Official Protocol Title:	An Open-Label, Multicenter Phase 2 Basket Study to Evaluate the Antitumor Activity and Safety of Lenvatinib in Children, Adolescents, and Young Adults with Relapsed or Refractory Solid Malignancies
NCT number:	NCT04447755
Document Date:	08 JUN 2022

Title Page

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Protocol Title: An Open-Label, Multicenter Phase 2 Basket Study to Evaluate the Antitumor Activity and Safety of Lenvatinib in Children, Adolescents, and Young Adults with Relapsed or Refractory Solid Malignancies

Protocol Number: 013-04 (E7080-G000-231)

Compound Number: MK-7902 (E7080/lenvatinib)

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

This study is co-funded by MSD and Eisai.

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	147052
EudraCT	2019-004441-33
NCT	NCT04447755

Approval Date: 08 June 2022

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 4	08-JUN-2022	Further enrollment of participants into the other solid tumors' cohort was discontinued due to insufficient antitumor activity of lenvatinib in this patient population, with FDA and EMA agreement obtained.
Amendment 3	11-AUG-2021	Global amendment to modify the futility rules for the three target tumor cohorts based on results from the futility analyses completed for the corresponding cohorts in Study E7080-A001-216 (Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including Central Nervous System Tumors). Changed the definition of evaluable participants for consistency with Study E7080-A001-216 and to accommodate a health authority request.
Amendment 2	14-OCT-2020	The study protocol has been revised to require (1) A minimum of 6 participants less than 17 years of age for each of the HGG, RMS, and EWS/pPNET target tumor cohorts, (2) Reduced PK sampling in children weighing <13 kg (3) Reduced PD sampling for children <16 kg (4) Medications known to prolong the QT interval are to be initiated cautiously; and (5) Added a requirement to normalize electrolytes prior to starting treatment per the lenvatinib SmPC and to also specify on study that electrolytes should be replenished as appropriate. Dose modification guidelines for QT interval prolongation to align with lenvatinib development program was also added.
Amendment 1/Czech Republic-specific amendment	18-AUG-2020	To address feedback from Czech Republic regulatory authorities.
Original Protocol	26-FEB-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

Further enrollment of participants into the other solid tumors' cohort was discontinued due to insufficient antitumor activity with lenvatinib for this patient population, with FDA and EMA agreement obtained.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.4 Beginning and End of Study Definition 9.7.2 Efficacy Interim Analysis	Added text indicating that enrollment into the other solid tumors cohort was discontinued	Insufficient antitumor activity of lenvatinib in participants in the other solid tumors' cohort; FDA and EMA agreement obtained.
10.7.3 Italy	Included details regarding maximum blood volumes and a reference to "Ethical Considerations for Clinical Trials on Medicinal Products Conducted With Minors" [European Commission 2017]	To address the Italian Health Authority's recommendation to stipulate maximum blood volumes to be taken from participants in Italy
1.3 Schedule of Activities 8 Study Assessments and Procedures 8.3 Safety Assessments	Added references to Appendix 7 (Country-specific Requirements) where needed	

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 8.3.6.1 Hematology and Clinical Chemistry	Updated text to clarify that hematology, blood chemistry, and urinalysis samples are to be obtained and assessed, and the results are to be reviewed, prior to study drug administration on C1D1 and within 72 hours prior to the visit for all subsequent cycles	To clarify timing of study assessments
1.1 Synopsis	Added a statement acknowledging that the EWS and HGG cohorts were not expanded.	For completeness; futility was concluded in the corresponding cohorts in Study E7080-A001-216.
5 Study Population	Added text regarding the collection and use of demographic data	To clarify the collection, use, and confidentiality of demographic data provided by the participants.
Title Page Section 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp and Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
8.4.7 Events of Clinical Interest	Added text to indicate that lenvatinib overdose is not considered an ECI	To clarify the reporting of lenvatinib overdose
10.3.2 Definition of AE	Formerly Section 10.3.1 Revised text to clarify that lenvatinib overdose without an associated AE is not reportable as an AE Added a reference to Section 8.5 (Treatment of Overdose)	

Section # and Name	Description of Change	Brief Rationale
8.4.5 Pregnancy and Exposure During Breastfeeding	Added text to ensure that any pregnancy complications, as well as the medical reason for elective termination of a pregnancy, are reported as AEs or SAEs Added 'ectopic pregnancy' to the list of pregnancy outcomes to be reported as serious events (Important Medical Events)	To ensure that all pregnancy complications, outcomes, and medical reasons for elective termination of a pregnancy are properly reported
1.1 Synopsis 4.4 Beginning and End of Study Definition	Replaced withdraws 'from the study' with withdraws 'consent'	To clarify the intent regarding the end of the study
8 Study Assessments and Procedures	Added text "or dental" "All study-related medical or dental decisions must be made by an investigator who is a qualified physician."	To correct a previous omission
1.1 Synopsis 6.1 Study Intervention(s) Administered	In the 'Use' column, replaced 'Experimental' with 'Test Product'	To align with EU CTR
4.4 Beginning and End of Study Definition	Added definition of end of study for analysis and reporting purposes Added definition of local start of the study for countries in the EEA	

Section # and Name	Description of Change	Brief Rationale
6.1 Study Intervention(s) Administered	Replaced 'IMP/NIMP' column header with 'IMP or NIMP/AxMP' Updated the abbreviations and added text to describe the use of IMP and NIMP/AxMP classifications	To align with EU CTR
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events	Added text stating that investigators need to document if an SAE was associated with a medication error, misuse, or abuse	
10.3.1 Definitions of Medication Error, Misuse, and Abuse	New section added	
8.2.1.2 Tumor Imaging During the Study	Added "pregnancy" to the list of reasons to discontinue imaging	For consistency with the reasons to discontinue imaging in Section 8.2.1.3
8.11.4 Discontinued Participants Continuing to be Monitored in the Study	Revised section title to "Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study"	To clarify the information that is included within this section
Title Page	Added NCT number	To include the ClinicalTrials.gov Identifier

Section # and Name	Description of Change	Brief Rationale
6.6.7 Management of Hepatotoxicity	Deleted redundant sentence "If hepatic failure occurs, the study drug must be discontinued."	To remove redundancy
8.10 Health Economics Medical Resource Utilization and Health Economics	Revised section title to "Medical Resource Utilization and Health Economics"	
Throughout document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-Label, Multicenter Phase 2 Basket Study to Evaluate the Antitumor Activity and Safety of Lenvatinib in Children, Adolescents, and Young Adults with Relapsed or Refractory Solid Malignancies

Short Title: Lenvatinib for Pediatric Patients with Relapsed/Refractory Solid Tumors

Acronym: Protocol 013 (E7080-G000-231)

Hypotheses, Objectives, and Endpoints:

In children, adolescents, and young adults with relapsed or refractory solid malignancies treated with lenvatinib:

Primary Objectives	Primary Endpoints
- To determine the ORR at Week 16, by each tumor type, per RECIST 1.1 or RANO (for HGG only) as assessed by the investigator.	- Objective Response, defined as a confirmed (≥4 weeks after initial response) CR or PR.
Secondary Objectives	Secondary Endpoints
- To evaluate ORR, by each tumor type, per RECIST 1.1 or RANO (for HGG only) as assessed by the investigator.	- Objective Response, defined as a confirmed (≥4 weeks after initial response) CR or PR.
- To evaluate PFS per RECIST 1.1 or RANO (for HGG only), by each tumor type.	- PFS defined as the time from the date of the first administration of lenvatinib until the date of first documentation of PD or death (whichever occurs first).
- To evaluate the BOR, DOR, DCR, and CBR, by each tumor type.	- BOR defined as the participant's best confirmed response (CR or PR) over the treatment period. - DOR defined as the time from the date of the first documented CR or PR to the date first documentation of progressive disease or death (whichever occurs first). - Disease control defined as a BOR of CR or PR, or SD. To be assigned a BOR of SD, the time from the first administration of study drug until the date of documented SD should be ≥7 weeks. - Clinical benefit defined as a BOR of CR or PR, or durable SD (SD duration ≥23 weeks since the first dose of the study treatment).

- To evaluate the safety of lenvatinib.	- AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECGs, urine dipstick, Lansky play scores or Karnofsky performance status scores, physical examination findings, dental examination findings, height, and closure of proximal tibial plates.
- To assess the palatability and acceptability of the suspension formulation of lenvatinib.	- Palatability questionnaire using a facial hedonic scale.
- To characterize the PK of lenvatinib.	- Assessment of population-based PK parameters of lenvatinib.

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Treatment of relapsed/refractory pediatric solid tumors including: HGG, RMS, or EWS/pPNET and other solid tumors, excluding osteosarcoma.
Population	Children, adolescents, and young adults with relapsed/refractory HGG, RMS, or EWS/pPNET, or other solid tumors, excluding osteosarcoma. Participants with HGG, RMS and EWS/pPNET may only be enrolled in the tumor-specific cohorts and may not be enrolled in the other solid tumors' cohort. Participants with CNS tumors other than HGG are eligible for enrollment into the other solid tumors' cohort.
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	None
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 42 months from the time the first participant (or their legally acceptable representative) provides documented informed consent/assent until the last participant's last study-related contact.

Number of Participants:

A minimum of 36 participants will be enrolled, 9 evaluable participants in each of 4 cohorts: HGG, RMS, EWS/pPNET, and other solid tumors. The final sample size of participants will depend on the number of tumor types that meet the futility bar and the antitumor activity in evaluable participants observed in the corresponding tumor cohort in Study E7080-A001-216. The enrollment in the HGG, RMS, and EWS/pPNET cohorts is capped at a maximum of 17 evaluable participants each. The enrollment for each tumor type expanded based on response in the other solid tumors' cohort is also capped at a maximum of 17 evaluable participants. Based on these factors and the projected enrollment period, it is estimated that up to approximately 150 participants could be enrolled. Participants 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.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin.</th><th>Regimen/ Treatment Period</th><th>Use</th></tr>
<tr><td></td><td>Lenvatinib</td><td>14 mg/m^2 (maximum daily dose of 24 mg)</td><td>Once Daily</td><td>Orally</td><td>Daily</td><td>Test Product</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>1 arm</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study from the time the participant provides documented informed consent/assent through the final contact.

After a Screening phase of up to 28 days, each participant will be assigned to receive study intervention with lenvatinib. Participants will continue to receive lenvatinib until disease progression is verified by the investigator using RECIST 1.1 or RANO (for participants with HGG) criteria, initiation of another anticancer therapy, development of unacceptable toxicity, or withdrawal of consent, whichever occurs first. Estimated time of lenvatinib treatment is 1 year. However, participants can continue on treatment with lenvatinib until a treatment discontinuation criterion is met.

At the end of treatment, each participant will be followed for 30 days for the occurrence of AEs/SAEs and for spontaneously reported pregnancy as described in Section 8.4.</td></tr>
</table>

	Participants who discontinue lenvatinib treatment for reasons other than radiographic disease progression or initiation of new anticancer therapy will have post-treatment follow-up imaging for disease status every 8 weeks for up to 24 weeks, then every 12 weeks thereafter until documentation of disease progression or start of a new anticancer agent, whichever occurs first, unless the participant withdraws consent, becomes lost to follow-up, or the study is terminated. Participants who discontinue lenvatinib treatment due to documented radiographic disease progression or initiation of new anticancer therapy will move to survival follow-up. Participants will be followed by telephone every 12 weeks for survival status until death unless the participant withdraws consent, becomes lost to follow-up, or the study is terminated. A database lock for the primary analysis will occur when all participants in all cohorts have discontinued the study or if the last evaluable participant has completed the Week 16 imaging assessment, whichever comes first. Enrollment will be stopped for a specific cohort/tumor type if no objective responses occur in the first 9 evaluable participants (i.e., the futility boundary is crossed), or a lack of antitumor activity is concluded for the corresponding tumor cohort in Study E7080-A001-216. EWS and HGG cohorts were not expanded because futility was concluded for the corresponding cohorts in Study E7080-A001-216. Further enrollment of participants into the other solid tumors' cohort was discontinued due to insufficient antitumor activity of lenvatinib in this patient population. The overall study ends when the last evaluable participant completes the last study-related telephone call or visit, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator). Additional details are in Section 4.1.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

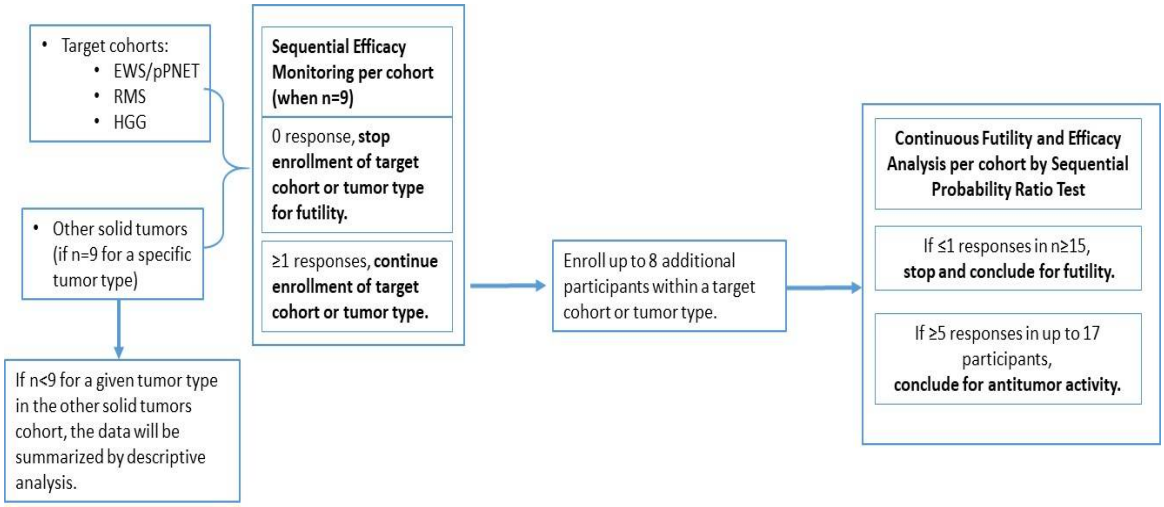
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 15.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



1. The enrollment period may last up to approximately 30 months from the time of enrollment of the first participant. Additionally, data cutoff may occur when the last evaluable participant (see Section 1.1 for definition of evaluable) enrolled in the study has completed the Week 16 imaging assessment or discontinues prior to Week 16 imaging assessment, whichever occurs first.
2. If no objective responses are observed at the time of enrollment of the ninth evaluable participant in a specific cohort or other tumor type, enrollment will be paused in said cohort or other tumor type until the IA for these 9 evaluable participants is completed. If at least 1 objective response is observed at the time of enrollment of the ninth evaluable participant in a specific cohort or other tumor type, enrollment may continue in said cohort or other tumor type.
3. In addition to the futility rules above, the enrollment of 3 target tumor cohorts will stop if a lack of antitumor activity is concluded for the corresponding tumor cohort in Study E7080-A001-216.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Study Period	**Screening**	**Intervention Cycle = 28 Days**									**Post-treatment Visits**			
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**	**EOT**	**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	**NOTES**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
Administrative Procedures														
Informed Consent/ Assent	X													Documented informed consent/assent may be obtained up to 4 weeks prior to C1D1 and must be obtained prior to performing any protocol-specified procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame for screening.
Inclusion/ Exclusion Criteria	X													See Appendix 7 for country-specific requirements.
Participant Identifi-cation Card	X													At the time of allocation, site personnel will add the allocation number to the identification card.
Demograph-ics	X													

Study Period	**Screening**	**Intervention Cycle = 28 Days**								**EOT**	**Post-treatment Visits**			**NOTES**
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**		**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
Medical/ surgical history	X													
Prior anticancer medication/ procedures	X													
Prior/ Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X		X	Concomitant medications will be recorded throughout the study and for 30 days after last dose. Off-study anticancer therapy will be recorded from study treatment discontinuation until time of death or until withdrawal from survival FU.
Cancer staging as appropriate for pediatric tumor type	X													

Study Period	**Screening**	**Intervention Cycle = 28 Days**									**Post-treatment Visits**			
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**	**EOT**	**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	**NOTES**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
Tanner Staging	X	X								X		X	X	Tanner Stage will be assessed for all participants aged ≥8 years (females) or ≥9 years (males) during screening or C1D1, at EOT, and during efficacy and survival FU. During efficacy and survival FU, perform annually until puberty has completed or through survival FU, whichever comes first. Assessment can be performed by a local healthcare provider and reported by telephone contact if clinic visits are not possible for post-treatment visits after the 30-day safety FU.
Allocation		X												

Study Period	**Screening**	**Intervention Cycle = 28 Days**								**EOT**	**Post-treatment Visits**			**NOTES**
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**		**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
Survival status			◄———	———	———	———	———	———	———	———►				Updated survival status may be requested at any time during the course of the study. Participants will be offered survival FU for at least 1 year. During survival FU, participants will be followed every 12 weeks until death, unless the participant becomes lost to FU, withdraws consent, or the study is terminated.
Study Intervention Administration														
Lenvatinib dispensing		◄———	———	———	———	———	———	———	———	———►				Lenvatinib dose based on BSA calculation at D1 of each cycle.
Lenvatinib administrat-ion (orally, once daily)		X	X	X	X	X	X	X	X					Lenvatinib may be taken at home except on C1D1, C1D15, and C2D1; on these days lenvatinib will be taken in the clinic. Participants will receive lenvatinib treatment until disease progression (by investigator assessment), intolerable toxicity, initiation of another anticancer therapy, or voluntary discontinuation by the participant at any time, whichever occurs first.

