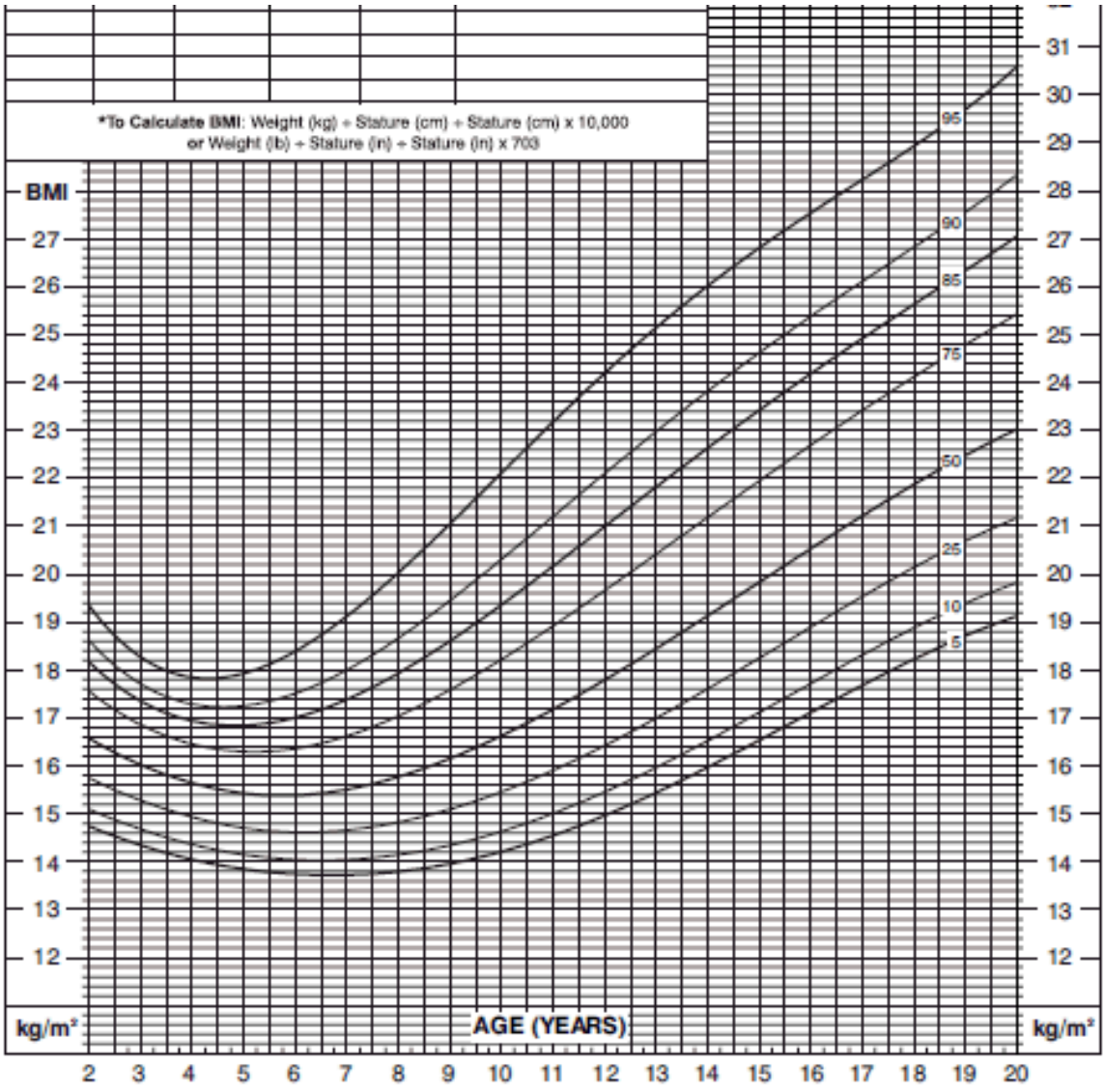
BP, blood pressure

* 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 8 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).

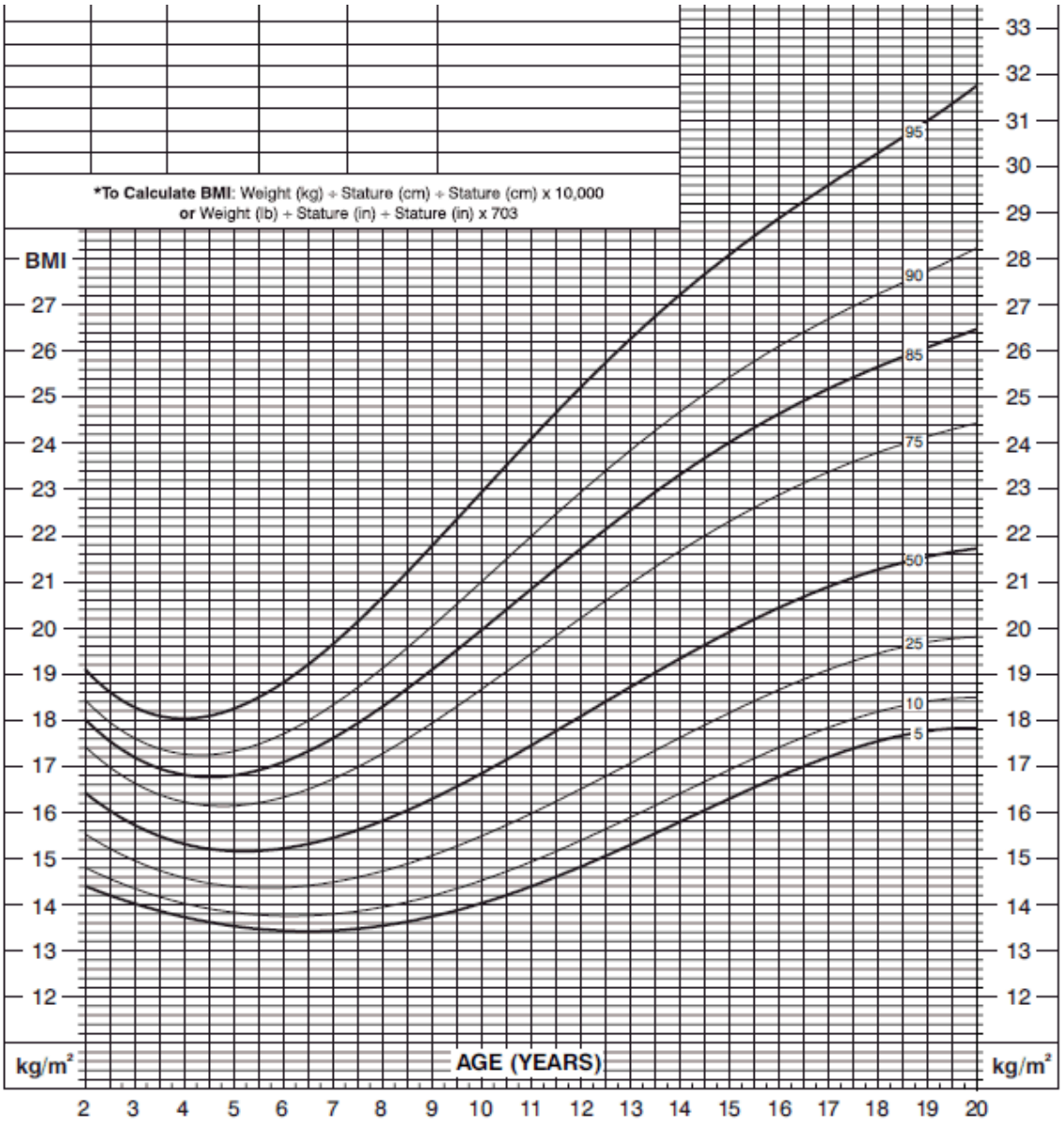
http://www.cdc.gov/growthcharts

Link for the charts is provided below

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

Appendix 9 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.ht

Appendix 10 Tanner's Staging

Boys Tanner Stage progression scale*

Genitalia:

1= The testes, scrotum and penis are about the same size and shape as they were when you were a child

2= The testes and scrotum are bigger. The skin of the scrotum has changed. The scrotum, the sack holding the testes, has gotten lower. The penis has gotten only a little bigger.

3= The penis has grown in length. The testes and scrotum have grown and dropped lower.

4= The penis has gotten even bigger. It is sider. The glans (the head of the penis) is bigger. The scrotum is darker than before. It is bigger because the testes are bigger.

5= The penis, scrotum, and testes are the size and shape of an adult man.

Pubic Hair:

1= There is no pubic hair at all.

2= There is a little soft, long, lightly-colored hair. Most of the hair is at the base of the penis.

This hair may be straight or a little curly.

3= The hair is darker in this stage. It is more curled. It has spread out and thinly covers a bigger area.

4= the hair is now as dark, curly, and course as that of an adult man. The area that the hair covers is not as big as that of an adult man. The hair has NOT spread out to the legs.

5= The hair has spread out to the legs. The hair is now like that of an adult man. It covers the same area as that of an adult man.

Girls Tanner Stage progression scale

Breast:

1= The nipple is raised a little. The rest of the breast is still flat.

2= This is the breast bud stage. In this stage, the nipple is raised more than in stage 1. The breast is a small mound. The areola is larger than stage 1.

3= The breast and areola are both larger than in stage 2. The areola does not stick out away from the breast.

4= The areola and the nipple make up a mound that sticks up above the shape of the breast. NOTE: This stage may not happen at all for some girls. Some girls develop from stage 3 to stage 5 with no stage 4

5= This is the mature adult stage. The breasts are fully developed. Only the nipple sticks out in this stage. The areola has moved back in the general shape of the breast.

Pubic Hair:

1= There is no pubic hair at all.

2= There is a little soft, long lightly-colored hair. This hair may be straight or a little curly.

3= The hair is darker in this stage. It is coarser more curled. It has spread out and thinly covers a bigger area.

4= the hair is now as dark, curly, and course as that of an adult female. The area that the hair covers is not as big as that of an adult female. The hair has NOT spread out to the legs.

5= The hair is now like that of an adult female. It covers the same area as that of an adult female. The hair usually forms a triangular (V) pattern as it spreads out to the legs.

*Adapted from: Morris, N.M., and Udry, J.R., (1980). Validation of a Self-Administered Instrument to Assess Stage of Adolescent Development. Journal of Youth and Adolescence, Vol. 9, No. 3: 271-80.

Appendix 11 Pharmacodynamic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic (PD), 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.

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

Sample Collection and Handling

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

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

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

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

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

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

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays

that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

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

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E7080-G000-230

Study Protocol Title: A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)

Investigational Product Name: E7080/Lenvatinib

IND Number: 146642

EudraCT Number: 2019-003696-19

SIGNATURES

Authors:

PPD

10-Mar-2020

Date

Oncology Business Group, Eisai Inc.

PPD

10-Mar-2020

Date

Oncology Business Group, Eisai Inc.

PPD

10-Mar-2020

Date

Oncology Business Group, Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7080-G000-230
Study Protocol Title:	A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)
Investigational Product Name:	E7080/Lenvatinib
IND Number:	146642
EudraCT Number:	2019-003696-19

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

Medical Institution

Investigator	Signature	Date

TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-G000-230
Study Protocol Title:	A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 JP
Sponsor's Investigational Product Name:	E7080/Lenvatinib
Indication:	Osteosarcoma
Phase:	2
Approval Date:	Original Protocol 08 Oct 2019
IND Number:	146642
EudraCT Number:	2019-003696-19
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.

1 CLINICAL PROTOCOL SYNOPSIS

Compound No. E7080

Name of Active Ingredient: Lenvatinib

Study Protocol Title

A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)

Investigator

Principal Investigator: Dr Nathalie Gaspar

Sites

Approximately 70 sites worldwide

Study Period and Phase of Development

Approximately 36 months

Phase 2

Objectives

Primary Objective

To evaluate whether lenvatinib in combination with ifosfamide and etoposide (Arm A) is superior to ifosfamide and etoposide (Arm B) in improving progression-free survival (PFS) rate at 4 months (PFS-4m) (by independent imaging review [IIR] using Response Evaluation Criteria In Solid Tumors [RECIST 1.1]), in children, adolescents, and young adults with relapsed or refractory osteosarcoma.

Secondary Objectives

The secondary objectives of the study are to:

1. Compare differences in PFS rate at 1 year (PFS-1y) between the 2 treatment arms
2. Compare differences in PFS Kaplan-Meier (K-M) survival curves and median PFS between the 2 treatment arms
3. Compare differences in overall survival (OS) and OS rate at 1 year (OS-1y) between the 2 treatment arms
4. Compare differences in objective response rate (ORR) at 4 months between the 2 treatment arms
5. Compare differences in safety and tolerability between the 2 treatment arms
6. Characterize the pharmacokinetics (PK) of lenvatinib, when administered in combination with ifosfamide and etoposide
7. Compare differences in health-related quality of life (HRQoL) as assessed by using the the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales and Cancer Module between the 2 treatment arms
8. Assess the palatability and acceptability of the suspension formulation of lenvatinib in pediatric subjects receiving the suspension formulation in the study

Exploratory Objectives

The exploratory objectives of the study are to:

1. Explore differences in duration of response (DOR), disease control rate (DCR), and clinical benefit rate (CBR) between the 2 treatment arms

2. Compare the proportion of subjects who achieve complete removal of baseline lesion(s) following completion of chemotherapy between the 2 treatment arms
3. Investigate the relationship between subject tumor biomarkers and clinical response and toxicity of lenvatinib in combination with ifosfamide and etoposide

Study Design

E7080-G000-230 is a multicenter, randomized, open-label, parallel-group, Phase 2 study to compare the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide in children, adolescents, and young adults with relapsed or refractory osteosarcoma.

Approximately 72 eligible subjects will be randomized to 1 of the following 2 treatment arms in a 1:1 ratio within the strata:

- Arm A: lenvatinib 14 mg/m^2 (orally, once daily) plus ifosfamide 3000 mg/m^2/day (intravenously [IV], Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)
- Arm B: ifosfamide 3000 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)

Randomization will follow a predefined randomization scheme based on the following stratification factors: time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 and ≥18 years).

Eisai will closely monitor enrolment, to ensure that at least 32 subjects <18 years of age at the time of informed consent are randomized.

The study will be conducted in 3 Phases: a Prerandomization Phase, a Randomization Phase, and an Extension Phase.

The **Prerandomization Phase** will consist of 2 periods: Screening and Baseline. The Prerandomization Phase will last no longer than 28 days. The Screening Period will establish protocol eligibility and the Baseline Period will confirm eligibility.

The **Randomization Phase** will consist of 2 periods: Treatment Period and Follow-up Period. The Randomization Phase will begin at the time of randomization of the first subject and will end on the data cutoff date for the PFS-1y and OS-1y analysis. After the data cutoff date for the PFS-1y and OS-1y has occurred, all subjects who are still on study treatment will enter the Extension Phase. Data cutoff (for PFS-1y and OS-1y analysis) will occur when the last subject has completed 18 cycles of treatment or discontinues before the end of Cycle 18, whichever occurs first.

The ***Treatment Period*** for each subject will begin at the time of randomization and will end at the completion of the Off-Treatment Visit which will occur within 30 days after the final dose of study treatment

Subjects will receive study treatment as continuous 21-day cycles in both treatment arms. Treatment cycles will be counted continuously regardless of dose interruptions. If chemotherapy administration is precluded on Day 1 of a treatment cycle, the subject may resume treatment once recovered at the discretion of investigator. Subsequent chemotherapy will be administered every 21 (±1) days starting from the timepoint it was resumed.

Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments. Subjects randomized to Arm A will continue to receive lenvatinib until disease progression (PD) confirmed by IIR, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor, whichever occurs first.

Disease progression (PD) must be confirmed by IIR prior to the investigator discontinuing study treatment for a subject. In situations where the investigator judges that alternative treatments must be

instituted immediately for a subject's safety, study drugs may be discontinued without waiting for IIR confirmation of radiographic evidence of PD. If possible, before discontinuation of the subject from the study, the investigator should consult with the sponsor.

The ***Follow-up Period*** begins the day after the Off-Treatment Visit and will continue as long as the subject is alive, unless the subject withdraws consent, or the sponsor terminates the study.

Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn, however, an investigator may consult public records to establish survival status if permitted by local regulations.

All adverse events (AEs) will be captured for 30 days after the last dose of study drug.

All subjects who discontinue study treatment early for reasons other than PD, will continue to undergo tumor assessments every 6 weeks until Week 18, then every 9 weeks until Week 54, thereafter, every 12 weeks until confirmation of disease progression by IIR as described in the tumor assessments in the assessment schedule, or until another anticancer therapy is initiated.

Subjects in both Arm A and Arm B will be followed for survival every 12 weeks (±1 week) and all subsequent anticancer treatments received will be recorded. Subjects who are being followed for survival at the time of data cutoff for the for PFS-1y and OS-1y analysis (ie, at the end of the Randomization Phase) will continue to be followed for survival during the Follow-up Period of the Extension Phase.

Extension Phase: The Extension Phase will consist of 2 periods: Treatment Period and Follow-up Period.

In the ***Treatment Period***, subjects still on lenvatinib in Arm A following the completion of the PFS-1y and OS-1y analysis (ie, at the end of the Randomization Phase) will continue to receive lenvatinib in 21-day cycles until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor. Tumor assessments will be performed according to the local standard of care. Independent imaging review (IIR) review and confirmation of radiographic evidence of PD will not be required, and scans will no longer be required to be sent to the imaging core laboratory (ICL). The Off-Treatment Visit will occur within 30 days after the final dose of study treatment. All AEs will be captured up to 30 days after last dose of study drug. In case the study is discontinued by the sponsor, the sponsor will continue to provide study drug (outside the study) for subjects requiring continuation of treatment.

The ***Follow-up Period*** will begin the day after the Off-Treatment Visit and will last until death or for 2 years after end of treatment for a subject, unless the study is terminated by the sponsor, or the subject discontinues due to withdrawal of consent, or is lost to follow-up. Subjects will be treated by the investigator according to the prevailing local standard of care. Subjects will be followed every 12 weeks (±1week) for survival and all subsequent anticancer treatments received will be recorded.

The definition of end of the study, as required by certain regulatory agencies, will be the date of data cutoff for the final analysis or the time of last subject last visit, whichever occurs later.

Number of Subjects

Approximately 72 subjects will be randomised (36 subjects in each arm).

For the primary endpoint (intent–to-treat analysis), at least 32 subjects <18 years old (at the time of informed consent) will be randomized.

Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of high grade osteosarcoma.
2. Refractory or relapsed osteosarcoma after 1 to 2 prior systemic treatments.
3. Measurable or evaluable disease per RECIST 1.1 that meets the following criteria:

- Must be accurately measurable with a minimum size (by long axis) of 10 mm using computed tomography/magnetic resonance imaging (CT/MRI) (lymph nodes must be accurately measurable with a minimum size [by short axis] of 15 mm).
- Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must have subsequently grown unequivocally to be deemed a target lesion.

4. Aged 2 years to ≤25 years at the time of informed consent.
5. Life expectancy of 12 weeks or more.
6. Lansky play score ≥50% or Karnofsky Performance Status score ≥50%. Use Karnofsky for subjects ≥16 years of age and Lansky for subjects <16 years of age. Subjects who are unable to walk because of paralysis, but who are up in wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
7. Adequate bone marrow function as evidenced by:
   a. absolute neutrophil count (ANC) $\geq 1.0\times10^9$/L.

      (subjects with bone marrow involvement should have ANC $\geq 0.8\times10^9$/L and leucocyte count $\geq 1\times10^9$/L).
   b. hemoglobin ≥8.0 g/dL (a hemoglobin of <8.0 g/dL is acceptable if it is corrected by growth factor or transfusion before Cycle 1 Day 1).
   c. platelet count $\geq 75\times10^9$/L.
8. Adequate blood coagulation function defined by International Normalized ratio (INR) ≤1.5 unless participant is receiving anticoagulant therapy, as long as INR is within therapeutic range of intended use of anticoagulants.
9. Adequate liver function as evidenced by:
   a. bilirubin ≤1.5 times the upper limit of normal (ULN).
   b. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3×ULN (in the case of liver metastases ≤5×ULN).
10. Adequate renal function as evidenced by:
    a. Serum creatinine based on age/gender as below. If serum creatinine is greater than maximum serum creatinine for age/gender as shown in the table below, then creatinine clearance (or radioisotope glomerular filtration rate [GFR]) must be >70 mL/min/1.73 m^2.

