STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7080-A001-216
Study Protocol Title:	A Phase 1/2 Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including CNS Tumors
Date:	22 Sep 2022
Version:	Final Version 2.0

DATE	Highlights of Major Changes Sections/Changes
22 Sep 2022	Version 2.0:
	Section 3.2 Added definition of being evaluable for an objective response. Added definition of evaluable participants.
	Section 3.2.2 and 3.2.3 Added ±1 week window for tumor assessment timepoints.
	Section 5.2.1 Added Evaluable Analysis Set for efficacy analysis of Phase 2 and updated Safety Analysis Set will be used for disposition, demographic and baseline characteristics, previous anticancer medications, prior and concomitant medications, procedures and radiotherapy, medical history, efficacy analysis of Phase 1 as well as all safety evaluations.
	Section 5.2.4 Updated to TNM will be listed only. Tumor-node-metastasis (TNM) staging, stage group of Ewing sarcoma/PNET and Rhabdomyosarcoma at diagnosis and WHO Grading of Glioma for subjects evaluated by RANO will be provided in listing only.
	Section 5.2.5 Prior medications definition updated to medications that started prior to the first dose of study drug and discontinued before the first dose of study drug.
	Section 5.4.1.2 Remove “As an example, if a subject had an SD at the timepoint 1, a PR at the timepoint 2, a CR at the timepoint 3, and another CR at the timepoint 4, then the BOR for this subject is CR, which was confirmed at timepoint 4” for conciseness.

	Section 5.4.2 Added DOR to the secondary endpoints in Phase 2. Updated the definition of more than 1 missed visit/adequate tumor assessment in Table 3 DOR and Censoring Rules.
	Section 5.4.3 Removed spider plot.
	Section 5.6.2 Combined the following tables into one table. Treatment-related TEAEs by decreasing frequency of PT Treatment-related TEAEs by decreasing frequency of PT with CTCAE Grades ≥3 Added bone and teeth abnormalities, removed impaired wound healing and weight loss in CSAE for Lenvatinib. Replaced CSAE with AEOSI, removed Edema, Rash and added Angioedema in AEOSI for Everolimus.
	Section 5.6.3.1 Shift table will include all chemistry parameters and hematology parameters. Shifts from Baseline to worst postbaseline CTCAE grade for all clinical chemistry parameters and hematology parameters.
	Section 5.6.3.4 Added height to the list of vital sign parameters that will be summarized. Added analysis for height percentiles. Updated the percentile categories for analysis of change in BP percentile categories for Shift in BP Percentile from Baseline to Worst Postbaseline Measurement (Subjects <18 Years Old).
	Section 5.6.4 Added descriptive statistics and changes from baseline for left ventricular shortening fraction assessed on echocardiogram and LVEF assessed on echocardiogram or MUGA scans will be

	presented. Percent reduction from baseline will also be summarized. In addition, Radiographic findings of proximal tibial growth plates and dental examination will also be summarized.
	Section 8.2.1.6 Added partial dates imputation rule for previous radiotherapy.
	Section 8.1 Updated visit window added efforts should be made to 1 week. Visit windows will be defined to be upper and lower bounds of 1 week of conduct tumor assessments on the day scheduled visit. (±7 day).
	Appendix Updated Summary of Efficacy Analyses of Phase 1 and Phase 2.

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ATC	anatomical therapeutic class
AUC	area under curve
BLQ	below limit of quantification
BMI	body mass index
BSA	body surface area
BOR	best overall response
C#/D#	Cycle#/Day#
CBR	clinical benefit rate
CI	confidence interval
C_{max}	concentration maximum
CNS	central nervous system
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DBP	diastolic blood pressure
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
HGG	high grade glioma
IDMC	independent data monitoring committee
KM	Kaplan-Meier
KPS	Karnofsky performance status
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MUGA	multiple gated acquisition

Abbreviation	Term
NA	not applicable
NE	not evaluable
ORR	objective response rate
PD	progressive disease
PK	pharmacokinetic
pPNET	peripheral primitive neuroectodermal tumor
PR	partial response
PSC	Protocol Steering Committee
PT	preferred term
QT	time from the beginning of the QRS complex to the end of the T wave
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	stable disease
SOC	System organ class
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs
TNM	tumor-node-metastasis staging system
WHO	World Health Organization

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze, and report results for the Phase 1/2 Study E7080-A001-216. This SAP is based on the Protocol Amendment 03 (16 Aug 2021) and final electronic Case Report Form (eCRF) (23 May 2022).

3.1 Study Objectives

3.1.1 Primary Objectives

3.1.1.1 Phase 1

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

3.1.1.2 Phase 2

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

3.1.2 Secondary Objectives

3.1.2.1 Phase 1

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

3.1.2.2 Phase 2

a. To assess other response variables including ORR at the time of data cutoff, disease control rate (DCR), clinical benefit rate (CBR), and duration of response (DOR).
b. To evaluate the tolerability and safety profile of lenvatinib in combination with everolimus in pediatric subjects with recurrent/refractory Ewing sarcoma/pPNET, rhabdomyosarcoma, and HGG.