Study Period	**Screening**	**Intervention Cycle = 28 Days**									**Post-treatment Visits**			
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**	**EOT**	**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	**NOTES**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
Efficacy Procedures														
Palatability Question-naire		X												To be completed once on C1D1 by all participants who receive suspension formulation, with the exception of participants using a nasogastric or gastrostomy tube. If the questionnaire is not completed on C1D1, it should be completed at the earliest next site visit. If the participant is unable to complete the questionnaire, this must be done by their parents or legal guardian.
Tumor Imaging (CT/MRI) and Tumor Assessment by investigator via RECIST 1.1 or RANO (HGG only)	X	◄———							———►			X		Imaging is performed at Screening, every 8 W (±7 days) from the date of lenvatinib initiation until Week 24, then every 12 W thereafter (±7 days) or sooner if there is evidence of PD). Imaging for participants who discontinue lenvatinib without documented PD will be performed every 8 W (±7 days) until Week 24, then every 12 W thereafter (±7 days) or until the start of a new anticancer agent, whichever occurs first.

Study Period	**Screening**	**Intervention Cycle = 28 Days**									**Post-treatment Visits**			
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**	**EOT**	**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	**NOTES**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
Brain CT/MRI (If clinically indicated)	X	←	—	—	—	—	—	—	→			X		Participants with HGG and participants with protocol-eligible treated brain metastases require brain scans at all tumor assessment timepoints.
Safety Procedures														
AEs/SAEs	X	←	—	—	—	—	—	—	→		X			AEs will be recorded from the date of documented informed consent, throughout the study, and for 30 days after last dose. SAEs irrespective of relationship to study treatment must be reported as soon as possible, but not later than 24 hours.
Physical examination	X	X		X	X	X	X	X	X	X				A comprehensive physical and oral examination (including a neurological examination) at Screening and at C1D1 and at visits indicated in the SoA. Only perform at C1D1 if the screening physical examination was performed >7 days prior to C1D1. A symptom-directed physical and oral examination will be performed on C1D1 and at any time during the study, as clinically indicated.

Study Period	**Screening**	**Intervention Cycle = 28 Days**								**EOT**	**Post-treatment Visits**			**NOTES**
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**		**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
Dental Evaluation	X	Per local standard of care, but no less than annually. ◄——————————►								X				Dental examination by a dentist or qualified dental professional should be conducted per local institutional guidelines during screening (can occur up to 4 weeks after first dose). Dental examination after screening should occur per local standard of care, but no less than annually, and at EOT unless the most recent dental examination was done within the last 6 months, then the dental examination is not required. Postbaseline dental examinations are not required for participants for whom permanent teeth (excluding third molars) are evaluated to be fully erupted at screening.

Study Period	**Screening**	**Intervention Cycle = 28 Days**									**Post-treatment Visits**			
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**	**EOT**	**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	**NOTES**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
Telephone Contact or Visit			X											On C1D8, participants will have a telephone or clinic visit to assess for early toxicity and BP can be measured at home or at a local pharmacy for reporting at this visit. An unscheduled visit can occur prior to C1D15 if necessary for safety.

Study Period	**Screening**	**Intervention Cycle = 28 Days**								**EOT**	**Post-treatment Visits**			**NOTES**
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**		**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
Vital Signs (BP, HR, RR, body temp, height, and weight)	X	X		X	X	X	X	X	X	X	X	X*	X*	Vital signs may be performed more frequently as clinically indicated. BP that is consistently above the 95th percentile for sex, age, and height/length requires further evaluation. Refer to hypertension guidelines in Section 6.6.2. BP monitoring will occur once every 2 weeks during the first 2 cycles, or more frequently if clinically indicated. Height and weight measurement will be obtained at C1D1 and thereafter at D1 of every cycle, and at EOT. *Height will also be monitored every 3 months in efficacy and survival follow-up until puberty has completed. Telephone contact is acceptable for height assessment if clinic visits are not possible at post-treatment visits after the 30-day safety FU.

Study Period	**Screening**	**Intervention Cycle = 28 Days**									**Post-treatment Visits**			
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**	**EOT**	**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	**NOTES**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
12-Lead ECG	X	X			X				X[a]	X	X			Single 12-lead ECG. If possible, participants must be in the recumbent position for a period of 5 minutes prior to the ECG. ECG should be conducted at Screening, C1D1, C2D1, and [a]D1 of every 4th cycle (ie, C6, C10, C14, etc.), EOT, and Safety FU. ECG at C1D1 and C2D1 should be conducted approximately 2 hours after lenvatinib dose. For high-risk participants (as defined in Section 8.3.4), conduct ECG monitoring in every cycle.
Echocardio-gram or MUGA scan	X	Performed every 16 ± 2 Weeks after the first dose of study drug or sooner, if clinically indicated. ◄——►								X				
Lansky Play Score/ Karnofsky Performance Score	X	X			X		X	X	X	X	X			Scores obtained on C1D1 prior to allocation may also be used as the screening value to determine eligibility. Lansky Play Score will be used for participants up to and including 16 years of age. Karnofsky Performance Score will be used for participants >16 years of age.

Study Period	**Screening**	**Intervention Cycle = 28 Days**									**Post-treatment Visits**			
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**	**EOT**	**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	**NOTES**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
Proximal Tibial growth plates x-ray	X									X[a]				For participants 2 to 17 years (≥18 years not required). X-ray of only 1 leg is required. [a]X-ray at EOT is required only for participants with open growth plates at screening and must be performed on the same leg as screening x-ray.
Laboratory Assessments														
Pregnancy Test	X	X			X		X	X	X	X	X			In WOCBP, a serum or urine pregnancy test (Appendix 2) will be performed at screening and at C1D1 prior to allocation (within 24 hours prior to the first dose of study drug), prior to D1 of every subsequent cycle, at EOT, and at the Safety FU visit. Results must be reviewed prior to administration of study drug on C1D1 and within 24 hours prior to dispensing study drug for all subsequent cycles.
Clinical Chemistry/ Hematology	X	X		X	X	X	X	X	X	X	X			Hematology and clinical chemistry can be performed within 7 days prior to the first dose of lenvatinib (C1D1) as part of the screening visit and do not

Study Period	**Screening**	**Intervention Cycle = 28 Days**								**EOT**	**Post-treatment Visits**			**NOTES**
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**		**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
														need to be repeated at C1D1, unless clinically indicated. Samples are to be obtained and assessed and the results reviewed prior to study drug administration on C1D1 and within 72 hours prior to the visit for all subsequent cycles. If ≥Grade 3 hematologic or clinical chemistry toxicity, repeat laboratory test and AEs assessment at least every 3 days (until improvement to <Grade 3). Results obtained on C1D1 prior to allocation may also be used as screening values to determine eligibility if assessed prior to allocation. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting treatment.

Study Period	**Screening**	**Intervention Cycle = 28 Days**								**EOT**	**Post-treatment Visits**			**NOTES**
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**		**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
INR or PT	X													INR or PT should only be performed as part of the screening assessment and as clinically indicated.
Urine Dipstick (or urinalysis) Testing	X	X		X	X	X	X	X	X	X	X			Dipstick is the preferred method for urinalysis. Urine dipstick/urinalysis testing can be performed within 7 days prior to the first dose of lenvatinib (C1D1) as part of the screening visit and does not need to be repeated at C1D1 (unless clinically indicated) and within 72 hours prior to the visit at subsequent cycles. Urine dipstick/urinalysis testing will be performed during screening, at C1D1, C1D15, C2D1, C2D15, and D1 of every subsequent cycle, or more frequently as clinically indicated, at the EOT and at the Safety FU visit. For participants with proteinuria ≥2+ (≥100 mg/dL), urine dipstick/urinalysis testing should be performed on D15 (or more

Study Period	**Screening**	**Intervention Cycle = 28 Days**									**Post-treatment Visits**			
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**	**EOT**	**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	**NOTES**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
														frequently as clinically indicated) until the results have been 1+ or negative for 2 treatment cycles. If a new event of proteinuria ≥2+ (≥100 mg/dL) occurs, refer to Section 6.6.3 for further management guidelines. Urine glucose should be performed as part of the urine dipstick/urinalysis.
TSH, Free T4	X				X			X	X[a]	X	X			The screening blood sample for thyroid function testing can be obtained within 7 days prior to the first dose of lenvatinib (C1D1) as part of the screening visit and does not need to be repeated at C1D1 (unless clinically indicated) and within 72 hours prior to the visit at subsequent cycles. TSH and free T4 should be assessed for all participants. Assessment should be obtained at screening C2D1, [a]every 2 cycles thereafter, at EOT and at the Safety FU visit. If not done locally, can be done at a central laboratory.

Study Period	**Screening**	**Intervention Cycle = 28 Days**									**Post-treatment Visits**			
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**	**EOT**	**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	**NOTES**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
Pharmacokinetics/Pharmacodynamics/Biomarkers														
PK blood samples, participants ≥13 kg body weight		X		X	X									PK blood samples drawn: • C1D1: 0.5-4 hours and 6-10 hours postdose (no predose required) • C1D15: predose, 0.5-4 hours and 6-10 hours postdose • C2D1: predose and 2-12 hours postdose. Postdose samples are not needed if the lenvatinib administration is skipped. If dose interruption is necessary at these time points, contact the Sponsor. See Appendix 7 for country-specific requirement.

Study Period	**Screening**	**Intervention Cycle = 28 Days**									**Post-treatment Visits**			
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**	**EOT**	**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	**NOTES**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
PK blood samples, participants <13 kg body weight		X		X	X									PK blood samples drawn: • C1D1: 0.5-4 hours postdose (no predose required) • C1D15: 6-10 hours postdose (no predose required) • C2D1: predose and 2-12 hours postdose. Postdose samples are not needed if the lenvatinib administration is skipped. If dose interruption is necessary at these time points, contact the Sponsor. See Appendix 7 for country-specific requirement.
Buccal swab (DNA) for Genetic Analysis		X												Collection of buccal swabs to obtain genomic DNA will be performed at C1D1 prior to allocation. If sampling is not performed predose, sampling may occur at any subsequent visit.
Blood for serum biomarkers, participants ≥16 kg body weight		X		X	X		X		X	X				Collect predose: C1D1, C1D15, C2D1, C3D1, C5D1, and at EOT. See Appendix 7 for country-specific requirement.

Study Period	**Screening**	**Intervention Cycle = 28 Days**									**Post-treatment Visits**			
Visit Timing/ Cycle No.		**1**			**2**		**3**	**4**	**5 – last**	**EOT**	**Safety FU**	**Efficacy (Imaging) FU Visits**	**Sur-vival FU**	**NOTES**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**At DC**	**30 days after last dose**	**Q8W for 24 weeks, then Q12W**	**Q12 W**	
Scheduling Window	**-28 to -1**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		**±7**	**±7**	**±7**	
Blood for serum biomarkers, participants <16 kg body weight		X			X		X							Collect predose: C1D1, C2D1, and C3D1. See Appendix 7 for country-specific requirement.
Archival Tumor Blocks or Slides		←								→				Providing archival tumor tissue is not required for participation in the study and is an optional collection. If an archival tumor tissue is available from a biopsy performed as standard of care prior to study treatment, it can be submitted to the central laboratory anytime during the study.

AE adverse event; BP blood pressure; BSA body surface area; C Cycle; CT computerized tomography; D Day; DC discontinuation; ECG electrocardiogram; EOT end of treatment visit; h hour, HR heart rate; INR International normalized ratio; MRI magnetic resonance imaging; P/C ratio urine protein to creatinine ratio; PK pharmacokinetics; PS performance score; PT prothrombin time; RANO Response Assessment in Neuro Oncology. RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; RR respiratory rate; SAE serious adverse event; T4 thyroxine; TSH thyroid stimulating hormone; W weeks; WOCBP women of childbearing potential.
Note: All procedures and assessments are to be performed prior to administration of lenvatinib unless otherwise indicated. Refer to Section 8.

2 INTRODUCTION

2.1 Study Rationale

Currently, treatment of solid tumors in pediatric patients includes supportive care, surgery, radiation therapy, immunotherapy, targeted therapy, stem cell transplant, and/or chemotherapy. Treatment of relapsed/refractory/progressive disease depends on factors such as age, performance status, initial response to therapy, time since original diagnosis/prior relapse, and whether tumor recurrence is local or diffuse.

The disease burden caused by several relapsed/refractory pediatric solid tumors is significant and represents an area of unmet need. For the majority of pediatric solid tumors, there is no accepted treatment regimen for relapsed/refractory disease and efficacy outcomes have plateaued with traditional cytotoxic chemotherapy. Five-year survival rates for many pediatric solid tumors other than neuroblastoma have not changed since the 1990s [Smith, M. A., et al 2010].

Pediatric solid tumors typically originate in rapidly growing normal tissue. The use of anticancer therapy on the developing body and subsequent cancer risk is of concern. Studies have shown that the risk of subsequent cancer increases with age, female gender, treatment era, increased age at diagnosis, and radiotherapy [Friedman, D. L., et al 2010]. For patients with solid tumors, the highest risk is for survivors of EWS/pPNET, followed by CNS and solid organ cancers.

There is a clear, unmet need for improved and targeted therapies, particularly in the relapsed/refractory setting.

The antitumor activity of lenvatinib in vivo has been shown in several xenograft models of pediatric solid tumors, namely EWS/pPNET, RMS, and osteosarcoma (lenvatinib IB). In the pediatric clinical study E7080-G000-207 (Study 207), lenvatinib monotherapy demonstrated antitumor activity in patients with relapsed/refractory osteosarcoma (Section 2.2.1.2). The data suggest that lenvatinib may have activity in the treatment of pediatric solid tumors when administered alone in patients with relapsed/refractory malignancies where no available therapeutic options exist. It is therefore warranted to further assess the activity of lenvatinib in pediatric solid tumors, aside from osteosarcoma, that are relapsed/refractory to standard therapy. The primary efficacy goal of this Phase 2 basket study is to assess the antitumor activity of lenvatinib monotherapy in children, adolescents, and young adults (≤21 years with relapsed/refractory solid tumors (excluding osteosarcoma, which is being evaluated in Study 207).

2.2 Background

Lenvatinib (also known as E7080 or MK-7902) is a potent multiple RTK inhibitor that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other pro-angiogenic and oncogenic pathway-related RTKs, including FGFR 1-4, PDGFRα, KIT, and RET.

Studies have also demonstrated that lenvatinib's mechanism of action includes immunomodulation in the TME. This includes decreases in immunosuppressive TAMs, activated cytotoxic T-cell increases, and activation of IFN-γ signaling, which contribute to lenvatinib's antitumor activity [Kato, Y., et al 2019] [Kimura, T., et al 2018].