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

    The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz, et al., 1985) using child length and stature data published by the CDC.
    b. Urine dipstick <2+ for proteinuria. Subjects who have ≥2+ proteinuria on dipstick urinalysis should undergo a spot protein-creatinine (P/C) ratio test that should be Grade <2 per

Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and if possible perform a 24-hour urine collection (children and adolescents ≤12 years of age must have ≤500 mg of protein/24 hours and subjects >12 years of age must have ≤1 g of protein/24 hours).

c. No clinical evidence of nephrotic syndrome.

11. Adequate cardiac function as evidenced by left ventricular ejection fraction ≥50% at baseline as determined by echocardiography.
12. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as:
    a. BP <95th percentile for sex, age, and height/length at screening (as per National Heart Lung and Blood Institute guidelines) and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1. Subjects >18 years of age should have BP ≤150/90 mm Hg at screening and no change in antihypertensive therapy within 1 week prior to Cycle 1 Day 1.
13. Washout before Cycle 1 Day 1 of 3 weeks in case of prior chemotherapy, 6 weeks if treatment included nitrosoureas; 4 weeks for definitive radiotherapy, 2 weeks for palliative radiotherapy; and 3 months from high-dose chemotherapy and stem cell rescue. Subjects must have recovered (to Grade ≤1, except for alopecia, ototoxicity, and Grade ≤2 peripheral neuropathy, per CTCAE v5.0) from the acute toxic effects of all prior anticancer therapy before Cycle 1 Day 1.
14. Written and signed informed consent from the parent(s) or legal guardian and assent from the minor subject. Written informed consent from subjects ≥18 years.
15. Willing and able to comply with the protocol, scheduled follow-up, and management of toxicity as judged by the investigator.

Exclusion Criteria

1. Any active infection or infectious illness unless fully recovered prior to Cycle 1 Day 1 (ie, no longer requiring systemic treatment).
2. Subjects with central nervous system metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy, surgery, or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 2 weeks before Cycle 1 Day 1.
3. Active second malignancy within 2 years prior to enrollment ([in addition to osteosarcoma], but not including definitively treated superficial melanoma, carcinoma-in-situ, basal or squamous cell carcinoma of the skin).
4. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
5. Has had major surgery within 3 weeks prior to Cycle 1 Day 1. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
6. Known hypersensitivity to any component(s) of the study drugs (lenvatinib, ifosfamide, and etoposide, or their ingredients).
7. Currently receiving any investigational drug or device in another clinical study or within 28 days prior to Cycle 1 Day 1.
8. A clinically significant ECG abnormality, including a marked baseline prolonged QT or QTc interval (eg, a repeated demonstration of a QTc interval >480 msec).
9. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that in the opinion of the investigator might affect the absorption of lenvatinib.
10. Pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula.
11. Gastrointestinal bleeding or active hemoptysis (bright red blood of at least ½ teaspoon) within

3 weeks prior to Cycle 1 Day 1.

12. Radiographic evidence of intratumoral cavitation, encasement, or invasion of a major blood vessel. Additionally, the degree of proximity to major blood vessels should be considered for exclusion because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.
13. History of ifosfamide-related Grade ≥3 nephrotoxicity or encephalopathy.
14. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
15. Known to be human immunodeficiency virus (HIV) positive. Note: HIV testing is required at screening only when mandated by local health authority.
16. Active viral hepatitis (B or C) as demonstrated by positive serology. Note: Testing for Hepatitis B or Hepatitis C is required at screening only when mandated by local health authority.
17. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG]) (human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG / hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
18. Females of childbearing potential* who:
    - Do not agree to use a highly effective method of contraception for the entire study period and for 28 days after lenvatinib discontinuation or 12 months after etoposide and ifosfamide discontinuation, ie:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
        - a contraceptive implant
        - an oral contraceptive. Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing with study drug and throughout the study and for 28 days after lenvatinib discontinuation or 12 months after etoposide and ifosfamide discontinuation

          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, or the subject has changed oral hormonal contraceptive product/dose within 4 weeks prior to study drug administration, 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.

    * All post pubertal females will be considered to be of childbearing potential unless they have early menopause (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).
19. 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 28 days after lenvatinib discontinuation or 6 months after discontinuation of etoposide and ifosfamide). No sperm

donation is allowed during the study period and for 28 days after lenvatinib discontinuation or 6 months after discontinuation of etoposide and ifsofamide.

Study Treatments

Body surface area (BSA) will be used to determine the amount of study drugs administered, and must be calculated on Day 1 of each cycle based on the subject's current height and body weight. The dose should be rounded to the nearest whole number.

Test Arm (Arm A): Lenvatinib + Ifosfamide + Etoposide

Lenvatinib 14 mg/m^2, orally administered once daily in each 21-day cycle.

Lenvatinib is provided as hard capsules containing 1 mg, 4 mg, or 10 mg lenvatinib. An extemporaneous suspension of lenvatinib capsules should be used for subjects unable to swallow capsules. After adjustment for BSA, the daily dose cannot exceed 24 mg QD.

Ifosfamide 3000 mg/m^2/day, IV, for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Etoposide 100 mg/m^2/day, IV, for 3 consecutive days (Day 1 to 3) , every 21 days, for a maximum of 5 cycles.

Treatment with lenvatinib will continue in 21-day cycles after chemotherapy is discontinued, until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor.

In case the study is discontinued by the sponsor, the sponsor will continue to provide study drug (outside the study) for subjects requiring continuation of treatment.

Control Arm (Arm B): Ifosfamide + Etoposide

Ifosfamide 3000 mg/m^2/day, IV, daily for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Etoposide 100 mg/m^2/day, IV, daily for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Duration of Treatment

A subject will remain on study treatment until 1 or more of the following events occur(s):

- Progressive disease (as confirmed by IIR)
- Unacceptable toxicity
- Subject request
- Withdrawal of consent
- Termination of the study by the Sponsor

Concomitant Drug/Therapy

Prohibited Concomitant Therapies and Drugs

Subjects should not receive other antitumor therapies while on study. If a subject receives additional antitumor therapies other than the study drug(s), such as chemotherapy, targeted therapies, immunotherapy, or antitumor interventions - such as surgery or palliative radiotherapy (other than as described below), this will be judged to represent evidence of disease progression, and continuation of the study medication and further participation in the study must be discussed and agreed upon with the sponsor.

For further information on the prohibited concomitant therapies for ifosfamide and etoposide, please refer to the respective prescribing information.

Granulocyte-colony stimulating factor (G-CSF) may be used to mitigate the toxicity of ifosfamide

and etoposide.

The following concomitant treatments/procedures are allowed:

a. Removal of existing (not new) osteosarcoma lesion (eg, surgical, radiofrequency ablation, cryotherapy, thermoablation, stereotaxic ratiotherapy, etc.) after completion of the Week 18 tumor assessment. Subjects in Arm A in the presence of clinical benefit, may continue treatment with lenvatinib after protocol permissible surgery.

b. Palliative radiotherapy is allowed for ≤2 significantly symptomatic nontarget lesions.

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

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

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

Assessments

Efficacy Assessments

Tumor assessment will be performed based on RECIST 1.1. Investigator–determined response assessments will be performed at each assessment time point and entered onto the case report form (CRF). Copies of all tumor assessment scans will be sent to an imaging core laboratory (ICL) designated by the sponsor for efficacy assessment and for confirmation of PD. Tumor assessments will be carried out following the guidelines provided by the ICL.

During the Screening Period, tumor assessments of the chest, abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed within 28 days prior to Cycle 1 Day 1. A brain scan (CT scan with contrast or MRI pre- and post-gadolinium) will be performed at screening as clinically indicated, and thereafter during the study as clinically indicated. Historical CT or MRI scans performed within 28 days prior to Cycle 1 Day 1 may be used as screening scans (baseline scans) to demonstrate eligibility, as long as they meet minimum standards as separately defined by the ICL.

Tumor assessments will then be performed every 6 weeks ±1 week following the start of treatment on Cycle 1 Day 1 during the chemotherapy treatment period until Week 18. Following completion of the chemotherapy treatment period (ie, after Week 18), the frequency of tumor assessments will be every 9 weeks ±1 week until Week 54 ±1 week. Thereafter, they will be performed every 12 weeks ±2 weeks until documentation of PD (please see schedule of assessments for details). At any point, the CT/MRI scan should be performed earlier than the scheduled time point, if clinically indicated. After data cutoff for PFS-1y and OS-1y analysis, tumor assessments should be performed following the prevailing local standard of care.

Disease progression per RECIST 1.1 during the randomization phase must be confirmed by IIR prior to the investigator discontinuing study treatment.

In the event that the investigator considers alternative treatments must be instituted immediately for management of urgent medical complications of PD, study drugs may be discontinued without waiting for independent confirmation of radiographic evidence of PD. Subjects who discontinue study treatment without PD will continue to undergo tumor assessments according to the schedule until PD is documented or another anticancer therapy is initiated.

Pharmacokinetic Assessments

Blood samples for plasma concentrations of lenvatinib will be collected from all subjects from

Arm A only as described in the Schedule of Assessments.

Pharmacodynamic and Other Biomarker Assessments

Pharmacodynamic serum and archived fixed tumor tissue samples for biomarker analysis will be collected from subjects randomized to Arm A only, as described in the Schedule of Assessments. Pharmacodynamic serum and tumor biomarkers assessed in this study will be based on those identified in other lenvatinib clinical studies. Pharmacodynamic biomarker analysis will be performed as described in a separate analysis plan.

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs), including all grades per National Cancer Institute (NCI) CTCAE v5.0 (for both increasing and decreasing severity), and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and physical examinations.

Progression of osteosarcoma and signs and symptoms clearly related to the progression of the osteosarcoma should not be captured as an AE. Disease progression is a study endpoint and should be captured in the CRF as per the guidelines for reporting disease progression.

Other Assessments

HRQoL assessment will be performed per the Schedule of Assessments. Impact of treatment on HRQoL will be assessed using the PedsQL (including the Generic Core Scales and Cancer Module).

Bioanalytical Methods

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

Statistical Methods

Primary Endpoint

- **PFS-4m rate (progression-free survival rate at 4 months) by IIR** is defined as the percentage of subjects who are alive and without PD at 4 months from the randomization date as determined by IIR of radiological imaging using RECIST 1.1. The PFS-4m rate is estimated on the full analysis set for this study using the K-M method.

Secondary Endpoints

- **PFS-1y rate (progression-free survival rate at 1 year) by IIR** is defined as the percentage of subjects who are alive and without PD at 1 year from the randomization date as determined by IIR of radiological imaging using RECIST 1.1. The PFS-1y rate is estimated on the full analysis set for this study using the K-M method.
- **Progression-free survival (PFS) by IIR** is defined as the time from the date of randomization to the date of the first documentation of PD or death (whichever occurs first) as determined by IIR using RECIST 1.1.
- **Overall survival (OS)** is defined as the time from the date of randomization to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cutoff will be censored at the date the subject was last known alive, or date of data cutoff, whichever occurs first. Overall survival rate at 1 year will be estimated.
- **Objective response rate (ORR) by IIR** at 4 months is defined as the proportion of subjects who have best overall response of complete response (CR) or partial response (PR) as determined by IIR using RECIST 1.1 within the first 4 months.

- **Safety** will be assessed summarizing the incidence of treatment-emergent adverse events (TEAEs) and SAEs together with all other safety parameters.
- Assessment of population-based PK parameters of lenvatinib.
- Score changes from baseline for all PedsQL scales including Generic Core Scales and Cancer Module. Scores will be calculated for total generic score, total cancer score, each physical function subscale including physical health, psychosocial health, emotional function, social function, school/work function in the Generic Core Scales, and each subscales in the cancer module.
- Palatibility and acceptability of the suspension formulation of lenvatinib in subjects receiving the suspension formulation in the study will be assessed using the Palatability Questionnaire (see Appendix 5).

Exploratory Endpoints

- **Duration of response (DOR) by IIR** is defined as the time from the date a response was first documented until the date of the first documentation of PD or date of death from any case.
- **Disease control rate (DCR) by IIR** is the proportion of subjects who have a best overall response of CR or PR or stable disease (SD). In this context, stable disease is defined as stable disease at ≥7 weeks after randomization to be considered best overall response.
- **Clinical benefit rate (CBR) by IIR** is the proportion of subjects who have best overall response of CR or PR or durable SD (duration of SD ≥23 weeks after randomization).
- Proportion of subjects who achieve complete removal of baseline lesions following completion of chemotherapy.
- **Blood and tumor biomarkers** will be assessed for identifying potential correlation with clinical outcomes-related endpoints.
- All efficacy endpoints listed above (except OS) evaluated based on investigator assessment using RECIST 1.1.

Analysis Sets

The Full Analysis Set (Intent-to-Treat Analysis [ITT]) includes all randomized subjects regardless of the treatment actually received. This is the primary analysis population used for the efficacy analyses which will be based on the ITT principle.

The Per Protocol Analysis Set includes those subjects from the ITT set who received at least 1 dose of any study drug, had no major protocol deviations and had both baseline and at least one postbaseline tumor assessment. Subjects for whom death occurred prior to the first postbaseline tumor assessment will also be included. The per protocol analysis set will be the secondary analysis set for efficacy endpoints.

The Safety Analysis Set includes subjects who received at least 1 dose of any study drug. This is the analysis population used for all safety analyses which will be based on as-treated principle.

Population Pharmacokinetic (PK) Analysis Set includes the subjects who have received at least 1 dose of lenvatinib with documented dosing history and have measurable plasma levels of lenvatinib.

The Pharmacodynamic Analysis Set includes subjects who received at least 1 dose of study drug and had sufficient pharmacodynamic data (eg, at least 1 evaluable/measurable pharmacodynamic parameter).

The HRQoL Analysis Set will consist of all randomized subjects who have received at least 1 dose of study medication, and have completed at least 1 patient-reported outcome (PRO) assessment beyond baseline. For PRO analysis, subjects will be analyzed as randomized and not according to treatment actually received.

Efficacy Analyses

Efficacy analyses will be based primarily on the Full Analysis Set.

All the statistical analysis will be conducted at the PFS-1y/OS-1y analysis data cutoff date (ie, when the last subject has completed 18 cycles of treatment or discontinues before the end of Cycle 18, whichever occurs first), including the analysis of PFS-4m rate. Additional follow-up analysis will be based on the date of data cutoff for the additional follow-up analysis for OS or at the time of last subject last visit, whichever occurs later.

Primary Analysis

The primary analysis of PFS-4m rate will be based upon data provided by IIR of tumor assessments. PFS-4m rate and their Greenwood standard errors will be evaluated using the K-M estimates from both treatment groups. The statistical significance of the difference in the 2 K-M PFS-4m rates comparing lenvatinib + chemotherapy agent (Test Arm) vs. chemotherapy agent alone (Control Arm) will be tested using a 2-sided 80% CI. This 2-sided 80% CI and a p-value will be constructed using the difference of these 2 K-M PFS-4m rates and the 2 corresponding Greenwood standard errors. Statistical significance of the difference is declared if the CI is entirely above 0. This is equivalent to a test using a 1-sided test at alpha=0.1. The 2-sided 95% CIs will also be provided for descriptive purposes. PFS-4m rate will also be analyzed using a binomial approach as a sensitivity analysis by excluding subjects whose PFS are censored prior to 18 weeks.

Secondary Analyses

PFS-1y rate will be analyzed using the same methods as the primary efficacy analysis. PFS censoring rules will follow FDA guidance of 2007, however, removal of baseline lesions after completion of Week 18 without progression is not a trigger for PFS censoring after 18 weeks (refer to Concomitant Drug/Therapy – allowed concomitant treatment/procedures).

Overall survival (OS) will be compared between treatment arm and control arm using the stratified logrank test with time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years) as strata. Median OS with 2-sided 80% and 95% CIs will be calculated using K-M product-limit estimates for each treatment arm, and the K-M estimates of OS will be plotted over time. The Cox regression model will be used to estimate the hazard ratio and its 80% and 95% CIs stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years). K-M estimates will also be presented for 4, 6, 9, and 12 months with 2-sided 80% and 95% CIs.

Median PFS and 2-sided 80% and 95% (as exploratory) CIs will be presented, and the K-M estimates of PFS will be plotted over time. The Cox regression model will be used to estimate the hazard ratio and its 80% and 95% CIs stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years). Kaplan-Meier (K-M) estimates will also be presented for 4, 6, 9, and 12 months with 2-sided 80% and 95% CIs.

The ORR will be compared between the test and control groups using either a chi-square test or a Cochran-Mantel-Haenszel test stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years), as appropriate. Corresponding odds ratios and their 2-sided 80% and 95% CIs comparing the groups will also be presented. The individual treatment group ORRs will also be calculated along with exact 95% confidence intervals using the Clopper and Pearson method.

Exploratory Analyses

Median DOR among responders for each arm will be presented along with its corresponding 2-sided 95% CIs. Disease Control Rate (DCR) and CBR will be calculated with exact 95% CIs using the Clopper and Pearson method. The differences of the above rates between 2 groups and corresponding two-sided 95% CIs will be calculated respectively.

Pharmacodynamic and Other Biomarker Analyses

Pharmacodynamic, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.

Blood serum samples may be analyzed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, or other assays/methods and new technology in an effort to identify biomarkers.

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

Data obtained from the pharmacodynamic samples will be used for research. The pharmacodynamic samples will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib and for potential diagnostic development. If the subject reaches 18 years of age prior to the date of final sample analyses they will be reconsented. No further analyses will be performed on these collected samples from subjects who either do not reconsent after their 18th birthday or cannot be reached for reconsenting and the sample will be destroyed. When the subject reaches the age of 18 years (or 16 years in the UK) while on the study, and becomes competent to give informed consent, his/her consent will be obtained using separate informed consent forms (ICFs) to continue on the study.

Pharmacokinetic Analyses

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

Lenvatinib data from Arm A of the study will be pooled with available data from other studies and subjected to population PK analysis. 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.

Other Analyses

Health-Related Quality of Life (HRQoL):

The PedsQL for all subjects(self- and proxy-rating) will be collected at baseline, at C2D1, C3D1, Week 18, C8D1, C18 D1, and at the Off-Treatment visit.

Interim Analyses

No interim analysis is planned for this study.

The safety monitoring will be conducted by the 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 recommendation whether to stop the study for safety will be reached by the IDMC based on their review of safety data with treatment information. The function and membership of the IDMC will be described in the IDMC charter.

Sample Size Rationale

A binomial-based comparison of 2 proportions using correction for continuity was used for sample size estimation. A total sample size of 72 subjects is estimated to achieve 80% statistical power at 1-sided alpha of 0.1 to detect a difference of 30% based on the assumption that PFS-4m for Arm A (lenvatinib arm) is 55% and for Arm B is 25%. Alpha is the type 1 error probability of declaring lenvatinib arm being effective when the true lenvatinib arm PFS-4m rate is only 25%.

