Amsterdam, 17 August 2023
EMA/367098/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Lenvima

Lenvatinib

Procedure no: EMEA/H/C/003727/P46/022

Kisplyx

Lenvatinib

Procedure no: EMEA/H/C/004224/P46/019

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 29/03/2023, the MAH submitted a completed paediatric study for lenvatinib, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure specific obligation.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study E7080-A001-216 a stand-alone study. The MAH confirms that Study E7080-A001-216 is part of the clinical development program for lenvatinib and is Study 3 in the approved Paediatric Investigation Plan (PIP) (EMEA-001119-PIP03-19-M03). The study was completed on 30th September 2022, which was the last visit of the last subject.

2.2. Information on the pharmaceutical formulation used in the study E7080-A001-216

Lenvatinib was provided as hard capsules containing lenvatinib 1 mg, 4 mg, or 10 mg for oral use.

Lenvatinib Batch/Lot Nos.:

1-mg capsules: P68005ZZC, P89008ZZD, P89009ZZC, P89010ZZC, P9Y012ZZB

4-mg capsules: P6005ZZB, P84008ZZE, P89013ZZC, P94004ZZC

10-mg capsules: P08006ZZA, P75009ZZB, P78024ZZI, P95003ZZD

For subjects who were unable to swallow capsules, lenvatinib capsules could be added to water or apple juice to prepare an extemporaneous oral suspension. Preparation of Lenvatinib suspension was described in E7080-A001-216 study protocol.

As per the section 4.2 of the approved Lenvima and Kisplyx SmPCs, the lenvatinib capsules may be added without breaking or crushing them to a tablespoon of water or apple juice in a small glass to produce a suspension. The capsules must be left in the liquid for at least 10 minutes and stirred for at least 3 minutes to dissolve the capsule shells. The suspension is to be swallowed. After drinking, the same amount of water or apple juice (one tablespoon) must be added to the glass and swirled a few times. The additional liquid must be swallowed.

Dosing nomograms based on BSA and dose level were used to prescribe lenvatinib to minimize intersubject dosing variability. The maximum daily dose of lenvatinib administered during the study could not exceed 18 mg at Dose Levels -1 and 1. Intrasubject dose escalation of lenvatinib was not allowed.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report for:

- E7080-A001-216 A Phase 1/2 Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including CNS Tumors

2.3.2. **Clinical study**

E7080-A001-216A Phase 1/2 Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including CNS Tumors

Description

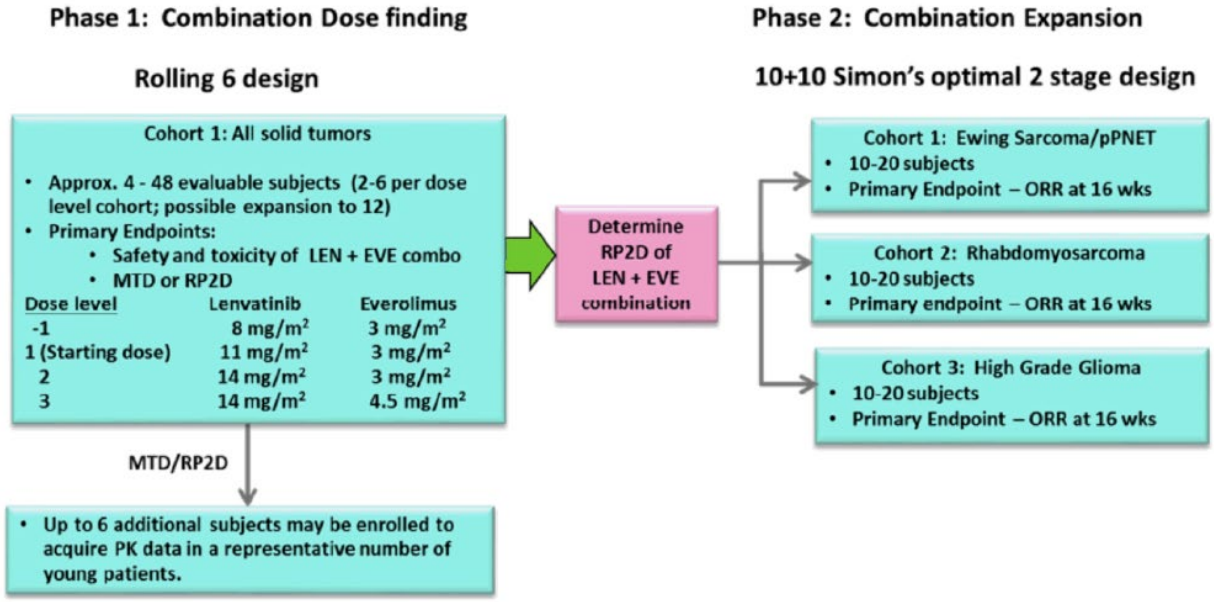


Figure 1 study E7080-A001-216 Design

Methods

Study treatment

Phase 1 Dose Escalation and Determination of the MTD

The Phase 1 component is a dose escalation study with treatment in sequential cohorts of escalating doses of lenvatinib in combination with everolimus, each administered once daily in 28-day treatment cycles. Pediatric subjects with a relapsed/refractory solid malignancy, including primary brain tumors are eligible to enrol. The initial dose level (Dose Level 1) for lenvatinib will be 11 mg/m2. The initial dose of everolimus will be 3 mg/m2. Dose Level 2 will escalate lenvatinib by approximately 25% to 14 mg/m2 and maintain everolimus at the same dose of 3 mg/m2. At Dose Levels -1 and 1, maximum daily dose of Lenvatinib will not exceed 18 mg daily. At Dose Level 2, maximum daily dose of lenvatinib allowed will not exceed 24 mg. Should Dose Level 2 be well tolerated, Dose Level 3 may be considered to test lenvatinib at 14 mg/m2 (capped at 24 mg) and escalate everolimus to 4.5 mg/m2. For everolimus dose levels of 3 mg/m2 and 4.5 mg/m2, the maximum daily dose of everolimus will not exceed 5 mg and 7 mg, respectively. If the MTD for combination of lenvatinib and everolimus has been

exceeded at Dose Level 1, then the subsequent cohort of subjects will be treated at Dose Level -1 with dose of lenvatinib 8 mg/ m2 and dose of everolimus 3 mg/ m2 (Table below). Intra-subject titration of everolimus will not be allowed on this study.

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

Table 1 Planned Dose-Escalation

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

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

Phase 2 Treatment Phase (Expansion Cohorts)

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

Phase 2 Cohorts 1 to 3 will use a 10+10 Simon's optimal 2-stage design for each cohort; 10 evaluable subjects will be enrolled to each stage. The Sponsor will closely monitor enrolment to ensure that at least 50% of subjects enrolled in each cohort are <18 years of age at the time of informed consent. The primary outcome measure for Ewing sarcoma/pPNET, rhabdomyosarcoma, and HGG will be ORR (complete or partial response) at 16 weeks.

If there are no responses among the 10 subjects in Stage 1, then the enrolment to that disease cohort will stop and conclude that the lenvatinib/everolimus combination therapy does not elicit a response in that disease cohort.

If there is at least 1 response in the first stage, then the second stage will enrol 10 additional evaluable subjects. If there are 2 or fewer responses among the 20 evaluable subjects, then lenvatinib/everolimus combination therapy will be declared a failure for that disease cohort.

Subjects will meet the criteria for being evaluable for an objective response if they have measurable disease present at baseline and at least 1 post-baseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease. Subjects who are not evaluable for objective response will be replaced.

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

Study Treatment Dose Reduction and Interruption Instructions

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

Doses in the Dose Adjustment column are based on a presumed starting dose of 11 mg/m2 lenvatinib and 3 mg/m2 everolimus. Dose reductions will occur in succession based on the previous dose level. Each dose level reduction due to toxicity at a given BSA is approximately 25% reduction from the previous dose. Once the study drug dose has been reduced, it may not be increased at a later date, unless the dose was mistakenly decreased; in this situation, the sponsor's approval is required to increase the dose.

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

Table 2 Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-related Toxicity

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

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

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

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

Objective(s)

Primary Objectives

Phase 1

- To determine a maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of lenvatinib administered in combination with everolimus once daily (QD) to pediatric subjects with recurrent/refractory malignant solid tumors
- To describe the toxicities of lenvatinib administered in combination with everolimus QD to pediatric subjects with recurrent/refractory malignant solid tumors

Phase 2

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

Secondary Objectives

Phase 1

- To preliminarily define the antitumor activity of lenvatinib in combination with everolimus in pediatric subjects with recurrent/refractory solid tumors
- To characterize the pharmacokinetics (PK) of oral lenvatinib and everolimus, when administered in combination to pediatric subjects with recurrent/refractory solid tumors

Phase 2

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

- To evaluate the tolerability and safety profile of lenvatinib in combination with everolimus inpediatric subjects with recurrent/refractory EWS, RMS, and HGGTo characterize the PK of lenvatinib and everolimus, when administered in combination to children with recurrent/refractory EWS, RMS, and HGG

Exploratory Objectives for Phases 1 and 2

- To evaluate blood, tumor, and safety (eg, hypertension) markers as correlative biomarkers of treatment effects and outcomes of lenvatinib in combination with everolimus
- To assess candidate alterations in genes and/or proteins that may contribute to tumor development and serve as predictive markers of response in archival tumor tissue from pediatric subjects
- To explore relationships between lenvatinib exposure and safety (eg, adverse events [AEs] of special interest)

Study design

Phase 1 Dose Escalation and Determination of the MTD

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

Dose level assignment will be based on:

1. the number of subjects currently enrolled in the dose level cohort,

2. the number of DLTs observed, and

3. the number of subjects at risk for developing a DLT (ie, subjects enrolled but who are not yet assessable for toxicity).

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

When subjects are not evaluable for toxicity, they will be replaced with the next available subject if escalation or de-escalation rules have not been fulfilled at the time the next

available subject is enrolled in the study.

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

Table 3 The Rolling 6 Design

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

DLT = dose-limiting toxicity

*If 6 subjects already entered at next lower dose level, the maximum tolerated dose (MTD) has been defined.

**If final dose level has been reached, the recommended dose has been reached.

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

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

Protocol Steering Committee

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

Toxicity Monitoring

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

Dose-Limiting Toxicity

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

A. Non-hematological DLT:

- Any Grade 3 or greater non-hematological toxicity attributable to the investigational drug with the specific exclusion of:
  - Grade 3 nausea and vomiting <3 days duration
  - Grade 3 diarrhea <3 days duration
  - Grade 3 weight loss
  - Grade 3 liver enzyme elevation, including ALT/aspartate aminotransferase (AST)/ gamma glutamyl transferase (GGT)/ bilirubin/alkaline phosphatase that returns to Grade <1 or baseline within 7 days
  - Grade 3 asymptomatic elevation in amylase or lipase that returns to Grade <1 or baseline within 7 days
  - Grade 3 elevation in triglycerides that returns to Grade<1 or baseline within 7 days
  - Grade 3 or 4 fever <5 days duration
  - Grade 3 infection <5 days duration
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation
  - Grade 3 proteinuria (UPC) ratio >1.9 unless confirmed with a second measurement within 72 hours
  - Grade 3 headache <3 days duration responsive to optimal management.
- Any Grade 2 non-hematological toxicity that persists for ≥7 days and is considered sufficiently medically significant or sufficiently intolerable by subjects despite optimal supportive care that it requires treatment interruption.
- Any dose interruption or reduction due to toxicity which results in administration of less than 75% of the planned dosage of lenvatinib and/or everolimus. considered a DLT.
- Dose-limiting hypertension: Any Grade 4 hypertension Confirmed systolic or diastolic BP more than 25 mmHg above 95th percentile for sex, age, height/length, or an elevated diastolic BP

(ie, >95th percentile for age) not controlled by a single antihypertensive medication within 14 days of use. An antihypertensive tablet or capsule that contains up to 2 antihypertensive ingredients was considered a single antihypertensive medication

B Hematologic Dose-Limiting Toxicity:

- In subjects evaluable for hematologic toxicity, DLT was defined as:

  - Grade 4 thrombocytopenia (platelet count <25,000/mm3) or Grade 4 neutropenia, not due to malignant infiltration.

  - Any Grade ≥2 arterial thromboembolic events (including cerebrovascular ischemia, peripheral or visceral arterial ischemia)

  - Note: Grade 3 or 4 febrile neutropenia was not considered a DLT

Dose-limiting toxicities were determined by the investigator and Eisai's medical monitor in consultation with the Protocol Steering Committee (PSC), as needed. Subjects who discontinued study treatment for any reason other than DLT (eg, early PD) during Cycle 1 (Day 1 to Day 28), and had not received at least 75% of the prescribed dose before discontinuation, were replaced.

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

Study population /Sample size

Study participants

Key eligibility criteria are provided below.

1. Histologically or cytologically confirmed diagnosis of the following tumor types:

a. Phase 1: Recurrent or refractory solid tumors (excluding hepatoblastoma and lymphomas), including primary CNS tumors; subjects had to have had either measurable or evaluable disease. Subjects with diffuse intrinsic pontine glioma, optic pathway glioma, or pineal tumors with elevated tumor markers (α-fetoprotein and ß-human chorionic gonadotropin did not require histological or cytological confirmation of diagnosis.

b. Phase 2: Recurrent or refractory tumors; subjects had to have had measurable disease

- Cohort 1: EWS

- Cohort 2: RMS

- Cohort 3: HGG (subjects with diffuse intrinsic pontine glioma were not eligible)

2. Measurable disease that met the following criteria (Phase 2):

a. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (for all tumor types except HGG)

- At least 1 lesion of ≥1.0 cm in the longest diameter for a nonlymph node or ≥1.5 cm in the short-axis diameter for a lymph node that is serially measurable according to RECIST 1.1 using computed tomography /magnetic resonance imaging (CT/MRI)

b. Response Assessment in Neuro-Oncology (RANO) for HGG (Wen, et al., 2010):

- At least 1 measurable lesion, defined as a bidimensionally contrast-enhancing lesion with clearly defined margins by CT/MRI scan, a minimal diameter of 1 cm, and visible on 2 axial slices (preferably at most 5 mm apart with 0 mm skip)

c. Lesions that had been treated with external beam radiotherapy or locoregional therapies such as radiofrequency ablation had to have shown evidence of PD based on RECIST 1.1 to be deemed as target lesions

Subjects also had to have adequate organ (eg, bone marrow, renal, hepatic, cardiac) function, adequate blood pressure (BP) control, minimum BSA of 0.6 m2 at study entry, Karnofsky performance status (KPS) score (for subjects aged >16 years) or Lansky play score (for subjects aged ≤16 years) of ≥ 50, appropriate washout periods and recovery following prior anticancer therapy, no prior lenvatinib treatment, no more than 2 prior VEGF/VEGFR targeted therapies for their cancer (Phase 2 only), no prior VEGF/VEGFR-targeted therapy in combination with an mTOR inhibitor (Phase 2 only), no major surgery planned, or clinically significant abnormalities that could have interfered with the subjects' participation in the study or analysis of their data as outlined in the protocol. Prior treatment with an mTOR inhibitor was permitted as long as the subject had PD following that treatment.