Refer to the IB/approved labeling for detailed background information on lenvatinib.

2.2.1 Pharmaceutical and Therapeutic Background

Angiogenesis, the formation of new blood vessels from a preexisting vascular network, is essential for tumor growth and metastasis. VEGF and its family of receptors (VEGFRs 1-3) play a major role in tumor angiogenesis [Ferrara, N., et al 2003] [Ellis, L. M. 2008] [Tammela, T. 2010]. Accumulated evidence suggests that FGF and its receptor tyrosine kinase, FGFR, also play important roles for tumor angiogenesis [Cross, M. J. 2001] [Lieu, C., et al 2011] [Limaverde-Sousa, G., et al 2014].

Lenvatinib is a potent multiple RTK inhibitor that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), FGFR1-4, PDGFRα, KIT, and RET. Among known kinase inhibitors in clinical use, lenvatinib is one of the only inhibitors currently labeled with a mechanism of action as an inhibitor of not only VEGFRs, but also FGFRs, both of which are currently believed to be very important for tumor angiogenesis. Pediatric tumors are highly vascularized. Serum VEGF was shown to be elevated in several pediatric solid tumors including pPNET and EWS [Pavlakovic, H., et al 2001] [El-Houseini, M. E., et al 2004]. High serum VEGF levels [El-Houseini, M. E., et al 2004] [DuBois, S. 2007] [Taylor, M., et al 2009] as well as soluble VEGFR2 plasma levels and circulating endothelial cells correlated with metastatic disease status in several pediatric tumor types [Taylor, M., et al 2009] and outcome in osteosarcoma [Taylor, J. G. 6th., et al 2009].

FGF2 is a critical signaling molecule for primitive neural crest cells. FGF2/FGFR1 activation induced growth inhibition, neuronal differentiation, and apoptosis in EWS/pPNET [Sturla, L. M., et al 2000] [Kim, M. S., et al 2004]. Basic fibroblast growth factor (bFGF)/FGFR1 strongly induced the motility and invasion of EWS/pPNET cells [Kamura, S., et al 2010]. Embryonal RMS patient biopsy specimens were found to overexpress FGFR3 [Hirotsu, M., et al 2009] and FGFR4 has been implicated in RMS [Cao, L., et al 2010] [Taylor, J. G. 6th., et al 2009].

High expression of PDGF and its receptors (PDGFRα) highlight the role of the PDGF pathway in several pediatric tumors (eg, osteosarcoma [Kubo, T., et al 2008], glioma [Mauro, A., et al 1991], diffuse pontine glioma [Zarghooni, M., et al 2010], nephroblastoma [Ghanem, M., et al 2010], and EWS/pPNET [Schaefer, K. L., et al 2008]). PDGFR expression is associated with clinical stage (nephroblastoma [Ghanem, M., et al 2010]) and metastases (EWS [Schaefer, K. L., et al 2008], medulloblastoma [MacDonald, T. J., et al 2001]), and correlates with event-free survival (eg, osteosarcoma [Kubo, T., et al 2008]).

Strong, diffuse staining for c-kit was seen in a proportion of synovial sarcomas, osteosarcomas, and EWS/pPNET, though to a lesser extent in neuroblastomas, Wilms'

tumors, and RMS, and was negative in alveolar soft part sarcomas and desmoplastic small round cell tumors [Smithey, B. E., et al 2002].

2.2.1.1 Epidemiology and Current Therapeutic Options

Cancer in children has a low overall incidence (18.6 cases per 100,000 children [National Cancer Institute 2018]), however, it is the leading cause of death in this population. Solid tumors constitute approximately 60% of childhood malignancies, with leukemia, lymphoma, and reticuloendothelial neoplasms accounting for the remaining 40% (SEER Cancer Statistics Review, 1975-2016, National Cancer Institute, posted April 2019).

Age affects the incidence of pediatric solid tumors. Across all age groups, CNS neoplasms constitute the majority; however, between 10 and 14 years of age, malignant bone tumors, soft tissue and other extraosseous sarcomas, other malignant epithelial, and neoplasms and melanomas are more common. Up to the age of 14 years, the most common solid tumor types are neuroblastoma and other peripheral nervous cell tumor and renal tumors, whereas between 15 and 19 years, germ cell and trophoblastic tumors neoplasms of the gonads, melanomas and other malignant epithelial neoplasms increase in frequency [Ries, L. A. G., et al 1999].

Some of the most common types of solid tumors found in children are brain tumors, RMS, and EWS/pPNET. Unfortunately, 5-year survival rates for pediatric solid tumors other than neuroblastoma have remained largely unchanged since the 1990s, and there is little evidence that more effective use of available cytotoxic agents will be sufficient for substantial progress[Smith, M. A., et al 2010].

2.2.1.1.1 High-grade Glioma

Brain and other CNS tumors are the most common form of solid tumors in children and account for the majority of cancer deaths in patients 19 years and younger. According to CBTRUS (2016), the overall incidence is 5.70 per 100,000 children younger than 19 years, which is approximately 6% of all brain tumors among affected individuals of any age [Ostrom, Q. T., et al 2016]. The incidence of HGG (including anaplastic astrocytoma, anaplastic oligodendrioglioma, glioblastoma, mixed glioma, and malignant glioma) according to CBTRUS (2016) is approximately 0.96 per 100,000 and is similar between the sexes [Ostrom, Q. T., et al 2016].

Pediatric HGG is a highly vascularized, very aggressive tumor type. Despite improvements in neurosurgery, radiotherapy, and chemotherapy, the outcome for children with HGG remains poor. The median duration of survival for newly diagnosed HGG is approximately 18 to 24 months [Qaddoumi, I., et al 2009]. Although numerous treatment approaches have been tested, outcomes have remained dismal, with 2-year survival rates in most trials ranging from 10% to 30% [MacDonald, T. J., et al 2011].

2.2.1.1.2 Rhabdomyosarcoma

Rhabdomyosarcoma is a malignant tumor of mesenchymal origin and is the most common soft tissue sarcoma in children. The incidence of RMS is 4.5 cases per 1 million children; approximately two-thirds of cases are diagnosed in children younger than 10 years of age and there is a slight male predominance. The 2 most common histological types of RMS are embryonal (57% of patients) and alveolar (23% of patients) [Dasgupta, R. 2012] [Ognjanovic, S., et al 2009]. Embryonal RMS occurs mainly in the 0- to 4-year age group (~4 cases per 1 million children, with a lower rate in adolescents, ~1.5 cases per 1 million adolescents), while the incidence of alveolar RMS is constant from ages 0 to 19 years, with approximately 1 case per 1 million children and adolescents. The reported median time to first relapse is approximately 1.5 years and has not changed in the past 2 decades [Dantonello, T. M., et al 2013] [Mazzoleni, S., et al 2005].

Current multimodality treatments for RMS, including chemotherapy, surgery, and radiotherapy, result in long-term survival of approximately 85% of patients with localized disease at presentation. However, up to one-third of these patients experience local or metastatic relapse, and survival after recurrence is usually poor, with little meaningful improvement of survival over the past 30 years [Winter, S., et al 2015].

2.2.1.1.3 Ewing's Sarcoma/pPNET

The EWS family of tumors encompasses a number of aggressive malignant tumors, including EWS/pPNET, Askin tumor, and neuroepithelioma. These tumors can occur in bone or soft tissue and are characterized by a nonrandom chromosomal rearrangement, the most frequent of which is EWS/FLI t(11;22)(q24;q12) translocation [Burchill, S. A. 2003].

Ewing sarcoma/pPNET is rare, with an overall age-adjusted incidence in children, adolescents, and young adults of approximately 3 per 1 million, per year, and has remained unchanged for more than 30 years [Esiashvili, N., et al 2008] [National Cancer Institute 2017]. It is the second most common primary bone cancer in the pediatric population after osteosarcoma and occurs most frequently in adolescents and young adults; the median age at initial diagnosis is 15 years [Esiashvili, N., et al 2008] [National Cancer Institute 2017] [Skubitz, K. M. 2007]. Ewing sarcoma is rare among individuals over the age of 30 years and under the age of 5 years [Bernstein, M., et al 2006]. The median time to first relapse after initial diagnosis is 17 to 18 months [Barker, L. M., et al 2005] [Stahl, M., et al 2011].

The presence of metastases is the most prominent adverse prognostic factor in EWS/pPNET. Metastases are detected in 15% to 33% of patients at the time of initial diagnosis [Ladenstein, R., et al 2010]. Additionally, 30% to 40% of patients with initially localized EWS/pPNET develop recurrent disease and 80% to 90% of patients have widespread disease [Stahl, M., et al 2011]. When systemic therapy is combined with adequate local control measures, applied to both primary and metastatic sites, the overall cure rate is 20% [National Cancer Institute 2017]. For patients with recurrent EWS/pPNET, the current 5-year OS rate is only 10% to 15% [Huang, M. 2011] [National Cancer Institute 2017].

2.2.1.2 Clinical Data on Lenvatinib in Children and Adolescent Patients

The safety, tolerability, and antitumor activity of lenvatinib in the pediatric population is being evaluated in Phase 1/2 Study 207. In the Phase 1 portion (Cohort 1), the recommended Phase 2 dose for lenvatinib as monotherapy in pediatric patients with solid tumors was determined to be 14 mg/m^2 (Section 4.3).

The Phase 2 portion of Study 207 assessed lenvatinib as a single agent in children, adolescents, and young adults with relapsed/refractory osteosarcoma (Cohort 2B; n 31). As of the data cutoff date of 02-AUG-2018, 9 of 28 evaluable participants (32.1%) achieved PFS at 4 months; median PFS was 3.0 months (95% CI: 1.8, 5.4) [Gaspar, N., et al 2018].

The safety profile of single-agent lenvatinib in pediatric patients is consistent with the known lenvatinib toxicities in adults, and PK data from Study 207 showed that exposure to lenvatinib in pediatric patients dosed by BSA is similar to adults receiving a fixed daily dose of lenvatinib [Gaspar, N., et al 2018] [Gaspar, N., et al 2017]. The recommended pediatric dose for single-agent lenvatinib is 14 mg/m^2 daily, which in terms of exposure, is equivalent to the adult daily dosage of 24 mg [Gaspar, N., et al 2017].

In the single-agent expansion cohort of patients with osteosarcoma treated at the RP2D of lenvatinib (n 31), TEAEs occurred in 29 patients (93.5%). The most frequently reported TEAEs (occurring in 40% or more of subjects), in descending order of frequency were decreased appetite, headache, vomiting, hypothyroidism, and proteinuria. Grade ≥3 TEAEs were reported in 20 subjects (64.5%), and such events in >2 subjects were back pain and tumor pain. Twenty-eight subjects (90.3%) had TEAEs reported by the investigator to be treatment-related, which were Grade ≥3 in 7 subjects (22.6%). The most frequently reported treatment-related TEAEs, occurring in 30% or more of subjects, were decreased appetite, hypertension, and hypothyroidism. Four subjects (12.9%) had Grade 5 AEs during treatment: cardio-respiratory arrest (n 2) and respiratory failure or respiratory distress (1 each). All were considered by the investigator to be secondary to disease progression and not related to study drug. Non-fatal SAEs occurred in 20 subjects (64.5%). Events that occurred in >1 participant each were: back pain (n 4), pneumothorax (n 4), dyspnea (n 3), tumor pain (n 3), and platelet count decreased (n 2). Additionally, there were no treatment-related fatal TEAEs.

In the single-agent expansion cohort of 31 patients with osteosarcoma, PFS at 4 months (PFS-4m) was 37.8% (95% CI: 20.0, 55.4) and median PFS was 3 months (95% CI: 1.8, 5.4). The median follow-up time for PFS was 16.6 months (95% CI: 5.5, 16.6). Thirty of the 31 patients enrolled in this cohort had measurable disease per RECIST 1.1. Two subjects had a BOR of PR (6.7%; 95% CI: 0.8, 22.1), and an additional 13 subjects had SD ≥7 weeks (43.3%). The median duration of objective response was 4.6 months (95% CI: NE, NE). Additionally, one participant had evaluable disease with a BOR of non-CR/non-PD.

Overall, the toxicity profile observed for single-agent lenvatinib in pediatric patients with refractory/relapsed solid tumors in the dose-finding cohort is consistent with the lenvatinib toxicity profile observed in adults.

2.2.2 Preclinical and Clinical Studies

Refer to the lenvatinib IB for preclinical and clinical study data for lenvatinib.

2.3 Benefit/Risk Assessment

As discussed in Sections 2.1 and 2.2.1.1, there is an unmet need for expanding treatment options for pediatric patients with relapsed/refractory solid tumors. Data from Study 207 indicate that pediatric patients with osteosarcoma may benefit from treatment with single-agent lenvatinib, and safety data suggest that toxicity is manageable in these patients. Therefore, it is planned to investigate the use of single-agent lenvatinib in other highly vascularized pediatric solid tumors that exhibit upregulation of VEGF/FGF/PDGF.

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In children, adolescents, and young adults with relapsed or refractory solid malignancies treated with lenvatinib:

Objectives	Endpoints
Primary	
• To determine the ORR at Week 16, by each tumor type, per RECIST 1.1 or RANO (for HGG only) as assessed by the investigator.	• Objective Response, defined as a confirmed (≥4 weeks after initial response) CR or PR.
Secondary	
• To evaluate ORR, by each tumor type, per RECIST 1.1 or RANO (for HGG only) as assessed by the investigator.	• Objective Response, defined as a confirmed (≥4 weeks after initial response) CR or PR.
• To evaluate PFS per RECIST 1.1 or RANO (for HGG only), by each tumor type.	• PFS defined as the time from the date of the first administration of lenvatinib until the date of first documentation of PD or death (whichever occurs first).

Objectives	Endpoints
• To evaluate the BOR, DOR, DCR, and CBR, by each tumor type.	• BOR defined as the participant's best confirmed response (CR or PR) over the treatment period. • DOR defined as the time from the date of the first documented CR or PR to the date first documentation of progressive disease or death (whichever occurs first). • Disease control defined as a BOR of CR or PR, or SD. To be assigned a BOR of SD, the time from the first administration of study drug until the date of documented SD should be ≥7 weeks. • Clinical benefit defined as a BOR of CR or PR, or durable SD (SD duration ≥23 weeks since the first dose of the study treatment).
• To evaluate the safety of lenvatinib.	• AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECGs, urine dipstick, Lansky play scores or Karnofsky performance status scores, physical examination findings, dental examination findings, height, and closure of proximal tibial plates.
• To assess the palatability and acceptability of the suspension formulation of lenvatinib.	• Palatability questionnaire using a facial hedonic scale.
• To characterize the PK of lenvatinib.	• Assessment of population-based PK parameters of lenvatinib.
Tertiary/Exploratory	
• To explore relationships between exposure and AE and efficacy.	• Plasma lenvatinib exposure parameters and assessment of AEs associated with lenvatinib treatment.
• To explore OS, by each tumor type.	• OS defined as the time from the date of the first administration of study drug until the date of death from any cause.

Objectives	Endpoints
• To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of lenvatinib.	• Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.

4 STUDY DESIGN

4.1 Overall Design

This is an open-label, multicenter, Phase 2 basket study to evaluate the antitumor activity and safety of lenvatinib in children, adolescents, and young adults between 2 to ≤21 years of age with relapsed or refractory malignant solid tumors. Four cohorts will be evaluated: HGG, RMS, EWS/pPNET, and any other solid tumors (aside from osteosarcoma).

A minimum of 36 participants will be enrolled, 9 evaluable participants in each of 4 cohorts: HGG, RMS, EWS/pPNET, and other solid tumors, as follows:

- HGG: at least 9 evaluable participants (a minimum of 6 participants <17 years of age)
- RMS: at least 9 evaluable participants (a minimum of 6 participants <17 years of age)
- EWS/pPNET: at least 9 evaluable participants (a minimum of 6 participants <17 years of age)
- Other solid tumor types: at least 9 evaluable participants (with any number of pediatric participants across all other tumor types).