2 TABLE OF CONTENTS

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANC	absolute neutrophil count
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
BSA	body surface area
CA	Competent Authorities
CBR	clinical benefit rate
CFR	Code of Federal Regulations
C_{max}	maximum drug or metabolite concentration
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP/CYP3A4	Cytochrome P450/cytochrome P4503A4
DCR	disease control rate
DOR	duration of response
DTC	differentiated thyroid cancer
ESMO	European Society for Medical Oncology
FGFR	fibroblast growth factor receptor
FGF	fibroblast growth factor
GFR	glomerular filtration rate
G-CSF	granulocyte-colony stimulating factor
HRQoL	health-related quality of life
HR	heart rate
ICF	informed consent form

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICL	imaging core laboratory
ID	identification
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IIR	independent imaging review
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenously
IVRS	interactive voice response system
KDR	kinase insert domain receptor
K-M	Kaplan-Meier
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
OS-1y	overall survival rate at 1 year
PD	progressive disease/disease progression
PDGFR	platelet-derived growth factor receptor
PedsQL	Pediatric Quality of Life Inventory
PFS	progression-free survival
PFS-4m	progression-free survival rate at 4 months
PFS-1y	progression-free survival rate at 1 year
PK	pharmacokinetic(s)
PR	partial response
PRES	posterior reversible leukoencephalopathy syndrome
PT	preferred term
QD	once daily

QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
RP2D	recommended Phase 2 dose
RPLS	reversible posterior leukoencephalopathy syndrome
RTK	receptor tyrosine kinase
RTKI	receptor tyrosine kinase inhibitor
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SmPC	summary of product characteristics
SOC	system organ class
SOP	standard operating procedure
SUSARs	suspected unexpected serious adverse reactions
TEAEs	treatment-emergent adverse events
TKI	tyrosine kinase inhibitors
TNM	tumor-node metastasis
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WHO DD	World Health Organization Drug Dictionary

4 ETHICS

4.1 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 the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice), Section 3, and any local regulations (eg, European Union [EU] Clinical Trials Directive 2001/20/EC or Code of Federal Regulations, Title 21 CFR Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate(s) [CRAs], 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.

Documented study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) 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 (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

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

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The definition of the end of the study is the date of the data cutoff for the final analysis or last subject/last visit, including discontinuation from the study for any reason, whichever occurs later.

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

4.2 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 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
- An IRB waiver request will be submitted before study initiation for non-US sites conducted under an Investigational New Drug (IND) application.
- 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.
- Other applicable regulatory authorities' requirements or directives

4.3 Subject Information and Informed Consent

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

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable 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 legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. In countries where specific laws for children are established for informed consent, those local laws will be applied. After the ICF and/or assent form and any other written information to be provided to subjects is read and explained to the subject or the subject's 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 and/or assent form, 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 ICF and/or assent form before any study-

specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (eg, EU Clinical Trials Directive 2001/20/EC or Code of Federal Regulations, Title 21, CFR Part 50). Each subject and the subject's parent(s) or legally acceptable representative must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

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

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

5 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 70 investigational sites worldwide.

The name, telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Regulatory Binder provided to each site.

6 INTRODUCTION

6.1 Osteosarcoma

Cancer is a relatively uncommon diagnosis in the pediatric population, and the overall incidence is low (18.6 cases per 100,000 children [Howlader, et al., 2019]). Solid tumors constitute approximately 60% of childhood malignancies (Howlader, et al., 2019). Malignant bone tumors are the fifth most common solid tumor type accounting for about 5% of childhood tumors (Howlader, et al., 2019; Kaatsch, 2010).

Osteosarcoma is the most commonly diagnosed primary malignancy of the bone in children and young adults, and accounts for approximately 5% of childhood tumors, with an estimated annual incidence of 4.4 cases per 1 million in people younger than 24 years (Mirabello, et al., 2009). Osteosarcoma occurs predominantly in adolescents and young adults. The median age at diagnosis is 20 years, with the incidence peaking at 15 to 19 years of age (ESMO, guidelines, 2014). According to the American Cancer Society, osteosarcoma in this age group is 8 per 1 million (Ward, et al., 2014).

There are both intrinsic and extrinsic factors that have been shown to contribute to the development of osteosarcoma. Studies have demonstrated that several genetic abnormalities, including the overexpression of vascular endothelial growth factor (VEGF) receptor (VEGFR), platelet-derived growth factor (PDGF) receptor (PDGFR), and c-fos, are associated with the development of osteosarcoma in laboratory models as well as humans (Gorlick and Khanna, 2010). However, osteosarcoma is not characterized by a single oncogenic driver. The vast majority of abnormal oncogenes and tumor-suppressor genes associated with osteosarcoma are also common in the most prevalent cancers (Gorlick and Khanna, 2010). Extrinsic factors such as ionizing radiation, which is used for the treatment of childhood solid tumors, have been well implicated in the development of a second malignancy, with osteosarcoma being the most likely to develop within the first 2 decades following treatment (Le Vu, et al., 1988).

The management of osteosarcoma is multimodal; patients not amenable to surgery or patients at second or third relapse have a poor prognosis. Metastatic osteosarcoma is common (10% to 20%) (NCCN, Bone cancer guidelines, 2020, Casali, et al., 2018), with the most frequent site being the lung (>85%). In the case of isolated lung metastases, more than a third of patients with a second surgical remission survive for >5 years (Casali, et al., 2018). Approximately 25% of all patients with primary metastatic osteosarcoma and >40% of those who achieve a complete surgical remission may become long-term survivors (Casali, et al., 2018) as compared with 65% to 70% of patients with localized disease (Meazza and Scanagatta, 2016).

About 30% to 40% of patients with localized disease and 80% of those with metastatic disease experience relapse (Casali, et al., 2018; NCCN, Bone cancer guidelines, 2020; Ferrari, 2003). The presence of solitary metastasis, time to first relapse, and complete resectability of disease at first recurrence are the most significant prognostic indicators for improved survival. Patients whose tumor is not amenable to surgery, or with second or third recurrence, or who have metastases to the bone, have a poor prognosis. In general, despite second-line treatment, the prognosis of recurrent disease in osteosarcoma has remained poor, with long-term postrelapse survival of <20% (Casali, et al., 2018; NCCN Bone Cancer Guidelines, 2020).

6.2 Current Therapeutic Options

There has been no substantial progress in the treatment of osteosarcoma since the 1980s. Current treatment utilizes multi-agent chemotherapy and surgical resection of all clinically detectable disease.

Treatment of Newly Diagnosed Disease

Newly diagnosed osteosarcoma is typically managed with neoadjuvant chemotherapy followed by surgical removal of the primary tumor and all clinically evident metastatic disease, followed by adjuvant chemotherapy. Surgical resection of all clinically detectable sites of disease is vital, regardless of number and site, as complete resection is predictive of

survival (Meazza and Scanagatta, 2016). For patients with unresectable disease at multiple sites, experimental therapy is also considered, due to the poor prognosis for these patients.

The most effective chemotherapy regimens include the combination of high-dose methotrexate, doxorubicin, and cisplatin and has become the standard treatment for high-grade osteosarcoma (Ferrari and Serra, 2015; Isakoff, et al., 2015; NCCN Bone Cancer Guidelines, 2020).

Treatment of Relapsed, Refractory, and Progressive Disease

Second-line treatment for relapsed disease consists of chemotherapy and/or surgical resection (Casali, et al., 2018; NCCN Bone Cancer Guidelines, 2020). The role of second-line chemotherapy for recurrent osteosarcoma is much less well defined than that of surgery, and there is no accepted standard regimen (Casali, et al., 2018). For patients with resectable solitary metastasis to the lung, surgical resection only may be adequate. For those with recurrent pulmonary metastases that are resectable, surgery is advised in addition to neoadjuvant or adjuvant chemotherapy, regardless of the number of previous lung relapses and the number of secondary pulmonary lesions (Briccoli, et al., 2005). Aggressive surgical resection of metastases and the ability to achieve a second surgical remission have consistently been shown essential for long-term survival following relapse (Kempf-Bielack, et al., 2005; Leary, et al., 2013; Bacci, et al., 2005; Chou, et al., 2005; Hawkins and Arndt, 2003).

As per the European Society for Medical Oncology (ESMO) guidelines for bone sarcoma, treatment options for recurrent osteosarcoma include ifosfamide ± etoposide ± carboplatin, and other active drugs (Casali, et al., 2018). Preferred regimens for second-line therapy per the National Comprehensive Cancer Network (NCCN) bone sarcoma guidelines include ifosfamide (high dose) with or without etoposide, regorafenib, sorafenib, and sorafenib plus everolimus (NCCN Bone Cancer Guidelines, 2020).

In the event of subsequent relapse, the NCCN guidelines (NCCN Bone Cancer Guidelines, 2020) and ESMO guidelines (Casali, et al., 2018) strongly encourage participation in clinical studies. Otherwise, patients with disease progression or relapse after second-line therapy are managed with surgical resection, palliative radiotherapy, or best supportive care.

6.3 Lenvatinib

E7080 (lenvatinib) is a potent multiple receptor tyrosine kinase (RTK) inhibitor (RTKI) that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other pro-angiogenic and oncogenic pathway-related RTKs, including fibroblast growth factor (FGF) receptor (FGFR) 1-4, PDGF receptor alpha (PDGFRα), KIT, and RET. Therefore, lenvatinib exerts it's in vivo antitumoural activity based on multiple mechanisms involved in and through effects related to angiogenesis (including reversion of resistance) and the tumor microenvironment, as well as direct inhibitory action on the tumour cells. Recent studies have also demonstrated lenvatinib's immunomodulatory activity in the tumor microenvironment. This includes decreases in immunosuppressive tumor-associated

macrophages, activated cytotoxic T cell increases, and activation of interferon-gamma signaling. These all contribute to lenvatinib's antitumor activity in immunocompetent mice (Kato, et al., 2019; Kimura, et al., 2018).

6.3.1 Clinical Data on Lenvatinib in Combination with Ifosfamide and Etoposide for Treatment of Relapsed or Refractory Osteosarcoma

The safety, tolerability and activity of single-agent lenvatinib, and lenvatinib in combination with chemotherapy (ifosfamide and etoposide), have been assessed in E7080-G000-207 (Study 207), a phase 1/2, multicenter, open-label study in children, adolescents and young adults with solid tumors, including relapsed or refractory osteosarcoma, and radioiodine- refractory differentiated thyroid carcinoma. The recommended phase 2 dose (RP2D) of lenvatinib was determined in the phase 1b portion as 14 mg/m^2 orally once daily when given as single-agent as well as in combination with etoposide (100 mg/m^2 IV once daily for 3 days) + ifosfamide (3000 mg/m^2 IV once daily for 3 days), administered on days 1 to 3 of each 21-day cycle, for 5 cycles. Safety and efficacy is being assessed in the Phase 2 portion of the study.

Data from Study 207 have shown that patients with osteosarcoma may benefit from treatment with lenvatinib. In the single agent expansion cohort in relapsed/refractory osteosarcoma, (n=31; Cohort 2B), 9 of 28 evaluable patients (32.1%) achieved progression-free survival (PFS) at 4 months (PFS-4m), median PFS was 3.0 months (95% CI: 1.8, 5.5). Two out of 29 subjects (6.9%) with measurable disease had a partial response (PR) (Gaspar, et al., 2018).

Among the 31 subjects included in the safety analysis set for the single-agent lenvatinib expansion cohort, the most common adverse events were: headache (48%), vomiting (45%), decreased appetite, diarrhea, and hypothyroidism (42% each), proteinuria (39%), increased blood TSH, hypertension, nausea, pyrexia, and weight decreased (36% each). Five subjects (16.1%) discontinued treatment due to TEAEs, and 8 subjects (25.8%) reported TEAEs leading to study drug dose reduction. There were no treatment-related fatal TEAEs (Gaspar, et al., 2018).

In a pooled analysis of subjects from Phase 1b and 2 receiving lenvatinib 14 mg/m^2 in combination with ifosfamide plus etoposide (N=35; full analysis set), the primary efficacy endpoint, PFS-4 rate based on RECIST 1.1 by investigator assessment, was 67.9% (95% CI: 47.6, 84.1). As of the data cutoff date of 23 Jul 2019, the objective response rate (ORR) was 12.5%, including 4 subjects with PR. Median PFS was 11.1 months (95% CI: 4.5, 12.6), and median overall survival (OS) was 16.3 months (95% CI: 12.6, NE) (Gaspar, et al., 2019).

Overall treatment with lenvatinib in combination with ifosfamide and etoposide in this patient population was associated with a manageable safety profile, and no unexpected toxicities were observed. Among the 31 subjects included in the safety analysis set, the most frequent treatment-emergent adverse events (TEAEs) were anemia (71%), nausea and vomiting (61% each), diarrhea (52%), neutropenia, platelet count decreased, and white blood cell count decreased (48% each). The most common treatment-related grade ≥3 TEAEs were anemia (52%), neutropenia (48%), platelet count decreased and white blood cell count

decreased (42% each), neutrophil count decreased (32%), and thrombocytopenia (29%). Eight subjects (25.8%) discontinued treatment due to TEAEs, and 15 subjects (48.4%) reported TEAEs leading to study drug dose reduction. There were no treatment-related fatal TEAEs (Gaspar, et al., 2019).

6.4 Study Rationale

Study 230, a randomized, controlled Phase 2 study, will evaluate the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide in children, adolescents, and young adults with relapsed or refractory osteosarcoma. Eligible patients aged 2 to 25 years old will receive ifosfamide and etoposide with or without lenvatinib (14 mg/m^2; RP2D from Study 207). Subjects randomized to Arm A can continue to receive lenvatinib until disease progression, intolerable toxicity, or withdrawal of consent. Approximately 72 subjects will be treated in the study. The primary objective of the study is to demonstrate that lenvatinib in combination with ifosfamide and etoposide has superior efficacy compared to ifosfamide and etoposide based on the PFS-4m rate in children, adolescents and young adults with relapsed or refractory osteosarcoma.

Pediatric solid tumors are highly vascularized. Angiogenesis and vasculogenesis are the fundamental processes by which new blood vessels are formed. As with normal tissue, the growing tumor requires an extensive network of capillaries to provide the necessary nutrients and oxygen. Moreover, the new intratumor blood vessels offer a way for tumor cells to enter the circulation and metastasize to distant organs and thus play an indispensable role in solid tumor growth and metastasis. Thus, inhibition of angiogenesis is a viable target for anticancer therapy. Moreover, vascular normalisation allows reoxygenation, hence the addition of an anti-VEGF to chemotherapy may result in increased uptake of drugs into tumor tissue (Tuettenberg, et al., 2006).

7 STUDY OBJECTIVES

7.1 Primary Objective

To evaluate whether lenvatinib in combination with ifosfamide and etoposide (Arm A) is superior to ifosfamide and etoposide (Arm B) in improving PFS-4m rate (by independent imaging review [IIR] using Response Evaluation Criteria In Solid Tumors [RECIST 1.1]), in children, adolescents, and young adults with relapsed or refractory osteosarcoma.

7.2 Secondary Objectives

The secondary objectives of the study are to:

1. Compare differences in PFS rate at 1 year (PFS-1y) between the 2 treatment arms
2. Compare differences in PFS Kaplan-Meier (K-M) survival curves and median PFS between the 2 treatment arms
3. Compare differences in OS and OS rate at 1 year (OS-1y) between the 2 treatment arms

4. Compare differences in objective response rate (ORR) at 4 months between the 2 treatment arms
5. Compare differences in safety and tolerability between the 2 treatment arms
6. Characterize the pharmacokinetics (PK) of lenvatinib, when administered in combination with ifosfamide and etoposide
7. Compare differences in health-related quality of life (HRQoL) as assessed by using the the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales and Cancer Module between the 2 treatment arms
8. Assess the palatability and acceptability of the suspension formulation of lenvatinib in pediatric subjects receiving the suspension formulation in the study

7.3 Exploratory Objective(s)

The exploratory objectives of the study are to:

1. Explore differences in duration of response (DOR), disease control rate (DCR), and clinical benefit rate (CBR) between the 2 treatment arms
2. Compare the proportion of subjects who achieve complete removal of baseline lesion(s) following completion of chemotherapy between the 2 treatment arms
3. Investigate the relationship between subject tumor biomarkers and clinical response and toxicity of lenvatinib in combination with ifosfamide and etoposide

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This is a multicenter, randomized, open-label, parallel-group, Phase 2 study to compare the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide in children, adolescents, and young adults with relapsed or refractory osteosarcoma.

Approximately 72 eligible subjects will be randomized to 1 of the following 2 treatment arms in a 1:1 ratio within the strata:

- Arm A: lenvatinib 14 mg/m^2 (orally, once daily) plus ifosfamide 3000 mg/m^2/day (intravenously [IV], Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)
- Arm B: ifosfamide 3000 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)

Randomization will follow a predefined randomization scheme based on the following stratification factors: time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 and ≥18 years).

Eisai will closely monitor enrolment, to ensure that at least 32 subjects <18 years of age at the time of informed consent are randomized.

The study will be conducted in 3 Phases: a Pre-randomization Phase, a Randomization Phase, and an Extension Phase.

The end of the study will be the date of data cutoff for the final analysis or the time of last subject last visit, whichever occurs later.

An overview of the study design is presented in Figure 1.

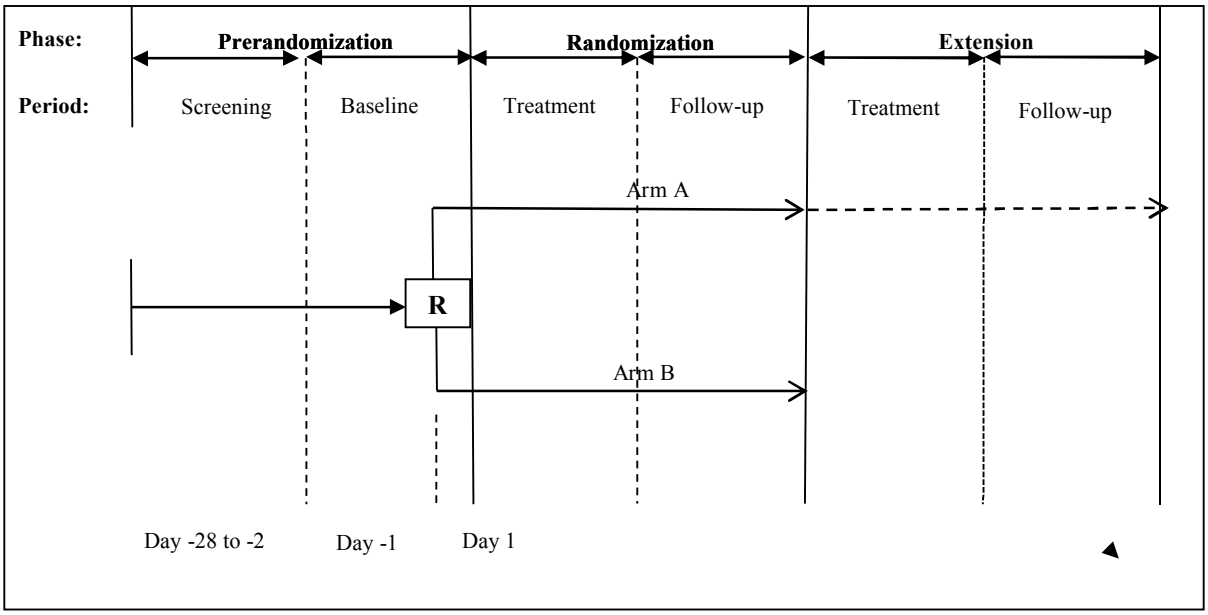

Figure 1 Overall Study Design

Follow-up can occur during the Randomization Phase (if the subject discontinued treatment during the Randomization Phase), or during the Extension Phase, after the termination of study treatment.
Arm A = lenvatinib+ifosfamide+ etoposide (ifosfamide+etoposide for maximum of 5 cycles; lenvatinib to be continued until disease progression, intolerable toxicity, subject request, withdrawal of consent, or study termination by the sponsor, whichever occurs first.
Arm B = ifosfamide+ etoposide (maximum of 5 cycles)
R = randomization

8.1.1 Prerandomization Phase

The Prerandomization Phase will consist of 2 periods: Screening and Baseline. The Prerandomization Phase will last no longer than 28 days. The Screening Period will establish protocol eligibility and the Baseline Period will confirm eligibility.

8.1.1.1 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 4.3.

Subjects must have a histologically or cytologically confirmed diagnosis of high grade refractory or relapsed osteosarcoma as detailed in the Inclusion Criteria (Section 8.3.1).