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

3.1.3 Exploratory Objectives for Phase 1 and Phase 2

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

3.2 Overall Study Design and Plan

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

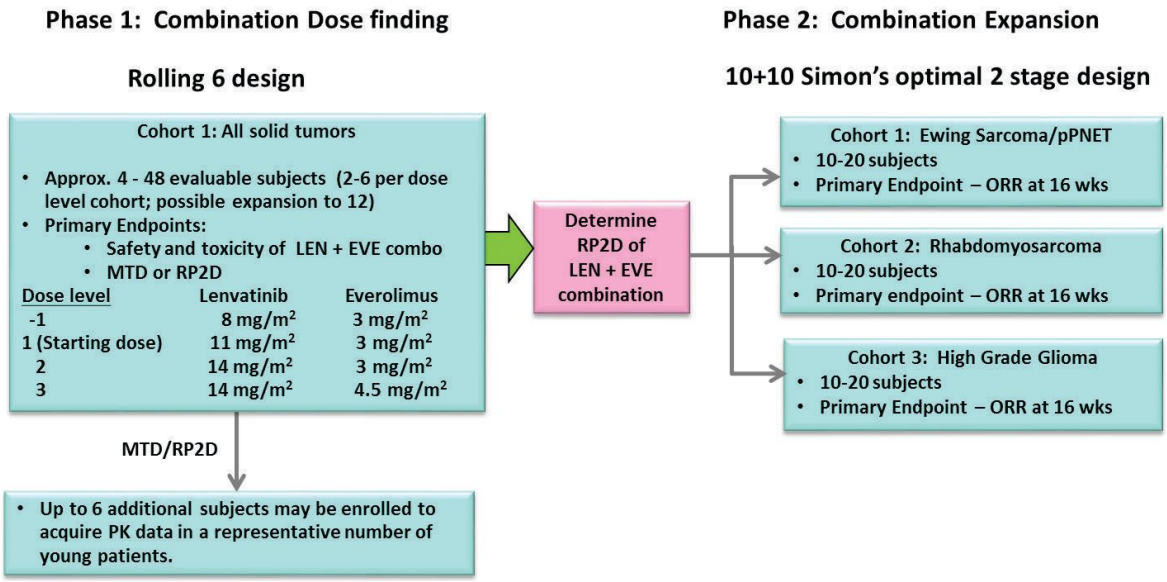

Figure 1 Study Design

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

Phase 1 Dose Escalation and Determination of the MTD

The Phase 1 component is a dose escalation study with treatment in sequential cohorts of escalating doses of lenvatinib in combination with everolimus, each administered once daily

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

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

Table 1 Planned Dose-Escalation

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

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

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

Dose level assignment will be based on:

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

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

suspended when a cohort of 6 potentially evaluable subjects has enrolled (ie, subjects enrolled but are not yet assessable for toxicity) or when the study endpoints have been met. When subjects are not evaluable for toxicity, they will be replaced with the next available subject if escalation or de-escalation rules have not been fulfilled at the time the next available subject is enrolled in the study.

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

Table 2 The Rolling 6 Design

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

DLT = dose-limiting toxicity

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

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

If 2 or more of a cohort 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 after 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 of having evaluable PK at the end of Phase I 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, up 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). Additional subjects enrolled for PK once the MTD or RP2D has been defined will not be included the DLT Rolling 6 analysis.

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.

Independent Data Monitoring Committee

In addition to Protocol Steering Committee, the safety monitoring will be conducted by the Independent Data Monitoring Committee (IDMC). The frequency of safety reviews will be defined in the IDMC charter. Minutes from the open meetings of the IDMC will be provided if requested by regulatory agencies. The function and membership of the IDMC will be described in the IDMC charter.

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 monitoring will occur at least weekly during the first 2 cycles.

Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) 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 nonhematological toxicities are defined differently (see Protocol Section 9.1 for definitions of nonhematological and hematological DLTs).

All DLTs must be reported to the sponsor within 24 hours of their occurrence. Determination of a DLT will be made by the investigator and the Eisai Medical Monitor in consultation with the PSC, as needed. Subjects who discontinue the study treatment for any reason other than DLT (eg, early disease progression) during Cycle 1 (Day 1 to Day 28), and have not received at least 75% of the prescribed dose prior to discontinuation, will be replaced.

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

Phase 2 Cohorts

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

Cohorts 1 – 3

Phase 2 Cohorts 1 to 3 will use a 10+10 Simon's optimal 2-stage design [Simon, 1989] for each cohort; 10 evaluable subjects will be enrolled in Stage 1 for each cohort. The primary outcome measure for Ewing sarcoma/pPNET, rhabdomyosarcoma, and HGG will be ORR (complete or partial response) at 16 weeks. If there are no responses among the 10 subjects in Stage 1, then the enrollment to that disease cohort will stop for futility. If there is at least 1 response in the first stage, then the second stage will enroll 10 additional evaluable subjects. If there are 2 or fewer responses among the 20 evaluable subjects, then lenvatinib/everolimus combination therapy will be declared a failure for that disease cohort. Subjects will meet the criteria for being evaluable for an objective response, if they have measurable disease present at baseline and at least 1 postbaseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease. Participants who are not evaluable for objective response will be replaced.

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

Dosing Nomogram

The dose nomogram (see Protocol Section 9.1 Table 3) provides the dose of lenvatinib to be administered for BSA increments starting from 0.6 m^2. BSA must be calculated on Day 1 of each cycle based on the subject's current height and body weight. The actual dose to be

administered is rounded to the nearest whole number. The total lenvatinib dose is capped at 18 mg daily (Dose Levels -1 and 1), and at 24 mg (Dose Levels 2 and 3).

The dose nomogram (see Protocol Section 9.1 Table 4) provides the dose of everolimus to be administered for BSA increments starting from 0.6 m^2. The total everolimus dose is capped at 5 mg daily for Dose Levels -1, 1, and 2, and at 7 mg daily for Dose Level 3.

Study Duration

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

Study duration for each subject is estimated to be:

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

3.2.1 Pretreatment Phase

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

3.2.1.1 Screening Period

Screening will occur between Day –28 and Day –2. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Protocol Section 5.3.

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

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

3.2.1.2 Baseline Period

The purpose of the Baseline Period is to confirm protocol eligibility as specified in the inclusion/exclusion criteria (as detailed in Protocol Section 9.3.1 and Section 9.3.2). Results of baseline assessments must be obtained prior to the first dose of study treatment (Cycle 1 Day 1). Baseline assessments can be performed on Day –1 or on Cycle 1 Day 1 prior to start of study treatment.