The final sample size of patients will depend on the number of tumor types that meet the futility bar and the antitumor activity observed in evaluable participants in the corresponding tumor cohort in Study E7080-A001-216. The enrollment in the HGG, RMS, and EWS/pPNET cohorts is capped at a maximum of 17 evaluable participants each. The enrollment for each tumor type expanded based on response in the other solid tumors' cohort is also capped at a maximum of 17 evaluable participants. Based on these factors and the projected enrollment period, it is estimated that up to approximately 150 participants could be enrolled. Participants 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.

Expansion portion of the study: This study uses a sequential monitoring procedure to evaluate for futility and to evaluate efficacy of lenvatinib by assessing antitumor activity. IAs will be performed after 9 evaluable participants are enrolled in each of the 3 target tumor

cohorts to assess ORR at Week 16. Separate IAs will be performed for each specific tumor type within the other solid tumors' cohort if 9 evaluable participants are enrolled for that tumor type. Assessment of ORR will be based on tumor response as assessed by the investigator using RECIST 1.1 for all tumor types except for HGG, which will be assessed by the investigator using RANO criteria. Enrollment within a cohort will be stopped for futility if no response is observed among the first 9 evaluable participants (i.e. if the futility boundary is crossed), or a lack of antitumor activity is concluded for the corresponding tumor cohort in Study E7080-A001-216. The results of the IAs will be reviewed by the Sponsor and recommendations will be given for expanding a cohort or a specific tumor type within the other solid tumors' cohort, to up to 17 evaluable participants, which will include the initial 9 evaluable participants from the cohort.

The enrollment period may last up to approximately 30 months from the time of enrollment of the first participant. Additionally, data cutoff may occur when the last evaluable participant (see Section 1.1 for definition of evaluable) enrolled in the study has completed the Week 16 imaging assessment or discontinues prior to the Week 16 imaging assessment, whichever occurs first.

If no objective responses are observed at the time of enrollment of the ninth evaluable participant in a specific cohort or other tumor type, enrollment will be paused in said cohort or other tumor type until the IA for these 9 evaluable participants is completed. If at least 1 objective response is observed at the time of enrollment of the ninth evaluable participant in a specific cohort or other tumor type, enrollment may continue in said cohort or other tumor type.

Participants will receive lenvatinib treatment until disease progression as assessed by the investigator per RECIST 1.1 or per RANO for participants with HGG, initiation of another anticancer therapy, development of unacceptable toxicity, or withdrawal of consent, whichever occurs first. The estimated time of treatment is 1 year (12 cycles). However, participants can continue on treatment with lenvatinib until a treatment discontinuation criterion is met.

The primary objective of the study is to evaluate ORR at Week 16 for each cohort separately as assessed per RECIST 1.1 or RANO (for HGG) by the investigator. On-study imaging assessments will be performed at screening, every 8 weeks from the date of lenvatinib initiation until Week 24, then every 12 weeks thereafter, or as clinically indicated (±7 days). All responses will be confirmed at a follow-up examination ≥28 days after the initial response. Images will be collected by a central imaging vendor for possible independent review of response; site assessment (RECIST 1.1 or RANO for HGG) will be considered for purposes of satisfying the primary efficacy endpoint.

Safety and tolerability will be assessed by clinical review of all relevant safety parameters including AEs, physical examinations, laboratory tests, vital signs, ECGs, Lansky Play Score and KPS, dental examination findings, height, and proximal tibial growth plate.

At the end of treatment, each participant will be followed 30 days for the occurrence of AEs/SAEs.

Participants who discontinue lenvatinib treatment for reasons other than radiographic disease progression or initiation of new anticancer therapy will have post-treatment tumor assessments performed every 8 weeks for 24 weeks, then every 12 weeks thereafter until documentation of disease progression or start of a new anticancer agent, whichever occurs first, unless the participant withdraws consent, becomes lost to follow-up, or the study is terminated.

Participants will be followed by telephone every 12 weeks for survival status until death unless the participant withdraws consent, becomes lost to follow-up, or the study is terminated.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

This Phase 2 basket study uses a sequential monitoring procedure to assess the antitumor activity of lenvatinib in children, adolescents, and young adults with relapsed/refractory malignancies for which there are no standard therapy regimens. The sequential monitoring design allows enrollment of a limited number of participants to determine drug activity, thereby preventing exposure of participants to a drug that is inactive for the specific tumor type. The safety of lenvatinib will be evaluated at the RP2D of single-agent lenvatinib (14 mg/m^2), as determined in Study 207.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use ORR, defined as the proportion of participants with confirmed objective response (an objective response of CR or PR at Week 16, based on RECIST 1.1 or RANO for HGG as assessed by the investigator) as the primary endpoint. For single-arm studies, ORR is commonly used to assess clinical activity of therapies in the treatment of pediatric solid tumors. The use of RECIST 1.1 and the use of RANO for HGG to assess ORR is typically considered acceptable by regulatory authorities.

Antitumor activity for participants with neuroblastoma enrolled in the other solid tumors' cohort will be determined by the following criteria and combined with RECIST-based efficacy for assessment of the study endpoints.

- CR: Complete resolution of all MIBG-positive lesions.
- PR: Resolution of at least 1 MIBG-positive lesion, with persistence of other MIBG-positive lesions.
- SD: No changes in MIBG scan in number of positive lesions.

- PD: Development of new MIBG-positive lesions.

DOR, BOR over the treatment period, DCR, CBR, and PFS are secondary endpoints that will serve as additional measures of efficacy and are commonly accepted endpoints by both regulatory authorities and the oncology community.

Overall survival, defined as the time from the first day of study intervention to death due to any cause, will be an exploratory endpoint.

4.2.1.1.1 RECIST 1.1

RECIST 1.1 will be used by the investigator when assessing images for determining eligibility and for efficacy measures using a maximum of 5 target lesions in total and 2 per organ (Section 8.2.1.4).

4.2.1.1.2 RANO

RANO criteria will be used by the investigator when assessing images for determining eligibility and for efficacy measures for HGG. A standard MRI-imaging protocol will be performed for use in the assessments, based on a published consensus [Ellingson, B. M.,Bendszus, M., et al 2015].

4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic cancer treatments are included as safety endpoints. These endpoints include, but are not limited to, the incidence, causality, and outcome of AEs/SAEs, changes in clinical laboratory values, vital signs, 12-lead ECGs, Lansky Play Score or KPS, results of physical examination findings, dental examination findings, height, and closure of proximal tibial plates.

4.2.1.3 Pharmacokinetic Endpoints

Based on lenvatinib PK data obtained in this study and from other studies, a population PK analysis will be performed.

4.2.1.4 Pharmacodynamic Endpoints

Blood samples for serum markers will be collected for participants as specified in the SoA (Section 1.3).

Biomarker discovery and/or validation will be performed to identify blood or tumor biomarkers that may be useful to predict participant response to study drug as well as for potential use in diagnostic development. Blood samples may undergo global proteomic and/or single-analyte ELISA or multiplex immunoassays based on the amount of sample available. Potential blood biomarkers to be explored include FGF ligands (eg, FGF2/bFGF, FGF19, FGF21, FGF23) and angiogenesis-related markers (eg, VEGF, Ang 1/2, sTie 2, HGF, PlGF). In addition, biomarkers identified in other lenvatinib clinical studies may also be assessed in samples collected from participants enrolled in this study. The decision to

perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

4.2.1.5 Planned Exploratory Biomarker Research

Much remains to be learned regarding how best to leverage lenvatinib in treating pediatric patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/PD biomarkers and generate information that may better guide single-agent and combination therapies. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict anti-tumor activity or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations.

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability) contributing towards the development/progression of cancer and/or driving response to therapy. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Evaluation of molecular targets and signaling pathways including angiogenesis and/or growth factor related signaling pathways related to lenvatinib may also be explored. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and blood RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment. Known gene signatures may be evaluated, and new signatures identified. Individual genes related to growth factor signaling pathways (eg, VEGF and FGF) may also be evaluated. MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and IHC using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses. Tumor or blood-derived proteins may be found to correlate with response to lenvatinib therapy. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for lenvatinib therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, circulating cytokines and angiogenic factors, and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunosorbent assay (ELISA) measure such proteins in serum. Correlation of expression with response to lenvatinib therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

The T-cell repertoire from tumor tissue and blood components may be evaluated.

4.3 Justification for Dose

The recommended dose for lenvatinib as a single agent in pediatric patients (2 to <18 years) with relapsed or refractory solid malignant tumors was determined in the Phase 1 portion of Study 207, using TiTE CRM. The recommended dose was defined as the dose with dose-limiting toxicity rate closest to the targeted 20% rate [Gaspar, N., et al 2017].

A total of 23 participants were enrolled in 3 dose levels: 11 mg/m^2 (n 5), 14 mg/m^2 (n 11), and 17 mg/m^2 (n 17). The most frequent tumor types were rhabdomyosarcoma (n 5), Ewing sarcoma (n 4), and neuroblastoma (n 3). BOR was stable disease (n 12).

Dose-limiting toxicities were reported in 3 participants at the 14 mg/m^2 dose during Cycle 1. All were considered related to lenvatinib. Dose-limiting toxicities were: 1 report each of Grade 3 ALT level increased, Grade 3 hypertension, and Grade 4 hypertension. All participants recovered after either interruption (ALT increase), reduction (Grade 3 hypertension) or discontinuation (Grade 4) of lenvatinib therapy. Based on these results, the recommended Phase 2 dose of lenvatinib in children, adolescents, and young adults was determined to be 14 mg/m^2, which is equivalent to the recommended daily dose of 24 mg/day of lenvatinib in adults with radioiodine-refractory DTC.

In this study, the lenvatinib daily dose will be calculated based on BSA, and the actual daily dose will not exceed 24 mg/day. Participants may receive lenvatinib until disease progression is radiographically documented by the investigator per RECIST 1.1 or per RANO criteria for participants with HGG, initiation of another anticancer therapy, development of unacceptable toxicity, or withdrawal of consent, whichever occurs first. The estimated time of lenvatinib

treatment is 1 year. However, participants continuing to derive benefit from lenvatinib treatment can continue to receive lenvatinib until a treatment discontinuation criterion is met.

4.4 Beginning and End of Study Definition

The study begins when the first participant (or their legally acceptable representative) provides documented informed consent/assent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

Enrollment will be stopped for a specific cohort/tumor type if no objective responses occur in the first 9 evaluable participants who have completed the Week 16 imaging assessment (or discontinued before Week 16 for progressive disease) or the futility boundary is crossed.

EWS and HGG cohorts were not expanded because futility was concluded for the corresponding cohorts in Study E7080-A001-216. Further enrollment of participants into the other solid tumors' cohort was discontinued due to insufficient antitumor activity of lenvatinib in this patient population.

4.4.1 Clinical Criteria for Early Study Termination

The enrollment period may last up to approximately 30 months from the time of enrollment of the first participant. Additionally, data cutoff may occur when the last evaluable participant (see Section 1.1 for definition of evaluable) enrolled in the study has completed the Week 16 imaging assessment or discontinues prior to the Week 16 imaging assessment, whichever occurs first).

If no objective responses are observed at the time of enrollment of the ninth evaluable participant in a specific cohort or other tumor type, enrollment will be paused in said cohort or other tumor type until the IA for these 9 evaluable participants is completed. If at least 1 objective response is observed at the time of enrollment of the ninth evaluable participant in a specific cohort or other tumor type, enrollment can continue in said cohort or other tumor type.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), our studies include people of varying age, race, ethnicity, and sex. The collection and use of these demographic data is to follow all local laws and guidelines in keeping with the needs for participant confidentiality while supporting the study of the disease, its related factors, and the IMP under investigation.

Male/female children, adolescents, and young adult participants with relapsed or refractory pediatric solid tumors (excluding osteosarcoma) between the ages of 2 and 21 years inclusive will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Has histologically or cytologically documented relapsed, or refractory pediatric solid malignancy excluding osteosarcoma.
   Participants with diffuse midline glioma (formerly known as diffuse intrinsic pontine glioma), optic pathway glioma, or pineal tumors with elevated tumor markers (AFP, ß-hCG, or hCG) do not require histological or cytological confirmation of diagnosis.
   Participants with diffuse midline glioma are not eligible for the HGG cohort and should only be enrolled in the other solid tumors' cohort.

2. Has measurable disease as defined by RECIST 1.1 or RANO for HGG, meeting the criteria below:

   - All tumor types except HGG and neuroblastoma: At least 1 lesion measuring ≥1.0 cm in the longest diameter for a non-lymph node or ≥1.5 cm in the short-axis diameter for a lymph node that is reproducibly measurable on CT or MRI scans.

   - HGG: At least 1 contrast-enhancing lesion with clearly defined margins on T1-weighted MRI scan, measuring ≥1.0 cm in 2 perpendicular diameters, and visible on at least 2 axial slices (preferably no more than 5 mm apart with 0 mm gap).

   - Participants with neuroblastoma who do not have measurable disease per RECIST 1.1 but have MIBG-positive evaluable disease may be enrolled.

   - Tumor lesions situated in a previously irradiated area or in an area subjected to other locoregional therapy are considered measurable only if progression has been observed in such lesions since the completion of therapy.

3. Has a performance status as defined below:

   - Lansky Play Score ≥50 for participants up to and including 16 years of age.
   - KPS ≥50 for participants >16 years of age.
   - Neurologic deficits in participants with primary CNS tumors must have been stable for at least 7 days prior to study enrollment. Participants who are unable to walk because of paralysis, but who can perform ADL while wheelchair bound, will be considered ambulatory for the purpose of assessing the performance score.

4. Demonstrate adequate organ function as defined below:

<table>
<tr><th>System</th><th>Laboratory Value</th></tr>
<tr><td colspan="2">Hematological</td></tr>
<tr><td colspan="2">For participants without bone marrow involvement</td></tr>
<tr><td>ANC</td><td>≥1000/µL</td></tr>
<tr><td>Platelets</td><td>≥75,000/µL</td></tr>
<tr><td>Hemoglobin</td><td>≥8.0 g/dL (a hemoglobin of <8.0 g/dL is acceptable if it is corrected by growth factor or transfusion before C1D1)</td></tr>
<tr><td colspan="2">For participants with known bone marrow involvement</td></tr>
<tr><td>ANC</td><td>≥800/µL and leucocyte count ≥1 × 10^9/L</td></tr>
<tr><td>Platelets</td><td>≥75,000/µL
(May receive transfusions provided they are not known to be refractory to platelet transfusions)</td></tr>
<tr><td>Hemoglobin</td><td>(May receive transfusions provided they are not known to be refractory to red cell transfusions.)</td></tr>
<tr><td colspan="2">Renal</td></tr>
<tr><td>Creatinine by age/gender[a]

<u>OR</u>
Measured or calculated[b] creatinine clearance</td><td>
<table>
<tr><th>Age</th><th colspan="2">Maximum Serum Creatinine (mg/dL)</th></tr>
<tr><th></th><th>Male</th><th>Female</th></tr>
<tr><td>2 to <6 years</td><td>0.8</td><td>0.8</td></tr>
<tr><td>6 to <10 years</td><td>1</td><td>1</td></tr>
<tr><td>10 to <13 years</td><td>1.2</td><td>1.2</td></tr>
<tr><td>13 to <16 years</td><td>1.5</td><td>1.4</td></tr>
<tr><td>≥16 years</td><td>1.7</td><td>1.4</td></tr>
</table>
<u>OR</u>
≥70 mL/min/1.73 m^2</td></tr>
<tr><td colspan="2">Hepatic</td></tr>
<tr><td>Total bilirubin</td><td>≤1.5 ×ULN for age, except for unconjugated hyperbilirubinemia of Gilbert’s syndrome</td></tr>
<tr><td>ALT and AST</td><td>ALT and AST ≤3 × ULN (in the case of liver metastases ≤5 × ULN)</td></tr>
</table>

System	Laboratory Value
Coagulation	
INR or PT	≤1.5 ×ULN (participants on anticoagulant therapy must remain within the therapeutic PT or INR range)

ALT alanine aminotransferase; ANC absolute neutrophil count; AST aspartate aminotransferase; GFR glomerular filtration rate; INR international normalized ratio; PT prothrombin time; ULN upper limit of normal.
a The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.
b Creatinine clearance should be calculated per institutional standards (see Appendix 7 for country specific requirements).