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

8.1.1.2 Baseline Period

The purpose of the Baseline Period is to confirm protocol eligibility as specified in the inclusion/exclusion criteria (as detailed in Section 8.3.1 and Section 8.3.2). Results of baseline assessments must be obtained prior to the first dose of study drug (Cycle 1 Day 1). Baseline assessments may be performed on Day -1 or on Cycle 1 Day 1 prior to dosing. Clinical laboratory tests (Table 4), including a pregnancy test (where applicable), should be performed within 72 hours prior to the first dose of study drug.

Subjects who complete the Baseline Period and continue to meet the criteria for inclusion/exclusion (as detailed in Section 8.3.1 and Section 8.3.2) will begin the Randomization Phase of this study.

8.1.2 Randomization Phase

The Randomization Phase will consist of 2 periods: Treatment Period and Follow-up Period. The Randomization Phase will begin at the time of randomization of the first subject and will end on the data cutoff date for the PFS-1y and OS-1y analysis. Data cutoff for PFS-1y and OS-1y analysis will occur when the last subject has completed 18 cycles of treatment or discontinues before the end of Cycle 18, whichever occurs first.

After the data cutoff date for the PFS-1y and OS-1y analysis has occurred, all subjects who are still on study treatment will enter the Extension Phase.

8.1.2.1 Treatment Period

The Treatment Period for each subject will begin at the time of randomization and will end at the completion of the Off-Treatment Visit which will occur within 30 days after the final dose of study treatment.

Subjects will receive study treatment as continuous 21-day cycles in both treatment arms. Treatment cycles will be counted continuously regardless of dose interruptions. If chemotherapy administration is precluded on Day 1 of a treatment cycle, the subject may resume treatment once recovered at the discretion of investigator. Subsequent chemotherapy will be administered every 21 (±1) days starting from the timepoint it was resumed. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments (Table 5). Subjects randomized to Arm A will continue to receive lenvatinib until disease progression (PD) confirmed by IIR, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor, whichever occurs first.

Disease progression (PD) must be confirmed by IIR prior to the investigator discontinuing study treatment for a subject. In situations where the investigator judges that alternative treatments must be instituted immediately for a subject's safety, study drugs may be discontinued without waiting for IIR confirmation of radiographic evidence of PD. If possible, before discontinuation of the subject from the study, the investigator should consult with the sponsor.

8.1.2.2 Follow-Up Period

The Follow-up Period begins the day after the Off-Treatment Visit and will continue as long as the subject is alive, unless the subject withdraws consent or the sponsor terminates the study.

Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn, however, an investigator may consult public records to establish survival status if permitted by local regulations.

All adverse events (AEs) will be captured for 30 days after the last dose of study drug.

All subjects who discontinue study treatment early for reasons other than PD, will continue to undergo tumor assessments every 6 weeks until Week 18, then every 9 weeks until Week 54, thereafter, every 12 weeks until IIR confirmation of radiographic evidence of PD as described in the tumor assessments in the assessment schedule, or until another anticancer therapy is initiated.

Subjects in both Arm A and Arm B will be followed for survival every 12 weeks (±1 week) and all subsequent anticancer treatments received will be recorded. Subjects who are being followed for survival at the time of data cutoff for the for PFS-1y and OS-1y analysis (ie, at the end of the Randomization Phase) will continue to be followed for survival during the Follow-up Period of the Extension Phase.

8.1.3 Extension Phase

The Extension Phase will consist of 2 periods: Treatment Period and Follow-up Period.

8.1.3.1 Treatment Period

In the Treatment Period, subjects still on lenvatinib in Arm A following the completion of the PFS-1y and OS-1y analysis (ie, at the end of the Randomization Phase) will continue to receive lenvatinib in 21-day cycles until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor. Tumor assessments will be performed according to the local standard of care. Independent imaging review (IIR) review and confirmation of radiographic evidence of PD will not be required, and scans will no longer be required to sent to the imaging core laboratory (ICL). The Off-Treatment Visit will occur within 30 days after the final dose of study treatment. All AEs will be captured up to 30 days after last dose of study drug. In case the study is

discontinued by the sponsor, the sponsor will continue to provide study drug (outside the study) for subjects requiring continuation of treatment.

8.1.3.2 Follow-Up Period

The Follow-up Period will begin the day after the Off-Treatment Visit and will last until death or for 2 years after end of treatment for a subject, unless the study is terminated by the sponsor, or the subject discontinues due to withdrawal of consent, or is lost to follow-up. Subjects will be treated by the investigator according to the prevailing local standard of care. Subjects will be followed every 12 weeks (±1week) for survival and all subsequent anticancer treatments received will be recorded.

8.2 Discussion of Study Design, Including Choice of Control Groups

The study has been designed as an open-label, randomized study to compare the safety and efficacy of lenvatinib in combination with the ifosfamide and etoposide with ifosfamide and etoposide alone in children, adolescents, and young adults with relapsed or refractory osteosarcoma. Ifosfamide and etoposide will be used as the control group since it is a recognized treatment option for patients with relapsed osteosarcoma.

Progression-free survival (PFS) rate at 4 months (PFS-4m) as compared to control, with blinded IIR of radiological imaging using RECIST 1.1 criteria will be evaluated as the primary endpoint. The endpoint was determined as appropriate for the study, given the unique biology of the osteosarcoma (bone lesions do not shrink) and the vital role of surgical resection of metastatic lesions, where possible, in the management of patients with this tumor. Pulmonary metastases are most common in osteosarcoma, and the ability to achieve a second surgical remission has consistently been shown essential for long-term survival following relapse (Kempf Bielack, et al., 2005; Leary, et al., 2013; Bacci, et al., 2005; Chou, et al., 2005; Hawkins and Arndt, 2003). The protocol allows for surgical resection of baseline lesions after completion of the Week 18 tumor assessment. This timepoint allows for surgical resection after completion of chemotherapy without confounding data due to subjects undergoing surgery. To avoid bias in efficacy assessment, the analysis for primary endpoint is based on tumor assessment by IIR, a central independent blinded assessment. Progression-free survival at 1 year (PFS-1y), PFS, and OS will also be evaluated in the study as secondary endpoints.

Pharmacodynamic serum and tumor biomarkers identified in other lenvatinib clinical studies will be assessed in samples collected from subjects enrolled in this study in the test arm only (Arm A: lenvatinib + ifosfamide + etoposide) and may be used for exploratory analysis for evaluation of response-related and/or safety-related outcomes.

The study will also assess health related quality of life (HRQoL) using validated questionnaires.

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg,

demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups.

8.3 Selection of Study Population

Approximately 72 subjects between 2 and ≤25 years of age will be randomised (36 subjects in each arm). Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

For evaluation of the primary endpoint (intent–to-treat analysis), at least 32 subjects <18 years old (at the time of informed consent) will be randomized.

8.3.1 Inclusion Criteria

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

1. Histologically or cytologically confirmed diagnosis of high grade osteosarcoma.
2. Refractory or relapsed osteosarcoma after 1 to 2 prior systemic treatments.
3. Measurable or evaluable disease per RECIST 1.1 that meets the following criteria:
   - Must be accurately measurable with a minimum size (by long axis) of 10 mm using computed tomography/magnetic resonance imaging (CT/MRI) (lymph nodes must be accurately measurable with a minimum size [by short axis] of 15 mm).
   - Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must have subsequently grown unequivocally to be deemed a target lesion.
4. Aged 2 years to ≤25 years at the time of informed consent.
5. Life expectancy of 12 weeks or more.
6. Lansky play score ≥50% or Karnofsky Performance Status score ≥50%. Use Karnofsky for subjects ≥16 years of age and Lansky for subjects <16 years of age. 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.
7. Adequate bone marrow function as evidenced by:
   a. absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L.

      (subjects with bone marrow involvement should have ANC $\geq 0.8 \times 10^9$/L and leucocyte count $\geq 1 \times 10^9$/L).
   b. hemoglobin ≥8.0 g/dL (a hemoglobin of <8.0 g/dL is acceptable if it is corrected by growth factor or transfusion before Cycle 1 Day 1).
   c. platelet count $\geq 75 \times 10^9$/L.
8. Adequate blood coagulation function defined by International Normalized ratio (INR) ≤1.5 unless participant is receiving anticoagulant therapy, as long as INR is within therapeutic range of intended use of anticoagulants.
9. Adequate liver function as evidenced by:
   a. bilirubin ≤1.5 times the upper limit of normal (ULN).

b. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3×ULN (in the case of liver metastases ≤5×ULN).

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

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

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

    b. Urine dipstick <2+ for proteinuria. Subjects who have ≥2+ proteinuria on dipstick urinalysis should undergo a spot protein-creatinine (P/C) ratio test that should be Grade <2 per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and if possible perform a 24-hour urine collection (children and adolescents ≤12 years of age must have ≤500 mg of protein/24 hours and subjects >12 years of age must have ≤1 g of protein/24 hours).
    c. No clinical evidence of nephrotic syndrome.
11. Adequate cardiac function as evidenced by left ventricular ejection fraction (LVEF) ≥50% at baseline as determined by echocardiography.
12. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as:
    a. BP <95th percentile for sex, age, and height/length at screening (as per National Heart Lung and Blood Institute guidelines) and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1. Subjects >18 years of age should have BP ≤150/90 mm Hg at screening and no change in antihypertensive therapy within 1 week prior to Cycle 1 Day 1.
13. Washout before Cycle 1 Day 1 of 3 weeks in case of prior chemotherapy, 6 weeks if treatment included nitrosoureas; 4 weeks for definitive radiotherapy, 2 weeks for palliative radiotherapy; and 3 months from high-dose chemotherapy and stem cell rescue. Subjects must have recovered (to Grade ≤1, except for alopecia, ototoxicity, and Grade ≤2 peripheral neuropathy, per CTCAE v5.0) from the acute toxic effects of all prior anticancer therapy before Cycle 1 Day 1.
14. Written and signed informed consent from the parent(s) or legal guardian and assent from the minor subject. Written informed consent from subjects ≥18 years.

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

8.3.2 Exclusion Criteria

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

1. Any active infection or infectious illness unless fully recovered prior to Cycle 1 Day 1 (ie, no longer requiring systemic treatment).
2. Subjects with central nervous system metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy, surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 2 weeks before Cycle 1 Day 1.
3. Active second malignancy within 2 years prior to enrollment ([in addition to osteosarcoma], but not including definitively treated superficial melanoma, carcinoma-in-situ, basal or squamous cell carcinoma of the skin).
4. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
5. Has had major surgery within 3 weeks prior to Cycle 1 Day 1. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
6. Known hypersensitivity to any component(s) of the study drugs (lenvatinib, ifosfamide, and etoposide, or their ingredients).
7. Currently receiving any investigational drug or device in another clinical study or within 28 days prior to Cycle 1 Day 1.
8. A clinically significant ECG abnormality, including a marked baseline prolonged QT or QTc interval (eg, a repeated demonstration of a QTc interval >480 msec).
9. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that in the opinion of the investigator might affect the absorption of lenvatinib.
10. Pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula.
11. Gastrointestinal bleeding or active hemoptysis (bright red blood of at least ½ teaspoon) within 3 weeks prior to Cycle 1 Day 1.
12. Radiographic evidence of intratumoral cavitation, encasement, or invasion of a major blood vessel. Additionally, the degree of proximity to major blood vessels should be considered for exclusion because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.
13. History of ifosfamide-related Grade ≥3 nephrotoxicity or encephalopathy.
14. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
15. Known to be human immunodeficiency virus (HIV) positive. Note: HIV testing is required at screening only when mandated by local health authority.

16. Active viral hepatitis (B or C) as demonstrated by positive serology. Note: Testing for Hepatitis B or Hepatitis C is required at screening only when mandated by local health authority.
17. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG]) (human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG /hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of any study drug.
18. Females of childbearing potential* who:
    - Do not agree to use a highly effective method of contraception for the entire study period and for 28 days after lenvatinib discontinuation or 12 months after etoposide and ifosfamide discontinuation, ie:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
        - A contraceptive implant
        - an oral contraceptive. Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing with study drug and throughout the study and for 28 days after lenvatinib discontinuation or 12 months after etoposide and ifosfamide discontinuation .

          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, or the subject has changed oral hormonal contraceptive product/dose within 4 weeks prior to study drug administration, 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.

    * All post pubertal females will be considered to be of childbearing potential unless they have early menopause (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).
19. 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 28 days after lenvatinib discontinuation or 6 months after discontinuation of etoposide and ifosfamide). No sperm donation is allowed during the study period and for 28 days after lenvatinib discontinuation or 6 months after discontinuation of etoposide and ifosfamide.

8.3.3 Removal of Subjects From Therapy or Assessment

Subjects will continue to receive study treatment until any of the following occur:

- Progressive disease (as confirmed by IIR)
- Unacceptable toxicity
- Subject request
- Withdrawal of consent
- Termination of the study by the Sponsor

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 protocol-specified off-treatment visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents.

During the Follow-Up Period, subjects who have discontinued study treatment without progression should have disease assessments as per the appropriate tumor assessment schedule in Table 5 and Table 6 from the date of the last assessment until PD is documented or another anticancer therapy is initiated. After data cutoff of PFS-1y and OS-1y, tumor assessments may be performed as clinically indicated per institutional guidelines, following the prevailing local standard of care, and IIR confirmation of radiographic evidence of PD will not be required.

All subjects will be followed for survival until death or for 2 years after end of treatment for a subject, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up after completion of the primary study analysis.

8.4 Treatment(s)

8.4.1 Treatment(s) Administered

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

Test Arm (Arm A): Lenvatinib + Ifosfamide + Etoposide

Lenvatinib 14 mg/m^2, orally administered once daily in each 21-day cycle.

Lenvatinib is provided as hard capsules containing 1 mg, 4 mg, or 10 mg lenvatinib. An extemporaneous suspension of lenvatinib capsules should be used for subjects unable to

swallow capsules. After adjustment for body surface area (BSA), the daily dose can not exceed 24 mg QD.

Ifosfamide 3000 mg/m^2/day, IV, for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Etoposide 100 mg/m^2/day, IV, for 3 consecutive days (Day 1 to 3) , every 21 days, for a maximum of 5 cycles.

Treatment with lenvatinib will continue in 21-day cycles after chemotherapy is discontinued, until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor. In case the study is discontinued by the sponsor, the sponsor will continue to provide study drug (outside the study) for subjects requiring continuation of treatment.

Control Arm (Arm B): Ifosfamide + Etoposide

Ifosfamide 3000 mg/m^2/day, IV, daily for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

Etoposide 100 mg/m^2/day, IV, daily for 3 consecutive days (Day 1 to 3), every 21 days, for a maximum of 5 cycles.

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

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

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

Subjects will receive study treatment as continuous 21-day cycles in both treatment arms. Treatment cycles will be counted continuously regardless of dose interruptions. If chemotherapy administration is precluded on Day 1 of a treatment cycle, the subject may resume treatment once recovered at the discretion of investigator. Subsequent chemotherapy will be administered every 21 (±1) days starting from the timepoint it was resumed.

8.4.1.1 Lenvatinib Dose Reduction and Interruption Instructions

Adverse events will be graded using CTCAE version 5.0.

Dose reduction and interruptions for subjects who experience lenvatinib related toxicity will be managed as described in Table 1.

The starting dose of lenvatinib is 14 mg/m^2. Dose reductions occur in succession based on the previous dose level. Each dose level reduction is a 20% reduction from the previous dose.

Once the study drug dose level 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.

Refer to the subsections below for management of hypertension, posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (PRES/RPLS), proteinuria, hepatotoxicity, thromboembolic events, hypocalcemia, gastrointestinal symptoms and acute abdominal pain, and hemorrhage, as appropriate, before consulting the dose modification table below.

Table 1 Criteria for Temporary Discontinuation of Study Drug, Dose Reduction, and Resumption of Treatment

Dose Modification Guidelines for Lenvatinib 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] or Grade 3[e]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	11.2 mg/m^2 (or 20% reduction of the starting dose) orally QD (one-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	9.0 mg/m^2 (or 20% reduction of the previous dose) orally QD (one-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	7.2 mg/m^2 (or 20% reduction of the previous dose) orally QD (one-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with sponsor
Grade 4[f]: Discontinue Study Treatment		

Note: For grading see CTCAE version 5.0. Collect all CTC grades of adverse events, decreasing and increasing grade.

BMI = body mass index, CTCAE = Common Terminology Criteria for Adverse Events

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, hypertension, 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 1 weight 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 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. Obesity is defined as body mass index (BMI) percentiles corresponding to 30 kg/m², related to the age of the children (Cole, et al., 2000) or BMI ≥ the 95th percentile for children and teens of the same age and sex (Ogden, et al., 2002) (Appendix 8 and Appendix 9).

e: 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.

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

8.4.1.1.1 BLOOD PRESSURE

For children, blood pressure varies by the sex and age of the child and it is closely related to height and weight. Blood pressure will be assessed in terms of percentile for sex, age and height/length. Guidelines to sex, age, and height-specific percentiles of blood pressure are provided in Appendix 6 and Appendix 7. Blood pressure that is consistently above the 95th percentile [for subjects age 18 to 25 years BP ≤140/90 mm Hg] for age and height/length

requires further evaluation. A referral to a cardiologist is recommended for patients who develop hypertension during the study. Ideally, cardiovascular assessments and the management of hypertension should be supervised by a cardiologist. Exercise, excitement, coughing, crying, and struggling may raise the systolic pressure of children as much as 40 to 50 mmHg greater than their usual level. Variability in blood pressure in children of approximately the same age and body build should be expected and serial measurements should always be obtained when evaluating a patient with hypertension.

8.4.1.1.2 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 mm Hg] for sex, age, and height/length at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1 Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be conducted as detailed in the Schedule of Procedures/ Assessments (Table 5 and Table 6). Hypertension will be graded using CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

If the subject's initial BP measurement is elevated (systolic BP ≥95th percentile [BP ≥140 mm Hg] or diastolic BP ≥95th percentile [BP ≥90 mm Hg]), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥95th percentile [BP ≥140 mm Hg] or diastolic BP ≥95th percentile [BP ≥90 mm Hg]) is confirmed on 2 assessments obtained 30 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when systolic BP ≥95th percentile [BP ≥140 mm Hg] or diastolic BP ≥95th percentile [BP ≥90 mm Hg] is first observed on 2 assessments obtained 30 minutes apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instances where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥99th percentile [BP ≥160/100 mm Hg], significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant comorbidities). Once the

subject has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

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

The following guidelines should be followed for the management of systolic BP ≥99th percentile (BP ≥160 mm Hg) or diastolic BP ≥99th percentile (BP ≥100 mm Hg) confirmed on repeat measurements after at least 30 minutes:

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

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

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

    - If systolic BP ≥99th percentile (BP ≥160 mm Hg) or diastolic BP ≥99th percentile (BP ≥100 mm Hg) recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP <95th percentile (BP ≤150 mm Hg) and diastolic BP <95th percentile (BP ≤95 mm Hg) and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥99th percentile (BP ≥160 mm Hg) or diastolic BP ≥99th percentile (BP ≥100 mm Hg) recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction only when systolic BP <95th percentile (BP ≤150 mm Hg and diastolic BP <95th percentile (BP ≤95 mm Hg) and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

- Additional dose reduction should be discussed with the Sponsor.