Sample size

Phase 1

Determination of the Maximum Tolerated Dose: The total number of subjects required for the Phase 1 portion of this study will depend upon the toxicities observed as the study progresses. The minimum number of evaluable subjects required for this study is 4. The projected maximum number of evaluable subjects required is 48. Once the MTD or RP2D has been defined, up to 6 additional subjects with recurrent or refractory solid tumors may be enrolled to acquire PK data in a representative number of young subjects.

Therefore, a maximum of 54 subjects are expected to be enrolled in the 4 dose escalation levels, and PK expansion. The Phase 1 part of the study is expected to be completed within 18 months. In the event that each of Dose Levels -1, 1, 2, and 3 are expanded to 12 subjects, an absolute maximum of 54 subjects would be required allowing for 20% to be non-evaluable and including up to 6 additional subjects for PK analysis.

Phase 2

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

Treatments

Lenvatinib

Provided as hard capsules containing 1 mg, 4 mg, or 10 mg lenvatinib for oral use. An extemporaneous suspension of lenvatinib capsules was used for children unable to swallow whole capsules.

Everolimus

Provided as dispersible tablets containing 2 mg, 3 mg, or 5 mg everolimus (tablets for oral suspension).

Each subject's dose of lenvatinib and everolimus was based on body surface area (BSA). At study entry, subjects had to have a minimum BSA of 0.6 m2. At Dose Levels -1 and 1, the maximum daily dose of lenvatinib administered could not exceed 18 mg and maximum daily dose of everolimus could

not exceed 5 mg. Lenvatinib and everolimus were administered orally once daily in continuous 28-day cycles. The sequence of administration was not important.

Outcomes/endpoints

Primary endpoints

Primary Endpoints for Phase 1

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

Primary Endpoint for Phase 2

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

Secondary endpoints

Secondary Endpoints for Phase 1 and Phase 2

- ORR at the time of data cutoff
- DCR, defined as the proportion of subjects who have the BOR of CR or PR or stable disease (SD) (SD duration ≥7 weeks since the first dose of the study treatment)
- CBR, defined as the proportion of subjects who have the BOR of CR or PR or durable SD (SD duration ≥23 weeks since the first dose of the study treatment)
- -DOR, defined as the time from the date of the first documented CR or PR to the date of the disease progression objectively documented or death (whichever occurs first)
- Plasma PK of lenvatinib and trough concentrations of everolimus when administered in combination
- Safety and toxicity of lenvatinib in combination with everolimus in Phase 2

Exploratory endpoints

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

Statistical Methods

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

Statistical analysis plan

All descriptive statistics for continuous variables will be reported using n, mean, SD, median, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects

For Phase 1, data cutoff will occur when the MTD/RP2D for the lenvatinib/everolimus combination is determined, or if the PK expansion is needed, will occur when the last subject in the PK expansion completes 1 cycle of treatment or discontinues before the end of Cycle 1, whichever occurs first. Additional subjects enrolled for PK once the MTD or RP2D has been defined will not be included in the DLT analysis.

For each cohort in Phase 2, there will be 1 futility analysis: this is planned after the first 10 subjects have completed at least 4 treatment cycles and, if applicable, a confirmatory scan has been performed (in case of a PR or CR at week 16), or have discontinued study drug early (i.e. before Week 16). At the futility analysis, if there are no responders (CR/PR), then enrollment for that cohort will be discontinued for lack of efficacy. If 1 or more responses are observed, accrual will continue up to a total of 20 subjects. Data cut-off for the primary study analysis for each cohort in Phase 2 will occur when all subjects in Stage 1 and/or Stage 2, as applicable, have completed at least 4 treatment cycles and, if applicable, a confirmatory scan has been performed (in case of a PR or CR at Week 16), or have discontinued study drug early.

Results

Recruitment/ Number analysed

Phase 1 (Combination Dose-Finding)

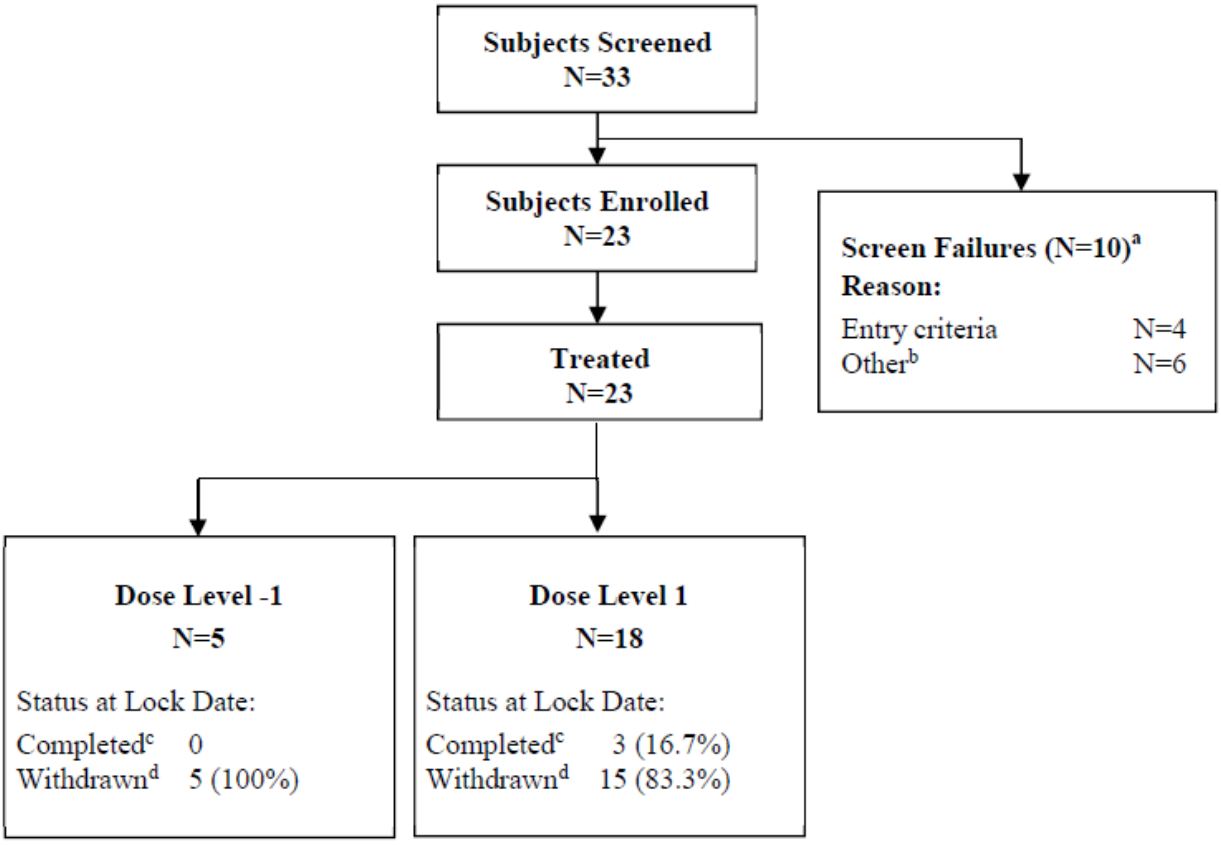
In Phase 1, a total of 33 subjects signed an ICF and were screened for inclusion in the study.

Of the 10 screen failures, 4 subjects failed to meet inclusion or exclusion criteria, and 6 subjects were excluded for another reason.

The remaining 23 enrolled subjects were all treated at 1 of 2 dose levels (Dose Level -1 or Dose Level 1) and received at least 1 dose of study treatment. Nine subjects discontinued treatment during or after completing the Treatment Phase (ie, Cycle 1).

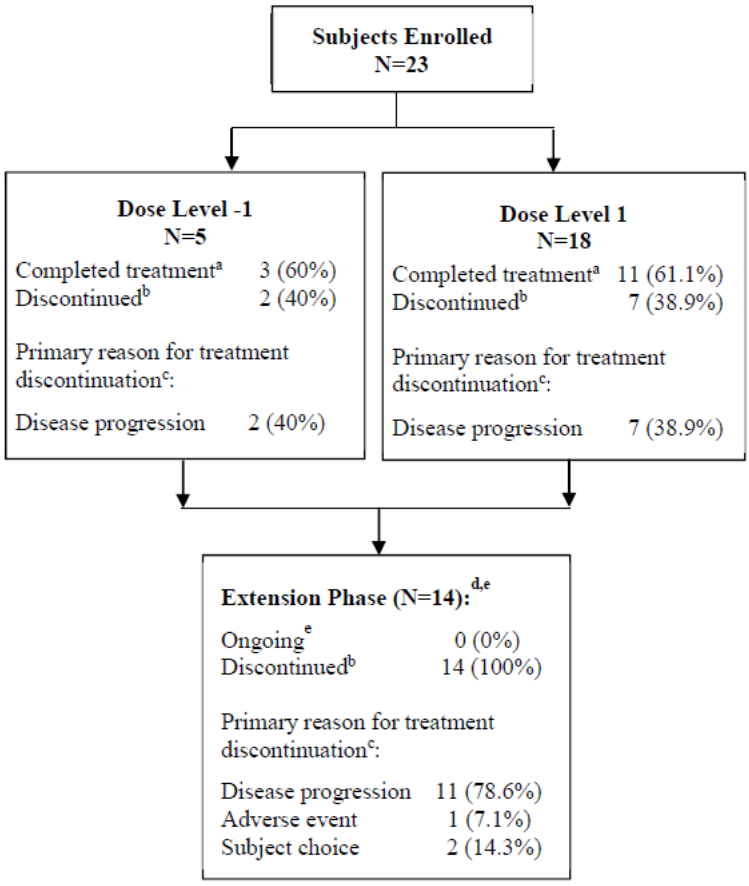
The primary reason for discontinuation in Cycle 1 was PD. The remaining 14 subjects completed the Treatment Phase (ie, Cycle 1) and entered the Extension Phase.

At the time of database lock, all 23 subjects had discontinued study treatment. The most requent reason for discontinuation of treatment was radiologic or clinical PD (20 subjects [87.0%]).



Database lock date: 14 Nov 2022.
Dose Level -1: Lenv 8 mg/m^2 + Ever 3 mg/m^2.
Dose Level 1: Lenv 11 mg/m^2 + Ever 3 mg/m^2.
eCRF = electronic case report form, EVER = everolimus, Lenv = lenvatinib.
a: Based on primary reason reported on the Screening Disposition eCRF.
b: Other reasons included, but were not limited to, rapid disease progression and subject choice.
c: Completed study refers to those subjects who were alive with survival follow-up for more than 1 year.
d: Withdrawn refers to subjects who were no longer being followed for survival as of the database lock date.
Source: Table 14.1.1.1.1 and Table 14.1.1.5.1.

Figure 2 Subject Disposition and Primary Reason for Withdrawal From the Study – Phase 1 (All Enrolled Subjects)



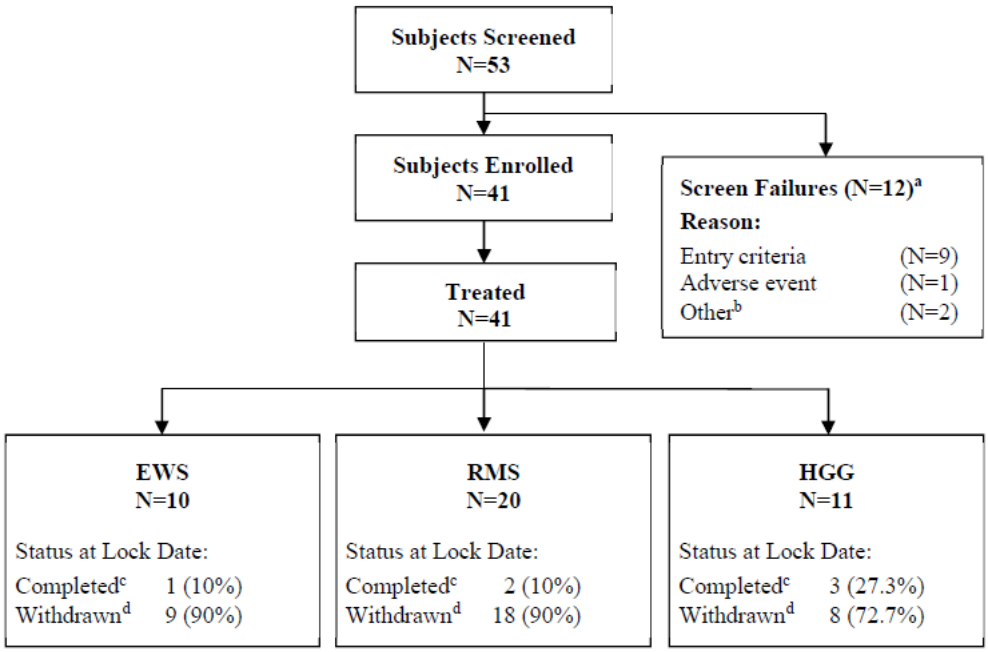
Database lock date: 14 Nov 2022.
Dose Level -1: Lenv 8 mg/m^2 + Ever 3 mg/m^2.
Dose Level 1: Lenv 11 mg/m^2 + Ever 3 mg/m^2.
eCRF = electronic case report form, EVER = everolimus, Lenv = lenvatinib.
Completed/discontinued treatment refers to completion/discontinuation of all study drugs.
a: 'Completed Treatment Phase' refers to subjects who completed 1 cycle of treatment. Subjects then transitioned to the Extension Phase and continued to receive study treatment at their original assigned dose level for lenvatinib and everolimus.
b: Discontinuation of treatment refers to subjects who discontinued both study drugs.
c: Based on primary reason reported on the *Screening Disposition* eCRF.
d: Extension Phase started after completion of Cycle 1.
e: Two subjects completed Cycle 1, entered the Extension Phase, and received treatment for 49 days (Subject PPD , Dose Level -1) and 504 days (Subject PPD , Dose Level 1), respectively; however, all of their exposure data were recorded in the Treatment Phase on the eCRF.
Source: Table 14.1.1.3.1 and Listing 16.2.1.2.1.