5. Has urine dipstick <2+ for proteinuria. Participants who have ≥2+ proteinuria on dipstick urinalysis should undergo a spot P/C ratio that should be Grade <2 per CTCAE v5.0, and if possible, perform a 24-hour urine collection (children and adolescents ≤12 years of age must have ≤500 mg of protein/24 hours and participants >12 years of age must have ≤1 g of protein/24 hours).

6. Has no clinical evidence of nephrotic syndrome.

7. Has adequate BP control with or without antihypertensive medications, defined as:

   - BP < the 95th percentile for sex, age, and height/length (≤150/90 mm Hg for participants aged 18 to 21 years) at Screening (as per NHLBI guidelines; Appendix 11 and Appendix 12) and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1.

8. Has adequate cardiac function:

   - Adequate cardiac function as evidenced by left ventricular shortening fraction of ≥27% by echocardiogram or LVEF ≥50% at C1D1 prior to allocation as determined by echocardiography or MUGA scan.

   - QT interval corrected for heart rate using Fridericia's formula (QTcF) ≤480 msec.

9. Has adequate neurologic function:

   - Participants with seizure disorder may be enrolled if on anticonvulsants and seizure disorder is well controlled.

10. Has fully recovered to CTCAE v5.0 Grade ≤1 (except for alopecia, ototoxicity, and Grade ≤2 peripheral neuropathy) from the acute toxic effects of all prior anticancer therapy and must meet the following minimum duration from prior anticancer-directed therapy prior to enrollment. If after the required timeframe, the numerical eligibility criteria are met, eg, blood count criteria, the participant is considered to have recovered adequately.

    a. Cytotoxic chemotherapy or other chemotherapy known to be myelosuppressive: ≥21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).

    b. Anticancer agents not known to be myelosuppressive (eg, not associated with reduced platelet or absolute neutrophil counts): ≥7 days after the last dose of agent.

    c. Monoclonal antibodies: ≥21 days or 3 half-lives (whichever is shorter) of the antibody must have elapsed after the last dose of a monoclonal antibody (including checkpoint inhibitors; Appendix 14). Toxicity related to prior antibody therapy must be recovered to Grade ≤1.

    d. Corticosteroids: If used to modify immune AEs related to prior therapy, ≥14 days must have elapsed since last dose of corticosteroid. For reasons other than immune AEs, participants receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible.

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

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

    g. Stem cell infusions (with or without total body irradiation):

        - Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including donor leukocytes infusion or boost infusion: ≥84 days after infusion and no evidence of graft versus host disease.

        - Autologous stem cell infusion including boost infusion: ≥42 days.

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

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

j. Radiopharmaceutical therapy (eg, ^{131}I-MIBG): ≥42 days after systemically administered radiopharmaceutical therapy.

k. VEGF/VEGFR-targeted therapies:

- Must not have received prior exposure to lenvatinib
- No more than 2 prior VEGF/VEGFR-targeted therapies

Demographics

11. Male or female ≥2 years to ≤ 21 years of age, on the day the main informed consent/assent is signed.

Male Participants

12. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after the last dose of study intervention:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Female Participants

13. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 30 days post lenvatinib.

- A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours before the first dose of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Informed Consent/Assent

14. Is willing and able to provide (and/or their parents or legal guardians) documented informed consent/assent for the study. Documented informed consent is required from participants ≥18 years.

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

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has had major surgery within 3 weeks prior to C1D1.
   Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.

2. Has GI bleeding or active hemoptysis (bright red blood of at least half teaspoon) within 21 days prior to enrollment.

3. Has CNS tumors with a history of symptomatic tumor hemorrhage.

4. Has evidence of new intracranial hemorrhage of more than punctate size on MRI assessment obtained within 28 days prior to study enrollment.

5. Has radiographic evidence of encasement or invasion of a major blood vessel or of intratumoral cavitation.
   Note: The degree of proximity to major blood vessels should be considered for exclusion because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.

6. Has evidence of untreated CNS metastases (exception: participants with primary CNS tumors and leptomeningeal disease).

7. Has GI malabsorption, GI anastomosis, or any other condition that in the opinion of the investigator might affect the absorption of lenvatinib.

8. Has preexisting ≥Grade 3 GI or non-GI fistula.

9. Has any active infection requiring systemic therapy.

10. Is known to be HIV positive. Note: HIV testing is required at screening only when mandated by local health authority (see Appendix 7 for country-specific requirements).

11. Has known active viral hepatitis B virus (eg, HBsAg reactive) or Hepatitis C virus (eg, HCV RNA [qualitative] is detected) infection. Note: Testing for hepatitis B or hepatitis C is required at screening only when mandated by local health authority (see Appendix 7 for country-specific requirements).

12. Has clinically significant cardiovascular disease within 6 months from first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability. Note: Medically controlled arrhythmia would be permitted.

13. Has non-healing wound, tumor ulceration, unhealed or incompletely healed fracture, or a compound (open) bone fracture at the time of enrollment.

Prior/Concomitant Therapy

Prior/Concurrent Clinical Study Experience

14. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the date of allocation.

    Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

Diagnostic Assessments

Other Exclusions

15. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

16. Has known hypersensitivity to any component of the investigational product (lenvatinib or ingredients).

17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting. Lenvatinib capsules may be administered with or without food.

5.3.2 Contraception

Lenvatinib may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

Participants should be informed that taking the study intervention may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, WOCBP must adhere to the contraception requirement (Appendix 5) from the day of study intervention initiation throughout the study period up and up to 30 days post

lenvatinib. If there is any question that a WOCBP will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.3.3 Pregnancy

If a participant inadvertently becomes pregnant while on lenvatinib, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor as described in Section 8.4. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 8.4.

5.3.4 Use in Nursing Women

It is unknown whether lenvatinib is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

5.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who is not evaluable for objective response will be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies will be packaged to support enrollment . Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Lenvatinib	Drug	Capsule	1 mg, 4 mg, 10 mg	14 mg/m^2	Oral	Once daily	Test Product	IMP	Central

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

After adjustments for body surface area, the lenvatinib daily dose will not exceed 24 mg.

A participant who is not evaluable for objective response will be replaced.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 6 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Lenvatinib is a capsule for oral administration and does not require preparation. For participants unable to swallow capsules a suspension can be prepared. See the Pharmacy Manual for additional information.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Treatment allocation will occur centrally using an interactive response technology. Participants will be assigned to 1 of 4 cohorts based on their malignancy.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Interruption from the protocol-specified lenvatinib treatment ≥28 days requires consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Treatment (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs, etc.) for AEs or therapy to ameliorate symptoms may be administered at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study medication. Prophylactic use of G-CSFs is not permitted.

Administration of systemic corticosteroids for PD is not permitted.

- Administration of systemic corticosteroids will be limited to premedication or the short-term treatment of acute medical conditions in accordance with approved indications, institutional, or national guidelines.

- Inhaled steroids are allowed for management of asthma.

Palliative radiotherapy of up to 2 painful preexisting, nontarget bone metastases will be permitted without being considered PD.

6.5.1 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during screening and while on treatment during the study:

- Concurrent anticancer therapies such as chemotherapy, TKIs, radiotherapy (with the exception of palliative radiotherapy as specified in Section 6.5), antitumor interventions (surgical resection, surgical debulking of tumor, etc.), or cancer immunotherapy.
- Concurrent other investigational drugs.

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

If participants receive additional anticancer therapies, this will be judged to represent evidence of disease progression, and study medication will be discontinued. These participants should complete all off-treatment assessments and continue to be followed for survival in the Survival Follow-up Period.

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

6.5.2 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

6.6 Dose Modification

Lenvatinib dose reduction and interruption for participants who experience lenvatinib-related toxicity will be in accordance with the dose modifications described in Table 3. AEs will be graded using CTCAE v5.0.

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.

Dose reductions will occur in succession based on the previous dose. Each reduction is a 20% reduction from the previous dose. Once the dose has been reduced, it cannot be increased at a later date, unless the dose has been mistakenly decreased; in this situation, Sponsor's approval is required to increase the dose. An interruption of lenvatinib >28 days will require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

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

Dose Modification Guidelines for Lenvatinib-Related Toxicity		
Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d] or Grade 3[e]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1 or tolerable Grade 2	11.2 mg/m^2 (or 20% reduction of the starting dose) orally QD (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1 or tolerable Grade 2	9.0 mg/m^2 (or 20% reduction of the previous dose) orally QD (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1 or tolerable Grade 2	7.2 mg/m^2 (or 20% reduction of the previous dose) orally QD (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with Sponsor
Grade 4[f]: Discontinue Study Treatment		

Abbreviations: BMI = body mass index; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; QD = once daily.

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

a An interruption of study treatment > 28 days will require Sponsor`s approval before treatment can be resumed.

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

c Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.

d Obese participants with weight loss do not need to return to the baseline weight or 10% of baseline weight (ie, Grade 1 weight loss). These participants will restart lenvatinib at a lower dose once their weight remains stable for at least 1 week and they reached the normal BMI (if the weight loss occurred, but it is still above normal BMI, they can restart lenvatinib 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. Refer to Appendix 13 for BMI-for-age percentiles.

e For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with the Sponsor.

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

6.6.1 Blood Pressure

For children, BP varies by the sex and age of the child and it is closely related to height and weight. BP will be assessed in terms of percentile for sex, age, and height/length. Guidelines to sex, age, and height/length-specific percentiles of BP are provided in Appendix 11 and Appendix 12. BP that is consistently above the 95th percentile based on sex, age, and height/length (or BP ≥140/90 mm Hg for participants 18 to 21 years old) requires further evaluation. A referral to a cardiologist is recommended for participants who develop hypertension during the study. Ideally, cardiovascular assessments and the management of hypertension should be supervised by a cardiologist. Exercise, excitement, coughing, crying, and struggling may raise the systolic pressure of children as much as 40 to 50 mm Hg greater than their usual level. Variability in BP in children of approximately the same age and body build should be expected, and serial measurements should always be obtained when evaluating a participant with hypertension. **BP values for the management of hypertension for participants 18 to 21 years old are included in parentheses in Section 6.6.2.**

6.6.2 Management of Hypertension

Hypertension is a recognized side-effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that participants enrolled to receive treatment with lenvatinib have BP <95th percentile (BP ≤150/90 mm Hg) for sex, age, and height/length at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1 Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be conducted as detailed in the SoA (Section 1.3). Hypertension will be graded using CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

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

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

diastolic BP ≥95th percentile (BP ≥90 mm Hg) is first observed on 2 assessments obtained 30 minutes apart. For those participants already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

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

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

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

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

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

- If systolic BP ≥99th percentile (BP ≥160 mm Hg) or diastolic BP ≥99th percentile (BP ≥100 mm Hg) persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at a lower dose QD (1 dose level reduction [20%] as specified in Table 3) only when systolic BP <95th percentile (BP ≤150 mm Hg) and diastolic BP <95th percentile (BP ≤95 mm Hg) and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

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

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

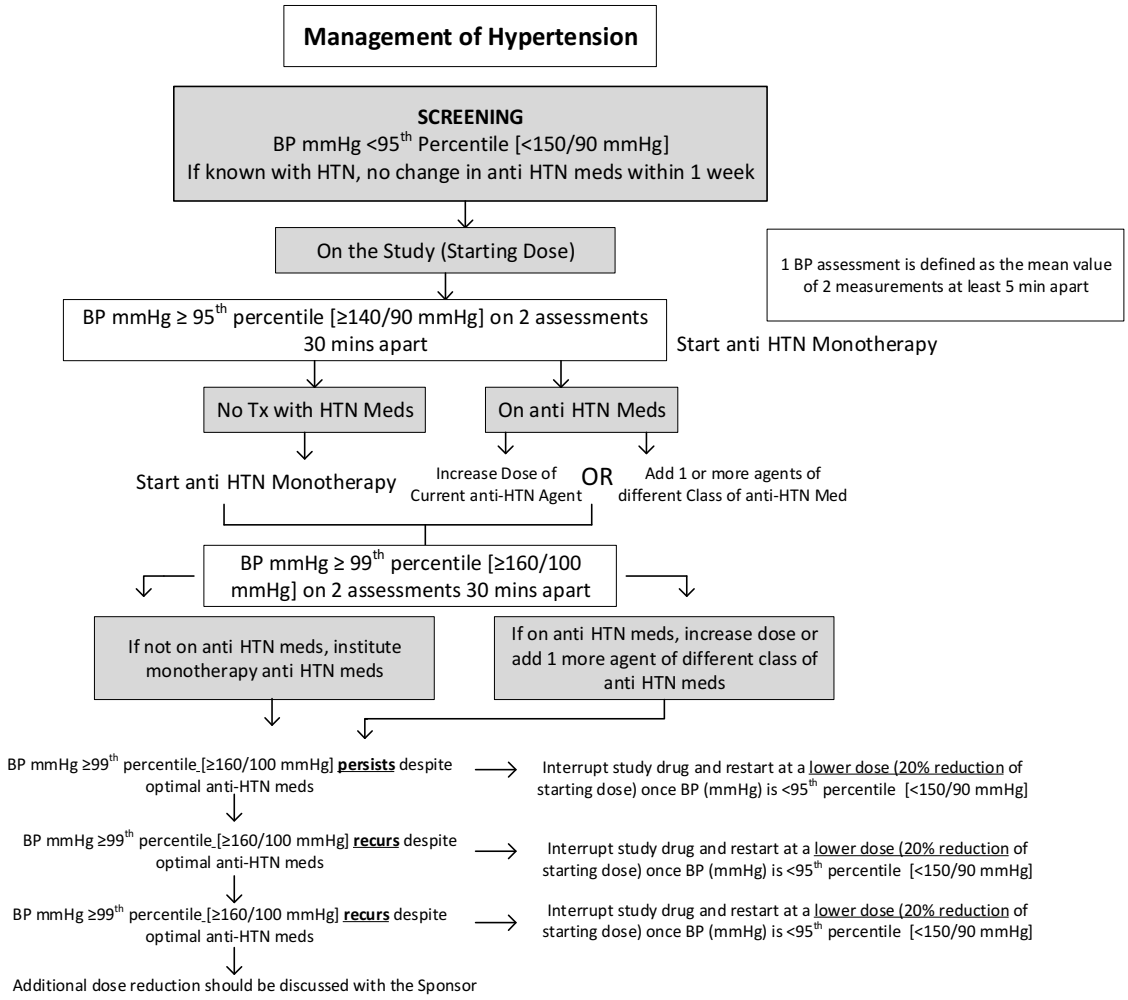
- If systolic BP ≥99th percentile (BP ≥160 mm Hg) or diastolic BP ≥99th percentile (BP ≥100 mm Hg) recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then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

- Additional dose reduction should be discussed with the Sponsor.

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

- Institute appropriate medical management
- Discontinue lenvatinib

Figure 2 Procedures Associated with Management of Hypertension



Abbreviations: BP blood pressure; HTN hypertension; Tx treatment.

6.6.3 Management of Proteinuria

Regular assessment for proteinuria should be conducted as detailed in the SoA (Table 1). Guidelines for assessment and management of proteinuria are summarized as follows:

Grading of Proteinuria

- Grading according to CTCAE v5.0 will be based on the protein-creatinine ratio or 24-hour urinary protein result if available. For participants ≥18 years of age, if the participant has 4+ proteinuria by dipstick (≥1000 mg/dL by urinalysis), a 24-hour urinary protein result is required to confirm Grade 3 proteinuria.

Management of Proteinuria

- Management of lenvatinib administration will be based on the grade of proteinuria according to Table 3.

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

Detection and Confirmation

- Perform urine dipstick testing per the SoA (Table 1). Urine dipstick testing is the preferred method for testing for urinary protein, however, urinalysis may be used if the use of urine dipsticks is not feasible.