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

3.2.2 Treatment Phase

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

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

3.2.3 Extension Phase

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

3.2.4 Treatment Discontinuation Criteria

Subjects may remain on study treatment as long as they do not meet any of the following criteria: 1) experience objective progression of disease (according to Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 or Response Assessment in Neuro-Oncology [RANO] criteria, as appropriate), 2) exhibit no clinical benefit (in the opinion of the investigator), 3) experience unacceptable toxicity leading to withdrawal from the study, 4) withdraw or are withdrawn from the study for any reason, or, 5) termination of the study program.

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

3.2.5 Off-Treatment Visit

After subject discontinues treatment, an Off-Treatment Visit and the procedures noted in the Schedule of Assessments (See Protocol Section 9.5.2.1, Tables 7 and 8) should be completed within 28 days after the last dose of study treatment.

3.2.6 Posttreatment Phase

3.2.6.1 Follow-Up Period

The posttreatment follow up will begin when the subject discontinues study treatment and all off-treatment assessments have been completed. Subjects who discontinue study treatment for reasons other than disease progression will be followed for documented disease progression for 1 year or until another anticancer therapy is initiated whichever occurs first. Subjects will be followed for survival every 3 months until death or for 1 year, whichever occurs first, unless the study is terminated or if the subject discontinues due to withdrawal of consent or is lost to follow up.

After data cutoff, tumor assessments may be performed as clinically indicated using the institutional guidelines, following the prevailing local standard of care.

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

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

4 DETERMINATION OF SAMPLE SIZE

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

5 STATISTICAL METHODS

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. The statistical analyses of the study data as described in this section will be performed as further outlined in this SAP, which will be finalized before database lock and included in the CSR.

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.

5.1 Study Endpoints

5.1.1 Primary Endpoints

5.1.1.1 Primary Endpoints for Phase 1

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

5.1.1.2 Primary Endpoint for Phase 2

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

5.1.2 Secondary Endpoints

Secondary endpoints for Phase 1 and Phase 2 are listed below.

- 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.

5.1.3 Exploratory Endpoints

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

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The following analysis sets will be defined:

- **Evaluable Analysis Set,** defined as all evaluable subjects, who have measurable disease present at baseline and at least 1 postbaseline efficacy assessment, unless they have discontinued prior to the first efficacy assessment due to progressive disease. Efficacy analyses in Phase 2 will primarily be based on the Evaluable Analysis Set.
- **Safety Analysis Set,** defined as all subjects who received at least 1 dose of study drug (lenvatinib or everolimus). This will be the analysis set for disposition, demographic and baseline characteristics, previous anticancer medications, prior and concomitant medications, procedures and radiotherapy, medical history, efficacy analysis in Phase 1 as well as all safety evaluations.
- **Pharmacokinetic (PK) Analysis Set,** defined as subjects in the Safety Analysis Set who had at least 1 measurable postdose plasma concentration with an adequately documented drug administration history.
- **Pharmacodynamic Analysis Set,** defined as all subjects in Safety Analysis Set who had evaluable pharmacodynamic data.

All analyses will be presented by planned dose level group in Phase 1 and separately for each study cohort in Phase 2, unless otherwise specified. A summary table and listing will also be provided to identify subjects in each analysis set.

5.2.2 Subject Disposition

Subject disposition will be summarized using the Safety Analysis Set.

The number of subjects who were screened, and the number and percentage of subjects who enrolled, treated, and discontinued study treatment at the time of data cutoff will be summarized. The subjects who discontinued study treatment will be tabulated according to the primary reason for discontinuation by dose level group and overall in Phase 1, and separately for each study cohort in Phase 2. The reasons for prematurely discontinuing either lenvatinib or everolimus will be provided in a listing.

The end of study status (e.g., alive, death, withdrew consent, or lost to follow-up) at the data cutoff will also be summarized using the data from the survival follow-up eCRF by dose level group and overall in Phase 1, and separately for each study cohort in Phase 2.

Additionally, all subjects who failed screening will be listed with the primary reason for failure. Subject listings with relevant disposition information will be provided.

5.2.3 Protocol Deviations

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

Important protocol deviations will be summarized and listed by dose level group in Phase 1 and separately for each cohort in Phase 2.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics for the Safety Analysis Set will be summarized by dose level group and overall in Phase 1, and separately for each study cohort in Phase 2.

The following demographic and baseline characteristics will be summarized as appropriate:

- Age (years)
- Age group (2 to <6 years, 6 to <12 years, 12 to <16 years, 16 to <18 years, 18 to 21 years, if applicable)
- Gender
- Race

- Ethnicity
- Baseline Karnofsky/Lanksy performance status score
- Height (cm)
- Height Percentile
- Baseline weight (kg)
- Baseline body mass index (BMI) (kg/m^2)
- Body Surface Area

Previous anticancer medication will be summarized by dose level group and overall in Phase 1, and separately for each study cohort in Phase 2 as follows:

- Number of previous therapy regimens
- Duration of most recent previous anticancer therapy (months)
- Best response for most recent previous anticancer therapy (CR, PR, SD, progressive disease (PD), not evaluable, not applicable, unknown)
- Time from end of most recent previous anticancer therapy to first dose of study drug (months)
- Previous anticancer therapy (administered as adjuvant, neoadjuvant, metastatic, locally advanced, maintenance and unknown)
- Previous anticancer therapy preferred term

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

- Number of subjects with any previous anthracycline therapy
- Duration of most recent previous anthracycline therapy (months)
- Time from end of most recent previous anthracycline therapy to first dose of study drug
- Previous anthracycline therapy preferred term

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

- Subjects with any previous radiotherapy
- Radiotherapy site (lymph node [neck/thoracic/abdominal and pelvic/other], bone [skull/spine/thorax/pelvis/extremities], brain, visceral [colorectal mass, lung mass, liver mass, chest, abdomen/pelvis], skin [trunk, extremity, head and neck], musculoskeletal [soft tissue-trunk, extremity, head and neck], miscellaneous)
- Tumor lesion at the site progressed since most recent previous radiotherapy (yes, no, not evaluated)
- Time from most recent previous radiotherapy to the first dose.