Figure 3 Subject Disposition and Primary Reason for Discontinuation of Study Treatment – Phase 1 (Safety Analysis Set)

Phase 2 (Combination Expansion)

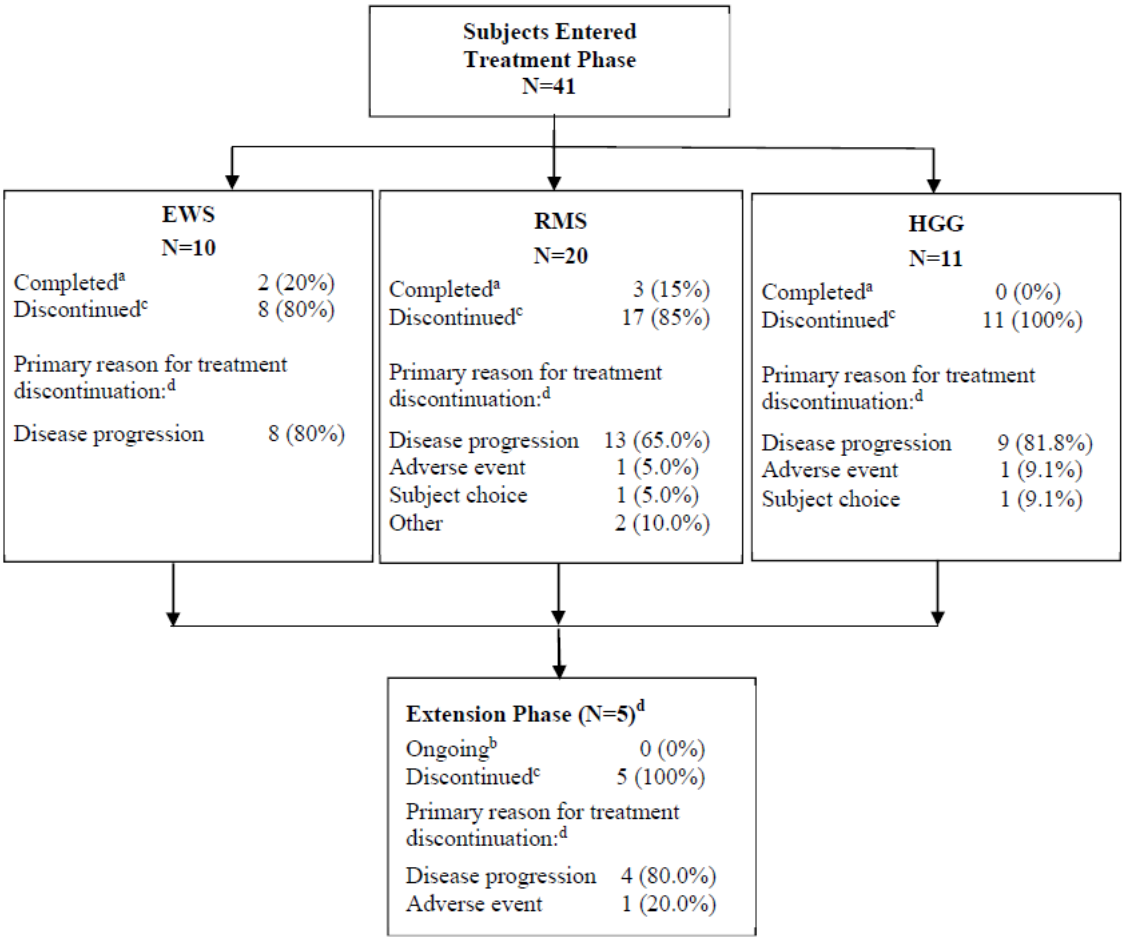
In Phase 2, a total of 53 subjects signed an ICF. Of the 12 screen failures, 9 subjects failed to meet inclusion or exclusion criteria, and 3 subjects were excluded for another reason.

The remaining 41 of the 53 subjects were entered into 1 of 3 cohorts and received at least 1 dose of study treatment. All 41 subjects discontinued treatment during or after completing the Treatment Phase (ie, Cycle 4). The primary reason for treatment discontinuation was radiologic or clinical PD (34 [82.9%]). Five subjects completed the Treatment Phase and entered the Extension Phase.



Database lock date: 14 Nov 2022.
All subjects received lenvatinib 11 mg/m^2 + everolimus 3 mg/m^2.
EWS = Ewing sarcoma, HGG = high-grade glioma, RMS = rhabdomyosarcoma.
a: Based on primary reason reported on the *Screening Disposition* electronic case report form.
b: Other reasons included worsening clinical status and disease progression.
c: Completed study refers to those subjects who were alive, with survival follow-up for >1 year.
d: 'Withdrawn' refers to subjects who were no longer being followed for survival as of the database lock date.
Source: Table 14.1.1.1.2 and Table 14.1.1.5.2; Listing 16.2.1.1.2 and Listing 16.2.1.3.2.

Figure 4 Subject Disposition and Primary Reason for Withdrawal From the Study – Phase 2 (All Enrolled Subjects)



Database lock date: 14 Nov 2022.
All subjects received lenvatinib 11 mg/m^2 + everolimus 3 mg/m^2.
Completed/discontinued treatment refers to completion/discontinuation of both study drugs.
EWS = Ewing sarcoma, HGG = high-grade glioma, RMS = rhabdomyosarcoma.
a: The Treatment Phase comprised 4 cycles of treatment. Subjects then transitioned to the Extension Phase, where they continued to receive study treatment or were followed for survival.
b: Ongoing refers to subjects who were still receiving at least 1 study drug at data cutoff date.
c: Discontinuation of treatment refers to subjects who discontinued both study drugs.
d: As reported on the *Subject Disposition* case report form.
Source: Table 14.1.1.3.2 and Listing 16.2.1.2.2.

Figure 5 Subject Disposition and Primary Reason for Discontinuation of Study Treatment – Phase 2 (Evaluable Analysis Set)

Baseline data

Phase I

Overall, the majority of subjects were white (n=14 [60.9%]) and had a KPS or Lansky play score of 80 or above (n=19 [82.6%]). Median BSA was 1.00. Of the 23 subjects enrolled, 21 (91.3%) were younger than 17 years and 11 subjects (47.8%) were male. There were no clinically relevant differences in baseline demographics.

Table 4 Selected Demographic and Baseline Characteristics – Phase 1 (Safety Analysis Set)

	Dose Level -1	Dose Level 1	
	Lenv 8 mg/m^2 + Ever 3 mg/m^2 (N=5) n (%)	Lenv 11 mg/m^2 + Ever 3 mg/m^2 (N=18) n (%)	Total (N=23) n (%)
Age (years)			
Mean (SD)	15.4 (3.5)	7.8 (4.4)	9.5 (5.2)
Median	15.0	7.0	9.0
Min, Max	12, 21	3, 19	3, 21
Age Group, n (%)			
≥2 years - <6 years	0 (0.0)	7 (38.9)	7 (30.4)
≥6 years - <17 years	4 (80.0)	10 (55.6)	14 (60.9)
≥17 years	1 (20.0)	1 (5.6)	2 (8.7)
Sex, n (%)			
Male	3 (60.0)	8 (44.4)	11 (47.8)
Female	2 (40.0)	10 (55.6)	12 (52.2)
Race, n (%)			
White	3 (60.0)	11 (61.1)	14 (60.9)
Black or African American	1 (20.0)	1 (5.6)	2 (8.7)
Asian	0 (0.0)	1 (5.6)	1 (4.3)
American Indian or Alaskan Native	0 (0.0)	1 (5.6)	1 (4.3)
Other[a]	1 (20.0)	4 (22.2)	5 (21.7)
Ethnicity, n (%)			
Hispanic or Latino	1 (20.0)	7 (38.9)	8 (34.8)
Not Hispanic or Latino	4 (80.0)	11 (61.1)	15 (65.2)
BSA (m^2)			
Mean (SD)	1.650 (0.1817)	0.955 (0.3581)	1.106 (0.4370)
Median	1.560	0.870	1.000
Min, Max	1.48, 1.92	0.60, 2.13	0.60, 2.13
KPS/Lansky play score, n (%)			
60	0 (0.0)	1 (5.6)	1 (4.3)
70	0 (0.0)	3 (16.7)	3 (13.0)
80	2 (40.0)	2 (11.1)	4 (17.4)
90	2 (40.0)	7 (38.9)	9 (39.1)
100	1 (20.0)	5 (27.8)	6 (26.1)

Database lock date: 14 Nov 2022.
Percentages are based on the total number of subjects within each relevant dose level group in the Safety Analysis Set.
BSA = body surface area, Ever = everolimus, Lenv = lenvatinib, KPS = Karnofsky performance status (score), max = maximum value, min = minimum value.
a: Other refers to Black/African American and White, Unknown, or Not Specified.
Source: Table 14.1.4.1.1.1.

Phase II

Efficacy Overall, the majority of subjects (n=31 [75.6%]) were white, male (n=22 [53.7%]), and had a KPS or Lansky play score of 80 or above (n=34 [82.9%]). Of the 41 subjects enrolled, 25 (61.0%) were younger than 17 years. There were no clinically relevant differences in baseline demographics between the cohorts except for sex. Seven subjects (70.0%) and 12 subjects (60.0%) in the EWS and RMS cohorts, respectively, were male, while 3 subjects (27.3%) in the HGG cohort were male. These gender differences are consistent with the known demographic characteristics of the diseases under study results

Table 5 Selected Demographic and Baseline Characteristics – Phase 2 (Safety Analysis Set)

	EWS (N=10) n (%)	RMS (N=20) n (%)	HGG (N=11) n (%)	Total (N=41) n (%)
Age (years)				
Mean (SD)	14.6 (5.0)	12.7 (6.1)	13.5 (3.3)	13.4 (5.2)
Median	16.5	15.0	14.0	15.0
Min, Max	3, 19	2, 21	9, 18	2, 21
Age Group, n (%)				
≥2 years - <6 years	1 (10.0)	2 (10.0)	0 (0.0)	3 (7.3)
≥6 years - <17 years	4 (40.0)	10 (50.0)	8 (72.7)	22 (53.7)
≥17 years	5 (50.0)	8 (40.0)	3 (27.3)	16 (39.0)
Sex, n (%)				
Male	7 (70.0)	12 (60.0)	3 (27.3)	22 (53.7)
Female	3 (30.0)	8 (40.0)	8 (72.7)	19 (46.3)
Race, n (%)				
White	9 (90.0)	16 (80.0)	6 (54.5)	31 (75.6)
Black or African American	0 (0.0)	1 (5.0)	3 (27.3)	4 (9.8)
Asian	1 (10.0)	0 (0.0)	0 (0.0)	1 (2.4)
Other[a]	0 (0.0)	3 (15.0)	2 (18.2)	5 (12.2)
Ethnicity, n (%)				
Hispanic or Latino	2 (20.0)	2 (10.0)	0 (0.0)	4 (9.8)
Not Hispanic or Latino	8 (80.0)	18 (90.0)	11 (100)	37 (90.2)
BSA (m^2)				
Mean (SD)	1.620 (0.5004)	1.409 (0.5054)	1.605 (0.3691)	1.513 (0.4716)
Median	1.680	1.525	1.550	1.630
Min, Max	0.65, 2.34	0.60, 2.15	1.02, 2.27	0.60, 2.34
KPS/Lansky play score, n (%)				
50	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
60	0 (0.0)	0 (0.0)	2 (18.2)	2 (4.9)
70	1 (10.0)	2 (10.0)	1 (9.1)	4 (9.8)
80	2 (20.0)	6 (30.0)	3 (27.3)	11 (26.8)
90	4 (40.0)	4 (20.0)	4 (36.4)	12 (29.3)
100	3 (30.0)	7 (35.0)	1 (9.1)	11 (26.8)

Database lock date: 14 Nov 2022.
Percentages are based on the total number of subjects within each relevant cohort in the Safety Analysis Set.
BSA = body surface area, EWS = Ewing sarcoma, HGG = high-grade glioma, KPS = Karnofsky performance status, max = maximum value, min = minimum value, RMS = rhabdomyosarcoma.
a: Other refers to Black/African American and White, Unknown, and Not Specified.
Source: Table 14.1.4.1.1.2.

Efficacy results

Assessment of antitumor activity was the primary objective for Phase 2 and preliminary antitumor activity was a secondary objective for Phase 1.

Primary Endpoint Results (Phase II)

The primary endpoint in Phase 2 was ORR at Week 16.

No PRs or CRs were observed in the EWS or HGG cohorts at Week 16; therefore, these 2 cohorts were discontinued for futility after Stage 1.

In the RMS cohort, 1 subject in Stage 1 had a confirmed PR by Week 16; therefore, the cohort was expanded to 20 subjects. One additional subject in Stage 2 had a PR by Week 16. Thus, a total of 2 subjects with RMS had a BOR of PR by Week 16, for an ORR of 10.0% for that cohort.

Given there were only 2 PRs in the RMS cohort, the success criteria were not met; therefore, treatment was declared a failure for this cohort per protocol.

Table 6 Objective Response Rate per Investigator Assessment at Week 16 – Phase 2 (Evaluable Analysis Set)

Objective Response (n, %)	EWS (N=10) n (%)	RMS (N=20) n (%)	HGG (N=10) n (%)	Total (N=40) n (%)
Best Overall Response[a]				
Complete Response (CR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial Response (PR)	0 (0.0)	2 (10.0)	0 (0.0)	2 (5.0)
Stable Disease (SD)	4 (40.0)	6 (30.0)	3 (30.0)	13 (32.5)
Progressive Disease (PD)	6 (60.0)	8 (40.0)	6 (60.0)	20 (50.0)
Unknown/Not Evaluable (NE)[b]	0 (0.0)	4 (20.0)	1 (10.0)	5 (12.5)
No Postbaseline Tumor Assessment	0 (0.0)	2 (10.0)	1 (10.0)	3 (7.5)
Early SD (SD <7 Weeks)	0 (0.0)	2 (10.0)	0 (0.0)	2 (5.0)
ORR (CR + PR), n (%)	0 (0.0)	2 (10.0)	0 (0.0)	2 (5.0)
95% CI of ORR[c]	(0.0, 30.8)	(1.2, 31.7)	(0.0, 30.8)	(0.6, 16.9)

Database lock date: 14 Nov 2022.
Tumor assessments were based on RECIST 1.1 for EWS and RMS, and RANO for HGG.
EWS = Ewing sarcoma, HGG = high-grade glioma, ORR = objective response rate, RANO = Response Assessment in Neuro-Oncology, RECIST = Response Evaluation Criteria for Solid Tumors.
a: Percentages based on total number of subjects in the Safety Analysis Set within the relevant cohort.
b: Rows containing only zeroes are omitted from the in-text table.
c: 95% CI was constructed using the Clopper and Pearson method.
Source: Table 14.2.1.1.2.