- For participants ≥18 years of age, a 24-hour urine collection (initiated as soon as possible and at least within 72 hours) or an immediate spot P/C test AND for participants <18 years of age, an immediate spot P/C test, and if possible, a 24-hour urine collection (initiated as soon as possible and at least within 72 hours) is required in the following situations:

    - The first (initial) occurrence of ≥2+ (≥100 mg/dL) proteinuria on urine dipstick (or urinalysis) while on lenvatinib.

    - A subsequent increase in severity of urine dipstick or urinalysis proteinuria occurring on the same lenvatinib dose level.

    - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+ (≥100 mg/dL).

      Note: For participants ≥18 years of age, a 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when P/C test is ≥2.4.

Monitoring

- Urine dipstick or urinalysis testing for participants with proteinuria ≥2+(≥100 mg/dL) should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+(10 mg/dL) or negative for 2 consecutive 28-day treatment cycles.

- Proteinuria monitoring can be performed at the local laboratory or investigator site but must be managed by the site physician.

6.6.4 Management of Gastrointestinal Symptoms and Acute Abdominal Pain

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

For AEs of abdominal pain believed related to lenvatinib or more specific AEs believed related to lenvatinib that result in the symptom of abdominal pain, follow instructions

contained in Table 3 regarding lenvatinib dose reduction and interruption. For Grade 4 AEs that result in abdominal pain, lenvatinib must be discontinued.

GI symptoms including diarrhea should be managed by providing symptomatic treatment. If the symptoms persist (eg, diarrhea for more than 10 days), guidelines in Table 3 should be followed. GI symptoms should be monitored closely and evaluated using CT, contrast-enhanced MRI, ultrasound, or other diagnostic imaging if clinically indicated, at the investigator's discretion.

6.6.5 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, deep vein thrombosis signs including lower-extremity swelling, redness, and warmth to touch or tenderness. In case any of these symptoms appear, participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 3 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences a Grade 3 or life-threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, lenvatinib must be discontinued.

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

6.6.6 Management of Posterior Reversible Encephalopathy Syndrome (PRES)/Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

PRES/RPLS is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurologic disturbances. Mild to severe hypertension may be present. An MRI is necessary to confirm the diagnosis of PRES/RPLS. The key diagnostic imaging feature for PRES, which can differentiate this entity from disease progression secondary to CNS tumors, is based on imaging evidence of new, bilateral/symmetric vasogenic edema without correlation with the location of the tumor/surgical cavity. Appropriate measures should be taken to control BP (see Section 6.6.1), and neurologic consultation is advised. In participants with signs or symptoms of PRES/RPLS, dose modification guidelines as per Table 3 should be followed.

6.6.7 Management of Hepatotoxicity

Regular monitoring of liver function tests (ALT, AST, and bilirubin levels) should be conducted as detailed in the SoA (Table 1) and as clinically indicated. If signs/symptoms indicating liver injury occur, dose modification guidelines contained in Table 3 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure (any grade per CTCAE v5) occurs, lenvatinib must be discontinued.

6.6.8 Management of Hypocalcemia

Serum calcium should be monitored monthly per the SoA (Table 1). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

Corrected calcium ([4 serum albumin in g/dL] × 0.8 + serum calcium)

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

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

6.6.9 Management of Hemorrhage

Dose modification guidelines in Table 3 for lenvatinib-related AEs should be followed for the management of hemorrhage. Lenvatinib should either be resumed at a reduced dose or discontinued, depending on the severity and persistence of hemorrhage.

6.6.10 Management of Fistula Formation and Gastrointestinal Perforation

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

6.6.11 Management of QT Prolongation

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

6.6.12 Management of Osteonecrosis of the Jaw

Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgement of adequate resolution (See Section 6.7)

6.7 Other Allowed Dose Interruptions for Lenvatinib

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

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least **2 days after, once there is evidence of adequate healing and no risk of bleeding.**
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 2 weeks after, once there is evidence of adequate healing and no risk of bleeding.
- For scheduled dental surgery or invasive dental procedures, stop lenvatinib for at least 1 week before the procedure, then restart lenvatinib when deemed clinically appropriate.

6.8 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.9 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.10 Standard Policies

Not applicable.

6.10.1 Study Site Retention Samples

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of study treatment will still continue to participate in the study as specified in Section 1.3 and Section 8.11.4.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect

occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 1.3 and Section 8.11.4.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant interrupts study intervention administration for more than 28 consecutive days.

  Note: Exceptions can be made with Sponsor consultation.
- The participant has a medical condition or personal circumstance, which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant experiences objective progression of disease (according to RECIST 1.1 or RANO criteria, for HGG).
- The participant exhibits no clinical benefit (in the opinion of the investigator).
- The participant experiences unacceptable toxicity leading to withdrawal from the study.
- The study is terminated by the Sponsor.
- Administrative reasons.

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, he/she shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical or dental decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will be provided in the laboratory manual. Refer to Appendix 7 for country-specific requirements.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent, and assent if applicable, from each potential participant or their legally acceptable representative prior to participating in this clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent/assent is in place.

8.1.1.1 General Informed Consent/Assent

Informed consent/assent given by the participant or their legally acceptable representative must be documented on a consent/assent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent/assent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial informed consent/assent form, any subsequent revised informed consent/assent form, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent/assent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The assent, as applicable will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent/assent. At the time of intervention allocation, site personnel will add the treatment/allocation number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical and surgical history will be obtained by the investigator or qualified designee. The medical and surgical history will collect all active conditions and any condition that is considered to be clinically significant by the investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 30 days before the first dose of study intervention. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and will not be listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. Concomitant medications will be recorded for 30 days after the last dose of study intervention.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.11.1.

8.1.7 Assignment of Treatment/Allocation Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/allocation number. The treatment/allocation number identifies the participant for all procedures occurring after treatment allocation. Once a treatment/allocation number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/allocation number.

8.1.8 Study Intervention Administration

Lenvatinib may be taken at home except on C1D1, C1D15, and C2D1; on these days lenvatinib will be taken in the clinic. An extemporaneous suspension of lenvatinib capsules should be used for participants unable to swallow capsules, as detailed in the Pharmacy Manual. Refer to Section 8.1.8.1 for further details.

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

$$\text{Scheduled dose (mg/m}^2\text{)} \times \text{BSA (m}^2\text{)} \quad \text{lenvatinib dose (mg)}$$

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

8.1.8.1 Timing of Dose Administration

Lenvatinib capsules are to be taken orally once daily at approximately the same time without regard to food intake from C1D1 onwards. Participants should not take lenvatinib on PK sampling days prior to their appointment (ie, C1D1, C1D15, and C2D1). On C1D1, C1D15 and C2D1, participants should be instructed to bring their lenvatinib to the clinic. Lenvatinib should be administered at the study site at approximately the same time of day to accommodate PK sample collection timing.

If a participant misses a dose, it may be taken within 12 hours after the usual time of the dose. If more than 12 hours have elapsed from the time of the usual daily dose, lenvatinib should be taken the next day at the usual time. In the event a participant vomits after lenvatinib administration, the participant should not take another dose until the next scheduled dose.

8.1.8.2 Compliance

Lenvatinib compliance will be calculated by the Sponsor based on the study drug accountability documented by the site staff and monitored by the Sponsor/designee. The objective is 100% compliance and investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the EOT visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or anti-tumor activity parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1.12 Demography

Participant demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, and race/ethnicity (recorded in accordance with prevailing regulations). Tanner staging will be collected at the Screening Visit or C1D1, at EOT, and during efficacy and survival FU. During efficacy and survival FU, perform annually until puberty has completed or through survival FU, whichever comes first. Telephone contact is acceptable for assessment if clinic visits are not possible at post-treatment visits after the 30-day safety FU.

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

In addition to survival, evaluation of antitumor activity will be assessed based on imaging evaluation of changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. The process for image collection can be found in the SIM.

For participants with non-CNS solid tumors:

- CT scans of the chest, abdomen and pelvis are required.
- As an alternative to CT (i.e., when iodinated contrast is contraindicated or when mandated by local practice), MRI of the abdomen and pelvis, along with a noncontrast CT of the chest is an acceptable alternative.
- If brain imaging is performed to document the stability of existing metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.
- Any additional anatomical areas as clinically indicated.

For participants with CNS Tumors:

- MRI of the brain is required for the HGG cohort. MRI of the brain is strongly preferred over CT for non-HGG CNS tumors.
- Any additional anatomical areas as clinically indicated.

Tumor imaging will be performed at the timepoints specified in Section 1.3, or as clinically indicated. Tumor imaging of the chest is to be acquired by CT scan. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. **MRI is the strongly preferred modality for imaging the brain. For HGG participants, MRI is mandatory to allow for RANO assessment.** Refer to the SIM for mandatory acquisition parameters. The same imaging technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on imaging. Note: for the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of allocation. Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of allocation.

Participant eligibility will be determined based on confirmation by the investigator that the participant has measurable disease per RECIST 1.1 for all tumor types except for HGG, which will be evaluated per RANO criteria. In addition, participants with neuroblastoma who do not have measurable disease per RECIST 1.1 but have MIBG-positive evaluable disease may be enrolled (see Section 4.2.1.1).

8.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed the end of Week 8 ±7 days. Subsequent tumor imaging should be performed every 8 weeks until Week 24, then every 12 weeks (±7days) thereafter during treatment (or sooner if there is evidence of PD). Imaging timing should follow calendar days from C1D1, and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator, the start of new anticancer treatment, pregnancy, withdrawal of consent, or death, whichever occurs first.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

8.2.1.3 End-of-Treatment and Follow-up Tumor Imaging

For participants who discontinue study intervention, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study intervention due to documented disease progression, this is the final required tumor imaging.

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment calculated from the date of allocation until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response (except for HGG), for date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention). RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ.

8.2.1.5 RANO Assessment of Disease

RANO criteria will be used for participants with HGG as the primary measure for assessment of tumor response for date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention). A standard MRI-imaging protocol will be performed for use in the assessments. Refer to Appendix 8 for RANO response criteria.

8.2.2 Palatability and Acceptability of Lenvatinib Suspension Formulation

The palatability and acceptability of lenvatinib suspension formulation will be assessed using a palatability questionnaire. All participants who receive suspension formulation, with the exception of participants using a NG or G tube, must complete the questionnaire according to the SoA. If the participant is unable to complete the questionnaire, this must be done by a parent or legal guardian. Measurement of palatability will be assessed using a facial hedonic scale [Guinard, J. X. 2001].

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the laboratory manual. Refer to Appendix 7 for country-specific requirements.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A comprehensive physical and oral examination or symptom-directed physical and oral examination will be performed as designated in the SoA (Section 1.3). A complete physical and oral examination at C1D1 will be performed only if the screening physical and oral examination was performed >7 days prior to C1D1.

A comprehensive physical and oral examination will include evaluations of the head, eyes, ears, nose, mouth including maxillary and mandibular mucosa, throat, neck, chest (including heart and lungs), abdomen, limbs, and skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Dental Examination

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

Dental examination by a dentist or qualified dental professional should be conducted per local institutional guidelines during screening and thereafter per local standard of care, but no less than annually, and at EOT. The baseline dental examination can occur up to 4 weeks after the first dose of study intervention. If the most recent dental examination is within 6 months prior to the EOT visit, the dental examination is not required.

Post-screening dental examinations are not required for participants for whom permanent teeth (excluding third molars) are evaluated to be fully erupted at screening.

8.3.3 Vital Signs

Vital sign measurements (ie, systolic and diastolic BP [mm Hg], pulse rate [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), weight [kg], and height [cm]) will be obtained at the visits designated in the SoA (Section 1.3) by a validated method.

- BP and heart rate will be measured after the participant has been resting for approximately 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

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

- At the C1D8 contact (clinic or telephone visit), and if required between clinic visits, participants will have BP measured. If the participant does not return to the study site for this BP measurement, BP may be measured, for example, at home or at a local pharmacy, and the results will be reviewed with the investigator or designee. The investigator/site may provide a diary as a tool to aid the participant in collecting BP evaluations between clinic visits. The sponsor will not provide diaries to the site. If BP result raises concerns, the investigator may require additional follow-up, including an on-site BP re-test, or other clinically appropriate intervention(s).

- Height and weight will be assessed at C1D1 and thereafter on Day 1 of every cycle during treatment, and at the EOT Visit. Height will also be monitored every 3 months in efficacy and survival follow-up until puberty has completed. Telephone contact is acceptable for height assessment if clinic visits are not possible at post-treatment visits after the 30-day safety FU.

8.3.4 Electrocardiograms

Electrocardiograms will be obtained as designated in the SoA (Section 1.3):

- Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Where possible, participants must be in the recumbent position for a period of 5 minutes prior to the ECG. The Fridericia correction method for calculating QTc will be used.

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

- An ECG abnormality may meet the criteria of an AE as described in this protocol (see Appendix 3) and the Case Report Form Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the appropriate CRF.

8.3.5 Echocardiograms or Multigated Acquisition Scans

A MUGA scan (using a technetium-based tracer) or an ECHO will be performed to further assess LVEF as designated in the SoA (Section 1.3). MUGA or ECHO scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality. However, whichever modality is used for the initial assessment should be repeated for all subsequent LVEF assessments for that participant. LVEFs as assessed by the institution will be entered on the eCRF. Investigator assessment will be based on institutional reports.

8.3.6 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days for all AEs and all SAEs (or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever occurs first) after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the laboratory manual. Refer to the SoA for the timing of laboratory assessments.

See Appendix 7 for country-specific requirement.

8.3.6.1 Hematology and Clinical Chemistry

Hematology (complete blood count with differential) and clinical chemistry will be performed within 7 days prior to the first dose of study intervention and do not need to be repeated at C1D1 (unless clinically indicated) and within 72 hours prior to all subsequent visits (Appendix 2). All clinical laboratory tests during the study will be performed by local laboratories. All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and sent to the local laboratory on the day of collection, unless otherwise instructed.

All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained and assessed and the results reviewed prior to study drug

administration on C1D1 and within 72 hours prior to the visit for all subsequent cycles. If ≥Grade 3 hematologic or clinical chemistry toxicity, repeat laboratory test and AEs assessment at least every 3 days (until improvement to <Grade 3). Refer to Table 3 for the management of lenvatinib-related toxicity.

Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting treatment.

8.3.6.2 Urine Dipstick/Urinalysis

Urine dipstick (preferred method)/urinalysis testing during screening can be performed within 7 days prior to the first dose of lenvatinib (C1D1) as part of the screening visit and does not need to be repeated at C1D1 (unless clinically indicated) and within 72 hours prior to the visit at subsequent cycles.

Urine dipstick/urinalysis testing will be performed during screening and on Days 1 and 15 of Cycles 1 and 2, on Day 1 of every cycle thereafter or more frequently as clinically indicated, at EOT and at the Safety Follow-up visit (Section 1.3). For participants with proteinuria ≥2+(≥100 mg/dL), urine dipstick/urinalysis testing should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive months. If a new event of proteinuria ≥2+(≥100 mg/dL) occurs, the participant must resume the Day 15 urine dipstick/urinalysis testing for evaluation of proteinuria until results are 1+(≥10 mg/dL) or negative for 2 consecutive months. Participants who have ≥2+(≥100 mg/dL) proteinuria on dipstick urinalysis should perform a spot P/C test and if possible, undergo a 24-hour urine collection. Urine glucose should be performed as part of urine dipstick/urinalysis.

For participants with proteinuria ≥2+(≥100 mg/dL), see Section 6.6.3 for management of proteinuria.

8.3.6.3 Thyroid Function Testing

The screening blood sample for thyroid function testing can be obtained within 7 days prior to the first dose of lenvatinib (C1D1) as part of the screening visit and does not need to be repeated at C1D1 (unless clinically indicated) and within 72 hours prior to all subsequent visits.

Thyroid function tests (TSH and free T4) should be assessed at Screening, C2D1, every 2 cycles thereafter, at EOT, and at the Safety Follow-up visit. Participants may be dosed while thyroid function test results are pending; however, the results must be reviewed by the investigator when available.