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

- Institute appropriate medical management
- Discontinue lenvatinib

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

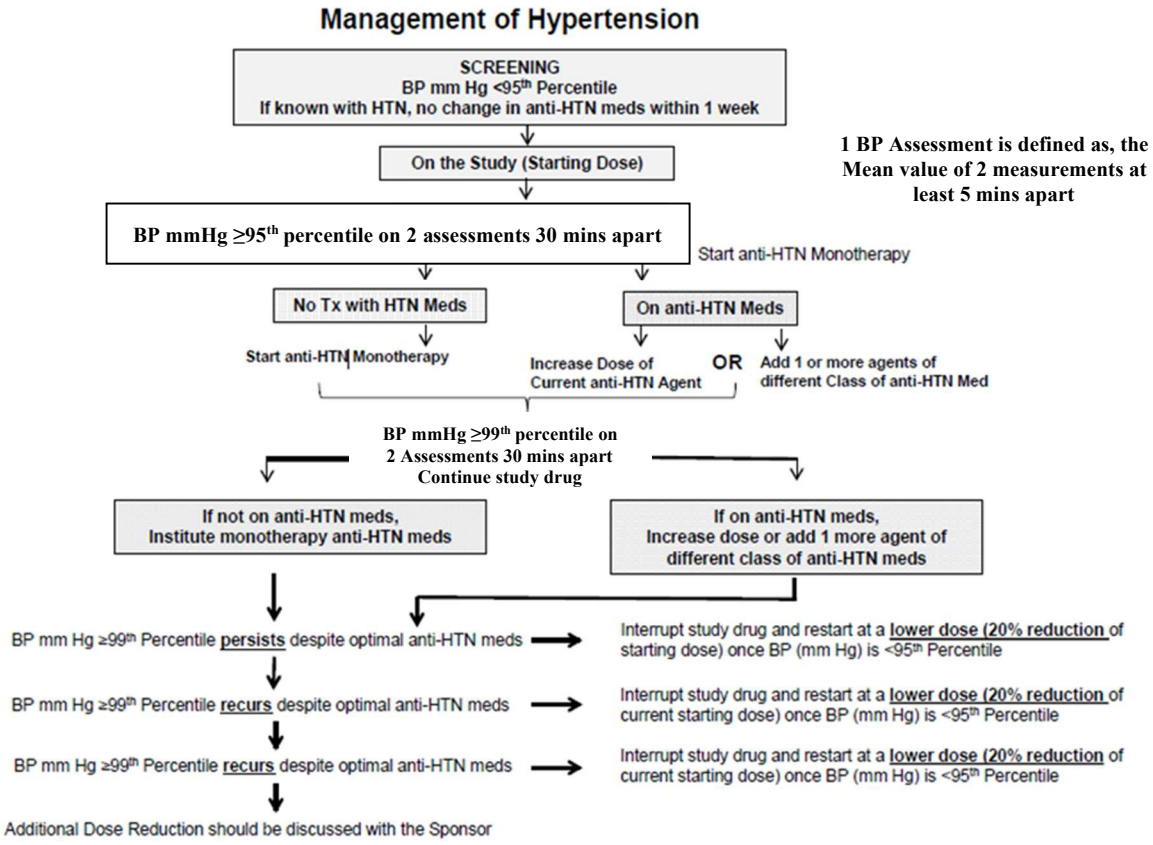

Figure 2 Management of Hypertension

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

8.4.1.1.3 MANAGEMENT OF POSTERIOR REVERSIBLE LEUKOENCEPHALOPATHY SYNDROME/REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME

Posterior Reversible Leukoencephalopathy Syndrome (PRES)/Reversible Posterior Leukoencephalopathy Syndrome (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. An MRI is

necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP (see Section 8.4.1.1.1 and 8.4.1.1.2), and neurologic consultation is advised. In subjects with signs or symptoms of PRES/RPLS, dose modification guidelines as per Table 1 should be followed.

8.4.1.1.4 MANAGEMENT OF PROTEINURIA

Regular assessment for proteinuria should be conducted as detailed in the Schedule of Assessments (Table 5 and Table 6). Guidelines for assessment and management of proteinuria are summarized as follows:

Grading of Proteinuria

- Grading according to CTCAE 5.0 (Cancer Therapy Evaluation Program, 2017) will be based on the protein-creatinine ratio or 24-hour urinary protein result, if available. For subjects ≥18 years of age, if the subject has 4+ proteinuria by dipstick, a 24-hour urinary protein result is required to confirm Grade 3 proteinuria.

Management of Proteinuria

- Management of lenvatinib administration will be based on the grade of proteinuria according to Table 1.
- In the event of nephrotic syndrome, lenvatinib must be discontinued.

Detection and Confirmation

- Perform urine dipstick testing per the Schedule of Assessments (Table 5 and Table 6)
- For subjects ≥18 years of age, a 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot urine protein-to-creatinine ratio [UPCR] test) AND for subjects <18 years of age, an immediate spot UPCR test, and if possible, a 24-hour urine collection (initiated as soon as possible and at least within 72 hours) is required in the following situations:
  - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on lenvatinib
  - A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
  - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+
- For subjects ≥18 years of age, a 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Monitoring

- Urine dipstick testing for subjects with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.

- Proteinuria monitoring can be performed at the local laboratory or investigator site, but must be managed by the site physician.

8.4.1.1.5 MANAGEMENT OF HEPATOTOXICITY

Regular monitoring of liver function tests (ALT, AST, bilirubin levels) should be conducted as detailed in the Schedule of Assessments (Table 5 and Table 6) 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 1). Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study drug must be discontinued.

8.4.1.1.6 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 1). Appropriate supportive care should be provided together with close monitoring. If a subject experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, study drug must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study drug discontinuation.

8.4.1.1.7 MANAGEMENT OF HYPOCALCEMIA

Serum calcium should be monitored monthly per the Schedule of Assessments (Table 5 and Table 6). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

Corrected calcium = ([4 – serum albumin in g/dL] ×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.

8.4.1.1.8 MANAGEMENT OF GASTROINTESTINAL SYMPTOMS AND ACUTE ABDOMINAL PAIN

Initial management of acute abdominal pain in these study subjects should be focused on treating the underlying cause where possible, ensuring appropriate hydration/rehydration, and symptomatic pain improvement consistent with subject's age and in accordance to local and

institutional standards of care. Appropriate supportive care should be provided together with close monitoring.

For adverse events of abdominal pain believed related to lenvatinib or more specific adverse events believed related to lenvatinib that result in the symptom of abdominal pain, follow instructions contained in Table 1 regarding study treatment dose reduction and interruption. For Grade 4 adverse events that result in abdominal pain, study drug 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), dose modification guidelines should be followed as per Table 1. 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.

Lenvatinib should be discontinued in any subject who develops gastrointestinal perforation of any grade or Grade ≥4 fistula.

8.4.1.1.9 MANAGEMENT OF HEMORRHAGE

Dose modification guidelines as per Table 1 for lenvatinib related adverse events should be followed for the management of hemorrhage. Either resume lenvatinib at a reduced dose or discontinue lenvatinib, depending on the severity and persistence of hemorrhage.

8.4.1.2 Management of Ifosfamide-Etoposide Associated Toxicity

Blood counts should be closely monitored during and prior to the next cycle of chemotherapy. Chemotherapy-associated myelosuppression should be managed by granulocyte-colony stimulating factor (G-CSF). It is recommended that pegylated G-CSF or G-CSF be administered at least 24 to 72 hours after completion of ifosfamide-etoposide chemotherapy; use of G-CSF is recommended until white blood cell (WBC) counts are $\geq 1 \times 10^9$/L. Guidelines for dose modification for ifosfamide and etoposide associated toxicities are provided in the Table 2 below.

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

Table 2 Criteria for Dose Modification of Chemotherapy Dose

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

ANC = absolute neutrophil count, RBC = red blood cell, ULN = upper limit normal.

8.4.2 Identity of Investigational Product(s)

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 4 provides instructions for the preparation of the lenvatinib suspension.

8.4.2.1 Chemical Name of E7080

- Test 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

8.4.2.2 Comparator Drug

Cytotoxic Chemotherapy: Ifosfamide and Etoposide

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

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

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

Anti-emetic or any other prophylaxis should be administered in accordance with institutional guidelines.

8.4.2.3 Labeling for Study Drug

Lenvatinib and the combination chemotherapy drugs, ifosfamide and etoposide, where supplied by the sponsor 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.

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

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

8.4.2.4 Storage Conditions

Lenvatinib will be stored in accordance with the labeled storage conditions. The expiry date for lenvatinib will be established based on manufacturing date and is based on formulation testing. The expiry date of of the lenvatinib will either be on the label and in the interactive voice response system (IVRS) system.

Ifosfamide and etoposide will be stored in accordance with the labeled storage conditions. The expiry date of the ifosfamide and etoposide will be the same as the commercial products provided.

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

8.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study. All subjects who provide signed informed consent and/or assent to participate in this study and satisfy all eligibility requirements (see Section 8.3) will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

After the Baseline Period, subjects will be randomized to 1 of the following 2 treatment arms in a 1:1 ratio:

- Arm A: lenvatinib 14 mg/m^2 (orally, once daily) plus ifosfamide 3000 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)
- Arm B: ifosfamide 3000 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m^2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)

Randomization will be performed centrally by an IVRS. Randomization will follow a predefined randomization scheme based on the following stratification factors: time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 and ≥18 years). Time to first relapse/refractory disease will be calculated starting from date of initial diagnosis.

8.4.4 Selection of Doses in the Study

The dose of lenvatinib, ifosfamide and etoposide in this study is the RP2D (14 mg/m^2 + ifosfamide 3000 mg/m^2 + etoposide 100 mg/m^2) established in Study 207. The dose of lenvatinib is the same as the RP2D for lenvatinib monotherapy, also established in Study 207.

8.4.5 Selection and Timing of Dose for Each Subject

Lenvatinib capsules are to be taken orally once a day at approximately the same time in the morning without regard to food intake for 21 days from Cycle 1 onward. If a subject misses a dose, it may be taken within the 12 hours following the usual time of the morning dose. If more than 12 hours have elapsed from the time of the usual daily dose, lenvatinib should be taken the next day at the usual time in the morning. In the event a subject vomits after study drug administration, the subject should not take another dose until the next scheduled dose.

Study drugs should be administered at the clinic on PK sampling days. All scheduled visits must be conducted as per protocol, irrespective of treatment interruption.

8.4.6 Blinding

The study will not be blinded.

8.4.7 Prior and Concomitant Therapy

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

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

Aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and low-molecular-weight heparin (LMWH) are permissible but should be used with caution. Granulocyte colony-stimulating factor (g-CSF) or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell (RBC) counts.

8.4.7.1 Drug-Drug Interactions

The weak inhibitory effect on CYP enzymes (in vitro) exhibited by lenvatinib suggests a low risk of lenvatinib interference with the PK of other drugs co-administered in usual clinical practice. There is no clinically meaningful drug-drug interaction (DDI) risk when lenvatinib is co-administered with CYP3A substrates such as midazolam. Simultaneous CYP3A4/P-gp inhibitions by ketoconazole slightly (15% to 19%) increased systemic exposure to lenvatinib after oral administration as measured by AUC and C_{max} in humans. Since no change was observed in half-life, t_{max}, or t_{lag}, the slight increase in systemic exposure is probably related

to a decrease in first pass metabolism. However, since the magnitude of the change is small, coadministration of lenvatinib with CYP3A4/P-gp inhibitors is not of clinical concern. Similarly, PK data did not suggest any major effects of rifampin on the exposure or disposition of lenvatinib. Following administration of a single dose of lenvatinib with a single dose of rifampin, lenvatinib exposure increased about 31%. In contrast, following administration of multiple doses of rifampin, free lenvatinib exposure was reduced about 9% and about 18% for total lenvatinib. These findings suggest that there is no clinically meaningful influence of either P-gp inhibition (single dose of rifampin) or simultaneous P-gp and CYP3A4 induction (multiple doses of rifampin) on lenvatinib PK.

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

8.4.7.2 Prohibited Concomitant Therapies and Drugs

Subjects should not receive other antitumor therapies while on study. If a subject receives additional antitumor therapies other than the study drug(s), such as chemotherapy, targeted therapies, immunotherapy, or antitumor interventions - such as surgery or palliative radiotherapy (other than as described below), this will be judged to represent evidence of disease progression, and continuation of the study medication and further participation in the study must be discussed and agreed upon with the sponsor.

For further information on the prohibited concomitant therapies for ifosfamide and etoposide, please refer to the respective prescribing information.

8.4.7.3 Permitted Concomitant Treatment/Procedures

The following concomitant treatments/procedures are allowed:

a. Removal of existing (not new) osteosarcoma lesion (eg, surgical, radiofrequency ablation, cryotherapy, thermoablation, stereotaxic ratiotherapy, etc.) after completion of the Week 18 tumor assessment. Subjects in Arm A in the presence of clinical benefit, may continue treatment with lenvatinib after protocol permissible surgery.

b. Palliative radiotherapy is allowed for ≤2 significantly symptomatic nontarget lesions.

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

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

Any additional procedural or subject specific particularities should be discussed with the investigator and the sponsor.

8.4.8 Treatment Compliance

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

8.4.9 Drug Supplies and Accountability

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

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, or a completed Investigator and Site Information Form
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572 or Investigator and Site Information Form
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

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

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

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to the site but not dispensed to the

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

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Products Regulatory Agency [MHRA]). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator or the designated pharmacist by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

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

8.5 Study Assessments

8.5.1 Assessments

8.5.1.1 Screening/Baseline Assessments

8.5.1.1.1 DEMOGRAPHY

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

8.5.1.1.2 BASELINE ASSESSMENTS

Baseline assessments will be performed at Day -1 or at Cycle 1 Day 1 prior to treatment. Assessments will include confirmation of subject eligibility with the inclusion and exclusion criteria, medical and surgical history, prior medications and procedures, pregnancy test

(serum or urine) within 72 hours of the first dose of study medication), Lansky play score (see Appendix 2) or Karnofsky performance status score (see Appendix 3), tumor-node metastasis (TNM) Staging (at initial diagnosis of the disease), vital signs, clinical chemistry and hematology, urine dipstick testing, height, Tanner's staging (see Appendix 10), proximal tibial growth plates, and pharmacodynamic biomarkers (for Arm A only).

8.5.1.1.3 MEDICAL HISTORY

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 5, and Table 6). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

8.5.1.2 Efficacy Assessments

8.5.1.2.1 TUMOR RESPONSE ASSESSMENTS

Tumor assessment will be performed based on RECIST 1.1 (Appendix 1). Investigator-determined response assessments will be performed at each assessment time point and entered onto the appropriate CRF. Copies of all tumor assessment scans will be sent to an ICL designated by the sponsor for efficacy assessment and for confirmation of PD. Tumor assessments will be carried out following the guidelines provided by the ICL. Subjects must have evaluable disease or measurable disease based on RECIST 1.1.

At Screening

During the Screening Period, tumor assessments of the chest, abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed within 28 days prior to Cycle 1 Day 1. 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.

Brain scans by MRI with and without contrast enhancement or CT with contrast enhancement will be performed at screening as clinically indicated.

Historical scans (within 28 days prior to the Cycle 1 Day 1) may be used to demonstrate eligibility as long as they meet minimum standards as separately defined by the ICL.

During Treatment Phase

CT/MRI scans of, chest, abdomen, pelvis, and other known sites of disease plus any areas of newly suspected disease will be performed using the same methodology as at screening every 6 weeks ±1 week, following the start of treatment on Cycle 1 Day 1 during the chemotherapy treatment period until Week 18. Following completion of the chemotherapy treatment period (ie, after Week 18), the frequency of tumor assessments will be every 9 weeks ±1 week until Week 54 ±1 week. Thereafter, they will be performed every 12 weeks ±2 weeks until documentation of PD. At any point, scans should be performed earlier than the scheduled time point, if clinically indicated.

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

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

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

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

Brain scans by MRI with and without contrast enhancement or CT with contrast enhancement will be performed as clinically indicated. If protocol eligible brain metastases are present at screening, a CT/MRI of the brain must be performed at all tumor assessment time points (eg, every 6, 9, or 12 weeks).

Disease progression per RECIST 1.1 during the randomization phase must be confirmed by IIR prior to the investigator discontinuing study treatment for a subject. In the event that the investigator considers alternative treatments must be instituted immediately for management of urgent medical complications of PD, study drugs may be discontinued without waiting for independent confirmation of radiographic evidence of PD. Subjects who discontinue study treatment without PD will continue to undergo tumor assessments according to the schedule until PD is documented or another anticancer therapy is initiated. If possible, before discontinuation of the subject from the study, the investigator should consult with the sponsor.

During Post-treatment Follow-up

Subjects who discontinue treatment without PD will have tumor assessments performed as per the appropriate tumor assessment schedule) or sooner if clinically indicated, for documented PD or until another anticancer therapy is initiated, whichever occurs first.

After data cutoff for PFS-1y and OS-1y analysis, tumor assessments may be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care. All subjects will be followed for survival for 2 years after end of treatment or until death, unless the study is terminated by the sponsor, or the subject discontinues due to withdrawal of consent, or is lost to follow-up.

8.5.1.2.2 PALATABILITY AND ACCEPTABILITY OF LENVATINIB SUSPENSION FORMULATION

The palatability and acceptability of lenvatinib suspension formulation will be assessed using the Palatability Questionnaire (see Appendix 5). All subjects who receive suspension formulation with the exception of subjects using a nasogastric or gastrostomy tube, must complete the questionnaire according to the Schedule of Assessments. If the subject is unable to complete the questionnaire, this must be done by a parent or legal guardian. Measurement of palatability will be assessed using the Hedonic scale (Guinard, 2001) which is a Visual Analog Scale (VAS).

8.5.1.3 Pharmacokinetic, Pharmacodynamic, and Other Biomarker Assessments

8.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (2 mL each) will be collected from all subjects from Arm A only at the time points shown in Table 3. Pharmacokinetic blood samples will also be drawn pretreatment on the day of tumor assessment as described in the Table 3. Actual time and date of PK blood collection as well as time of drug administration will be recorded on the appropriate page of the CRF. Exposure parameters such as area under the concentration × time curve (AUC) will be derived from posterior estimates of the PK parameters from the final population PK

model. For the time points shown in Table 3, subjects or their parents will be instructed not to take the dose of lenvatinib prior to arriving at the study site. Lenvatinib capsule administration will be recorded in the eCRF. The Cycle 1 Day 1 and Day 15 doses of lenvatinib will be administered at the study site at approximately the same time of day in order to accommodate PK sample collection timing. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in a separate Laboratory Manual.

Table 3 Lenvatinib Pharmacokinetic Sampling Time Points

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

Note: All predose samples are to be drawn approximately 24 hours following the dose administered on the previous day.
h = hour(s).
a. If dose interruption is necessary in these time points, please contact the sponsor.

Only samples from all subjects randomized to Arm A will be collected. Lenvatinib will be quantified using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method.

8.5.1.3.2 Pharmacodynamic and Other Biomarker Assessments

Pharmacodynamic serum and archived fixed tumor tissue samples for biomarker analysis will be collected from study subjects randomized to Arm A (ie, lenvatinib + ifosfamide + etoposide), as specified in the Schedule of Procedures/Assessments. Pharmacodynamic serum and tumor biomarkers identified in other lenvatinib clinical studies will be assessed in samples collected from subjects enrolled in this study. Pharmacodynamic biomarker analysis will be performed as described in an analysis plan provided separately.

Blood biomarker samples may be used for exploratory analysis for evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development (see Appendix 11).

8.5.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all grades per National Cancer Institute (NCI) CTCAE v5.0 (for both increasing and decreasing severity), and serious adverse events (SAEs); regular laboratory evaluation of hematology, blood chemistry, and urine values; periodic measurement of vital signs and 12-lead ECGs; and echocardiograms, Lansky play score or Karnofsky performance status score, physical examinations, and height assessments as detailed in the Schedule of Assessments (Table 5 and Table 6).

Clinical and laboratory toxicities/symptomatology will be graded according to CTCAE v5.0 (Cancer Therapy Evaluation Program, 2017).

8.5.1.4.1 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 drug is lenvatinib.

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 PD.
- 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, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit and for 30 days after the subject's last dose. Refer to Section 8.5.4.1 for the time period after the end of treatment for SAE collection.

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 (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed for 30 days after the subject's last study drug dose, or until resolution, whichever comes first. Subjects with onset of an AE or deterioration of a preexisting AE during the AE collection period will be followed until resolution to baseline, start of a new anticancer treatment, or death. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

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

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v5.0 (Cancer Therapy Evaluation Program, 2017). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

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.