Secondary Endpoints results

Phase I

In Phase 1, 18 subjects with measurable disease and 5 subjects with evaluable disease at Baseline were evaluated for BOR. No objective responses, per investigator assessment, occurred at either dose level.

At Dose Level -1, 1 subject with measurable disease had a BOR of SD. At Dose Level 1, 7 subjects with measurable disease had a BOR of SD and 2 subjects with evaluable disease had a BOR of non-CR/non-PD. The remainder had PD, except for 1 subject whose BOR was not evaluable.

The DCR for subjects with either measurable or evaluable disease was 20.0% at Dose Level -1 and 50.0% at Dose Level 1, and the CBR was 20.0% at Dose Level -1 and 22.2% at Dose Level 1.

Table 7 Summary of Tumor Response per Investigator Assessment –Phase 1 (Safety Analysis Set) Dose Level

Objective Response (n, %)	Dose Level -1 Lenv 8 mg/m^2 + Ever 3 mg/m^2 (N=5) n (%)	Dose Level 1 Lenv 11 mg/m^2 + Ever 3 mg/m^2 (N=18) n (%)	Total (N=23) n (%)
Subjects with Measurable Disease[a]	3 (60.0)	15 (83.3)	18 (78.3)
Best Overall Response[b]			
Complete Response (CR)	0 (0.0)	0 (0.0)	0 (0.0)

Partial Response (PR)	0 (0.0)	0 (0.0)	0 (0.0)
Stable Disease (SD)	1 (20.0)	7 (38.9)	8 (34.8)
Progressive Disease (PD)	2 (40.0)	7 (38.9)	9 (39.1)
Not Evaluable (NE)[c]	0 (0.0)	1 (5.6)	1 (4.3)
Subjects with Evaluable Disease[a]	2 (40.0)	3 (16.7)	5 (21.7)
Best Overall Response[d]			
Complete Response (CR)	0 (0.0)	0 (0.0)	0 (0.0)
Non-CR/Non-PD or IR/SD	0 (0.0)	2 (11.1)	2 (8.7)
Progressive Disease (PD)	2 (40.0)	1 (5.6)	3 (13.0)
Not Evaluable (NE)[c]	0 (0.0)	0 (0.0)	0 (0.0)
Objective Response Rate (CR + PR), n (%)[b]	0 (0.0)	0 (0.0)	0 (0.0)
95% CI of ORR[e]	(0.0, 70.8)	(0.0, 21.8)	(0.0, 18.5)
Subjects with either Measurable or Evaluable Disease[a]	5 (100)	18 (100)	23 (100)
Disease Control Rate, n (%)[a,f]	1 (20.0)	9 (50.0)	10 (43.5)
95% CI of Disease Control Rate[e]	(0.5, 71.6)	(26.0, 74.0)	(23.2, 65.5)
Clinical Benefit Rate, n (%)[a,g]	1 (20.0)	4 (22.2)	5 (21.7)
95% CI of Clinical Benefit Rate[e]	(0.5, 71.6)	(6.4, 47.6)	(7.5, 43.7)

Database lock date: 14 Nov 2022.

Tumor assessments are based on RECIST 1.1 (for non-HGG) and RANO (for HGG).
Ever = everolimus, HGG = high=grade glioma, IR/SD = incomplete response/stable disease,
Lenv = lenvatinib, ORR = objective response rate, RANO = Response Assessment in Neuro-Oncology,
RECIST = Response Evaluation Criteria in Solid Tumors, RMS = rhabdomyosarcoma.

a: Percentages based on total number of subjects within the relevant dose level group in the Safety Analysis Set.

b: Based on the total number of subjects with measurable disease at Baseline (with target lesions at Baseline +/- nontarget lesions at Baseline)

c: Not Evaluable defined as best overall response of NE or SD <7 weeks posttreatment.

d: Based on the total number of subjects with evaluable disease at Baseline (with only nontarget lesions at Baseline).

e: 95% CI was constructed using the Clopper and Pearson method.

f: DCR defined as CR +PR + SD ≥7 weeks for measurable disease and CR + Non-CR/Non-PD ≥7 weeks for evaluable disease.

g: CBR defined as CR + PR + durable SD lasting ≥23 weeks for measurable disease and CR + durable Non-CR/Non-PD lasting ≥23 weeks for evaluable disease.

Source: Table 14.2.1.1.1.

Phase II

At data cutoff for Phase 2, 2 subjects in the Evaluable Analysis Set, both with RMS, had a confirmed PR per investigator assessment, for an ORR in that cohort of 10% and an overall ORR in Phase 2 of 5.0% (Table below). The duration of response for the 2 subjects with PR was 2.10 and 2.76 months, respectively.

An additional 13 subjects (32.5%) had a BOR of SD, which was similarly distributed across disease types. The DCR for subjects with EWS, RMS and HGG was 40.0%, 40%, and 30.0%, respectively, and the CBR was 20.0%, 10%, and 0%, respectively.

Table 8 Summary of Tumor Response per Investigator Assessment at Data Cutoff – Phase 2 (Evaluable Analysis Set)

Response Assessment	EWS (N=10) n (%)	RMS (N=20) n (%)	HGG (N=10) n (%)	Total (N=40) n (%)
Best Overall Response[a]				
Complete Response (CR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial Response (PR)	0 (0.0)	2 (10.0)	0 (0.0)	2 (5.0)
Stable Disease (SD)	4 (40.0)	6 (30.0)	3 (30.0)	13 (32.5)
Progressive Disease (PD)	6 (60.0)	8 (40.0)	6 (60.0)	20 (50.0)
Unknown/Not Evaluable (NE)[b]	0 (0.0)	4 (20.0)	1 (10.0)	5 (12.5)
No Postbaseline Tumor Assessment	0 (0.0)	2 (10.0)	1 (10.0)	3 (7.5)
Early SD (SD <7 weeks)	0 (0.0)	2 (10.0)	0 (0.0)	2 (5.0)
ORR (CR + PR), n (%)	0 (0.0)	2 (10.0)	0 (0.0)	2 (5.0)
95% CI of ORR[c]	(0.0, 30.8)	(1.2, 31.7)	(0.0, 30.8)	(0.6, 16.9)
Duration of Objective Response, mo	n=0	n=2	n=0	n=2
Median (95% CI)	N/A	2.4 (2.1, NE)	N/A	2.4 (2.1, NE)
Range (Min, Max)	N/A	(2.10, 2.76)	N/A	(2.10, 2.76)
Disease Control Rate, [a,d] n (%)	4 (40.0)	8 (40.0)	3 (30.0)	15 (37.5)
95% CI of DCR[b]	(12.2, 73.8)	(19.1, 63.9)	(6.7, 65.2)	(22.7, 54.2)
Clinical Benefit Rate, [a,e] n (%)	2 (20.0)	2 (10.0)	0 (0.0)	4 (10.0)
95% CI of CBR[b]	(2.5, 55.6)	(1.2, 31.7)	(0.0, 30.8)	(2.8, 23.7)

Database lock date: 14 Nov 2022.
Tumor assessments based on RECIST 1.1 for EWS and RMS, and RANO for HGG.
EWS = Ewing sarcoma, HGG = high-grade glioma, Max = maximum value, Min = minimum value, N/A = not applicable, ORR = objective response rate, RANO = Response Assessment in Neuro-Oncology, RECIST = Response Evaluation Criteria for Solid Tumors, RMS = rhabdomyosarcoma.
a: Percentages were based on the total number of subjects in the Safety Analysis Set within the relevant cohort.
b: Rows containing only zeroes are omitted from the in-text table.
c: 95% CI was constructed using the Clopper and Pearson method.
d: DCR defined as CR +PR +SD ≥7 weeks.
e: CBR defined as CR + PR + durable SD (SD ≥23 weeks).
Source: Table 14.2.1.2.2.

Futility analyses (phase 2)

In Phase 2, the futility assessment for the 10 subjects in Stage 1 was determined in evaluable patients. Per protocol, subjects evaluable for ORR included only those subjects with measurable disease at Baseline who had their disease re-evaluated at postbaseline time point assessments, unless they discontinued for PD before the first efficacy assessment.

Futility analysis for Ewing's sarcoma cohort

All 10 subjects enrolled in the EWS cohort were evaluable. Of these 10 subjects, 9 discontinued treatment because of radiologic PD and 1 discontinued for clinical PD (subject required radiation therapy to the only site of measurable disease for pain management).

Subject received only 1 dose of lenvatinib and, due to administrative reasons, was not treated with everolimus. On Day 2, this subject was hospitalized for worsening chest pain and fever, assessed by the investigator as related to PD, and study treatment was held. On Day 12, the subject discontinued study treatment to receive palliative radiotherapy to a target lesion. At the Week 3 (Day 15) tumor assessment, the subject had radiologic PD.

Thus, the sponsor confirmed that all subjects included in the assessment of futility met the protocol criteria of 'evaluable'.

Futility analysis for RMS cohort

A total of 20 subjects were enrolled and treated in the RMS cohort.

Of the first 10 evaluable subjects, 1 subject achieved a PR at Week 8, which was confirmed at Week 13; this subject discontinued study treatment at Week 20 for PD. Per Simon's 2-stage design, the RMS cohort was expanded to enrol an additional 10 subjects in Stage 2. Of these additional 10 evaluable subjects, 1 subject () achieved a PR at Week 8, which was confirmed at Week 14. Overall, the primary reason for discontinuation was disease progression (n=16) of the remaining subjects, 2 subjects discontinued treatment with stable disease as per subject choice at Week 8, 1 discontinued treatment at Week 16 with stable disease to have surgery, and 1 discontinued due to subject choice at Week 8 with stable disease, this subject went on to receive another systemic anticancer treatment thereafter.

Futility analysis for high-grade glioma cohort

A total of 11 subjects were enrolled and treated in the HGG cohort as part of Stage 1.

Of these 11 subjects, 10 were deemed evaluable for objective response. One subject discontinued treatment after 2 weeks for subject choice and was replaced. There were no objective responses (CR/PR) by Week 16, and the primary reason for treatment discontinuation was PD (n=9).

The remaining subject discontinued treatment at Week 17 because of an AE. Based on the data for these 11 subjects, futility for the HGG cohort was declared in Phase 2, as there were no objective responses by the Week 16 tumor assessment time point.

Safety results

Dose-Limiting Toxicity (Phase 1)

The primary objective of Phase 1 was determination of the MTD, based on assessment of DLTs in Cycle 1.

Per protocol, 3 subjects were initially enrolled at Dose Level 1 (lenvatinib 11 mg/m2 + everolimus 3 mg/m2). Two of the 3 subjects had AEs that met the criteria for DLT, namely Grade 3 proteinuria (n=1) and Grade 3 headache (n=1). On C1D6, 1 subject with Grade 3 headache was hospitalized. The subject received acetaminophen 650 mg and the event improved to Grade 1 on C1D7. Lenvatinib was interrupted for 1 day and the subject completed Cycle 1 at a reduced lenvatinib dose of 8 mg/m2 without recurrence of headache.

Per the rolling-6 design, enrolment continued at the de-escalated dose level of Lenvatinib 8 mg/m2 + everolimus 3.0 mg/m2 (Dose Level -1). Five subjects were enrolled at that dose level, with no further DLTs.

Since the DLT of Grade 3 headache was readily reversible with acetaminophen 650 mg, the classification of the Grade 3 headache as a DLT was reassessed. The PSC and Eisai personnel reviewed safety and PK data for all 8 subjects enrolled in the study at that time, in addition to safety and PK data from Studies 205 and 207, and concurred that the DLT of Grade 3 headache was not dose-dependent.

An independent review of safety and PK data for Studies 216, 205, and 207 was conducted in June 2018. Accrual into Study 216 was temporarily suspended pending independent review of the data.

The independent review concluded that:

1. Safety data indicated that Dose Level -1 was safe

2. Grade 3 headache was not dose-dependent3. Grade 3 headache should not be considered a DLT

4. Enrolment in Study 216 should reopen at Dose Level 1 (11 mg/m2 + everolimus mg/m2) once the protocol was amended

As a result, the protocol was amended (Amendment 01) to revise the definition of a DLT to exclude Grade 3 headache <3 days' duration and responsive to optimal management.

Following approval of Protocol Amendment 01, enrolment re-opened at Dose Level 1 (lenvatinib 11 mg/m2 + everolimus 3 mg/m2) and out of the 3 additional subjects, 1 subject had DLTs of Grade 3 hypertriglyceridemia and Grade 4 hypercholesterolemia. Per protocol, given that the 2 DLTs out of 6 subjects at Dose Level 1 were of different classes of adverse events, the cohort was expanded to a total of 12 subjects. No further DLTs occurred at this dose level.

Thus, 2 out of 12 subjects out of 12 at Dose Level 1, had DLTs as shown in Table below.

Based on these findings, Dose Level 1, ie, lenvatinib 11 mg/m2 + everolimus 3 mg/m2, both administered once daily, was determined by the PSC to be both the MTD and the RP2D for the subsequent Phase 2 portion of the study. Maximum daily doses were capped at Lenvatinib 18 mg per day and everolimus 5 mg per day. Per protocol, once the RP2D was defined, 6 additional subjects were enrolled at Dose Level 1 to attain the goal of having evaluable PK data from minimally 6 subjects aged 2 to <6 years old.

Table 9 Dose-Limiting Toxicities in Cycle 1 – Phase 1 (Safety Analysis Set)

Table 9 Dose-Limiting Toxicities in Cycle 1 – Phase 1 (Safety Analysis Set)

Subject ID	Assigned Dose Level	DLT (AE Preferred Term)	Study Day of DLT [a]	Grade	Study Drug Action Taken		Outcome
					Lenv	Ever	
PPD	L: 11 mg/m^2	Proteinuria	15	1	None	None	Not recovered
8, PPD	E: 3 mg/m^2	Proteinuria	22	3	Interrupted	Interrupted	Recovering
		Proteinuria	27	1	None	None	Recovered
PPD	L:[b] 11 mg/m^2	Hypertriglyceridemia	15	3	Interrupted	Reduced	Recovered
7, PPD	E: 3 mg/m^2	Hypercholesterolemia	15	4	Interrupted	Reduced	Recovered

Database lock date: 14 Nov 2022.
Adverse events coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 and graded using Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.
For subjects who had multiple occurrences of the same event, only the first occurrence is presented in the in-text table.
BSA = body surface area, DLT = dose-limiting toxicity, E = everolimus, F = female, L = lenvatinib, M = male, W = white.
a: Study Day listed is first day (start) of the event.
b: Subject received an actual dose of lenvatinib 9 mg on C1D1, which is equivalent to 10.71 mg/m^2.
Source: Listing 16.2.5.1.1 and Listing 16.2.7.6.2.1.

TEAEs
Phase 1

All subjects reported at least 1 TEAE. A total of 19 subjects (82.6%) had at least one Grade ≥3 TEAE.