8.3.6.4 Lansky Play Score or Karnofsky Performance Status

A Lansky play score or KPS score will be obtained at Screening, at C1D1 prior to allocation, on Day 1 of all subsequent cycles, at the EOT, and at the Safety Follow-up Visit. Scores obtained on C1D1 prior to allocation may also be used as the screening value to determine eligibility. Lansky Play Score will be used for participants up to and including 16 years of age; refer to Appendix 9. KPS will be used for participants >16 years of age; refer to Appendix 10.

8.3.6.5 Proximal Tibial Growth Plate Measurement

Proximal tibial growth plates x-rays will be taken during Screening for participants 2 to 17 years (≥18 years not required). X-ray of only 1 leg is required. X-ray at EOT is only required for participants with open growth plates at screening and must be performed on the same leg as the screening x-ray.

8.3.6.6 Pregnancy Test

Pregnancy tests will be performed at screening and at C1D1 prior to allocation (within 24 hours prior to the first dose of study drug), and repeated on Day 1 of each cycle, from Cycle 2 onward, at the EOT, and at the Safety Follow-up visit.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent but before intervention allocation must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation through 30 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation through 30 days following cessation of study intervention.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through 30 days following cessation of study intervention.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 4.

Table 4 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.7 Events of Clinical Interest

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

Lenvatinib overdose is not considered an ECI.

8.5 Treatment of Overdose

For the purposes of this study, an overdose will be defined as any lenvatinib dose above the protocol-prescribed dose if associated with an AE.

There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients receiving single doses of lenvatinib as high as 40 mg were similar to those in clinical studies at the recommended dose for DTC, renal cell carcinoma, and hepatocellular carcinoma.

No specific information is available on the treatment of overdose of lenvatinib.

All reports of lenvatinib overdose with an AE must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper.

8.6 Pharmacokinetics

PK blood samples will be collected as specified in the SoA (Section 1.3). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in the laboratory manual.

Plasma concentrations of lenvatinib will be measured. Lenvatinib will be analyzed using a population PK approach.

Lenvatinib will be quantified by the use of validated High-Performance Liquid Chromatography-tandem mass spectroscopy methods.

If at some point prospective PK blood sample collection is no longer required, sites will be notified.

8.7 Pharmacodynamics

PD blood samples will be collected as specified in the SoA (Section 1.3). Sample collection, storage, and shipment instructions for PD samples will be provided in the laboratory manual.

8.8 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Buccal swab (DNA) for Genetic Analysis
- Blood for Serum Biomarkers
- Archival Tumor Blocks or Slides (optional)

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the operations/laboratory manual.

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be collected for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.

8.9 Future Biomedical Research Sample Collection

Not applicable.

8.10 Medical Resource Utilization and Health Economics

Not applicable.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Screening

Documented consent/assent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 7 days prior to the first dose of study intervention. Exceptions are hepatitis testing and HIV testing which may be performed up to 28 days prior to the first dose of study intervention, if mandated by local health authority (see Appendix 7 for country-specific requirements).

- Evaluation of Lansky play score or KPS is to be performed within 7 days prior to the first dose of study intervention.

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Providing archival tumor tissue is not required for participation in the study and is an optional collection. If an archival tumor tissue is available from a biopsy performed as standard of care prior to study treatment, it can be submitted to the central laboratory anytime during the study.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

8.11.2 Treatment Period

The estimated duration of lenvatinib treatment is 1 year. However, participants receiving clinical benefit from lenvatinib treatment can continue treatment with lenvatinib until a treatment discontinuation criterion is met.

8.11.3 Telephone Contact or Visit

A telephone contact or visit will be scheduled to report BP and record AEs. Blood pressure can be taken, for example, at home or at a local pharmacy, and will be reviewed with the investigator or medically qualified designee (consistent with local requirements) on C1D8 to assess participants for development of early toxicity, as outlined in the SoA (Section 1.3). An unscheduled visit can occur prior to C1D15 if deemed necessary for safety by the investigator.

8.11.4 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

The EOT visit will take place at the time lenvatinib is discontinued for any reason.

If the EOT visit takes place approximately 30 days from the last dose of lenvatinib, a separate Safety Follow-up visit is not required. All procedures required at the EOT and at the Safety Follow-up visit will be performed as a single visit.

8.11.5 Post-treatment Visits

8.11.5.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first.

8.11.5.2 Efficacy Follow-up Visits

Participants who discontinue lenvatinib for a reason other than disease progression and/or initiation of new anticancer therapy will move into the Efficacy Follow-up Phase and will be assessed as outlined in the SoA (Section 1.3) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study, whichever occurs first. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

8.11.5.3 Survival Follow-up Assessments

Participants will be offered survival follow-up for at least 1 year. Participant survival follow-up status will be assessed approximately every 12 weeks until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the efficacy follow-up phase, the first survival follow-up assessment will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last).

- For participants who completed assessments in the efficacy follow-up phase, the first survival follow-up assessment will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.11.6 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. A separate molecular profiling analysis plan will be developed to explicitly address exploratory biomarker objectives.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below; the comprehensive plan is provided in Sections 9.1-9.12.

Study Design Overview	An Open-Label, Multicenter Phase 2 Basket Study to Evaluate the antitumor activity and Safety of Lenvatinib in Children, Adolescents, and Young Adults with Relapsed or Refractory Solid Malignancies
Treatment Assignment	A minimum of 36 evaluable participants will be enrolled: 9 evaluable participants in each of the tumor types. The final sample size of participants will depend on the number of tumor types that meet the futility bar and the antitumor activity in evaluable participants observed in the corresponding tumor cohort in Study E7080-A001-216. The enrollment in the HGG, RMS, and EWS/pPNET cohorts is capped at a maximum of 17 evaluable participants each. The enrollment for each tumor type expanded based on response in the other solid tumors' cohort is also capped at a maximum of 17 evaluable participants. Based on these factors and the projected enrollment period, it is estimated that up to approximately 150 participants could be enrolled. The participants will receive lenvatinib 14 mg/m^2 orally once daily (equivalent to 24 mg QD, the adult daily dose).
Analysis Populations	Antitumor activity: Evaluable Analysis Set (EAS), defined as all evaluable participants, 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. Safety: Safety Analysis Set, defined as all participants who received at least 1 dose of the study drug. Pharmacokinetic (PK): PK Analysis Set, defined as participants in Safety Analysis Set who had at least 1 measurable postdose plasma concentration with an adequately documented dosing history.
Primary Endpoint(s)	The **Primary Endpoint** will be assessed for each tumor type: ORR, defined as the proportion of participants with a confirmed (≥4 weeks after initial response) CR or PR per RECIST 1.1 or RANO for HGG as assessed by investigator, at Week 16.
Key Secondary Endpoints	• ORR • BOR • DOR • DCR • CBR • PFS per RECIST 1.1 or RANO for HGG • AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECGs, urine dipstick, Lansky play scores or Karnofsky performance status scores, physical examination findings, dental examination findings, height, and closure of proximal tibial plates. • Palatability questionnaire using a facial hedonic scale.

Statistical Methods for Key Efficacy Analyses	To evaluate for efficacy of lenvatinib, data on antitumor activity will be analyzed by each tumor type. Objective responses will count only confirmed CR and PR at Week 16. Estimated ORR and its exact 95% CI using the method of Clopper and Pearson will be presented. The ORR, DCR, and CBR will be provided with exact 95% CIs using the method of Clopper and Pearson, and the DOR will be analyzed for responders using Kaplan-Meier approach. PFS will be analyzed using Kaplan-Meier product-limit estimates. The cumulative PFS probabilities will be plotted over time as appropriate.
Statistical Methods for Key Safety Analyses	The incidence of treatment-emergent adverse events (TEAEs) and SAEs will be summarized by system organ class and preferred term. Continuous measures such as changes from baseline in laboratory test data, vital signs, 12-lead ECGs, cardiac function by echocardiography or MUGA scan, urine dipstick, and Lansky play scores or KPS scores will be summarized using descriptive statistics (mean, standard deviation, etc.) for baseline, on-treatment, and change-from-baseline values.
Interim Analyses	Multiple interim analyses may be performed in this study due to the sequential monitoring procedure. Results will be reviewed by the study team. Within each tumor type, the study will enroll a minimum of 9 evaluable participants.
Multiplicity	No additional multiplicity adjustment is required for this study.
Sample Size and Power	CCI [redacted]

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study is being conducted as an open-label study (ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned).

The Clinical Biostatistics department will generate the allocation schedule(s) for study treatment assignment. Allocation will be implemented in an IVRS. Participants will be allocated by nonrandom assignment.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy Endpoints

Primary Endpoints

- **ORR**: defined as the proportion of participants with a confirmed (≥4 weeks after initial response) CR or PR per RECIST 1.1 or RANO for HGG as assessed by investigator, at Week 16.

Secondary Endpoints

- **ORR**.
- **BOR**: defined as the participant's best confirmed response (CR or PR) over the treatment period.
- **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).
- **DCR:** defined as the percentage of participants who have a BOR of CR, PR, or SD. To be assigned a best overall response of SD, the time from the first administration of study drug until the date of documented SD should be ≥7 weeks.
- **CBR**: defined as the percentage of participants who have a BOR of CR, PR, or durable SD (SD duration ≥23 weeks since the first dose of the study treatment).
- **PFS:** defined as the time from the date of the first administration of study drug until the date of first documentation of PD per RECIST 1.1 or RANO for HGG or death (whichever occurs first).

Tertiary/Exploratory Endpoints

- **OS:** defined as the time from the date of the first administration of study drug until the date of death from any cause.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECGs, urine dipstick, Lansky play scores or KPS scores, physical examination findings, dental examination findings, height, and closure of proximal tibial plates.

9.4.3 Pharmacokinetic Endpoints

PK blood samples will be collected as outlined in the SoA (Section 1.3). Lenvatinib concentration versus time data will be tabulated, summarized, and graphically presented.

Lenvatinib data will be pooled with available data from other studies and subjected to population PK analysis. The PK model will be parameterized in terms of clearance and volume of distribution. Details of the population PK analysis, if performed, will be provided in a separate analysis plan.

9.4.4 Palatability and Acceptability Questionnaire

Measurement of palatability will be assessed using a facial hedonic scale [Guinard, J. X. 2001] in participants receiving the suspension formulation in the study.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The EAS population will serve as the primary population for the analysis of antitumor activity data within each tumor type in this study. EAS is defined as all evaluable participants, 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 Details on the approach to handling missing data are provided in Table 5.

9.5.2 Safety Analysis Population

The Safety Analysis Set population will be used for the analysis of safety data in this study. The safety analysis set population is defined as all participants who received at least 1 dose of the study drug.

At least 1 laboratory or vital sign measurement obtained after at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement at C1D1 prior to allocation is also required.

9.5.3 Pharmacokinetic Analysis Population

The population for PK analysis includes participants in safety analysis set who had at least 1 measurable post dose plasma concentration with an adequately documented dosing history.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary efficacy objectives. Methods related to exploratory objectives will be described in the sSAP.

Antitumor activity data will be analyzed by each tumor type. The data cutoff for the primary study analysis for a given tumor type will be determined by the study team, based on the review of data at each interim analysis and predetermined futility guidance.

Only those participants who have measurable disease present at baseline and have their disease re-evaluated at postbaseline visits will be considered evaluable for ORR. These participants will have their response classified according to RECIST 1.1 or RANO for participants with HGG.

Primary Efficacy Analysis

ORR: Objective responses will count only confirmed CR and PR at Week 16. Estimated ORR and its exact 95% CI using the method of Clopper and Pearson will be presented.

Secondary Efficacy Analyses

The BOR will be provided with the descriptive statistics. The ORR, DCR, and CBR will be provided with exact 95% CIs using the method of Clopper and Pearson, and the DOR will be analyzed for responders using Kaplan-Meier approach.

The secondary endpoint of PFS will be analyzed using Kaplan-Meier product-limit estimates. Median PFS and the cumulative probability of PFS at 4, 6, 12, and 24 months will be presented with 2-sided, 95% CIs when an adequate number of at-risk participants at those time points warrant the estimate. The cumulative PFS probabilities will be plotted over time as appropriate.

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 5.

Table 5 Table Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses – Within tumor type			
ORR (RECIST 1.1 or RANO for HGG) at Week 16	Summary statistics using Clopper and Pearson method	EAS	Participants in EAS with missing data are considered nonresponders.
Secondary Analyses – Within tumor type			
ORR	Summary statistics using Clopper and Pearson method	EAS	Participants in EAS with missing data are considered nonresponders.
BOR	Summary statistics using Clopper and Pearson method	EAS	Missing observation in EAS population are counted as nonresponders.
DCR	Summary statistics using Clopper and Pearson method	EAS	Missing observation in EAS population are counted as nonresponders.
CBR	Summary statistics using Clopper and Pearson method	EAS	Missing observation in EAS population are counted as nonresponders.
DOR	Summary statistics using Kaplan-Meier method	All responders in EAS	Nonresponders are excluded in analysis.
PFS (RECIST 1.1 or RANO for HGG)	Summary statistics using Kaplan-Meier method	EAS	Censored at last assessment.

Abbreviations: BOR=best overall response; CBR=clinical benefit rate; DCR = disease control rate; DOR = duration of response; EAS = evaluable analysis set; ORR=overall response rate; PFS = progression-free survival; RANO= Response Assessment in Neuro-Oncology; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, laboratory tests, and vital signs. Safety summaries will be pooled across all indications. The additional safety analyses for each tumor type might be conducted if desired and will be documented in the sSAP. The safety analysis population will be used for the analysis of safety data. TEAE is defined as all AEs from the treatment start date until 30 days after last dose (30 days for SAE). The incidence of TEAEs and SAEs will be summarized by system organ class and preferred term. Continuous measures such as changes from baseline in laboratory test data, vital signs, 12-lead ECGs, cardiac function by echocardiography or MUGA scan, urine dipstick, and Lansky play scores or KPS scores will be summarized using descriptive statistics (mean, standard deviation, etc.) for baseline, on-treatment, and change-from-baseline values.

9.6.3 Summary of Baseline Characteristics, Demographics, and Other Analyses

Baseline characteristics will be assessed by the use of tables and/or graphs for each tumor type with at least 9 evaluable participants enrolled. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, allocated, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age, gender), baseline characteristics, and prior and concomitant medications, medical/surgical history will be summarized by descriptive statistics or categorical tables.

9.6.4 Statistical Methods for Pharmacokinetic, Pharmacodynamic, and Other Biomarker Analyses

Plasma concentrations of lenvatinib versus time data will be tabulated with descriptive statistics and the individual data graphed. Plasma concentrations of lenvatinib versus time data will be analyzed using a population PK approach to estimate population PK parameters. The analysis will be detailed in an analysis plan at a later date.

Pharmacokinetic data will be summarized using n, mean, standard deviation, percent coefficient of variation, geometric mean, median, minimum, and maximum.