8.5.1.4.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

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

- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events 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

8.5.1.4.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 5 and Table 6) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 4 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Bicarbonate, chloride, potassium, sodium, calcium, magnesium, phosphorus
Liver function tests	ALT, alkaline phosphatase, AST, conjugated (direct) bilirubin[a], total bilirubin, INR[b]
Renal function tests	BUN or urea, creatinine
Other chemistries	Albumin, amylase, glucose, LDH, lipase, total protein
Thyroid function tests[c]	Thyroid stimulating hormone, free T4 level
Urinalysis for microscopy[d]	RBCs
Urine dipstick testing[d,e]	Blood, protein, glucose
Other	Pregnancy test (serum or urine β–hCG)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, β hCG = beta-human chorionic gonadotropin, INR = International Normalized ratio, LDH = lactate dehydrogenase, RBC = red blood cells, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cells.

a. Direct bilirubin should be assessed if total bilirubin is elevated.
b. INR should only be performed as part of the screening assessment. During the study, INR should be performed if clinically indicated.
c. Thyroid function will be assessed every 2 cycles for all subjects.
d. 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
e. 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 at qualified local laboratories. All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and sent to the local laboratory on the day of collection unless otherwise instructed.

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

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 8.5.1.4.1 and the CRF Completion Guidelines. In these instances, the

AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF (see Section 8.5.4.3.2).

8.5.1.4.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute]), body temperature (in centigrade), weight (kg), and height (cm) will be obtained at the visits designated in the Schedule of Assessments (Table 5 and Table 6) by a validated method. Blood pressure and pulse will be measured after the subject has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

Only 1 BP measurement is needed for subjects with systolic BP <95th percentile (BP <140 mm Hg) and diastolic BP <95th percentile (BP <90 mmHg). If the subject's initial BP measurement is elevated (systolic BP ≥95th percentile [≥140 mmHg] or diastolic BP ≥95th percentile [≥90 mmHg]), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥95th percentile [≥140 mm Hg] or diastolic BP ≥95th percentile [≥90 mm Hg]), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

8.5.1.4.5 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 5 and Table 6). 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.

8.5.1.4.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Assessments (Table 5 and Table 6). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3×4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. If possible, subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 8.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Serious Adverse Events and Other Events of Interest), the study site must fax the SAE report including the ECG report to the number indicated in the Investigator File using the SAE reporting form (see Section 8.5.4.1).

8.5.1.4.7 OTHER SAFETY ASSESSMENTS

Pregnancy Test

A serum β-hCG test will be performed for females of childbearing potential (see definition included in the Inclusion/Exclusion criteria, Sections 8.3.1 and 8.3.2). A serum or urine pregnancy test will be performed at Screening, Baseline (or within 72 hours prior to the first dose of study medication), on Day 1 of each cycle from Cycle 2 onwards, and at the Off-treatment Visit in women of childbearing potential. Blood and urine samples will be taken at designated time points as specified in the Schedule of Assessments (Table 5 and Table 6).

Echocardiogram

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

8.5.1.5 Other Assessments

Health-related quality of life (HRQoL) assessment will be performed per the Schedule of Assessments (Table 5 and Table 6). Impact of treatment on HRQoL will be assessed using the PedsQL (including the Generic Core Scales and Cancer Module). Data will be collected as parent-report for toddlers (2 to 4 years) and as self-report for subjects aged ≥5 years. Self-report is the preferred data collection for all subjects aged ≥5, however to improve adherence of participation, it is also acceptable to collect the data as proxy report by observers including parents and caregivers.

The PedsQL is a modular instrument designed to measure HRQoL in pediatric and adults population. The PedsQL 4.0 Generic Core Scales are multidimensional child self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL disease specific modules. The PedsQL 3.0 Cancer Module was designed to measure pediatric cancer specific HRQOL.

It is best practice and strongly recommended that the PedsQL measurement modules are administered to randomized subjects prior to drug administration or any other interaction with site staff.

8.5.2 Schedule of Procedures/Assessments

8.5.2.1 Schedule of Procedures/Assessments

Table 5 presents the schedule of procedures/assessments for the Randomization Phase of the study.

Table 6 presents the schedule of procedures/assessments for the Extension Phase of the study.

Table 5 Schedule of Assessments in study E7080-G000-230 – Randomization Phase

Phase	**Prerandomization**		**Randomization [a] (All cycles are 21 days in duration)**																	
Period	**Screening[b]**	**Baseline[c]**	**Treatment[d]**																**Off-Tx**	**Follow-up[e]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18+**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6-X**		
Day	**-28 to -2**	**-1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Procedures/Assessments																				
Informed consent	X																			
Inclusion/exclusion	X	X																		
Randomization (IVRS)			X																	
Demographic data	X																			
Medical/surgical history	X	X																		
Prior medication/ procedures	X	X																		
Pregnancy test[f]	X	X				X			X			X			X			X	X	
Lansky play score/ Karnofsky PS[g]	X	X	X			X			X			X			X			X		
TNM Staging	X																			
Physical examination[h]	X	X	X		X	X		X	X			X			X			X	X	
Vital signs[i]	X	X	X		X	X		X	X			X			X			X	X	
12-lead ECG[j]	X		X			X												X	X	
Echocardiogram[k]	X	Performed every 16±2 weeks following the first dose of study drug or sooner, if clinically indicated																	X	
Clinical chemistry and hematology[l]	X	X			X	X		X	X			X			X			X	X	
Urine dipstick testing[m]	X	X			X	X		X	X			X			X			X	X	
PK blood samples[n]			X		X	X														
Study treatment[o]			Arm A: Combination of lenvatinib (QD) + ifosfamide + etoposide (Days 1-3 of Cycles 1-5 only) [based on BSA calculations at Day 1 of each Cycle]; after Cycle 5 subjects will receive lenvatinib alone. Arm B: Ifosfamide + etoposide (Days 1-3 of Cycles 1-5 only) [based on BSA calculations at Day 1 of each Cycle]																	

Table 5 Schedule of Assessments in study E7080-G000-230 – Randomization Phase

Phase	**Prerandomization**		**Randomization [a] (All cycles are 21 days in duration)**																	
Period	**Screening[b]**	**Baseline[c]**	**Treatment[d]**																**Off-Tx**	**Follow-up[e]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18+**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6-X**		
Day	**-28 to -2**	**-1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Procedures/Assessments																				
Palatability Questionnaire[p]			X																	
Tumor assessments: CT/MRI[q]	X		CT chest and CT/MRI of other areas of known disease at Screening plus any areas of newly suspected disease should be performed every 6±1 week or sooner if clinically indicated until Week 18±1 week, then every 9±1 weeks until Week 54±1 week. Thereafter, to be performed every 12±2 weeks until documentation of PD.																X	
Brain CT/MRI[r]	X		Brain scans will be performed at screening as clinically indicated, and thereafter during treatment if clinically indicated. For subjects with protocol-eligible, treated brain metastases at Screening, brain scans should be performed at all tumor assessment time points.																	
Height[s]		X	X									X						X	X	X
Tanner Stage[t]		X																	X	X
Proximal Tibial growth plates x-ray[s]		X																	X	
HRQoL		X	HRQoL will be collected on C2D1, C3D1, Week 18, C8D1, and C18D1																X	
Pharmacodynamic biomarkers[u]		X		X		X						X						X		
Archival tumor block or slides[v]		X																		X
Survival[w]				X																X
Concomitant medications[x]	Throughout																			X
AEs/SAEs[y]	Throughout																			X

AE = adverse event, BP = blood pressure, C1D1 = Cycle 1 Day 1, C1D2 = Cycle 1 Day 2, C1D8 = Cycle 1/Day 8, C1D15 = Cycle 1 Day 15, CR = complete response, CT = computerized tomography, h = hour, HR = heart rate, HRQoL = Health-Related Quality of Life, IV = intravenous, IVRS = Interactive Voice Response System, MRI = magnetic resonance imaging, PD = progressive disease/disease progression, PK = pharmacokinetics, PR = partial response, PS =

Table 5 Schedule of Assessments in study E7080-G000-230 – Randomization Phase

Phase	Prerandomization		Randomization [a] (All cycles are 21 days in duration)																	
Period	Screening[b]	Baseline[c]	Treatment[d]																Off-Tx	Follow-up[e]
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+		
Cycle			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6-X		
Day	-28 to -2	-1	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1		
Procedures/Assessments																				

performance score, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1, RR = respiratory rate, SAE = serious adverse event, TNM = tumor-node-metastasis, Tx = treatment.

a. During Cycle 1, efforts should be made to conduct study visits on the day scheduled (±1 day); from Cycle 2 onwards, efforts should be made to conduct study visits on the day scheduled (±3 days).
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. For subjects randomized to Arm A, subjects benefiting from study treatment in the opinion of the investigator will continue lenvatinib treatment until PD, intolerable toxicity, noncompliance with safety or efficacy assessments, voluntary discontinuation by the subject at any time, or study termination by the sponsor, whichever occurs first.
e. Subjects will be followed every 12 weeks until documentation of PD or until death as per the protocol.
f. A serum or urine pregnancy test will be performed at the Screening and Baseline Visits (or within 72 hours prior to the first dose of study medication), on Day 1 of each cycle from Cycle 2 onwards, if pregnancy is suspected, and at the Off-treatment Visit in women of childbearing potential.
g. A Lansky play score or Karnofsky performance status score will be obtained at the Screening, Baseline, and C1D1 Visit, and Day 1 of every subsequent cycle visit thereafter.
h. A comprehensive physical examination (including a neurological examination) will be performed at the Screening and Baseline Visits (only if screening physical examination was performed >7 days prior to C1D1), C1D15, C2D1, C2D15, and Day 1 visit of each subsequent cycle, and at the Off-treatment Visit. A symptom-directed physical examination will be performed on C1D1 and at any time during the study, as clinically indicated.
i. Assessments will include vital signs (resting BP, HR, RR, and body temperature) and weight. Blood pressure that is consistently above the 95th percentile for sex, age, and height/length requires further evaluation. Refer to hypertension management guidelines in Section 8.4.1.1.2.
j. Single 12-lead ECG. If possible, subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. ECG should be conducted at Screening, C1D1, C2D1, D1 of every 4th cycle (ie, C6, C10, C14, etc.). ECG at C1D1 and C2D1 should be conducted approximately 2 hours after lenvatinib dose. For high risk subjects (as defined in lenvatinib product label), conduct ECG monitoring in every cycle.
k. An echocardiogram is performed during screening, every 16±2 weeks, and at the Off-Treatment visit, or sooner if clinically indicated.

Table 5 Schedule of Assessments in study E7080-G000-230 – Randomization Phase

Phase	Prerandomization		Randomization [a] (All cycles are 21 days in duration)																	
Period	Screening[b]	Baseline[c]	Treatment[d]																Off-Tx	Follow-up[e]
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+		
Cycle			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6-X		
Day	-28 to -2	-1	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1		
Procedures/Assessments																				

l. Clinical chemistry and hematology results must be reviewed by the investigator prior to administration of study drug on C1D1 and within 48 hours after administering any 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). TSH should be assessed for all subjects.

m. Urine dipstick testing should be performed at Screening, Baseline, C1D15, C2D1, C2D15, and Day 1 of every subsequent cycle, or more frequently as clinically indicated, and at the Off-treatment Visit. For subjects with a history of proteinuria ≥2+, urine dipstick testing should be performed until the results have been 1+ or negative for 2 treatment cycles. If a new event of proteinuria ≥2+ occurs, refer to Section 8.4.1.1.4 for further management guidelines. Urine glucose should be performed as part of the urine dipstick.

n. Sampling (one 2 mL sample per time point) for PK analysis of lenvatinib will be performed (in subjects in Arm A only) on Cycle 1 Day 1 at 0.5 to 4 hours and 6 to 10 hours postdose, on Cycle 1 Day 15 at predose, 0.5 to 4 hours and 6 to 10 hours postdose, and on Cycle 2 Day 1 at predose. All predose samples are to be drawn approximately 24 hours following the dose administered on the previous day. If dose interruption is necessary at these time points, please contact the sponsor.

o. Subjects randomized to Arm A will continue to receive lenvatinib only after completion of 5 cycles with lenvatinib+ifosfamide+etoposide until progressive disease, unacceptable toxicity, subject request, study termination by the sponsor, subject noncompliance with safety or efficacy assessments, or withdrawal of consent. Subjects randomized to Arm B will be off-treatment after 5 cycles of ifosfamide+etoposide.

p. All subjects who receive suspension formulation, with the exception of subjects using a nasogastric or gastrostomy tube, must complete the Palatability Questionnaire according to the Schedule of Assessments. If the subject is unable to complete the questionnaire this must be done by their parents or their legal guardian.

q. **Screening**: Tumor assessments of the chest, abdomen, pelvis, and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1. Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans should be performed with IV gadolinium chelate. **Treatment Phase**: Tumor assessments of the chest, and other areas of known disease at Screening or newly suspected disease should be performed every 6±1 weeks from C1D1 until Week 18±1 week, then every 9±1 weeks until Week 54±1 week, and thereafter, every 12±2 weeks until documentation of PD during the Treatment Phase (or sooner if there is evidence of progressive disease) and should utilize the same methodology (CT or MRI) and scan

Table 5 Schedule of Assessments in study E7080-G000-230 – Randomization Phase

Phase	Prerandomization		Randomization [a] (All cycles are 21 days in duration)																	
Period	Screening[b]	Baseline[c]	Treatment[d]																Off-Tx	Follow-up[e]
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+		
Cycle			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6-X		
Day	-28 to -2	-1	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1		
Procedures/Assessments																				

acquisition techniques (including use or nonuse of IV contrast) as was used for the screening assessments. Tumor response will be assessed according to RECIST 1.1. Subjects who discontinue must complete the off-treatment tumor assessment. Any CR or PR must be confirmed not less than 4 weeks following the initial achievement of the response. After treatment discontinuation, tumor assessment should continue to be performed according to the schedule: every 6±1 weeks until Week 18±1 week, then every 9±1 weeks until Week 54±1 week, thereafter, to be performed every 12±2 weeks until documentation of progression or start of a new anticancer agent.

r. Brain CT with contrast or MRI pre- and post- gadolinium contrast will be performed at the Screening Visit as clinically indicated, and thereafter during treatment as clinically indicated. For subjects with protocol-eligible treated brain metastases, brain CT/MRI will be performed at all tumor assessment time points.

s. Height will be assessed at the Baseline Visit, Day 1 of every 4 cycles during the Treatment Phase, at the Off-treatment Visit and every 3 months during the Post-treatment Follow-up. Proximal tibial growth plates x-rays should be conducted at baseline and at the Off-treatment Visit. If the growth plates are closed at baseline then the subject does not need a reassessment at the Off-treatment Visit. Tibial growth plate x-rays will be optional for Germany.

t. Tanner Stage will be assessed at the Baseline Visit, at the Off-treatment Visit, and annually thereafter during the Post-treatment Follow-up.

u. Blood samples will be collected only from subjects in Arm A at the Baseline Visit, C1D8, Day 1 of Cycles 2, 4, and 6, for assessment for blood serum sample to measure factors implicated in angiogenesis.

v. An archival tumor sample from the most recent surgery or biopsy for identification of predictive biomarkers and pathology review may be collected from subjects in Arm A at any time during the study, unless no such material is available.

w. Survival data will be collected every 3 months until death as per the protocol. All anticancer therapies will be collected.

x. Concomitant medications will be recorded throughout the study and for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of Survival Follow-up.

y. AEs will be recorded from the date of signed informed consent, throughout the study, and for 30 days after last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 hours.

Table 6 presents the Schedule of Procedures/Assessments for the Extension Phase of the study.

Table 6 Schedule of Assessments in study E7080-G000-230 – Extension Phase

Phase	**Extension[a]**		
Period	**Treatment Period [a]**		**Follow-up Period**
Visit	**98**	**99**	
Cycle	**Cycle X +1 and beyond**	**Off-Tx Visit**	
Day	**1**		
Procedures/Assessments			
Pregnancy test[b]	X	X	
Lansky play score/ Karnofsky PS[c]	X	X	
Physical examination[d]	X	X	
Vital signs[e]	X	X	
12-lead ECG[f]	As clinically indicated		
Echocardiogram[g]	As clinically indicated		
Clinical chemistry and hematology[h]	X	X	
Urine dipstick testing[i]	X	X	
Study treatment[j]	Arm A: Lenvatinib[a]		
Tumor assessments: CT/MRI[k]	After data cutoff, tumor assessments may be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care.		
Brain CT/MRI[l]	After data cutoff, tumor assessments may be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care.		
Height[m]	To be checked every 4 cycles	X	X
Tanner Stage[n]		X	X
Proximal Tibial growth plates x-ray[o]		X	
Survival[p]	X		X
Concomitant medications[q]	Throughout		X
AEs/SAEs[r]	Throughout		X

AE = adverse event, CT = computerized tomography, ICL = imaging core laboratory, MRI = magnetic resonance imaging, PD = disease progression, PS = performance status, SAE = serious adverse event.

a. Subjects benefiting from study treatment in the opinion of the investigator will continue treatment until PD, intolerable toxicity, subject request, subject

Table 6 Schedule of Assessments in study E7080-G000-230 – Extension Phase

Phase	Extension[a]		
Period	Treatment Period [a]		Follow-up Period
Visit	98	99	
Cycle	Cycle X +1 and beyond	Off-Tx Visit	
Day	1		

noncompliance with safety or efficacy assessments, voluntary discontinuation by the subject at any time, or study termination by the sponsor, whichever occurs first.

b. A serum or urine pregnancy test will be performed on Day 1 of each cycle and at the Off-treatment Visit in women of childbearing potential.
c. A Lansky play score or Karnofsky performance status score will be obtained at Day 1 of every cycle visit.
d. A physical examination will be performed at Day 1 visit of each cycle, and at the Off-treatment Visit. A symptom-directed physical examination will be performed at any time as clinically indicated.
e. Assessments will include vital signs (resting BP, HR, RR, and body temperature), and weight. Blood pressure that is consistently above the 95th percentile for sex, age, and height/length requires further evaluation. Refer to hypertension management guidelines in Section 8.4.1.1.2.
f. Single 12-lead ECG. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.
g. An echocardiogram is performed as clinically indicated.
h. Clinical chemistry and hematology results must be reviewed within 48 hours after administering any 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). TSH should be assessed for all subjects.
i. Urine dipstick testing should be performed on Day 1 of every cycle, or more frequently as clinically indicated, and at the Off-treatment Visit. For subjects with a history of proteinuria ≥2+, urine dipstick testing should be performed until the results have been 1+ or negative for 2 consecutive cycles. If a new event of proteinuria ≥2+ occurs, refer to Section 8.4.1.1.4 for further management guidelines. Urine glucose should be performed as part of the urine dipstick.
j. Subjects randomized to Arm A will continue to receive lenvatinib only until progressive disease, unacceptable toxicity, or withdrawal of consent.
k. After data cutoff, tumor assessments may be performed as clinically indicated as per the institutional guidelines, following the prevailing local standard of care. The scans will no longer be required to be sent to the ICL.
l. Brain CT with contrast or MRI pre- and post- gadolinium contrast will be performed as per the institutional guidelines, following the prevailing local standard of care.
m. Height will be assessed at the Baseline Visit, Day 1 of every 4 cycles during the Treatment Phase, at the Off-treatment Visit and every 3 months during the Post-treatment Follow-up.
n. Tanner Stage will be assessed at the Baseline Visit, at the Off-treatment Visit, and annually thereafter during the Post-treatment Follow-up.
o. Proximal tibial growth plates x-rays should be conducted at baseline and at the Off-treatment Visit. If the growth plates are closed at baseline then the subject does not need a reassessment at the Off-treatment Visit. Tibial growth plate x-rays will be optional for Germany.
p. Survival data will be collected every 3 months until death as per the protocol. All anticancer therapies will be collected.
q. Concomitant medications will be recorded throughout the study and for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of Survival Follow-up.

Table 6 Schedule of Assessments in study E7080-G000-230 – Extension Phase

Phase	Extension[a]		
Period	Treatment Period [a]		Follow-up Period
Visit	98	99	
Cycle	Cycle X +1 and beyond	Off-Tx Visit	
Day	1		

r. AEs will be recorded from the date of signed informed consent, throughout the study, and for 30 days after last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 hours.