- Duration of most recent previous radiotherapy

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

- Solid tumor diagnosis classification
- Time since first diagnosis of solid tumor to date of first dose (months)
- Time since metastatic diagnosis to date of the first dose (months)
- Age at diagnosis (in years)
- Target lesions [yes/no] and nontarget lesions [yes/no] based on the measurable disease criteria at study entry using RECIST 1.1. or RANO as appropriate.

Tumor-node-metastasis (TNM) staging, stage group of Ewing sarcoma/PNET and Rhabdomyosarcoma at diagnosis and WHO Grading of Glioma for subjects evaluated by RANO will be provided in listing only.

Previous anticancer therapies, anthracycline therapy, previous radiotherapies, and disease history and characteristics at study entry will also be listed for each subject.

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

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded using the WHO Drug Dictionary (using the 2018 B2 version or later). The number (percentage) of subjects who have taken prior and concomitant antihypertensive, antidiarrheal and anthracycline medications will be summarized on the Safety Analysis Set, by the Anatomical Therapeutic Chemical (ATC) Classification, WHO drug dictionary preferred term, and by dose level in Phase 1 and by cohort in Phase 2. Other prior and concomitant medications, excluding antihypertensive, antidiarrheal and anthracycline will be summarized similarly. If a subject has taken prior and concomitant medications more than once within the same preferred term, the subject will be counted only once for the respective preferred term. Prior medications will be defined as medications that stopped prior to the first dose of study drug. Concomitant medications will be defined as medications that (i) have started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (ii) have started on or after the date of the first dose of study drug up to 28 days following the last dose. Medications that cannot be determined to be prior/concomitant due to missing or incomplete dates will be regarded as concomitant (see Section 5.3.5.2).

Data listings will be provided for all prior and concomitant medications.

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

5.2.6 Treatment Compliance

Not collected on CRF.

5.3 Data Analysis General Considerations

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

5.3.1 Pooling of Centers

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

5.3.2 Adjustments for Covariates

No adjustment for covariates will be made for this study.

5.3.3 Multiple Comparisons/Multiplicity

No multiplicity adjustment will be made for this study.

5.3.4 Examination of Subgroups

Subgroup analyses may be conducted if appropriate.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

5.3.5.1 Adverse Events

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

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

5.3.5.2 Concomitant Medications

Medications will be considered concomitant if:

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

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

5.3.6 Other Considerations

5.3.6.1 BSA Dose Adjustment and Dose Capping

Subjects in Phase 1 will receive study drug as described in Protocol Section 9.1, Tables 3 (lenvatinib) and 4 (everolimus).

The actual dose level of lenvatinib and everolimus could be different from the planned dose level due to the adjustment of BSA and dose capping. The actual dose level of lenvatinib and everolimus will be calculated from actual daily dose and BSA. The subject with dose capping will be listed. For Phase 1 and Phase 2 the planned dose level will be used for column grouping across all analyses.

5.3.6.2 Summarization of Safety Data

Regarding summarization of mean and mean change from Baseline for laboratory, vital sign, and ECG data, if 2 or fewer subjects in each of the treatment groups have data for a given cycle, the applicable cycle(s) will not be summarized, and the table will be curtailed. For example, if at Cycle 10 the 3 treatment groups have 4, 3 and 1 subjects, respectively, then Cycle 10 will be summarized for all treatment groups. If at Cycle 11, the 3 treatment groups have 2, 2 and 1 subject, respectively, and at subsequent cycles no treatment has 3 or more subjects, then the table will not be produced for Cycle 11 and all subsequent cycles. However, for shift tables and other analyses of worst postbaseline values, all data will be included.

5.4 Primary, Secondary and Exploratory Analyses

5.4.1 Primary Analyses

5.4.1.1 Dose-Finding Analysis in Phase 1

The primary objective of Phase 1 is to determine the MTD and to establish RP2D of lenvatinib administered in combination with everolimus. The study will utilize the rolling 6 design detailed in SAP Section 3.2.

5.4.1.2 Primary Efficacy Analysis for Phase 2

Efficacy analyses for Phase 2 will be performed separately for each study cohort.

The primary objective of Phase 2 is to estimate the antitumor activity of lenvatinib in combination with everolimus in pediatric subjects with Ewing sarcoma/peripheral primitive neuroectodermal tumor (pPNET), rhabdomyosarcoma, and HGG using the ORR at 16 weeks. The ORR at Week 16 is defined as the proportion of subjects who have the BOR of CR or PR at Week 16.

Subjects must have measurable disease present at baseline for Phase 2. Those who have their disease re-evaluated at postbaseline visits will be considered evaluable for objective response. Estimated ORR and its exact 95% CI using the Clopper-Pearson [Clopper and Pearson, 1934] method will be presented.

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

Tumor response data utilized in the primary analysis of ORR will be obtained from investigator's assessment of the imaging scans. No independent tumor assessments will be performed as part of this study. Tumor response will be assessed by RECIST 1.1 criteria [Eisenhauer, et al., 2009] in pediatric subjects with Ewing sarcoma/peripheral primitive neuroectodermal tumor (pPNET) and rhabdomyosarcoma, and RANO criteria will be used for subjects with HGG [Wen, et al., 2010]. Efficacy analyses in Phase 2 will primarily be based on the Evaluable Analysis Set .

The BOR is determined once all data for a subject is known. For this study, a confirmation of CR or PR is required for both RECIST 1.1 and RANO. The confirmation assessments should be made ≥4 weeks after the initial response assessment. The BOR is determined by sequentially checking two adjacent assessments (≥4 weeks apart).