One subject, at Dose Level 1, had a Grade 5 TEAE (see Section 12.4.1.1 for details). Serious AEs, including fatal and nonfatal events, were reported for 14 subjects (60.9%), 2 (40%) at Dose Level -1 and 12 (66.7%) at Dose Level 1. A total of 12 subjects had a treatment interruption and 6 had a dose reduction of lenvatinib, everolimus, or both for a TEAE. However, only 2 subjects, both at Dose Level 1, discontinued treatment with lenvatinib and/or everolimus for a TEAE. These results indicate that the majority of TEAEs were manageable using appropriate supportive care and dose modifications, as applicable.

Table 10 Overview of Treatment-Emergent Adverse Events – Phase 1 (Safety Analysis Set)

	Dose Level -1	Dose Level 1	
	Lenv 8 mg/m^2 + Ever 3 mg/m^2 (N=5) n (%)	Lenv 11 mg/m^2 + Ever 3 mg/m^2 (N=18) n (%)	Total (N=23) n (%)
Subjects with Any TEAEs	5 (100)	18 (100)	23 (100)
Subjects with DLT[a]	0 (0.0)	2 (11.1)	2 (8.7)
Subjects with Treatment-Related TEAEs	5 (100)	18 (100)	23 (100)
Subjects with Any TEAEs with Worst CTCAE Grade of:			
≥3	4 (80.0)	15 (83.3)	19 (82.6)
3	3 (60.0)	12 (66.7)	15 (65.2)
4	1 (20.0)	2 (11.1)	3 (13.0)
5	0 (0.0)	1 (5.6)	1 (4.3)
Subjects with Any Serious TEAEs[b]	2 (40.0)	12 (66.7)	14 (60.9)
Subjects with Any Fatal TEAEs	0 (0.0)	1 (5.6)	1 (4.3)
Subjects with Any Nonfatal Serious TEAEs	2 (40.0)	12 (66.7)	14 (60.9)
Subjects with[b]			
TEAEs Leading to Study Drug Discontinuation[c]	0 (0.0)	2 (11.1)	2 (8.7)
Discontinuation of Lenvatinib[d]	0 (0.0)	1 (5.6)	1 (4.3)
Discontinuation of Everolimus[e]	0 (0.0)	2 (11.1)	2 (8.7)
Discontinuation of Lenvatinib and Everolimus[f]	0 (0.0)	1 (5.6)	1 (4.3)
TEAEs Leading to Study Dose Modification[c,g]	0 (0.0)	12 (66.7)	12 (52.2)
Modification of Lenvatinib[d]	0 (0.0)	12 (66.7)	12 (52.2)
Modification of Everolimus[e]	0 (0.0)	12 (66.7)	12 (52.2)
Modification of Lenvatinib and Everolimus[f]	0 (0.0)	12 (66.7)	12 (52.2)
TEAEs Leading to Dose Reduction[c]	0 (0.0)	6 (33.3)	6 (26.1)
Reduction of Lenvatinib[d]	0 (0.0)	5 (27.8)	5 (21.7)
Reduction of Everolimus[e]	0 (0.0)	2 (11.1)	2 (8.7)
Reduction of Lenvatinib and Everolimus[f]	0 (0.0)	1 (5.6)	1 (4.3)
TEAEs Leading to Study Drug Interruption[c]	0 (0.0)	12 (66.7)	12 (52.2)
Interruption of Lenvatinib[d]	0 (0.0)	10 (55.6)	10 (43.5)
Interruption of Everolimus[e]	0 (0.0)	11 (61.1)	11 (47.8)
Interruption of Lenvatinib and Everolimus[f]	0 (0.0)	9 (50.0)	9 (39.1)

Database lock date: 14 Nov 2022.
Percentages based on total number of subjects within the relevant dose level group in the Safety Analysis Set.
For each row category, subjects with 2 or more adverse events in that category were counted only once.
Adverse events (AE) graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
DLT = dose-limiting toxicity, Ever = everolimus, Lenv = lenvatinib, TEAE = treatment-emergent AE.
a: Adverse events that met the criteria defined per protocol as dose-limiting toxicity.
b: Each subject may have been counted in multiple categories.
c: Lenvatinib or everolimus.
d: Regardless of action taken for everolimus.
e: Regardless of action taken for lenvatinib.
f: Due to the same adverse event.
g: Modification refers to either dose reduction or interruption.
Source: Table 14.3.1.2.1.1 and Table 14.3.1.2.2.1.

Phase 2

An overview of TEAEs that occurred in Phase 2 is presented in Table below. A total of 40 subjects (97.6%) reported at least 1 TEAE. A total of 33 subjects (8, 17, and 8 in the EWS, RMS, and HGG cohorts, respectively) had at least one Grade ≥3 TEAE. One subject, with RMS, had a Grade 5 TEAE (see Section 12.4.1.1 for details).

Serious AEs, including fatal and nonfatal events, were reported for 22 subjects (53.7%): 6, 8, and 8 subjects in the EWS, RMS, and HGG cohorts, respectively. A total of 28 subjects (68.3%) had a dose modification (treatment interruption or dose reduction) of lenvatinib and/or everolimus for a TEAE. However, only 4 subjects (9.8%)—2 each in the RMS and HGG cohorts—discontinued treatment with lenvatinib, everolimus, or both for a TEAE. These results indicate that the majority of TEAEs were manageable using appropriate supportive care and dose modifications, as applicable. See Section 12.4.1.4 for details of the TEAEs that led to dose modification and treatment discontinuation.

Table 11 Overview of Treatment-Emergent Adverse Events – Phase 2 (Safety Analysis Set)

	EWS (N=10) n (%)	RMS (N=20) n (%)	HGG (N=11) n (%)	Total (N=41) n (%)
Subjects with Any TEAEs	10 (100)	19 (95.0)	11 (100)	40 (97.6)
Subjects with a treatment-related TEAEs	8 (80.0)	19 (95.0)	11 (100)	38 (92.7)
Subjects with Any TEAEs with Worst CTCAE Grade of:	10 (100)	19 (95.0)	11 (100)	40 (97.6)
≥3	8 (80.0)	17 (85.0)	8 (72.7)	33 (80.5)
3	6 (60.0)	11 (55.0)	4 (36.4)	21 (51.2)
4	2 (20.0)	5 (25.0)	4 (36.4)	11 (26.8)
5	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Subjects with Any Serious TEAEs[a]	6 (60.0)	8 (40.0)	8 (72.7)	22 (53.7)
Subjects with Any Fatal TEAEs	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Subjects with Any Nonfatal Serious TEAEs	6 (60.0)	8 (40.0)	8 (72.7)	22 (53.7)
Subjects with:[a]				
TEAEs Leading to Study Drug Discontinuation[b]	0 (0.0)	2 (10.0)	2 (18.2)	4 (9.8)
Discontinuation of Lenvatinib[c]	0 (0.0)	2 (10.0)	2 (18.2)	4 (9.8)
Discontinuation of Everolimus[d]	0 (0.0)	2 (10.0)	2 (18.2)	4 (9.8)
Discontinuation of Lenvatinib and Everolimus[e]	0 (0.0)	2 (10.0)	0 (0.0)	2 (4.9)
TEAEs Leading to Study Drug Modification[b,f]	7 (70.0)	13 (65.0)	8 (72.7)	28 (68.3)
Modification of Lenvatinib[c]	7 (70.0)	12 (60.0)	8 (72.7)	27 (65.9)
Modification of Everolimus[d]	6 (60.0)	12 (60.0)	7 (63.6)	25 (61.0)
Modification of Lenvatinib and Everolimus[e]	6 (60.0)	11 (55.0)	7 (63.6)	24 (58.5)
TEAEs Leading to Dose Reduction[b]	0 (0.0)	9 (45.0)	4 (36.4)	13 (31.7)
Reduction of Lenvatinib[c]	0 (0.0)	7 (35.0)	3 (27.3)	10 (24.4)
Reduction of Everolimus[d]	0 (0.0)	5 (25.0)	3 (27.3)	8 (19.5)
Reduction of Lenvatinib and Everolimus[e]	0 (0.0)	1 (5.0)	1 (9.1)	2 (4.9)
TEAEs Leading to Study Drug Interruption[b]	7 (70.0)	11 (55.0)	7 (63.6)	25 (61.0)
Interruption of Lenvatinib[c]	7 (70.0)	8 (40.0)	7 (63.6)	22 (53.7)
Interruption of Everolimus[d]	6 (60.0)	10 (50.0)	6 (54.5)	22 (53.7)
Interruption of Lenvatinib and Everolimus[e]	6 (60.0)	7 (35.0)	6 (54.5)	19 (46.3)

Database lock date: 14 Nov 2022.
Percentages based on total number of subjects within the relevant cohort in the Safety Analysis Set.
For each row category, subjects with 2 or more adverse events (AEs) in that category were counted only once.
AEs graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
EWS = Ewing sarcoma, HGG = high-grade glioma, RMS = rhabdomyosarcoma, TEAE = treatment-emergent AE.
a: Each subject may have been counted in multiple categories.
b: Lenvatinib or everolimus.
c: Regardless of action taken for everolimus.
d: Regardless of action taken for lenvatinib.
e: Due to the same AE.
f: Modification refers to either dose reduction or interruption.
Source: Table 14.3.1.2.1.2 and Table 14.3.1.2.2.2.

Most common adverse events

Phase 1

Treatment-emergent AEs occurred in all 23 subjects in Phase 1. Results should be interpreted with caution, due to the small sample size and the fact that subjects at Dose Level 1 received study treatment for a longer duration than did subjects at Dose Level -1 (median, 7.00 and 11.71 weeks, respectively).

A summary of TEAEs that occurred in ≥25% of subjects at either dose level is shown in Table below. The most frequently reported TEAEs, occurring in 50% or more of subjects overall (in descending order of frequency), were hypertension (73.9%), vomiting (60.9%), diarrhea (56.5%), hypertriglyceridemia (56.5%), abdominal pain (52.2%), headache (52.2%), and hypothyroidism (52.2%). The majority of remaining TEAEs occurred in 3 or fewer subjects each.

Table 12 Overall and Grade 3 or Higher Incidence of Treatment-Emergent Adverse Events that Occurred in 25% or More of Subjects*, by System Organ Class and Preferred Term – Phase 1 (Safety Analysis Set)

System Organ Class Preferred Term	Dose Level -1 Lenv 8 mg/m^2 + Ever 3 mg/m^2 (N=5) n (%)		Dose Level 1 Lenv 11 mg/m^2 + Ever 3 mg/m^2 (N=18) n (%)		Total (N=23) n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Subjects with any TEAE	*5 (100)*	*4 (80.0)*	*18 (100)*	*15 (83.3)*	*23 (100)*	*19 (82.6)*
Blood and lymphatic system disorders	**2 (40.0)**	**1 (20.0)**	**6 (33.3)**	**3 (16.7)**	**8 (34.8)**	**4 (17.4)**
Anaemia	2 (40.0)	1 (20.0)	6 (33.3)	3 (16.7)	8 (34.8)	4 (17.4)
Cardiac disorders	**3 (60.0)**	**0 (0.0)**	**5 (27.8)**	**0 (0.0)**	**8 (34.8)**	**0 (0.0)**
Sinus tachycardia	2 (40.0)	0 (0.0)	4 (22.2)	0 (0.0)	6 (26.1)	0 (0.0)
Endocrine disorders	**2 (40.0)**	**0 (0.0)**	**10 (55.6)**	**0 (0.0)**	**12 (52.2)**	**0 (0.0)**
Hypothyroidism	2 (40.0)	0 (0.0)	10 (55.6)	0 (0.0)	12 (52.2)	0 (0.0)
Gastrointestinal disorders	**5 (100)**	**1 (20.0)**	**16 (88.9)**	**1 (5.6)**	**21 (91.3)**	**2 (8.7)**
Abdominal pain	3 (60.0)	0 (0.0)	9 (50.0)	0 (0.0)	12 (52.2)	0 (0.0)
Constipation	2 (40.0)	0 (0.0)	3 (16.7)	0 (0.0)	5 (21.7)	0 (0.0)
Diarrhoea	3 (60.0)	0 (0.0)	10 (55.6)	1 (5.6)	13 (56.5)	1 (4.3)
Nausea	4 (80.0)	0 (0.0)	5 (27.8)	0 (0.0)	9 (39.1)	0 (0.0)
Stomatitis	4 (80.0)	0 (0.0)	5 (27.8)	0 (0.0)	9 (39.1)	0 (0.0)
Vomiting	3 (60.0)	1 (20.0)	11 (61.1)	0 (0.0)	14 (60.9)	1 (4.3)
General disorders and administration site conditions	**4 (80.0)**	**1 (20.0)**	**9 (50.0)**	**3 (16.7)**	**13 (56.5)**	**4 (17.4)**
Fatigue	3 (60.0)	0 (0.0)	6 (33.3)	0 (0.0)	9 (39.1)	0 (0.0)
Pain	3 (60.0)	1 (20.0)	3 (16.7)	2 (11.1)	6 (26.1)	3 (13.0)
Pyrexia	1 (20.0)	0 (0.0)	5 (27.8)	0 (0.0)	6 (26.1)	0 (0.0)
Infections and infestations	**3 (60.0)**	**1 (20.0)**	**9 (50.0)**	**1 (5.6)**	**12 (52.2)**	**2 (8.7)**
Urinary tract infection	2 (40.0)	0 (0.0)	1 (5.6)	0 (0.0)	3 (13.0)	0 (0.0)