8.5.2.2 Description of Procedures/Assessments Schedule

Refer to Table 5 for schedule and description of procedures in the Randomization Phase and Table 6 for the Extension Phase.

8.5.3 Appropriateness of Measurements

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

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

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

8.5.4.1 Reporting of Serious Adverse Events

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

Serious adverse events, regardless of causality assessment, must be collected for 30 days after the subject's last dose. 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 relevant follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the relevant 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 and/or the designated CRO monitor to be filed in the sponsor's Trial Master File.

8.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

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

If an adverse outcome of a pregnancy is suspected to be related to study drug 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, a spontaneous abortion or an induced abortion done due to safety concerns for either mother or fetus 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 8.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the 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 24 hours from the date the investigator becomes aware of the outcome.

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

8.5.4.3 Reporting of Events Associated with Special Situations

8.5.4.3.1 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 8.5.4.1) even if the AEs do not meet serious criteria. Abuse and Intentional Overdose, even if asymptomatic, are 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.

8.5.4.3.2 Reporting of Abnormal Hepatic Tests of Clinical Interest

The following combination of abnormal laboratory tests*, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing and whether nonserious or serious, should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 8.5.4.1). If the event does not meet serious criteria, the seriousness criteria on the SAE form should be indicated as "nonserious."

- Elevated AST or ALT lab value that is greater than or equal to 3× the upper limit of normal

  AND

- Elevated total bilirubin lab value that is greater than or equal to 2× the upper limit of normal

  AND AT THE SAME TIME

- Alkaline phosphatase lab value that is less than 2× the upper limit of normal

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology. In addition to reporting the abnormal hepatic laboratory tests on a SAE form, the site should also consult the medical monitor for guidance on assessment and follow-up. At a minimum, laboratory testing should be repeated at least once weekly until improvement or identification of a cause unrelated to study drug use that is unlikely to improve.

8.5.4.4 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.

8.5.4.5 Breaking the Blind

Not applicable

8.5.4.6 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 SUSARs will be reported, as required, to the competent authorities of all involved European member states.

8.5.5 Completion/Discontinuation of Subjects

A subject (or subject's parent or guardian) may elect to discontinue study drug at any time for safety, medical, or personal reasons. Subjects who choose to discontinue study drug prior to PD will be followed in the post-study treatment follow-up period and continue to undergo regularly scheduled disease assessment until documentation of PD or start of an alternative anticancer treatment. All subjects who discontinue study drug will be followed for OS and all post progression cancer treatments administered will be recorded. Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Assessments (Table 5 and Table 6).

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

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, progression of disease, withdrawal of consent, pregnancy, study terminated by sponsor, or administrative/other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

8.5.6 Abuse or Diversion of Study Drug

Not applicable.

8.5.7 Confirmation of Medical Care by Another Physician

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

8.6 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.

8.6.1 Data Collection

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

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

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

8.6.2 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.

8.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed, the database is locked and released, a snapshot of the database is obtained and released, and randomization codes have been released and applied. 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).

8.7.1 Statistical and Analytical Plans

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

8.7.1.1 Study Endpoints

8.7.1.1.1 PRIMARY ENDPOINT

- Progression-free survival rate at 4 months (PFS-4m rate) by IIR is defined as the percentage of subjects who are alive and without PD at 4 months from the randomization date as determined by IIR of radiological imaging using RECIST 1.1. The PFS-4m rate is estimated on the full analysis set for this study using the K-M method.

8.7.1.1.2 SECONDARY ENDPOINTS

- Progression-free survival rate at 1 year (PFS-1y rate) by IIR is defined as the percentage of subjects who are alive and without PD at 1 year from the randomization date as determined by IIR of radiological imaging using RECIST 1.1. The PFS-1y rate is estimated on the full analysis set for this study using the K-M method.
- Progression-free survival (PFS) by IIR is defined as the time from the date of randomization to the date of the first documentation of PD or death (whichever occurs first) as determined by IIR using RECIST 1.1.
- Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cutoff will be censored at the date the subject was last known alive, or date of data cutoff, whichever occurs first. Overall survival rate at 1 year will be estimated.
- Objective response rate (ORR) by IIR at 4 months is defined as the proportion of subjects who have best overall response of complete response (CR) or partial response (PR) as determined by IIR using RECIST 1.1 within the first 4 months.
- Safety will be assessed summarising the incidence of TEAEs and SAEs together with all other safety parameters.
- Assessment of population-based PK parameters of lenvatinib.
- Score changes from baseline for all PedsQL scales including Generic Core Scales and Cancer Module. Scores will be calculated for total generic score, total cancer score, each physical function subscale including physical health, psychosocial health, emotional function, social function, school/work function in the Generic Core Scales, and each subscales in the cancer module.
- Palatibility and acceptability of the suspension formulation of lenvatinib in subjects receiving the suspension formulation in the study will be assessed using the Palatability Questionnaire (see Appendix 5).

8.7.1.1.3 EXPLORATORY ENDPOINTS

- Duration of response (DOR) by IIR is defined as the time from the date a response was first documented until the date of the first documentation of PD or date of death from any case.
- Disease control rate (DCR) by IIR is the proportion of subjects who have a best overall response of CR or PR or stable disease (SD). In this context, stable disease is defined as stable disease at ≥7 weeks after randomization to be considered best overall response.
- Clinical benefit rate (CBR) by IIR is the proportion of subjects who have best overall response of CR or PR or durable SD (duration of SD ≥23 weeks after randomization).
- Proportion of subjects who achieve complete removal of baseline lesions following completion of chemotherapy.
- Blood and tumor biomarkers will be assessed for identifying potential correlation with clinical outcomes-related endpoints.
- All efficacy endpoints above (except OS) will be evaluated by both IIR and investigator assessment using RECIST 1.1.

8.7.1.2 Definitions of Analysis Sets

The Full Analysis Set (Intent-to-Treat Analysis [ITT]) includes all randomized subjects regardless of the treatment actually received. This is the primary analysis population used for the efficacy analyses which will be based on the ITT principle.

The Per Protocol Analysis Set includes those subjects from the ITT set who received at least 1 dose of any study drug, had no major protocol deviations, and had both baseline and at least one postbaseline tumor assessment. Subjects for whom death occurred prior to the first postbaseline tumor assessment will also be included. The per protocol analysis set will be the secondary analysis set for efficacy endpoints.

The Safety Analysis Set includes subjects who received at least 1 dose of any study drug. This is the analysis population used for all safety analyses which will be based on as-treated principle.

Population Pharmacokinetic (PK) Analysis Set includes the subjects who have received at least 1 dose of lenvatinib with documented dosing history and have measurable plasma levels of lenvatinib.

The Pharmacodynamic Analysis Set includes subjects who received at least 1 dose of study drug and had sufficient pharmacodynamic data (eg, at least 1 evaluable/measurable pharmacodynamic parameter).

The HRQoL Analysis Set will consist of all randomized subjects who have received at least 1 dose of study medication, and have completed at least 1 patient-reported outcome (PRO) assessment beyond baseline. For PRO analysis, subjects will be analyzed as randomized and not according to treatment actually received.

8.7.1.3 Subject Disposition

Reasons for screening failure will be summarized.

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

8.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Full Analysis Set will be summarized using descriptive statistics. Continuous demographic and baseline variables (including age, sex, race, height, and weight) will be summarized using n (number of subjects with available data), mean, standard deviation, median, quartiles 1 and 3, and range (minimum and maximum) unless otherwise specified. Categorical variables will be summarized by number and percentage.

8.7.1.5 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). Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) class indicating therapeutic classification. Prior medications will be defined as medications that started prior to the first dose of study drug and were either continued during the study or stopped prior to the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. All medications will be will be summarized and listed by drug and drug class and by treatment arm.

8.7.1.6 Efficacy Analyses

Efficacy analyses will be based primarily on the Full Analysis Set.

All the statistical analysis will be conducted at the PFS-1y/OS-1y analysis data cutoff date (ie, when the last subject has completed 18 cycles of treatment or discontinues before the end of Cycle 18, whichever occurs first), including the analysis of PFS-4m rate. Additional follow-up analysis will based on the date of data cutoff for the additional follow-up analysis for OS or at the time of last subject last visit, whichever occurs later.

8.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis of PFS-4m rate will be based upon data provided by IIR of tumor assessments. PFS-4m rate and their Greenwood standard errors will be evaluated using the K-M estimates from both treatment groups. The statistical significance of the difference in the 2 K-M PFS-4m rates comparing lenvatinib + chemotherapy agent (Test Arm) vs. chemotherapy agent alone (Control Arm) will be tested using a 2-sided 80% CI. This 2-sided

80% CI and a p-value will be constructed using the difference of these 2 K-M PFS-4m rates and the 2 corresponding Greenwood standard errors. Statistical significance of the difference is declared if the CI is entirely above 0. This is equivalent to a test using a 1-sided test at alpha=0.1. The 2-sided 95% CIs will also be provided for descriptive purposes. PFS-4m rate will also be analyzed using a binomial approach as a sensitivity analysis by excluding subjects whose PFS are censored prior to 18 weeks.

8.7.1.6.2 SECONDARY EFFICACY ANALYSES

PFS-1y rate will be analyzed using the same methods as the primary efficacy analysis. PFS censoring rules will follow FDA guidance of 2007, however, removal of baseline lesions after completion of Week 18 without progression is not a trigger for PFS censoring after 18 weeks. (refer to Section 8.4.7.3 for allowed concomitant treatments/procedure in the study).

Overall survival (OS) will be compared between treatment arm and control arm using the stratified logrank test with time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years) as strata. Median OS with 2-sided 80% and 95% CIs will be calculated using K-M product-limit estimates for each treatment arm, and the K-M estimates of OS will be plotted over time. The Cox regression model will be used to estimate the hazard ratio and its 80% and 95% CIs stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years). Kaplan-Meier (K-M) estimates will also be presented for 4, 6, 9 and 12 months with 2-sided 80% and 95% CIs.

Overall PFS will be analyzed similarly to OS. Median PFS and 2-sided 80% and 95% (as exploratory) CIs will be presented, and the K-M estimates of PFS will be plotted over time. The Cox regression model will be used to estimate the hazard ratio and its 80% and 95% CIs stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years). K-M estimates will also be presented for 4, 6, 9, and 12 months with 2-sided 80% and 95% CIs.

The ORR will be compared between the test and control groups using either a chi-square test or a Cochran-Mantel-Haenszel test stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 or ≥18 years), as appropriate. Corresponding odds ratios and their 2-sided 80% and 95% CIs comparing the groups will also be presented. The individual treatment group ORRs will also be calculated along with exact 95% confidence intervals using the Clopper and Pearson method.

8.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Median DOR among responders for each arm will be presented along with its corresponding 2-sided 95% CIs. Disease Control Rate (DCR) and CBR will be calculated with exact 95% CIs using the Clopper and Pearson method. The differences of the above rates between 2 groups and corresponding two-sided 95% CIs will be calculated respectively.

8.7.1.7 Pharmacokinetic, Pharmacodynamic, and Other Biomarker Analyses

8.7.1.7.1 PHARMACOKINETIC ANALYSES

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

Lenvatinib data from Arm A of the study will be pooled with available data from other studies and subjected to population PK analysis. 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.

8.7.1.7.2 PHARMACODYNAMIC AND OTHER BIOMARKER ANALYSES

Pharmacodynamic, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.

Pharmacodynamic serum and archived, fixed tumor tissue biomarkers will be collected from subjects in Arm A only as described in the Schedule of Assessments. Pharmacodynamic serum and tumor biomarkers in this study will be identified as in other lenvatinib clinical studies.

Blood serum samples may be analyzed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, or other assays/methods and new technology in an effort to identify biomarkers.

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

Data obtained from the pharmacodynamic samples will be used for research. The pharmacodynamic samples will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib and for potential diagnostic development. If the subject reaches 18 years of age prior to the date of final sample analyses they will be reconsented. No further analyses will be performed on these collected samples from subjects who either do not reconsent after their 18th birthday or cannot be reached for reconsenting and the sample will be destroyed. When the subject reaches the age of 18 years (or 16 years in the UK) while on the study, and becomes competent to give informed consent, his/her consent will be obtained using separate ICFs to continue on the study.

8.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment group, will be summarized on an “as treated” basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%]

for categorical variables), as appropriate. Safety variables include TEAEs, clinical laboratory parameters, vital signs, 12-lead ECG results, Lansky play scores or Karnofsky performance scores, physical examination, height, closure of proximal tibial plates, and LVEF. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

8.7.1.8.1 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 adverse events will be summarized.

8.7.1.8.2 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 (Version 20.1 or higher) 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 (and within 30 days of the last study treatment), having been absent at pretreatment (Baseline) or

- Re-emerges 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 TEAEs will be summarized by treatment group. 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 highest CTCAE grade.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

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-related TEAEs will also be summarized by highest CTCAE grade.

Adverse events will be summarized using the Safety Analysis Set. The number of AEs and number and incidence (%) of subjects with AEs will be summarized by treatment group and

overall. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by SOC and by PT will be calculated. Incidence (%) by causal relationship with study drug and by severity (CTCAE v5.0) will also be calculated. For clinically significant events, time of onset, and recovery will be reported.

Adverse events will be summarized for descriptive purposes by age (2 to <6, 6 to <18, and ≥18), and sex.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. All deaths will also be summarized.

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

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

8.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 8.5.1.4.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 8.5.1.4.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on shift tables that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

8.7.1.8.4 VITAL SIGNS

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

Percentiles for BP values (only for subjects <18 years old) will also be summarized using a shift table of worst postbaseline from Baseline measurement by categories (<90th percentile,

90th to 95th percentile, 95th to ≤99th percentile, systolic BP or diastolic BP >99th percentile). See Appendix 6 and Appendix 7 for detail on percentiles.

8.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for electrocardiogram parameters (HR, PR, QRS, QT, QTcB, QTcF and RR) and changes from Baseline will be presented by visit. Electrocardiogram (ECG) findings will be summarized. A shift table of worst postbaseline values from Baseline for ECG findings will be provided.

QTc Bazett and QTc Fridericia will be summarized. QTc Bazett and QTc Fridericia will be categorized as both maximum increases from Baseline and maximum postbaseline values.

8.7.1.8.6 OTHER SAFETY ANALYSES

Descriptive summary statistics for LVEF changes from baseline will be calculated and summarized.

The shift of worst postbaseline proteinuria from Baseline will be summarized.

Thyroid-stimulating hormone values will be summarized in 2 categories (≤ULN and >ULN).

Lansky play scores or Karnofsky Performance Status score scores will be summarized by shifts from Baseline to worst postbaseline visit.

Radiographic findings of proximal tibial growth plates will be listed and analyzed if appropriate.

8.7.1.9 Other Analyses

8.7.1.9.1 HEALTH-RELATED QUALITY OF LIFE

Descriptive statistics will be presented for all PedsQL endpoints at each analysis time period by treatment arm. Baseline is defined as the later value of Day -1 or at Cycle 1 Day 1 prior to treatment.

This will be collected at baseline, at C2D1, C3D1, Week 18, C8D1, C18 D1 and at the Off-Treatment Visit. Score change from baseline in PedsQL at each analysis timepoint will be analyzed. Primary timepoint for assessment is at week 18 for all PedsQL endpoints.

Detailed HRQoL analysis plan will be provided in a separate analysis plan and the results will be provided in a stand-alone report.

8.7.1.9.2 PALATABILITY AND ACCEPTABILITY QUESTIONNAIRE

Measurement of palatability will be assessed using the Hedonic scale (Guinard, 2001) which is a Visual Analog Scale (VAS) in subjects receiving the suspension formulation in the study.

8.7.2 Determination of Sample Size

A binomial-based comparison of 2 proportions using correction for continuity was used for sample size estimation. A total sample size of 72 subjects is estimated to achieve 80% statistical power at 1-sided alpha of 0.1 to detect a difference of 30% based on the assumption that PFS-4m for Arm A (lenvatinib arm) is 55% and for Arm B is 25%. Alpha is the type 1 error probability of declaring lenvatinib arm being effective when the true lenvatinib arm PFS-4m rate is only 25%.

8.7.3 Interim Analysis

No interim analysis is planned for this study.

The safety monitoring will be conducted by the independent data monitoring committee (IDMC). The frequency of the 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 recommendation of whether to stop the study for safety will be reached by the IDMC based on their review of safety data with treatment information. The function and membership of the IDMC will be described in the IDMC charter.

8.7.4 Other Statistical/Analytical Issues

Not applicable.

8.7.5 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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10 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

10.1 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 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.

10.2 Adherence to the Protocol

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

10.3 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 IVRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source
- Electronic Patient-Reported Outcome by self-reported measures

10.4 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.

10.5 Identification of Source Data

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

10.6 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 for US sites), Investigator and Site Information Form (for non-US sites), 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.

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.

10.7 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.

10.8 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.

10.9 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.

10.10 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.

10.11 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.

10.12 Subject Insurance and Indemnity

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

11 APPENDICES

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

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

Appendix 2 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 3 Karnofsky Performance Status Scale Definitions Rating (%) Criteria

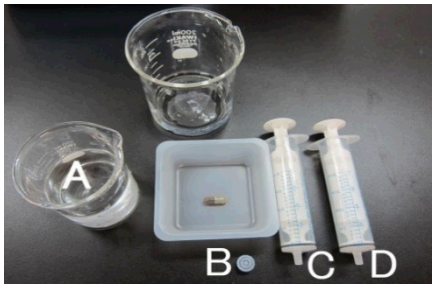
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and 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.

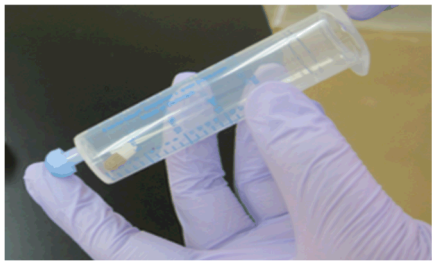
Appendix 4 Preparation of Lenvatinib suspension

Preparation of suspension Prepare the suspension as illustrated by either method. Prepare the suspension with water or apple juice. The suspension should be directly injected into the mouth of the subjects and should not be washed down with additional fluid. The suspension should be taken immediately after preparation.

a. Procedure for suspension administration by syringe

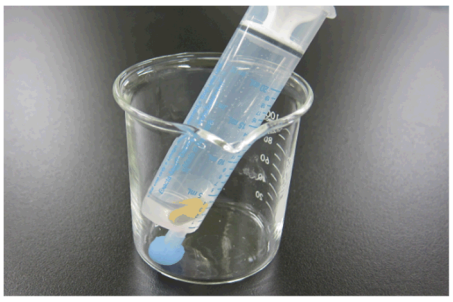


A: Water or apple juice
B: Cap
C: Syringe (20 mL, Baxa preferred)
D: Syringe for rinse (20 mL, Baxa preferred)

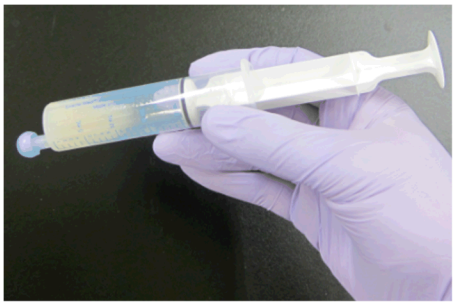


Place one capsule* into a syringe. The tip port of the syringe needs to be closed with a cap.
* One to five capsules are allowed to be placed in a syringe.

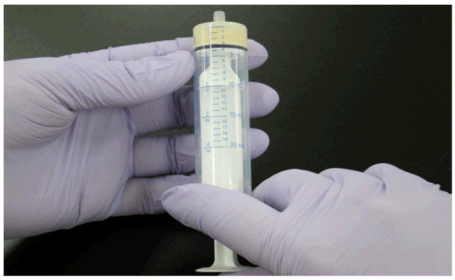
Three (3) mL of water or apple juice is added into the syringe using another (new) syringe.