5.4.2 Secondary Efficacy Analyses

5.4.2.1 Phase 1

The secondary efficacy analyses in Phase 1 subjects will be summarized by planned dose level and overall if appropriate and listed by dose level group and based on the Safety Analysis Set. Subjects with measurable disease (target lesions at baseline with or without nontarget lesions at baseline) and evaluable disease (only nontarget disease at baseline) will be summarized separately for their best overall response. The response will be classified according to RECIST 1.1 and RANO defined categories for subjects.

- BOR will be analyzed separately for subjects with measurable disease and for subjects with only evaluable disease.
  - To be assigned a best overall response of SD (measurable disease), Non-CR/Non-PD or IR/SD (evaluable disease), the time from the first administration of study drug until the date of documented SD, Non-CR/Non-PD, or IR/SD should be ≥7 weeks. IR/SD is Incomplete Response/Stable Disease from RANO.
- ORR at the time of cut off: defined as the proportion of subjects with measurable disease at screening/baseline achieving a best overall response of confirmed PR or CR at the time of data cutoff. ORR will be estimated by dose level, and by exact Clopper-Pearson 95% CI if appropriate.

- DCR: For subjects with measurable disease, defined as the proportion of subjects who achieved a best overall response of CR, PR, or SD (minimum duration of SD ≥7 weeks). For subjects with evaluable disease, defined as the proportion of subjects:
  - those assessed by RECIST 1.1 who have a BOR of CR, or Non-CR/Non-PD ≥7 weeks
  - those assessed by RANO who have a BOR of CR, or IR/SD ≥7 weeks.

  The count and percentage will be summarized by dose level, and by exact Clopper-Pearson 95% CI if appropriate.

- Clinical Benefit Rate (CBR): For subjects with measurable disease, defined as the proportion of subjects with measurable disease who have a BOR of CR or PR, or durable SD lasting ≥23 weeks. For subjects with evaluable disease, defined as the proportion of subjects:
  - those assessed by RECIST 1.1 who have a BOR of CR, or Non-CR/Non-PD lasting ≥23 weeks,
  - those assessed by RANO who have a BOR of CR, or IR/SD lasting ≥23 weeks.

  The count and percentage will be summarized by dose level, and by exact Clopper-Pearson 95% CI if appropriate.

- DOR: defined as the time from the date of first documented confirmed CR or PR to disease progression objectively documented or death (whichever comes first). The DOR will be analyzed using the Kaplan-Meier (KM) (Kaplan and Meier, 1958) method among the responders (CR or PR). The DOR will be analyzed using the KM approach among the responders (CR or PR) according to the rules in Table 3.

5.4.2.2 Phase 2

Subjects must have measurable disease at baseline for enrollment in Phase 2. The secondary efficacy endpoints ORR at the time of data cutoff, DCR, CBR and DOR will be performed for subjects in the Evaluable Analysis Set.

- ORR at the time of data cutoff: defined as the proportion of subjects achieving a best overall response of confirmed PR or CR at the time of data cutoff. ORR and corresponding exact 95% CI using the Clopper-Pearson method will estimated for all Phase 2 treatment disease cohorts.
- DCR: defined as the proportion of subjects who have a BOR of CR or PR or stable disease (SD). To be assigned a best overall response of SD, the time from the first dose of study treatment until the date of documented SD should be ≥7 weeks. The count and percentage with exact Clopper-Pearson 95% CI for the DCR will be summarized for all Phase 2 treatment disease cohorts.
- CBR: defined as the proportion of subjects with who have a BOR of CR or PR or durable SD lasting ≥23 weeks. The count and percentage with exact Clopper–Pearson 95% CI for the CBR will be summarized for each Phase 2 treatment disease cohort.

- DOR: defined as the time from the date of first documented confirmed CR or PR to disease progression objectively documented or death (whichever comes first). The DOR will be analyzed using the Kaplan-Meier (KM) (Kaplan and Meier, 1958) method among the responders (CR or PR) according to the rules in Table 3.

- **Table 3 DOR and Censoring Rules**

No.	Situation	Date of Progression or Censoring	Outcome
1	Progression documented between scheduled visits, on or prior to new anticancer therapy	Date of first radiologic PD assessment	PFS Event
2	No progression at the time of data cutoff	Date of last adequate radiologic assessment on or prior to data cutoff	Censored
3	New anticancer therapy started before the first PD or death	Date of last adequate radiologic assessment on or prior to the start of new anticancer therapy	Censored
4	Death before first PD assessment, on or prior to start of new anticancer therapy	Date of death	PFS Event
5	Death between adequate assessment*	Date of death	PFS Event
6	Death or progression after more than one missed visit/tumor assessment**	Date of last adequate radiologic assessment before missed tumor assessments	Censored

Note:

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

** More than 1 missed visit/adequate tumor assessment of subjects is defined as having the duration between the last adequate tumor assessment and PD or death being longer than 125 days in Treatment Phase of Phase 2 and longer than 181 days in Extension Phase for both Phase I and II.

If a subject had PFS event (#1, #4 or #5), the earliest event date will be used.

The priority of the censoring rules is described as follows:

- If a subject missed two or more tumor assessments before PD or death (#6), the subject will be censored at the date of the last adequate tumor assessment before the missed tumor assessments.

  Note that if a subject is censored by both this criterion and start of new anticancer therapy criterion, the earliest censoring date will be used.

- If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (#2, #3, #6).

5.4.3 Exploratory Efficacy Analyses

5.4.3.1 Biomarkers, Archival Tumor Tissue, Lenvatinib Exposure and AEs of Special Interest

- 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).

A separate analysis plan will be developed for these analyses.

5.4.3.2 Other Exploratory Efficacy Analyses

- Graphical displays will be prepared for the maximum tumor shrinkage in target lesions, defined as the maximum percentage change from Baseline in the sum of the diameters of the target lesions at data cutoff.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analysis

Lenvatinib and everolimus concentration versus time data will be tabulated and summarized and graphically presented (Box and Whisker plots).