System Organ Class Preferred Term	Dose Level -1 Lenv 8 mg/m^2 + Ever 3 mg/m^2 (N=5) n (%)		Dose Level 1 Lenv 11 mg/m^2 + Ever 3 mg/m^2 (N=18) n (%)		Total (N=23) n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Investigations	**4 (80.0)**	**1 (20.0)**	**15 (83.3)**	**7 (38.9)**	**19 (82.6)**	**8 (34.8)**
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	5 (27.8)	1 (5.6)	5 (21.7)	1 (4.3)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	5 (27.8)	0 (0.0)	5 (21.7)	0 (0.0)
Blood cholesterol increased	1 (20.0)	0 (0.0)	6 (33.3)	1 (5.6)	7 (30.4)	1 (4.3)
Electrocardiogram QT prolonged	2 (40.0)	0 (0.0)	2 (11.1)	1 (5.6)	4 (17.4)	1 (4.3)
Lymphocyte count decreased	3 (60.0)	1 (20.0)	6 (33.3)	4 (22.2)	9 (39.1)	5 (21.7)
Neutrophil count decreased	3 (60.0)	1 (20.0)	4 (22.2)	0 (0.0)	7 (30.4)	1 (4.3)
Platelet count decreased	2 (40.0)	1 (20.0)	7 (38.9)	2 (11.1)	9 (39.1)	3 (13.0)
Weight decreased	2 (40.0)	0 (0.0)	6 (33.3)	0 (0.0)	8 (34.8)	0 (0.0)
White blood cell count decreased	2 (40.0)	1 (20.0)	6 (33.3)	0 (0.0)	8 (34.8)	1 (4.3)
Metabolism and nutrition disorders	**4 (80.0)**	**0 (0.0)**	**15 (83.3)**	**5 (27.8)**	**19 (82.6)**	**5 (21.7)**
Decreased appetite	4 (80.0)	0 (0.0)	4 (22.2)	0 (0.0)	8 (34.8)	0 (0.0)
Dehydration	2 (40.0)	0 (0.0)	2 (11.1)	1 (5.6)	4 (17.4)	1 (4.3)
Hypertriglyceridaemia	2 (40.0)	0 (0.0)	11 (61.1)	3 (16.7)	13 (56.5)	3 (13.0)
Hyponatraemia	1 (20.0)	0 (0.0)	6 (33.3)	1 (5.6)	7 (30.4)	1 (4.3)
Musculoskeletal and connective tissue disorders	**5 (100)**	**1 (20.0)**	**10 (55.6)**	**5 (27.8)**	**15 (65.2)**	**6 (26.1)**
Back pain	4 (80.0)	1 (20.0)	3 (16.7)	2 (11.1)	7 (30.4)	3 (13.0)
Myalgia	3 (60.0)	0 (0.0)	2 (11.1)	1 (5.6)	5 (21.7)	1 (4.3)
Nervous system disorders	**5 (100)**	**2 (40.0)**	**11 (61.1)**	**4 (22.2)**	**16 (69.6)**	**6 (26.1)**
Headache	4 (80.0)	2 (40.0)	8 (44.4)	2 (11.1)	12 (52.2)	4 (17.4)
Psychiatric disorders	**2 (40.0)**	**0 (0.0)**	**4 (22.2)**	**1 (5.6)**	**6 (26.1)**	**1 (4.3)**
Depression	2 (40.0)	0 (0.0)	1 (5.6)	0 (0.0)	3 (13.0)	0 (0.0)
Insomnia	2 (40.0)	0 (0.0)	2 (11.1)	0 (0.0)	4 (17.4)	0 (0.0)
Renal and urinary disorders	**4 (80.0)**	**0 (0.0)**	**9 (50.0)**	**3 (16.7)**	**13 (56.5)**	**3 (13.0)**
Pollakiuria	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)	0 (0.0)
Proteinuria	1 (20.0)	0 (0.0)	8 (44.4)	3 (16.7)	9 (39.1)	3 (13.0)
Respiratory, thoracic and mediastinal disorders	**3 (60.0)**	**0 (0.0)**	**11 (61.1)**	**3 (16.7)**	**14 (60.9)**	**3 (13.0)**
Hypoxia	0 (0.0)	0 (0.0)	5 (27.8)	3 (16.7)	5 (21.7)	3 (13.0)
Nasal congestion	2 (40.0)	0 (0.0)	2 (11.1)	0 (0.0)	4 (17.4)	0 (0.0)
Vascular disorders	**4 (80.0)**	**1 (20.0)**	**13 (72.2)**	**1 (5.6)**	**17 (73.9)**	**2 (8.7)**
Hypertension	4 (80.0)	1 (20.0)	13 (72.2)	1 (5.6)	17 (73.9)	2 (8.7)

Database lock date: 14 Nov 2022.
* Cutoff is based on incidence of individual PTs in ≥25% of subjects in either dose level group. If all PTs within an SOC had an incidence of <25%, that SOC is not included in the in-text table, even if the SOC had an overall incidence of ≥25%.
Percentages are based on the total number of subjects within the relevant dose level group in the Safety Analysis Set.
Display is in alphabetical order of SOC and PT within the SOC.
Subjects with 2 or more TEAEs reported in the same SOC or PT were counted only once within that SOC or PT.
Adverse event terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1.
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
Ever = everolimus, Lenv = lenvatinib, PT = preferred term, SOC = system organ class; TEAE = treatment-emergent adverse event.
Source: Table 14.3.1.3.1.1.

Phase 2

Overall, TEAEs occurred in 40 subjects (97.6%) in Phase 2. A summary of TEAEs that occurred in ≥ 25% of subjects in any cohort is shown in Table below. The most frequently reported TEAEs, occurring in 40% or more of subjects overall (in descending order of frequency), were hypertriglyceridemia (56.1%), proteinuria (53.7%), lymphocyte count decreased (51.2%), diarrhea (48.8%), fatigue (48.8%), platelet count decreased (43.9%), blood cholesterol increased (41.5%), hypertension (41.5%), and vomiting (41.5%). The majority of remaining TEAEs occurred in 3 or fewer subjects each.

Table 13 Overall and Grade 3 or Higher Incidence of Treatment-Emergent Adverse Events that Occurred in 25% or More of Subjects*, by System Organ Class and Preferred Term – Phase 2 (Safety Analysis Set)

System Organ Class Preferred Term	Dose Level -1 Lenv 8 mg/m² + Ever 3 mg/m² (N=5) n (%)		Dose Level 1 Lenv 11 mg/m² + Ever 3 mg/m² (N=18) n (%)		Total (N=23) n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Subjects with any TEAE	*5 (100)*	*4 (80.0)*	*18 (100)*	*15 (83.3)*	*23 (100)*	*19 (82.6)*
Blood and lymphatic system disorders	**2 (40.0)**	**1 (20.0)**	**6 (33.3)**	**3 (16.7)**	**8 (34.8)**	**4 (17.4)**
Anaemia	2 (40.0)	1 (20.0)	6 (33.3)	3 (16.7)	8 (34.8)	4 (17.4)
Cardiac disorders	**3 (60.0)**	**0 (0.0)**	**5 (27.8)**	**0 (0.0)**	**8 (34.8)**	**0 (0.0)**
Sinus tachycardia	2 (40.0)	0 (0.0)	4 (22.2)	0 (0.0)	6 (26.1)	0 (0.0)
Endocrine disorders	**2 (40.0)**	**0 (0.0)**	**10 (55.6)**	**0 (0.0)**	**12 (52.2)**	**0 (0.0)**
Hypothyroidism	2 (40.0)	0 (0.0)	10 (55.6)	0 (0.0)	12 (52.2)	0 (0.0)
Gastrointestinal disorders	**5 (100)**	**1 (20.0)**	**16 (88.9)**	**1 (5.6)**	**21 (91.3)**	**2 (8.7)**
Abdominal pain	3 (60.0)	0 (0.0)	9 (50.0)	0 (0.0)	12 (52.2)	0 (0.0)
Constipation	2 (40.0)	0 (0.0)	3 (16.7)	0 (0.0)	5 (21.7)	0 (0.0)
Diarrhoea	3 (60.0)	0 (0.0)	10 (55.6)	1 (5.6)	13 (56.5)	1 (4.3)
Nausea	4 (80.0)	0 (0.0)	5 (27.8)	0 (0.0)	9 (39.1)	0 (0.0)
Stomatitis	4 (80.0)	0 (0.0)	5 (27.8)	0 (0.0)	9 (39.1)	0 (0.0)
Vomiting	3 (60.0)	1 (20.0)	11 (61.1)	0 (0.0)	14 (60.9)	1 (4.3)
General disorders and administration site conditions	**4 (80.0)**	**1 (20.0)**	**9 (50.0)**	**3 (16.7)**	**13 (56.5)**	**4 (17.4)**
Fatigue	3 (60.0)	0 (0.0)	6 (33.3)	0 (0.0)	9 (39.1)	0 (0.0)
Pain	3 (60.0)	1 (20.0)	3 (16.7)	2 (11.1)	6 (26.1)	3 (13.0)
Pyrexia	1 (20.0)	0 (0.0)	5 (27.8)	0 (0.0)	6 (26.1)	0 (0.0)
Infections and infestations	**3 (60.0)**	**1 (20.0)**	**9 (50.0)**	**1 (5.6)**	**12 (52.2)**	**2 (8.7)**
Urinary tract infection	2 (40.0)	0 (0.0)	1 (5.6)	0 (0.0)	3 (13.0)	0 (0.0)
Investigations	**4 (80.0)**	**1 (20.0)**	**15 (83.3)**	**7 (38.9)**	**19 (82.6)**	**8 (34.8)**
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	5 (27.8)	1 (5.6)	5 (21.7)	1 (4.3)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	5 (27.8)	0 (0.0)	5 (21.7)	0 (0.0)
Blood cholesterol increased	1 (20.0)	0 (0.0)	6 (33.3)	1 (5.6)	7 (30.4)	1 (4.3)
Electrocardiogram QT prolonged	2 (40.0)	0 (0.0)	2 (11.1)	1 (5.6)	4 (17.4)	1 (4.3)
Lymphocyte count decreased	3 (60.0)	1 (20.0)	6 (33.3)	4 (22.2)	9 (39.1)	5 (21.7)
Neutrophil count decreased	3 (60.0)	1 (20.0)	4 (22.2)	0 (0.0)	7 (30.4)	1 (4.3)
Platelet count decreased	2 (40.0)	1 (20.0)	7 (38.9)	2 (11.1)	9 (39.1)	3 (13.0)
Weight decreased	2 (40.0)	0 (0.0)	6 (33.3)	0 (0.0)	8 (34.8)	0 (0.0)
White blood cell count decreased	2 (40.0)	1 (20.0)	6 (33.3)	0 (0.0)	8 (34.8)	1 (4.3)
Metabolism and nutrition disorders	**4 (80.0)**	**0 (0.0)**	**15 (83.3)**	**5 (27.8)**	**19 (82.6)**	**5 (21.7)**
Decreased appetite	4 (80.0)	0 (0.0)	4 (22.2)	0 (0.0)	8 (34.8)	0 (0.0)
Dehydration	2 (40.0)	0 (0.0)	2 (11.1)	1 (5.6)	4 (17.4)	1 (4.3)
Hypertriglyceridaemia	2 (40.0)	0 (0.0)	11 (61.1)	3 (16.7)	13 (56.5)	3 (13.0)
Hyponatraemia	1 (20.0)	0 (0.0)	6 (33.3)	1 (5.6)	7 (30.4)	1 (4.3)
Musculoskeletal and connective tissue disorders	**5 (100)**	**1 (20.0)**	**10 (55.6)**	**5 (27.8)**	**15 (65.2)**	**6 (26.1)**
Back pain	4 (80.0)	1 (20.0)	3 (16.7)	2 (11.1)	7 (30.4)	3 (13.0)
Myalgia	3 (60.0)	0 (0.0)	2 (11.1)	1 (5.6)	5 (21.7)	1 (4.3)
Nervous system disorders	**5 (100)**	**2 (40.0)**	**11 (61.1)**	**4 (22.2)**	**16 (69.6)**	**6 (26.1)**
Headache	4 (80.0)	2 (40.0)	8 (44.4)	2 (11.1)	12 (52.2)	4 (17.4)

System Organ Class Preferred Term	Dose Level -1 Lenv 8 mg/m^2 + Ever 3 mg/m^2 (N=5) n (%)		Dose Level 1 Lenv 11 mg/m^2 + Ever 3 mg/m^2 (N=18) n (%)		Total (N=23) n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Psychiatric disorders	**2 (40.0)**	**0 (0.0)**	**4 (22.2)**	**1 (5.6)**	**6 (26.1)**	**1 (4.3)**
Depression	2 (40.0)	0 (0.0)	1 (5.6)	0 (0.0)	3 (13.0)	0 (0.0)
Insomnia	2 (40.0)	0 (0.0)	2 (11.1)	0 (0.0)	4 (17.4)	0 (0.0)
Renal and urinary disorders	**4 (80.0)**	**0 (0.0)**	**9 (50.0)**	**3 (16.7)**	**13 (56.5)**	**3 (13.0)**
Pollakiuria	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)	0 (0.0)
Proteinuria	1 (20.0)	0 (0.0)	8 (44.4)	3 (16.7)	9 (39.1)	3 (13.0)
Respiratory, thoracic and mediastinal disorders	**3 (60.0)**	**0 (0.0)**	**11 (61.1)**	**3 (16.7)**	**14 (60.9)**	**3 (13.0)**
Hypoxia	0 (0.0)	0 (0.0)	5 (27.8)	3 (16.7)	5 (21.7)	3 (13.0)
Nasal congestion	2 (40.0)	0 (0.0)	2 (11.1)	0 (0.0)	4 (17.4)	0 (0.0)
Vascular disorders	**4 (80.0)**	**1 (20.0)**	**13 (72.2)**	**1 (5.6)**	**17 (73.9)**	**2 (8.7)**
Hypertension	4 (80.0)	1 (20.0)	13 (72.2)	1 (5.6)	17 (73.9)	2 (8.7)

Database lock date: 14 Nov 2022.
* Cutoff is based on incidence of individual PTs in ≥25% of subjects in either dose level group. If all PTs within an SOC had an incidence of <25%, that SOC is not included in the in-text table, even if the SOC had an overall incidence of ≥25%.
Percentages are based on the total number of subjects within the relevant dose level group in the Safety Analysis Set.
Display is in alphabetical order of SOC and PT within the SOC.
Subjects with 2 or more TEAEs reported in the same SOC or PT were counted only once within that SOC or PT.
Adverse event terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1.
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
Ever = everolimus, Lenv = lenvatinib, PT = preferred term, SOC = system organ class; TEAE = treatment-emergent adverse event.
Source: Table 14.3.1.3.1.1.

Deaths, other serious adverse events, and other significant adverse events

Phase 1

As of the database lock date of 14 Nov 2022, 18 (78.3%) of the 23 subjects enrolled in Phase 1 had died (Table below). Of these, 4 subjects, all at Dose Level 1, died within 28 days of the last dose of study drug. Three of the 4 deaths were attributed to malignant neoplasm progression; 1 death was due to respiratory failure, which was not considered treatment related but related to disease progression.