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

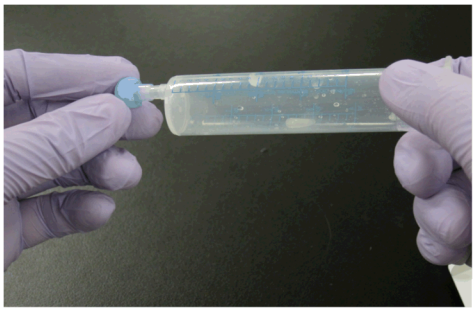


After 10 minutes leaving, shake the syringe for not less than 3 minutes to dissolve the capsule shell completely and to suspend granules (capsule shell needs to be dissolved. It is fine as long as granules are well suspended).

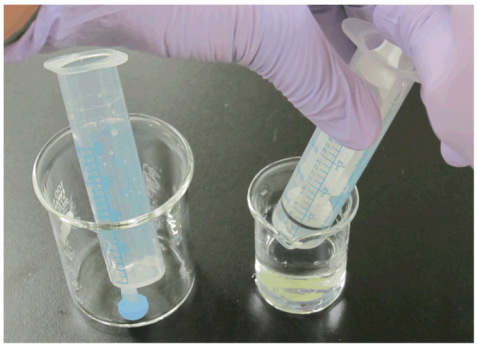


Remove the cap from the syringe.
By sliding the piston, push air out from the syringe, and then administer the 3mL of suspension from the syringe.

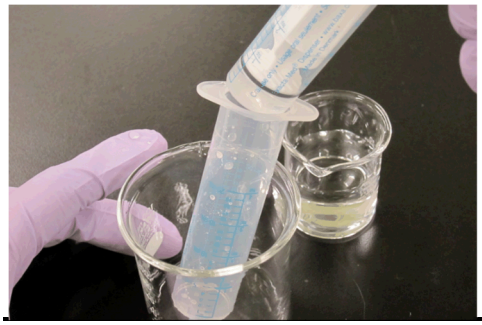
Rinse step



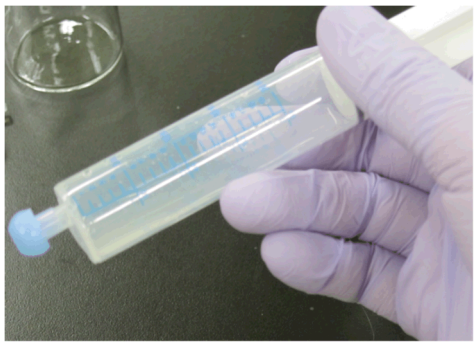
After the administration of 3mL suspension from the syringe, the cap (reuse) is to be connected with the syringe.



2 mL of water or apple juice is to be taken by another (new) syringe.



2 mL of water or apple juice is to be poured into the syringe (which was used for the 3mL suspension).

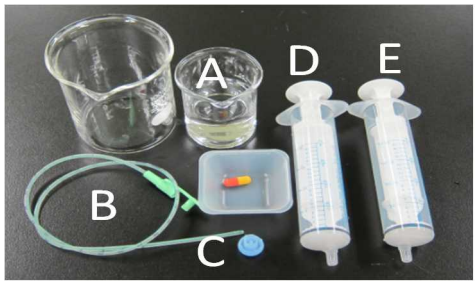


After connecting the cap (reuse), the syringe is to be shaken for 10 times.

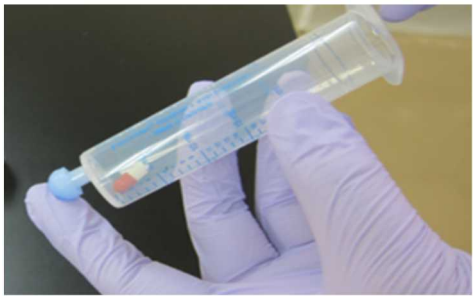
After removing the cap from the syringe, push air out from the syringe, and then 2 mL of rinse liquid is to be administered.

Total volume of suspension to be administrated is 5 ml (=3mL for suspension + 2mL for rinse) for one to five capsules.

b. Procedure of suspension administering by syringe with NG tube



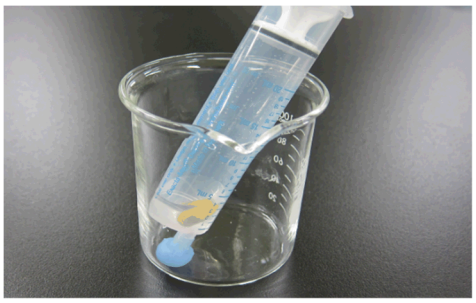
A: Water or apple juice
B: NG tube (Vygon, 6FR)
C: Cap
D: Syringe (20 mL, Baxa, preferred)
E: Syringe for rinse (20 mL, Baxa preferred)



Place one capsule* into a syringe. The tip port of the syringe needs to be closed with a cap.

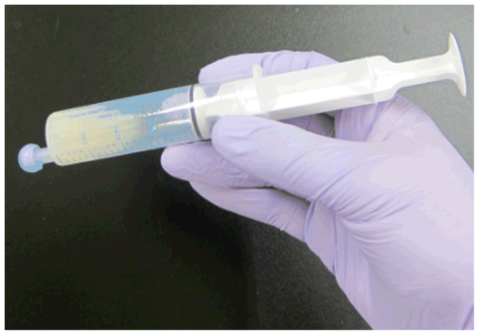
* One to five capsules are allowed to be placed in a syringe.

The 3 mL of water or apple juice is to be poured into the syringe using another (new) syringe.



Insert a piston into the syringe (cylinder) about 2 cm from the end.

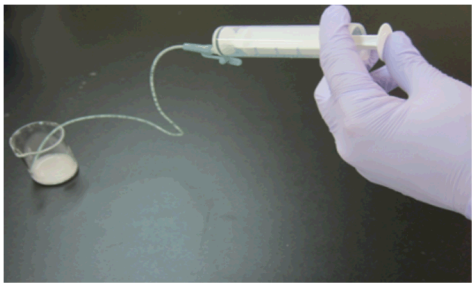
Leave the syringe for is not less than 10 minutes.



After 10 minutes leaving, shake the syringe for not less than 3 minutes to dissolve the capsule shell completely and to suspend granules (capsule shell needs to be dissolved, but it is fine as long as granules are well suspended).

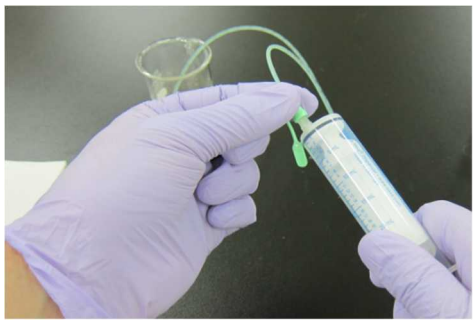
Remove the cap from the syringe.

By sliding the piston, push air out from the syringe.

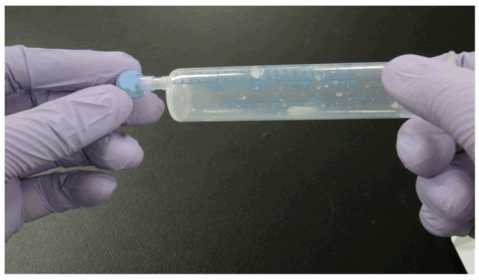


After connecting a NG tube with the syringe, administrate the 3 mL of suspension through the NG tube.

Rinse step



After pouring the suspension, the NG tube is to be taken off from the syringe.



The cap (reuse) is connected with the syringe

Two 2 mL of water or apple juice is to be poured into the syringe by using another (new) syringe.

After inserting the piston to the syringe (about 2cm from the end), shake the syringe for 10 times.

By sliding the piston, push out air from the syringe.

After connecting a NG tube, the 2 mL of rinse liquid is to be administered from the syringe through the NG tube.

Total volume of suspension to be administrated is 5 ml (=3mL for suspension + 2mL for rinse) for one to five capsules.

Appendix 5 Palatability Questionnaire

Study E7080-G000-230- Palatability Questionnaire

Subject ID:

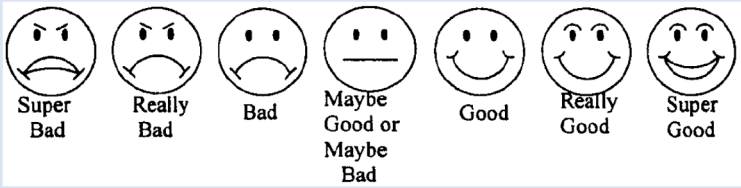
1	0	0	1				

Treatment Dose:

Visit Cycle:

Date:

Taste



(Please circle according to your experience)

Please provide reasons for your rating:

……

Appearance

(Please circle according to your experience)

Please provide reasons for your rating:

……

Smell

(Please circle according to your experience)

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

Appendix 6 Blood Pressure Levels for Boys by Age and Height Percentile

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

AGE (Year)	BP Percentile Ð	Systolic BP (mmHg) Percentile of Height 5th	10th	25th	50th	75th	90th	95th	Diastolic BP (mmHg) Percentile of Height 5th	10th	25th	50th	75th	90th	95th
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 7 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)	Ð	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63

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

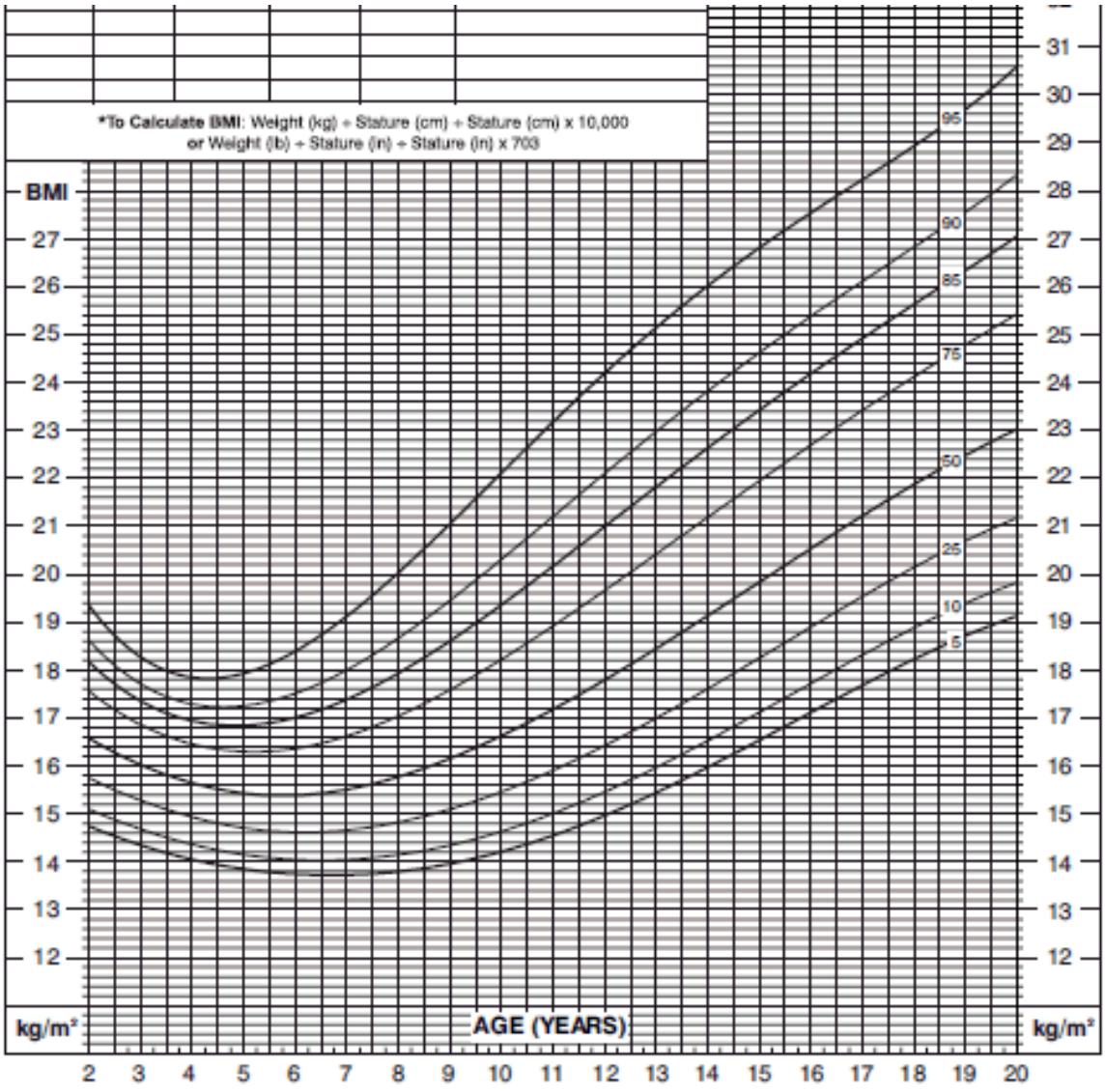
BP, blood pressure

* 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 8 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).

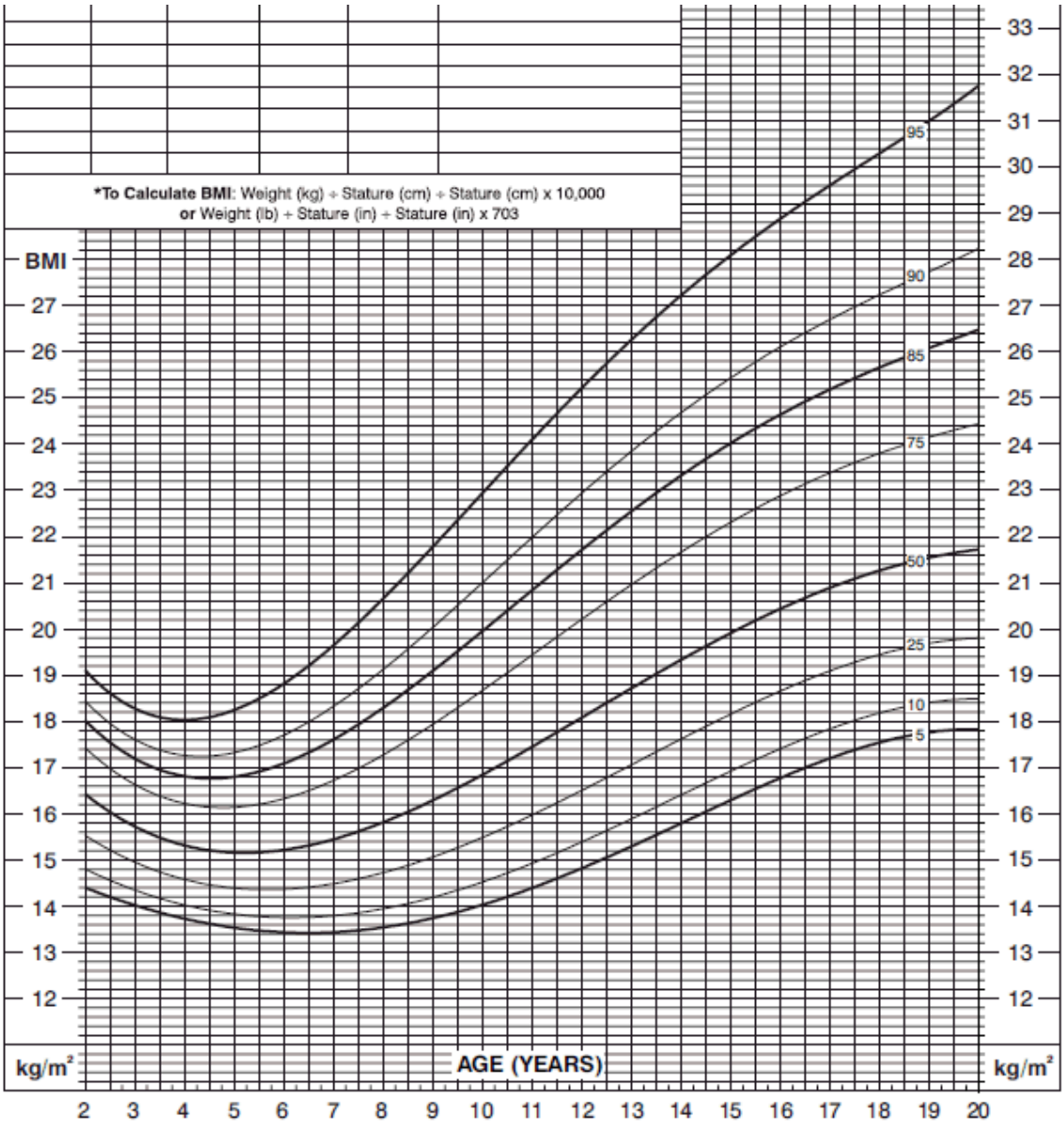
http://www.cdc.gov/growthcharts

Link for the charts is provided below

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

Appendix 9 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.ht

Appendix 10 Tanner's Staging

Boys Tanner Stage progression scale*

Genitalia:

1= The testes, scrotum and penis are about the same size and shape as they were when you were a child

2= The testes and scrotum are bigger. The skin of the scrotum has changed. The scrotum, the sack holding the testes, has gotten lower. The penis has gotten only a little bigger.

3= The penis has grown in length. The testes and scrotum have grown and dropped lower.

4= The penis has gotten even bigger. It is sider. The glans (the head of the penis) is bigger. The scrotum is darker than before. It is bigger because the testes are bigger.

5= The penis, scrotum, and testes are the size and shape of an adult man.

Pubic Hair:

1= There is no pubic hair at all.

2= There is a little soft, long, lightly-colored hair. Most of the hair is at the base of the penis.

This hair may be straight or a little curly.

3= The hair is darker in this stage. It is more curled. It has spread out and thinly covers a bigger area.

4= the hair is now as dark, curly, and course as that of an adult man. The area that the hair covers is not as big as that of an adult man. The hair has NOT spread out to the legs.

5= The hair has spread out to the legs. The hair is now like that of an adult man. It covers the same area as that of an adult man.

Girls Tanner Stage progression scale

Breast:

1= The nipple is raised a little. The rest of the breast is still flat.

2= This is the breast bud stage. In this stage, the nipple is raised more than in stage 1. The breast is a small mound. The areola is larger than stage 1.

3= The breast and areola are both larger than in stage 2. The areola does not stick out away from the breast.

4= The areola and the nipple make up a mound that sticks up above the shape of the breast. NOTE: This stage may not happen at all for some girls. Some girls develop from stage 3 to stage 5 with no stage 4

5= This is the mature adult stage. The breasts are fully developed. Only the nipple sticks out in this stage. The areola has moved back in the general shape of the breast.

Pubic Hair:

1= There is no pubic hair at all.

2= There is a little soft, long lightly-colored hair. This hair may be straight or a little curly.

3= The hair is darker in this stage. It is coarser more curled. It has spread out and thinly covers a bigger area.

4= the hair is now as dark, curly, and course as that of an adult female. The area that the hair covers is not as big as that of an adult female. The hair has NOT spread out to the legs.

5= The hair is now like that of an adult female. It covers the same area as that of an adult female. The hair usually forms a triangular (V) pattern as it spreads out to the legs.

*Adapted from: Morris, N.M., and Udry, J.R., (1980). Validation of a Self-Administered Instrument to Assess Stage of Adolescent Development. Journal of Youth and Adolescence, Vol. 9, No. 3: 271-80.

Appendix 11 Pharmacodynamic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic (PD), 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.

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

Sample Collection and Handling

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

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

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

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

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

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

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays

that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

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

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E7080-G000-230

Study Protocol Title: A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)

Investigational Product Name: E7080/Lenvatinib

IND Number: 146642

EudraCT Number: 2019-003696-19

SIGNATURES

Authors:

PPD

06-Nov-2019
Date

Oncology Business Group, Eisai Inc.

PPD

06 Nov 2019
Date

Oncology Business Group, Eisai Inc.

PPD

6 Nov 2019
Date

Oncology Business Group, Eisai Inc.

PPD

6 Nov 2019
Date

Oncology Business Group, Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7080-G000-230
Study Protocol Title:	A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)
Investigational Product Name:	E7080/Lenvatinib
IND Number:	146642
EudraCT Number:	2019-003696-19

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

Medical Institution

Investigator	Signature	Date