Plasma concentrations of lenvatinib from the intense sampling in Phase 1 will be used to determine the following PK parameters for Cycle 1, Day 1 and Cycle 1, Day 15: area under the plasma concentration time course profile (AUC_{0-t}), maximum observed concentration (C_{max}), time from drug administration to the maximum observed concentration (T_{max}). Other PK parameters (AUC_{0-inf}, half-life [$t_{1/2}$], clearance [CL/F], and volume of distribution [V_Z/F]) may be determined as data permit. The following graphical displays will be prepared:

- Trellis plots of plasma concentrations at Cycle 1, Day 1 and Cycle 1, Day 15
- Mean and SD of lenvatinib plasma concentration by planned dose level group over time
  (Cycle 1, Day 1 and Cycle 1, Day 15)
- Box and Whisker plots of PK parameters by planned dose level group at Cycle 1, Day 1 and Cycle 1, Day 15

For both lenvatinib and everolimus, data from Phase 1 and 2 of the study will be pooled with available data from other studies and subjected to population PK analysis. For each drug, the PK model will be parameterized in terms of clearance and volume of distribution. Details of the population PK analysis will not be included in the study SAP and will be provided in a separate analysis plan.

5.5.1.1 Pharmacodynamic, Pharmacokinetic, Pharmacogenomic, and Other Biomarker Analyses

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

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

5.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data will be presented by planned dose level in Phase 1 and study cohort in Phase 2 and summarized on an "as treated" basis using descriptive statistics (e.g., n, mean, SD, median, Q1, Q3, minimum, and maximum values for continuous variables; n (%) for categorical variables). Safety variables include study drug exposure, treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, 12-lead ECGs, cardiac function by echocardiography/MUGA scan, urine dipstick, and Lansky play scores or Karnofsky performance scores. Study Day 1 for all safety analyses is defined as the date of the first dose of study drug.

5.6.1 Extent of Exposure

5.6.1.1 Extent of Exposure of Study Drug

Parameters that represent the extent of exposure will be presented per dose level in Phase 1 and per study cohort in Phase 2, summarized separately for lenvatinib and everolimus. These include:

- No. of Cycles Received
- Cumulative No. of Cycles Received
- Duration of Treatment
- No. of Subject Weeks

Number of cycles received will be summarized by descriptive statistics and by categories. Duration of treatment (presented separately as days, weeks, and months) for oral drug Lenvatinib and everolimus will be summarized by descriptive statistics. Overall Duration of Treatment and No. of Subject Weeks will also be tabulated by dose level in Phase 1 and study cohort in Phase 2.

5.6.1.2 Study Drug Administration

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

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

The percentage of received dose relative to planned dose will be summarized separately for lenvatinib and everolimus by descriptive statistics. It is calculated as: dose intensity / planned dose level × 100. Interpretation: 100 means received dose was the same as the planned, 90 means that the actual dose was 90% of the planned.

5.6.1.3 Study Drug Dose Modifications

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

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

The first dose reduction is defined as the first time the subject's daily dose level was reduced to a nonzero value from its maximum designated prescribed BSA-adjusted dose level and did not go back to the maximum designated BSA-adjusted dose level due to a reason other than BSA adjustment or drug administration error. For example, lenvatinib 11 mg/m^2 followed by 0 mg/m^2 followed by 8 mg/m^2. If there is only dose interruption with no reduction in dose, such an event will not be considered as a dose reduction. The second and subsequent dose reductions will be defined accordingly. In addition, time to first dose reduction among subjects with dose reduction will also be summarized.

Dose interruptions defined as below:
1. Only includes the scenario that before and after dose 0 mg/m^2 (interruption period), the

dose levels are the same. For example: 11 mg/m^2 followed by 0 mg/m^2 and followed by 11 mg/m^2; 8 mg/m^2 followed by 0 mg/m^2 followed by 8 mg/m^2.

2. If dose level reduces from previous dose level after dose interruption period (dose 0 mg/m^2), it should count as dose reduction and not dose interruption. For example: 11 mg/m^2 followed by 0 mg/m^2 followed by 8 mg/m^2, the period with 0 mg/m^2 should not count as dose interruption instead it should count as dose reduction.

3. If after dose level 0 mg/m^2, the subject discontinued from treatment permanently, it should count as treatment discontinuation instead of dose interruption.

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

5.6.1.4 Dose Limiting Toxicity

DLTs will be recorded during Cycle 1 (Day 1 to Day 28) for subjects in Phase 1. The BSA, DLT (Yes/No/Not Evaluable) and reason(s) for each subject will be listed, as well as the date, and dosage of drug when the DLT occurred.

5.6.2 Adverse Events

The adverse event (AE) verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA version 21.1 or higher. Adverse events will be coded to the MedDRA lower level term (LLT) closet to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date on or after the first dose of study drug up to 28 days following the last dose of study drug, or a worsening in severity from Baseline (pretreatment). In addition, if an AE reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, it is also counted as TEAE. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be used to assess the severity of AEs.

Only those AEs that are treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings. TEAEs will be summarized by dose level in Phase 1 and by cohort in Phase 2.

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

to be related to study treatment or missing causality.

In summary, the following TEAE tables will be provided if appropriate:

- Overview of TEAEs
- TEAEs by SOC and PT
- TEAEs in decreasing frequency of PT
- TEAEs by SOC, PT, and CTCAE grade
- TEAEs with CTCAE Grades ≥3 by decreasing frequency of PT
- Overview of treatment-related TEAEs
- Treatment-related TEAEs by SOC and PT
- Treatment-related TEAEs by SOC, PT, and Worst CTCAE grade
- Treatment-related TEAEs by decreasing frequency of PT with CTCAE Grades ≥3

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

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

In summary, the following tables will be provided if appropriate:

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

- TEAEs leading to study drug dose reduction by SOC and PT

Clinically significant treatment-emergent AEs (CSAEs) for lenvatinib include: arterial TE (thromboembolic) events, bone and teeth abnormalities, cardiac dysfunction, hypothyroidism, GI (gastrointestinal) perforation, fistula formation, hemorrhage, hypertension, hypocalcemia, hepatotoxicity, palmar plantar erythrodysesthesia syndrome (PPE), proteinuria, QT prolongation, renal events, posterior reversible encephalopathy syndrome (PRES), and pneumothorax.