Table 14 Summary of All Deaths – Phase 1 (Safety Analysis Set)

	Dose Level -1 Lenv 8 mg/m^2 + Ever 3 mg/m^2 (N=5) n (%)	Dose Level 1 Lenv 11 mg/m^2 + Ever 3 mg/m^2 (N=18) n (%)	Total (N=23) n (%)
All Deaths	4 (80.0)	14 (77.8)	18 (78.3)
Deaths During Treatment or Within 28 Days of Last Dose	0 (0.0)	4 (22.2)	4 (17.4)
Deaths >28 Days of Last Dose	4 (80.0)	10 (55.6)	14 (60.9)
Primary Reason for Deaths During Treatment or Within 28 Days of Last Dose			
Progressive Disease[a]	0 (0.0)	3 (16.7)	3 (13.0)
Adverse Event[b]	0 (0.0)	1 (5.6)	1 (4.3)

Database lock date: 14 Nov 2022.
Percentages are based on the total number of subjects within each relevant treatment group in the Safety Analysis Set.
Ever = everolimus, Lenv = lenvatinib, MedDRA = Medical Dictionary for Regulatory Activities.
a: Includes TEAEs with MedDRA preferred terms of 'Malignant Neoplasm Progression', 'Neoplasm Progression' and 'Disease Progression'.
b: Include patients with a fatal TEAE other than MedDRA preferred terms of 'Malignant Neoplasm Progression', 'Neoplasm Progression' and 'Disease Progression'.
Source: Table 14.3.2.1.1.1.

Phase II

As of the database lock date of 14 Nov 2022, 34 (82.9%) of the 41 subjects enrolled in Phase 2 had died (Table below).

Of the 34 subjects who died, 8 deaths occurred within 28 days of the subjects' last dose of study drug. Seven subjects died due to malignant neoplasm progression and 1 subject died due to encephalopathy, which was not considered treatment related but related to disease progression.

Table 15 Summary of All Deaths – Phase 2 (Safety Analysis Set)

	EWS (N=10) n (%)	RMS (N=20) n (%)	HGG (N=11) n (%)	Total (N=41) n (%)
All Deaths	9 (90.0)	17 (85.0)	8 (72.7)	34 (82.9)
Deaths During Treatment or Within 28 Days of Last Dose	1 (10.0)	5 (25.0)	2 (18.2)	8 (19.5)
Deaths >28 Days of Last Dose[a]	8 (80.0)	12 (60.0)	6 (54.5)	26 (63.4)
Primary Reason for Deaths During Treatment or Within 28 Days of Last Dose				
Progressive Disease[b]	1 (10.0)	4 (20.0)	2 (18.2)	7 (17.1)
Adverse Event[c]	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)

Database lock date: 14 Nov 2022.
Percentages based on total number of subjects within each relevant cohort in the Safety Analysis Set.
EWS = Ewing sarcoma, HGG = high-grade glioma, RMS = rhabdomyosarcoma.
a: Cause of death was not captured on the case report form beyond the 28-day posttreatment reporting period.
b: Includes TEAEs with MedDRA preferred terms of 'Malignant Neoplasm Progression,' 'Neoplasm Progression,' and 'Disease Progression.'
c: Include patients with a fatal TEAE other than MedDRA preferred terms of 'Malignant Neoplasm Progression,' 'Neoplasm Progression,' and 'Disease Progression.'
Source: Table 14.3.2.1.1.2.

Other Serious Adverse Events

Phase I

Overall, 14 subjects (60.9%) reported a nonfatal SAE in Phase 1, 2 subjects at Dose Level -1 and 12 subjects at Dose Level 1 (Table below).

The most frequently reported nonfatal SAEs were hypoxia, pain, and seizure, each occurring in 3 subjects (13.0%). All subjects with seizures had either HGG or other CNS tumors. All other nonfatal SAEs occurred in 1 or 2 subjects each.

Treatment-related SAEs, as determined by the investigator, were reported in 4 subjects, all at Dose Level 1. These comprised 1 subject each with ALT and AST increased, headache, pneumothorax, and tendon rupture (Table 14.3.2.3.1.1).

Table 16 Nonfatal Treatment-Emergent Serious Adverse Events by Preferred Term – Phase 1 (Safety Analysis Set)

Any Nonfatal SAE	Dose Level -1 Lenv 8 mg/m^2 + Ever 3 mg/m^2 (N=5) n (%)	Dose Level 1 Lenv 11 mg/m^2 + Ever 3 mg/m^2 (N=18) n (%)	Total (N=23) n (%)
Subjects with Any Nonfatal SAEs	*2 (40.0)*	*12 (66.7)*	*14 (60.9)*
Hypoxia	0 (0.0)	3 (16.7)	3 (13.0)
Pain	1 (20.0)	2 (11.1)	3 (13.0)
Seizure	0 (0.0)	3 (16.7)	3 (13.0)
Back pain	0 (0.0)	2 (11.1)	2 (8.7)
Headache	1 (20.0)	1 (5.6)	2 (8.7)
Abdominal pain	0 (0.0)	1 (5.6)	1 (4.3)
Alanine aminotransferase increased	0 (0.0)	1 (5.6)	1 (4.3)
Aspartate aminotransferase increased	0 (0.0)	1 (5.6)	1 (4.3)
Dysarthria	0 (0.0)	1 (5.6)	1 (4.3)
Dysphagia	0 (0.0)	1 (5.6)	1 (4.3)
Hypotension	0 (0.0)	1 (5.6)	1 (4.3)
Malignant pleural effusion	0 (0.0)	1 (5.6)	1 (4.3)
Mental status changes	0 (0.0)	1 (5.6)	1 (4.3)
Musculoskeletal pain	0 (0.0)	1 (5.6)	1 (4.3)
Nausea	0 (0.0)	1 (5.6)	1 (4.3)
Nystagmus	0 (0.0)	1 (5.6)	1 (4.3)
Pneumonia aspiration	0 (0.0)	1 (5.6)	1 (4.3)
Pneumothorax	0 (0.0)	1 (5.6)	1 (4.3)
Tendon rupture	0 (0.0)	1 (5.6)	1 (4.3)
Tumour haemorrhage	0 (0.0)	1 (5.6)	1 (4.3)
Vomiting	0 (0.0)	1 (5.6)	1 (4.3)

Database lock date: 14 Nov 2022.
Percentages are based on the total number of subjects within each relevant treatment group in the Safety Analysis Set.
Display is in descending order of frequency for all subjects, then alphabetically.
Subjects with 2 or more nonfatal SAEs reported for the same preferred term were counted only once.
Adverse event terms were coded using Medical Dictionary for Regulatory Affairs (MedDRA) version 25.1.
Ever = everolimus, Lenv = lenvatinib, SAE = serious adverse event.
Source: Table 14.3.2.1.6.1.

Phase II

Overall, 22 subjects (53.7%)—6, 8, and 8 subjects in the EWS, RMS, and HGG cohorts, respectively—reported a nonfatal SAE in Phase 2 (Table below). The most frequently reported nonfatal SAEs were pyrexia (4; 9.8%) and pleural effusion (3; 7.3%). The remaining nonfatal SAEs occurred in 1 or 2 subjects each. Treatment-related SAEs, as determined by the investigator, were reported in 11 subjects— 3, 5, and 3 subjects in the EWS, RMS, and HGG cohorts, respectively. All of the treatment-related SAEs occurred in 1 subject each (Table 14.3.2.3.1.2).

Table 17 Nonfatal Treatment-Emergent Serious Adverse Events by Preferred Term – Phase 2 (Safety Analysis Set) (Safety Analysis Set)

Preferred Terms	EWS (N=10) n (%)	RMS (N=20) n (%)	HGG (N=11) n (%)	Total (N=41) n (%)
Subjects with Any Nonfatal SAEs	*6 (60.0)*	*8 (40.0)*	*8 (72.7)*	*22 (53.7)*
Pyrexia	3 (30.0)	1 (5.0)	0 (0.0)	4 (9.8)
Pleural effusion	2 (20.0)	1 (5.0)	0 (0.0)	3 (7.3)
Dehydration	1 (10.0)	1 (5.0)	0 (0.0)	2 (4.9)
Hypoxia	1 (10.0)	1 (5.0)	0 (0.0)	2 (4.9)
Pancreatitis	0 (0.0)	2 (10.0)	0 (0.0)	2 (4.9)
Seizure	0 (0.0)	0 (0.0)	2 (18.2)	2 (4.9)
Upper respiratory tract infection	0 (0.0)	2 (10.0)	0 (0.0)	2 (4.9)
Cancer pain	1 (10.0)	0 (0.0)	0 (0.0)	1 (2.4)
Cerebrospinal fluid leakage	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Cough	1 (10.0)	0 (0.0)	0 (0.0)	1 (2.4)
Deep vein thrombosis	0 (0.0)	0 (0.0)	1 (9.1)	1 (2.4)
Depressed level of consciousness	0 (0.0)	0 (0.0)	1 (9.1)	1 (2.4)
Diarrhoea	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Encephalopathy	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Eyelid oedema	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Face oedema	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Febrile neutropenia	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Haemothorax	1 (10.0)	0 (0.0)	0 (0.0)	1 (2.4)
Headache	0 (0.0)	0 (0.0)	1 (9.1)	1 (2.4)
Hydrocephalus	0 (0.0)	0 (0.0)	1 (9.1)	1 (2.4)
Hypophosphataemia	1 (10.0)	0 (0.0)	0 (0.0)	1 (2.4)
Hypothyroidism	0 (0.0)	0 (0.0)	1 (9.1)	1 (2.4)
Mouth haemorrhage	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Muscular weakness	0 (0.0)	0 (0.0)	1 (9.1)	1 (2.4)
Musculoskeletal chest pain	1 (10.0)	0 (0.0)	0 (0.0)	1 (2.4)
Myalgia	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Nausea	0 (0.0)	0 (0.0)	1 (9.1)	1 (2.4)
Optic neuritis	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Oral cavity fistula	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Pain	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Paraesthesia	0 (0.0)	0 (0.0)	1 (9.1)	1 (2.4)
Pneumatosis intestinalis	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Pneumonia	0 (0.0)	0 (0.0)	1 (9.1)	1 (2.4)
Pneumothorax	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Sepsis	1 (10.0)	0 (0.0)	0 (0.0)	1 (2.4)
Vomiting	0 (0.0)	0 (0.0)	1 (9.1)	1 (2.4)

Database lock date: 14 Nov 2022.
Percentages are based on the total number of subjects within each relevant treatment group in the Safety Analysis Set.
Display is in descending order of frequency, then alphabetically, for Total column.
Subjects with 2 or more nonfatal SAEs reported for the same preferred term were counted only once.
Adverse event terms coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1.
EWS = Ewing sarcoma, HGG = high-grade glioma, RMS = rhabdomyosarcoma, SAE = serious adverse event.
Source: Table 14.3.2.1.6.2.

Clinically significant adverse events for Lenvatinib

The following CSEs for lenvatinib were identified based on a detailed review of the safety data from the clinical and pharmacovigilance databases for this study and the overall clinical development program for lenvatinib: arterial thromboembolic events, bone and teeth abnormalities, cardiac dysfunction, fistula formation, gastrointestinal (GI) perforation, hemorrhage, hepatotoxicity, hypertension, hypocalcemia, hypothyroidism, palmar-plantar erythrodysesthesia syndrome (PPE), posterior reversible encephalopathy syndrome (PRES), pneumothorax, proteinuria, QT prolongation, and renal events (Section 5.6.2 of the SAP, Appendix 16.1.9).

Cardiac dysfunction was reported for 4 subjects, 1 in Phase 1 and 3 in Phase 2. Two of these events, both in Phase 2, were Grade ≥3. A fistula formation event–Grade 3 oral cavity fistula—occurred in only 1 subject with RMS in Phase 2.

There were no reported events for the following CSEs for lenvatinib in either Phase 1 or Phase 2: arterial thromboembolic events, bone and teeth abnormalities, GI perforation, PRES, and renal events.

Table 18 Treatment-Emergent Clinically Significant Events for Lenvatinib Identified by SMQ or CMQ –Phase 1 (Safety Analysis Set)

	Dose Level -1		Dose Level 1		Total	
	Lenv 8 mg/m^2 + Ever 3 mg/m^2 (N=5) n (%)		Lenv 11 mg/m^2 + Ever 3 mg/m^2 (N=18) n (%)		(N=23) n (%)	
Clinically Significant Event	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Subjects with any Clinically Significant TEAEs	4 (80.0)	1 (20.0)	18 (100)	8 (44.4)	22 (95.7)	9 (39.1)
Subjects with any TEAE in the CSE category of:						
Cardiac dysfunction	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)
Hemorrhage	1 (20.0)	0 (0.0)	5 (27.8)	1 (5.6)	6 (26.1)	1 (4.3)
Hepatotoxicity	0 (0.0)	0 (0.0)	8 (44.4)	2 (11.1)	8 (34.8)	2 (8.7)
Hypertension	4 (80.0)	1 (20.0)	13 (72.2)	1 (5.6)	17 (73.9)	2 (8.7)
Hypocalcemia	0 (0.0)	0 (0.0)	4 (22.2)	0 (0.0)	4 (17.4)	0 (0.0)
Hypothyroidism	2 (40.0)	0 (0.0)	10 (55.6)	0 (0.0)	12 (52.2)	0 (0.0)
Palmar-plantar erythrodysaesthesia	1 (20.0)	0 (0.0)	1 (5.6)	0 (0.0)	2 (8.7)	0 (0.0)
Pneumothorax	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	2 (8.7)	0 (0.0)
Proteinuria	1 (20.0)	0 (0.0)	8 (44.4)	3 (16.7)	9 (39.1)	3 (13.0)
QT prolongation	2 (40.0)	0 (0.0)	2 (11.1)	1 (5.6)	4 (17.4)	1 (4.3)

Database lock date: 14 Nov 2022.
Display is in alphabetical order of CSE category.
Rows that contained only zeroes have been omitted from the in-text table.
Adverse event terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1.
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
CMQ = customized MedDRA query, CSE = clinically significant event, Ever = everolimus, Lenv = lenvatinib, SMQ = standardized MedDRA query, TEAE = treatment-emergent adverse event.
Source: Table 14.3.2.6.1.1.

Table 19 Treatment-Emergent Clinically Significant Events for Lenvatinib Identified by SMQ or CMQ –Phase 2 (Safety Analysis Set)

Clinically Significant Event	EWS (N=10) n (%)		RMS (N=20) n (%)		HGG (N=11) n (%)		Total (N=41) n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Subjects with any Clinically Significant TEAEs	10 (100)	2 (20.0)	16 (80.0)	6 (30.0)	10 (90.9)	2 (18.2)	36 (87.8)	10 (24.4)
Subjects with any TEAE in the CSE category of:								
Cardiac Dysfunction	1 (10.0)	1 (10.0)	1 (5.0)	0 (0.0)	1 (9.1)	1 (9.1)	3 (7.3)	2 (4.9)
Fistula formation	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.4)
Hemorrhage	5 (50.0)	0 (0.0)	10 (50.0)	1 (5.0)	5 (45.5)	1 (9.1)	20 (48.8)	2 (4.9)
Hepatotoxicity	5 (50.0)	1 (10.0)	10 (50.0)	1 (5.0)	5 (45.5)	0 (0.0)	20 (48.8)	2 (4.9)
Hypertension	3 (30.0)	0 (0.0)	10 (50.0)	1 (5.0)	4 (36.4)	0 (0.0)	17 (41.5)	1 (2.4)
Hypocalcemia	5 (50.0)	0 (0.0)	4 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (22.0)	0 (0.0)
Hypothyroidism	2 (20.0)	0 (0.0)	8 (40.0)	0 (0.0)	6 (54.5)	0 (0.0)	16 (39.0)	0 (0.0)
Palmar-plantar erythrodysaesthesia	2 (20.0)	0 (0.0)	1 (5.0)	0 (0.0)	2 (18.2)	0 (0.0)	5 (12.2)	0 (0.0)
Pneumothorax	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.4)
Proteinuria	8 (80.0)	1 (10.0)	10 (50.0)	2 (10.0)	4 (36.4)	0 (0.0)	22 (53.7)	3 (7.3)
QT prolongation	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)

Database lock date: 14 Nov 2022.
Display is in alphabetical order of CSE category.
Adverse event terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1.
Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
CMQ = customized MedDRA query, CSE = clinically significant event, EWS = Ewing sarcoma, HGG = high-grade glioma, RMS = rhabdomyosarcoma, SMQ = standardized MedDRA query, TEAE = treatment-emergent adverse event.
Source: Table 14.3.2.6.1.2.