Adverse events of special interest (AEOSI) for everolimus include: Angioedema , Dyslipidemia, Pneumonitis, and Stomatitis.

The number and percentage of each category of treatment-emergent CSAEs for lenvatinib and AEOSI for everolimus will be summarized by overall, CTCAE grade and by dose level for Phase 1 and by cohort for Phase 2. Time to first onset of CSAEs for lenvatinib and AEOSI for everolimus will also be summarized.

The following tables will be provided only for CSAEs for lenvatinib and AEOSI for everolimus .

- Summary of CSAEs for lenvatinib and AEOSI for everolimus by category and PT
- Summary of serious CSAEs for lenvatinib and AEOSI for everolimus by category and PT
- Overview of CSAEs for lenvatinib and AEOSI for everolimus by category
- Incidence and Time to First Onset of CSAEs for lenvatinib and AEOSI for everolimus

The following tables will be provided only for subjects in Phase 1.

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

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

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

The following subject listings will be provided only for subjects in Phase 1.

- DLTs in Cycle 1
- TEAEs in Cycle 1

5.6.3 Laboratory Values

Laboratory values that are nonmissing and reported as "below the detectable limit" of an assay will be replaced by half the detectable limit in the summary tables. Laboratory results will be summarized using Système International (SI) units. Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Abnormal laboratory values will be identified as those outside the normal range. The abnormal values will be indicated in data listings. The CTCAE grade will also be included in the listing.

Laboratory tests during treatment are defined as laboratory tests conducted from the start of treatment to no more than 28 days after the last dose of study drug. Only laboratory parameters specified in the protocol will be summarized. Other laboratory parameters collected for some individual subjects will be presented in listings only. Baseline is defined as the last nonmissing result prior to the first administration of study drug.

For quantitative parameters, the actual value and the change from Baseline to each postbaseline visit will be summarized by visit and dose level (Phase 1)/study cohort (Phase 2) using descriptive statistics. Qualitative parameters will be summarized using frequencies (number and percentage of subjects), and changes from baseline to the worst postbaseline will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

5.6.3.1 Hematology and Clinical Chemistry

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

- Descriptive summary statistics for all major hematology and clinical parameters and their changes from Baseline will be calculated (n, mean, SD, median, Q1, Q3, min, max)
- Shifts from Baseline to worst postbaseline CTCAE grade (presented by each dose level in Phase 1 and overall, and each study cohort in Phase 2) for all clinical chemistry parameters and hematology parameters.

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

5.6.3.2 Thyroid-Stimulating Hormone

Thyroid-stimulating hormone values will be summarized separately at both Baseline and for worst postbaseline value in 2 categories (≤ULN and >ULN).

5.6.3.3 Urinalysis

The shift of Baseline to worst postbaseline proteinuria will be summarized. All urinalysis parameters (RBCs/high-power-field [HPF], blood, glucose, and protein [dipstick], 24-hour urine protein) will be provided by subject listing at each visit.

5.6.3.4 Vital Signs

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

Vital sign values will be evaluated on an individual basis by subject. Descriptive statistics for vital sign parameters (systolic [SBP] and diastolic [DBP] blood pressure (subjects <18 years old presented as percentile, other subjects ≥18 years old presented in mmHg), heart rate, respiratory rate, body temperature, height, weight and BSA), as well as changes from Baseline, will be presented for each cycle and day.

Percentiles for height measurements will also be summarized using a shift table of lowest postbaseline from Baseline measurement by categories (5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95th).

Percentiles for BP values (only for subjects <18 years old [see Protocol Appendix 7 and 8]) will also be summarized using a shift table of worst postbaseline from Baseline measurement by categories (<90th percentile, 90th to 95th percentile, 95th to <99th percentile, SBP or DBP ≥99th percentile). The overall percentile is taken as the worse of SBP/DBP percentiles.

5.6.3.5 Electrocardiograms

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

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

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

5.6.4 Other Safety Analyses

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

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

In addition, Radiographic findings of proximal tibial growth plates and dental examination will also be summarized.

5.7 Other Analyses

5.8 Exploratory Analyses

See Section 5.4.3 for Exploratory Efficacy Analyses.

6 INTERIM ANALYSES

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

7 CHANGES IN THE PLANNED ANALYSES

There is no change from the planned analyses defined in protocol.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Visit Windows

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

In Phase 1, tumor assessments for efficacy analysis are to be performed at Week 4 during Treatment Phase, and at Week 12, Week 24 and every 12 weeks thereafter or as clinically indicated in the Extension Phase. In Phase 2, tumor assessments for efficacy analysis are to be performed at Week 8 and Week 16 during Treatment Phase, and at Week 24 and every 12 weeks thereafter or as clinically indicated in the Extension Phase. All responses are to be confirmed at a follow-up examination after ≥28 days following the initial indication of response. Efforts should be made to conduct tumor assessments on the day scheduled (±7 days).