2.3.3. Discussion on clinical aspects

Design and conduct of the clinical study:

Study E7080-A001-216 was a multicenter, open-label, single-arm, Phase 1/2 study of lenvatinib in combination with everolimus in paediatric subjects with relapsed or refractory solid tumours. There were two parts in the study: a dose finding and an expansion part.

The Phase I part of the study used a rolling-6 design for dose finding. If there were no DLTs in the first 3 subjects enrolled under the rolling-6 design, then the fourth subject was allocated to the next higher dose level. If toxicity data were not available for the first 3 subjects or if 1 DLT was observed, the fourth subject was entered at the same dose level as the first 3.

In Phase II part, subjects were enrolled to each cohort using a 10+10 Simon's optimal 2-stage design; 10 evaluable subjects were initially enrolled to each of the 3 cohorts in Stage 1. Futility rules were in place (see below discussion on efficacy results) to avoid exposure of patients to suboptimal therapy.

All subjects who were still receiving study treatment following completion of Cycle 1 in Phase 1, or after completing 4 cycles of treatment in Phase 2, transitioned to the Extension Phase. During the Extension Phase, subjects continued to receive the same doses of study drug as assigned in the Treatment Phase, in 28-day cycles. Study treatment continued throughout the Extension Phase.

The primary objectives for Phase I were to identify the lenvatinib MTD and to describe the toxicities of lenvatinib administered in combination with everolimus QD to paediatric subjects with recurrent/refractory malignant solid tumours.

The primary objectives for Phase II were to estimate the antitumor activity of lenvatinib in combination with everolimus in paediatric subjects with selected recurrent/refractory malignant solid tumours, including Ewing sarcoma (EWS)/peripheral primitive neuroectodermal tumour (pPNET) (EWS), rhabdomyosarcoma (RMS), and high-grade glioma (HGG) using objective response rate (ORR) at Week 16 as the outcome measure.

The rationale for the type of tumours to be included in the trial refers to incidence of these tumours in paediatric population. Some of the most common types of solid tumours found in children are brain tumours, rhabdomyosarcoma (RMS), and Ewing sarcoma (EWS). Brain tumours are the most common

solid tumours in paediatrics and the leading cause of childhood cancer-related death, therefore the medical need is acknowledged. Various pre-clinical mouse model support the use of mTORi and VEGF inhibitors as treatment for cancer. In addition, the rationale for pediatric evaluation of lenvatinib in combination with everolimus was based on the positive results of the randomized trial (E7080-G000-205) in adults with advanced RCC.

Lenvatinib was provided as hard capsules containing lenvatinib 1 mg, 4 mg, or 10 mg for oral use. For subjects who were unable to swallow capsules, lenvatinib capsules could be added to water or apple juice to prepare an extemporaneous oral suspension. Dosing nomograms based on BSA and dose level were used to prescribe lenvatinib to minimize inter-subject dosing variability. The maximum daily dose of lenvatinib administered during the study could not exceed 18 mg at Dose Levels -1 and 1. Intrasubject dose escalation of lenvatinib was not allowed. Dose interruptions, dose reductions, or treatment discontinuation were allowed for subjects who experienced lenvatinib-related toxicity. Once the dose was reduced, it could not be increased at a later date.

To estimate the antitumor activity of lenvatinib in combination with everolimus in paediatric subjects with EWS, RMS, or HGG the ORR at 16 weeks was selected as primary efficacy endpoint. The ORR at Week 16 was defined as the proportion of subjects who had a BOR of CR or PR at Week 16. The response (CR or PR) had to be confirmed. Best overall response was assessed by the investigator using RECIST 1.1 or RANO (for HGG) and summarized and listed by dose level (Phase 1) or disease cohort (Phase 2). Subjects enrolled in Phase 2 were required to have measurable disease at Baseline.

The original protocol was approved in 16 March 2017. There were three protocol amendments; the date of the last protocol amendment is 16 august 2021, before the final CSR (24 March 2023). The full analysis set definition was changed in the last protocol amendment from "Full Analysis Set, defined as all subjects enrolled." To "Evaluable Analysis Set defined as all subjects, who have measurable disease present at baseline and at least 1 post-baseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease. This will be the analysis set for efficacy". This is unlikely to change the final conclusions of the study.

Efficacy data and additional analyses

Phase I

Enrolment in this cohort was initiated at Dose Level 1, 11 mg/m^2 lenvatinib plus 3 mg/ m2 everolimus. Two of the 3 subjects at Dose Level 1 had that met the criteria for DLT. Thus, the next subject was treated at a de-escalated level, ie, Dose Level -1 (8 mg/m2 lenvatinib plus 3 mg/m2 everolimus) and enrolment continued at this dose level. Five subjects were enrolled at Dose Level -1 with no further DLTs. Since there were no DLTs at Dose Level -1, and a DLT of Grade 3 headache was readily reversible with administration of acetaminophen 650 mg, the classification of the Grade 3 headache as a DLT was reassessed and the protocol amended (Amendment 01) to revise the definition of a DLT to exclude Grade 3 headache of <3 days' duration responsive to optimal management. Upon approval of Amendment 01, enrolment was re-initiated at Dose Level 1, and out of the 3 additional subjects, 1 subject had DLTs of Grade 3 hypertriglyceridemia and Grade 4 hypercholesterolemia. Per protocol, given that the DLTs were of different classes of adverse events, the cohort was expanded to a total of 12 subjects. No additional DLTs occurred and thus, lenvatinib 11 mg/m2 plus everolimus 3 mg/m2, both administered orally once daily, was established as the MTD for the combination and identified as the RP2D.

Assessment of antitumor activity was a secondary objective in Phase I. No subjects had a BOR of CR or PR per investigator assessment.

In Phase II, a 10+10 Simon's optimal 2-stage design was used to evaluate clinical activity in each of the disease cohorts, EWS, RMS, and HGG. Ten evaluable subjects were enrolled in each of the 3 cohorts in Stage 1. The primary outcome measure was ORR (complete or partial response) at 16 weeks. If there were no responses among the 10 subjects in Stage 1, then enrolment into that cohort was stopped for futility. If there was at least 1 response in the first stage, then an additional 10 evaluable subjects were enrolled in Stage 2. If there were 2 or fewer responses among the 20 evaluable subjects in a cohort, then combination treatment with lenvatinib and everolimus was declared a failure for that cohort.

Enrolment into 2 of the cohorts, EWS and HGG, was stopped for futility after Stage 1, as no subjects in either cohort had a complete or partial response. In the RMS cohort, 1 subject achieved a confirmed PR by Week 16 during Stage 1. Consequently, an additional 10 subjects were enrolled in the RMS cohort. One additional confirmed PR occurred among the 10 subjects during Stage 2, for an ORR in the RMS cohort of 10.0%. Since only 2 responses occurred, combination treatment with lenvatinib and everolimus was deemed a failure for that cohort. The primary reason for discontinuation of treatment was progressive disease; very few patients discontinue due to AEs or by choice.

Safety

The AE profile of combination of lenvatinib 11 mg/m2 daily + everolimus 3 mg/m2 daily was manageable. Overall, there were no new safety signals.

In phase 2, the most frequently reported TEAEs, occurring in 40% or more of subjects overall were hypertriglyceridemia, proteinuria, lymphocyte count decreased, diarrhoea, fatigue, platelet count decreased, blood cholesterol increased, hypertension, and vomiting.

In Phase 1, the most frequently reported nonfatal SAEs were hypoxia, pain, and seizure, each occurring in subjects. All subjects with seizures had either HGG or other CNS tumours. In Phase 2, most frequently reported nonfatal SAEs were pyrexia and pleural effusion.

In part 1, at database lock date of 14 Nov 2022, 18 (78.3%) of the 23 subjects enrolled in Phase 1 had died. Of these, 4 subjects (all at Dose Level 1) died within 28 days of the last dose of study drug. Three of the 4 deaths were attributed to malignant neoplasm progression; 1 death was due to respiratory failure, which was not considered treatment related but related to disease progression.

In part 2, of the 34 (82.9%, out of 41 enrolled) subjects who died, 8 deaths occurred within 28 days of the subjects' last dose of study drug. Seven subjects died due to malignant neoplasm progression and 1 subject died due to encephalopathy, which was not considered treatment related but related to disease progression.

Based on the established safety profiles of both drugs, certain AEs were prespecified as being of special interest. The CSEs for lenvatinib that occurred in >45% of subjects in either Phase 1 or Phase 2 were haemorrhage, hepatotoxicity, hypertension, hypothyroidism, and proteinuria. Most CSEs were Grade 1 or 2 and did not lead to treatment discontinuation.

The AESIs for everolimus that occurred in >30% of subjects were dyslipidemia and stomatitis. No events of angioedema occurred in either study phase. Most AESIs were low grade and few led to discontinuation of treatment.

3. Rapporteur's overall conclusion and recommendation

Study E7080-A001-216 was a trial to study lenvatinib in combination with everolimus in paediatric subjects with solid tumours.

The first part of the trial was a dose finding study and employed a rolling-6 design and DLT to select the dose; the data were monitored by a safety steering committee and Eisai employees. In addition, an ad-hoc independent review committee examined the data (which included safety and PK from studies 205 and 207 in addition to study 216) and informed on the conduct of the trial ie update the definition of DLT headache grade 3 from the list. Headache occurred in one subject in part 1 at dose level 1 (lenvatinib 11 mg/m2 + everolimus 3 mg/m2). The study resumed after protocol amendment and eventually the selected dose was Dose Level 1, ie, lenvatinib 11 mg/m2 + everolimus 3 mg/m2. Despite the changes in the protocol conduct, the approach to identity the RP2D appears reasonable.

Enrolment into EWS and HGG cohorts was stopped for futility after Stage 1 (10 subjects), as no subjects in either cohort had a complete or partial response. In the RMS cohort, 1 subject achieved a confirmed PR, therefore an additional 10 subjects were enrolled in the RMS cohort. One confirmed PR occurred among these 10 additional 10 patients resulting in ORR of 10.0% in this cohort. Since only 2 responses occurred, combination treatment with lenvatinib and everolimus was deemed a failure for that cohort.

The activity/efficacy results from the Study 216 appear consistent with literature data in patients with relapsed/refractory EWS, RMS and HGG that suggest a limited response to therapy (including VEGFR inhibitors) beyond chemotherapy.

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide description of the additional clarifications requested per study as part of this procedure. (see section "Additional clarification requested")

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH did not suggest an extension of indication to paediatric patients nor any changes to the SmPC. The MAH previously committed to update the SmPC when the outcome of study 230 from the PIP becomes available and to submit a Type 2 variation in 2023, the expected timelines for such submission should be specified. Further, the MAH should discuss the potential relevance of data from the currently submitted study E7080-A001-216 for inclusion in the SmPC (e.g. safety, PK) and to provide a text proposal to include information whenever relevant.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

The MAH would like to clarify that following the submission and receipt of a positive PDCO opinion for the final compliance check for the agreed paediatric investigation plan (PIP) EMEA-001119-PIP02-12-M08 (conditions: papillary thyroid cancer, follicular thyroid cancer and osteosarcoma), a Type II variation (variation category C.I.4, eCTD seq #0142), was recently submitted on 16 June 2023 for the Lenvima license.

This variation proposes to update the Product Information (Annex I –Summary of Product Characteristics (sections 4.2, 4.8, 5.1 and 5.2) and Annex IIIB –Package Leaflet (section 2)) to reflect the results of the two completed paediatric clinical studies performed in compliance with the agreed

paediatric investigation plan (PIP) EMEA-001119-PIP02-12-M08; studies E7080-G000-207 (hereafter Study 207) and Study E7080-G000-230 (hereafter Study 230).

The MAH is currently preparing a final compliance check for the second PIP; EMEA001119-PIP03-19-M03 (condition: solid tumours). After the PDCO opinion has been received, an additional Type II variation (variation category C.I.4) is planned to update the SmPC for both Lenvima and Kisplyx licenses to reflect the results of the paediatric studies E7080-A001-216 (hereafter Study 216) and E7080-G000-231 (hereafter Study 231).

The MAH is not planning to seek a paediatric indication for differentiated thyroid cancer (DTC) or any other type of cancer, based on the results of EMEA-001119-PIP02-12-M08 Studies 207 and 230. In addition, there is no plan to seek a paediatric indication based on the results of EMEA-001119-PIP03-19-M03 Studies 216 and 231 for solid tumours.

The proposed SmPC wording will be provided in the planned Type II variation.

5. Rapporteur's overall conclusion and recommendation

The MAH has submitted a type II variation (Lenvima II-50) to update sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to update paediatric information based on final results from studies E7080-G000-207 (Study 207) and E7080-G000-230 (Study 230). These two studies were performed to comply with the agreed paediatric investigation plan (PIP) EMEA-001119-PIP02-12-M08.

Studies E7080-A001-216 (Study 216) and E7080-G000-231 (Study 231) are both part of the second lenvatinib PIP, EMEA-001119-PIP03-19-M03.

The MAH commits to submit an additional Type II variation (variation category C.I.4) to update the SmPC for both Lenvima and Kisplyx to reflect the results of these paediatric studies E7080-A001-216 and E7080-G000-231.

The update of the both Kisplyx and Lenvima SmPCs with the same information in paediatric population is expected.

☒ Fulfilled with recommendation

The MAH is recommended to submit as committed the update of the relevant SmPC sections to propose inclusion additional information in paediatric patients based on the results of the studies E7080-A001-216 (Study 216) and E7080-G000-231 (Study 231). This should be provided without any delay and by 31 December 2023 (pending the PDCO compliance check).