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

8.2 Safety and Efficacy Data Handling

8.2.1 Partial dates

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

8.2.1.1 Diagnosis date

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

8.2.1.2 Date of Death

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day

- If both the day and the month are missing, "Jan 1" will be used to replace the missing information

- If the entire date is missing, the date of death will be imputed as the last known date the subject was known to be alive + 1 day

8.2.1.3 Date of Progression

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day

- If the day and month are missing or a date is completely missing, it will be considered as missing and no date will be imputed

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

8.2.1.4 Date of Last Tumor Assessment

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day

- If the day and month are missing or a date is completely missing, it will be considered as missing and no date will be imputed

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

8.2.1.5 Date of Start of Subsequent Anticancer Therapy

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

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

8.2.1.6 Date of Previous Radiotherapy

- If only the start day of the month is missing, the 1st of the month will be used to replace the missing day

- If both the start day and month are missing, "Jan 1" will be used to replace the missing information
- If only the stop day of the month is missing, the latest possible day of the month will be used to replace the missing day
- If both the stop day and month are missing, "Dec 31" will be used to replace the missing information

In case the date of treatment start day is present (complete date), the imputed radiotherapy stop date will be compared with the date of treatment start day. The earlier date of imputed radiotherapy stop date and date of treatment start day will be considered as the stop date of radiotherapy.

8.3 Definitions, Derived Variables, and Data Sets

8.3.1 Baseline

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

8.3.2 Date/Time Definitions

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

1 month = 30.4375 days

- Time from first diagnosis to first dose (months) is:

  (Date of first dose – Date of first diagnosis) / 30.4375
- Time from first metastatic diagnosis to first dose (months) is:

  (Date of first dose – Date of first metastatic diagnosis) / 30.4375
- Time from last medication to first dose (months) is:

  (Date of first dose – End date of last medication) / 30.4375
- Time from last anthracycline therapy to first dose (months) is:

  (Date of first dose – Start date of the last anthracycline therapy) /30.4375
- Time from last radiotherapy to first dose (months) is:

  (Date of first dose – End date of the last radiotherapy) / 30.4375

8.3.3 Creatinine Clearance

The pediatric Schwartz equation for creatinine clearance is:

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

8.3.4 Last Known Alive Date

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

8.4 Pharmacokinetics/Pharmacodynamics Data Handling

8.4.1 Lower Limit of Quantification of Lenvatinib Plasma Concentration

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

The LLOQ of everolimus whole blood concentration is 0.300 ng/mL.

8.4.2 BLQ Handling for Developing Concentration-Time Profiles

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

9 PROGRAMMING SPECIFICATIONS

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

10 STATISTICAL SOFTWARE

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

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

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13 APPENDICES

13.1 Summary of Efficacy Analyses of Phase 1

Efficacy Variable	Analysis Set	Statistical Method	Tumor Assessments
ORR at data cutoff	Safety Analysis Set	Number (percentage) of subjects (with PR + CR) at data cutoff and its exact 95% CI using method of Clopper and Pearson.	Investigator
DOR	Safety Analysis Set	Median, Q1, and Q3 DOR will be presented (KM method), with 2-sided 95% CIs (Brookmeyer and Crowley, 1982).	Investigator
DCR	Safety Analysis Set	Number (percentage) of subjects (measurable disease with CR + PR + stable disease [SD]≥7 weeks, evaluable disease with CR + Non-CR/Non-PD for RECIST1.1 or IR/SD ≥7 weeks for RANO) and its exact 95% CI using method of Clopper and Pearson.	Investigator
CBR	Safety Analysis Set	Number (percentage) of subjects (measurable disease with CR+ PR + SD≥23weeks, evaluable disease with CR + Non-CR/Non-PD for RECIST1.1 or IR/SD ≥23 weeks for RANO) and its exact 95% CI using method of Clopper and Pearson.	Investigator

13.2 Summary of Efficacy Analyses of Phase 2

Efficacy Variable	Analysis Set	Statistical Method	Tumor Assessments
ORR at Week 16	Evaluable Analysis Set	Number (percentage) of subjects (with PR + CR) at Week 16 and its exact 95% CI using method of Clopper and Pearson.	Investigator
ORR at data cutoff	Evaluable Analysis Set	Number (percentage) of subjects (with PR + CR) at data cutoff and its exact 95% CI using method of Clopper and Pearson.	Investigator
DOR	Evaluable Analysis Set	Median, Q1, and Q3 DOR will be presented (KM method), with 2-sided 95% CIs (Brookmeyer and Crowley, 1982).	Investigator
DCR	Evaluable Analysis Set	Number (percentage) of subjects (measurable disease with CR + PR + stable disease [SD]≥7 weeks) and its exact 95% CI using method of Clopper and Pearson.	Investigator
CBR	Evaluable Analysis Set	Number (percentage) of subjects (measurable disease with CR+ PR + SD≥23weeks) and its exact 95% CI using method of Clopper and Pearson.	Investigator

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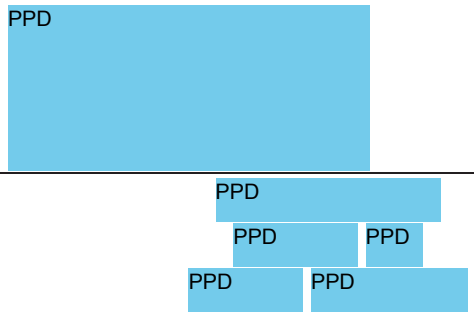

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Date

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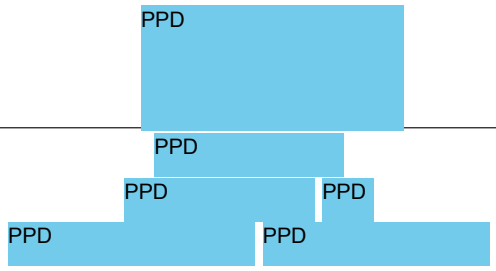

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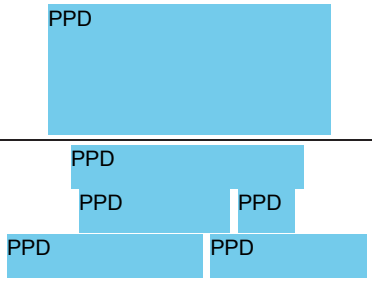

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