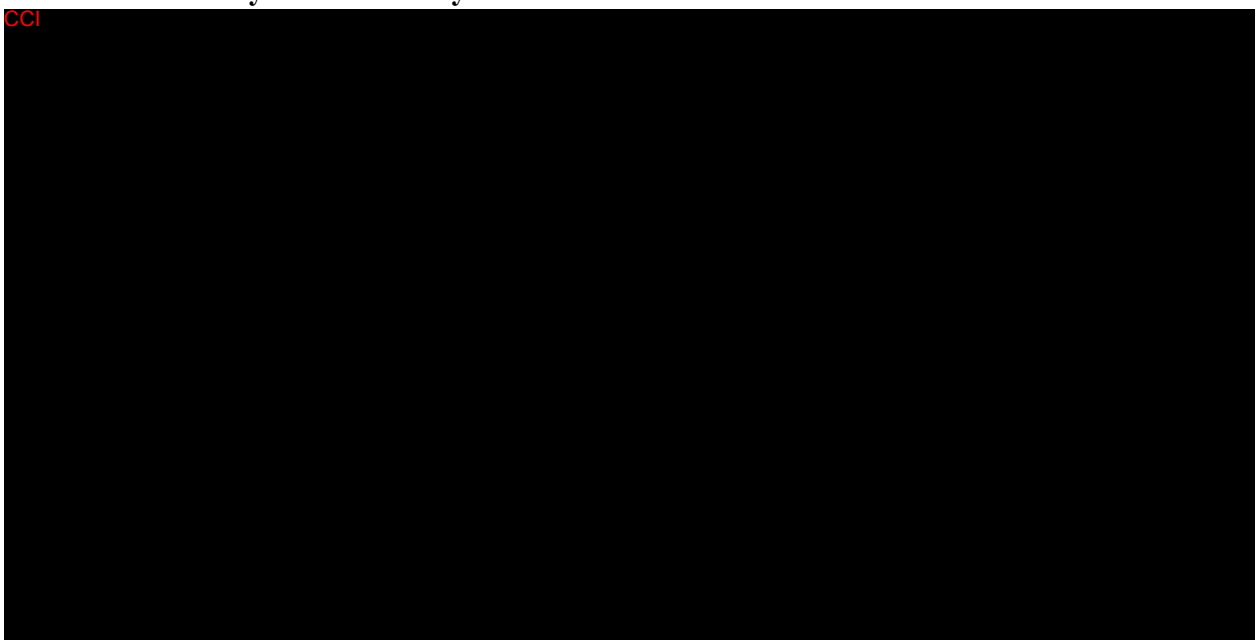
9.7 Interim Analyses

9.7.1 Safety Interim Analyses

The DMC will review accumulating safety data periodically to provide an opportunity to terminate the study early if there are safety concerns. The timing of the safety monitoring will be specified in the DMC charter.

9.7.2 Efficacy Interim Analysis

CCI



CCI

[redacted]

CCI

[redacted]

9.8 Multiplicity

No multiplicity adjustment is required because each disease indication will be evaluated independently.

9.9 Sample Size and Power Calculations

CCI

[redacted]

CCI

[redacted]

9.10 Subgroup Analyses

No subgroup analysis is planned.

9.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

Extent of exposure for a participant will be measured by number of cycles and number of days in which the participant receives the study medication. Summary statistics will be provided on extent of exposure for the safety analysis population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

scientific/research misconduct or serious GCP non compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time and labor intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the study team regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7) and recommend to the study team whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their

disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator’s knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent/assent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 7 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count Red Blood Cell (RBC) Count Hemoglobin Hematocrit International Normalized Ratio (INR) or prothrombin time (PT)[a]	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
Chemistry	**Renal Function Tests**	**Electrolytes[c]**	**Liver Function Tests**	**Other Chemistries**
	Blood urea nitrogen (BUN)[b] Creatinine	Potassium Carbon dioxide (CO_2) or bicarbonate[d] Sodium Calcium Chloride Magnesium Phosphorous	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Total bilirubin Direct bilirubin[e]	Albumin Amylase Lipase Glucose[f] Lactate dehydrogenase Total protein
Thyroid Function Tests	Thyroid-stimulating hormone (TSH) Free thyroxine (T4)			
Urine dipstick/urinalysis testing,[f, g]	• Glucose, protein, blood • Urinalysis for microscopy[g]: Microscopic examination for RBCs/high-power field.			
Other Screening Tests	• Serum or urine β human chorionic gonadotropin (β-hCG) pregnancy test (as needed for women of child-bearing potential [WOCBP]).			

NOTES:
a. INR or PT should only be performed as part of the screening assessment and as clinically indicated.
b. Urea is acceptable if BUN is not available as per institutional standard.
c. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting treatment.
d. Perform only if considered local standard of care.
e. Direct bilirubin should be assessed if total bilirubin is elevated.
f. If urine protein is ≥2+, then a spot test for protein-creatinine ratio and if possible, a 24-hour urine collection should be done to quantify the 24-hour urine protein excretion.
g. If urine dipstick/urinalysis testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. Lenvatinib overdose without an associated adverse event is not reportable as an AE. Refer to Section 8.5 for the definition of overdose.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study)

- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of causality

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b,c] • IUS[c] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin-releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable

10.7 Appendix 7: Country-specific Requirements

10.7.1 Sweden

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

If applicable, the 2009 Schwartz equation must be used to estimate GFR for participants aged <18 years (ie, eGFR 36.5 x height [cm]/plasma creatinine [µmol/L]) [Schwartz, G. J., et al 2009].

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

10.7.2 Czech Republic

Section 5.2 Exclusion Criteria

11. Known to be HIV positive. Note: HIV testing is required at screening.

12. Has known active viral hepatitis B virus (eg, HBsAg reactive) or Hepatitis C virus (eg, HCV RNA [qualitative] is detected) infection. Note: Testing for hepatitis B or hepatitis C is required at screening.

Section 8.11.1 Screening

Laboratory tests are to be performed within 7 days prior to the first dose of study intervention. Exceptions are hepatitis testing and HIV testing which may be performed up to 28 days prior to the first dose of study intervention.

10.7.3 Italy

- eGFR for pediatric subjects under 18 years old should be calculated exclusively with the Bedside Schwartz equation for participants in Italy.

- The blood volume to be taken from a pediatric participant must not exceed the allowable maximum outlined in “Ethical Considerations for Clinical Trials on Medicinal Products Conducted With Minors” (3% of the total blood volume over a 4-week period or 1% at any single time)[European Commission 2017]. If the blood volume is insufficient to conduct all planned analyses, safety laboratory tests should be prioritized for participants in Italy.

10.8 Appendix 8: Response Assessment in Neuro-Oncology (RANO) Response Criteria

For HGG, treatment response assessment will be based on the RANO criteria [Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, 2010], using a combination of clinical and imaging data. At baseline, tumor burden is documented by selection of lesions that will be followed quantitatively (target lesions) and qualitatively (nontarget). At each visit afterward, imaging assessment consists of evaluating target and nontarget lesions, searching for new lesions, and review of the abnormalities on Fluid Attenuated Inversion Recovery (T2/FLAIR) images. These assessments are combined into a radiographic response, which is then combined with clinical performance status and steroid dose information to determine the overall response for each visit. Endpoint information, such as the best overall response, is determined from the sequence of visit responses as described in the SAP.

Scan acquisition

Imaging will be acquired using the standardized Brain Tumor Imaging Protocol [Ellingson, B. M.,Bendszus, M., et al 2015]. It will include pre- and post-contrast T1-weighted MRI, as well as T2/FLAIR and diffusion-weighted imaging. The same technique should be used at baseline and all follow-up scans.

Lesion measurements

Lesions should be measured on T1 weighted post-gadolinium images, in the axial plane. The 2 maximal perpendicular outer diameters of each enhancing lesion should be measured. In lesions that have cystic components, areas of necrosis, or surgical cavities, every effort should be made to measure only the solid portions of the lesion, excluding the non-solid components. In particular, if a patient has a surgical cavity surrounded by enhancement, the cavity should not be included in the measurement. If there is nodular enhancement associated with the cavity, the nodular component alone should be measured.

Baseline tumor documentation

Reviewers will document baseline tumor on post-contrast T1-weighted and T2/FLAIR images. They first identify all lesions, determine whether they are measurable (can be measured), and from these choose target lesions (will be measured throughout the trial). To be considered measurable, a lesion has to show enhancement, have 2 perpendicular diameters ≥10 mm, and be suitable for reproducible repeated measurements. Enhancing non-measurable lesions include all other enhancement that is strongly believed to represent tumor, but that does not meet the requirements above. Up to 5 lesions can be selected as target. Selected target lesions are measured, and the sum of products of diameters (SPD) calculated. Enhancing nontarget lesions are identified by location only. Because T2/FLAIR abnormalities are typically more diffuse than tumor enhancement, the T2/FLAIR images will be used for comparison when evaluating later visits, without identification of discrete lesions.

Radiographic response assessment

Target lesion response is determined by the change in the sum of diameters from baseline and from nadir (smallest measurement seen until the visit being evaluated) (Table 8).

Table 8 Target Lesion Response

Response	Definition
Complete Response (CR)	All target lesions have completely disappeared.
Partial Response (PR)	SPD decreased by ≥50% from baseline value.
Stable Disease (SD)	SPD <50% decreased from baseline, but <25% increased from nadir.
Progressive Disease (PD)	SPD increased by ≥25% from nadir value.
Non-evaluable (NE)	The sum of diameters cannot be meaningfully evaluated (for example, because of technical factors such as scan quality that obscure one or more target lesions).

Nontarget lesion response is determined by visual inspection of enhancing nontarget lesions collectively and classification into a response category (Table 9).

Table 9 Lesion Response for Enhancing Nontarget Lesions

Response	Definition
Complete Response (CR)	All enhancing nontarget lesions have disappeared completely.
Stable Disease (SD)	Enhancing lesions present, showing no definite growth from the visit where they were smallest.
Progressive Disease (PD)	Unequivocal progression of enhancing lesions (see below).
Non-evaluable (NE)	The sum of diameters cannot be meaningfully evaluated (for example, because of technical factors such as scan quality that obscure one or more target lesions).
Note on PD: The general approach is that nontarget lesions can be the basis for a determination of PD if it is clear, in the context of the entire scan, that there has been a sufficient increase in the tumor burden to demonstrate that treatment has failed.	

New lesions are assessed in a binary yes/no fashion. If any new enhancing lesions are present, and the reviewer is confident that these are due to the presence of new malignancy, the response is “Yes,” otherwise, it is “No.” New lesions do not need to meet the size criteria for being considered measurable at baseline, but must, in the best judgment of the reviewer, be true tumor lesions rather than benign or incidental findings, or caused by some comorbidity. If the lesion is uncertain, it should be followed. If later scans reveal it to be a true lesion, the record can be retrospectively updated to show the new lesion at the time it was first identified.

The T2/FLAIR images are reviewed to determine whether there has been an unequivocal increase in tumor-related T2/FLAIR abnormality. This is performed with reference to the scan at which the T2/FLAIR abnormality is smallest (analogous to the nadir measurement for target lesions), and classified as increase, decreased, or unchanged. Because of the frequently

diffuse nature of the T2/FLAIR abnormality, it is performed at the scan level rather than by evaluation of discrete T2/FLAIR lesions. The reviewer must be confident that any recorded increase in T2/FLAIR abnormality is due to tumor rather than some alternative etiology (such as infection, infarction, demyelination, or other causes). If there is question about whether a change seen on T2/FLAIR represents progression, the participant continues to the next scheduled scan. If the subsequent scan confirms progression, the date of progression can be assigned retrospectively to the visit where the T2/FLAIR changes were first observed.

Target, nontarget, and new lesions are combined into a radiographic response (Table 10).

Table 10 Radiographic Response

Target Lesions	Enhancing Nontarget Lesions	FLAIR/T2 Lesions	New Lesions	Radiographic Response
CR	CR	No increase	No	CR
CR	SD or NE	No increase	No	PR
PR	CR, SD, or NE	No increase	No	PR
SD	CR, SD, or NE	No increase	No	SD
NE	CR, SD, or NE	No increase	No	NE
PD	Any	Any	Yes/No	PD
Any	PD	Any	Yes/No	PD
Any	Any	Any	Yes	PD
Any	Any	Increased	Yes/No	PD
NA[a]	CR	No increase	No	CR
NA[a]	SD	No increase	No	SD
NA[a]	NA[a]	No increase	No	NED[b]

[a] NA – No lesions of this type were present at baseline.
[b] NED (No evidence of disease) – No enhancing lesions were present at baseline, and no new lesions have appeared.

Pseudoprogression associated with radiotherapy

If new or increased enhancement is seen within 12 weeks of the completion of radiation therapy, but the participant is clinically stable and the investigator believes that the changes may be due to pseudoprogression, the participant may remain on treatment. A second scan should be performed, at least 6 weeks after the initial scan. If the enhancement continues to grow on this scan, progression is considered to have been confirmed at the time of the initial scan that showed increased enhancement. If the enhancement has stabilized or decreased on this second scan, the initial scan will be considered to have been confirmed as pseudoprogression. For endpoint assessment purposes, the initial scan will be equivalent to SD. On subsequent scans, in cases of confirmed pseudoprogression, all scans prior to the scan at which pseudoprogression was seen will be excluded when choosing the nadir value against which the size of enhancing lesions is compared.

If the new or increased enhancement occurs in an area that is known to be outside the irradiated area (outside the 80% isodose line), or if the participant shows clinical deterioration not caused by a comorbid condition or changes in steroid dosing, pseudoprogression will not be considered.

Overall Response

To make a final response determination, the radiographic response (Table 10) is combined with assessments of clinical status and of corticosteroid dose (Table 11).

Clinical status is measured using the Karnofsky Performance Scale. A participant's status is considered "stable" if there has been no definite decline in age-adjusted performance from their baseline state and is considered "worsening" if there has been definite decline in age-adjusted performance that is not attributable to a non-tumor-related cause. Examples of definite decline include a decline from 100 or 90 to 70 or less, a decline of at least 20 points from 80 or less, or a decline from any baseline to 50 or less, unless attributable to comorbid events or changes in corticosteroid dose.

Steroid dose is defined as the average daily dose since last visit. A dose of "none" means no corticosteroids above physiologic replacement dose. The dose is considered "stable" if it is unchanged or decreased from the visit at which the scans showed the smallest tumor burden. The dose is considered "increased" if it has increased from the visit at which the scans showed the smallest tumor burden.

For any overall response except PD, all the components of the definition (radiological, neurological, and steroid dose) must be present. However, either radiological progression or clinical deterioration (not attributable to a non-tumor-related cause) qualifies a participant for PD. However, an increase in steroid dose alone is not sufficient for an overall visit response of PD in the absence of clinical or radiological evidence of progression. A participant with a radiological response of SD, and without neurological evidence of progression, but requiring an increased dose of steroids, would still be considered SD overall at that visit (because increase in steroids alone is not PD). However, the participant will be reassessed at the next visit. If either radiological or neurological progression is documented at that next visit, the visit at which the increased dose was first observed would be retroactively reassessed as PD overall.

Table 11 Overall Response

Radiographic Response	Clinical Performance	Steroid Dose	Overall Response
CR	Stable	None	CR
CR	Stable	Stable or increased	PR
PR	Stable	Stable	PR
PR	Stable	Increased	SD
SD	Stable	Stable	SD
SD	Stable	Increased	SD or PD[a]
PD	Any	Any	PD
Any	Worsening	Any	PD
NE	Stable	Increased	NE or PD[a]
NED	Stable	Increased	NED or PD[a]

[a] PD should not be based on an increase in steroid dose alone, unless confirmed by radiographic or clinical deterioration. If the steroid dose is increased while the radiographic assessment and clinical performance are stable, the participant should be re-evaluated at the next visit. If clinical or radiographic deterioration has occurred, progression can be retrospectively assigned at the visit when the steroid dose was increased.

Pseudoresponse and response confirmation

Pseudoresponse is a phenomenon observed in patients treated with antiangiogenic therapy and manifests as a transient decrease in tumor enhancement that does not reflect a true reduction in tumor burden. To avoid mistaken reporting of pseudoresponse as objective response, a visit response of PR or CR must be confirmed with a scan performed at least 4 weeks later that shows the same category of response or better. That is, a PR can be confirmed with a subsequent PR or CR, and a CR must be confirmed with a subsequent CR.

10.9 Appendix 9: Lansky Play Score

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

100 Fully active, normal.

90 Minor restrictions in physically strenuous activity.

80 Active, but tires more quickly.

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

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

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

40 Mostly in bed; participates in quiet activities.

30 In bed; needs assistance even for quiet play.

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

10 No play; does not get out of bed.

0 Unresponsive.

Adapted from: [Lansky, S. B., et al 1987].

10.10 Appendix 10: Karnofsky Performance Status Scale Definitions Rating (%) Criteria

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

Adapted from: [Crooks, V., et al 1991] [Hollen, P. J., et al 1994] [O'Toole, D. M. 1991].

10.11 Appendix 11 Blood Pressure Levels for Boys by Age and Height Percentile

	BP	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
AGE	Percentile	Percentile of Height							Percentile of Height						
(Year)	Ð	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

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

Abbreviations: BP blood pressure; SD standard deviation.

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

10.12 Appendix 12: Blood Pressure Levels for Girls by Age and Height Percentile

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

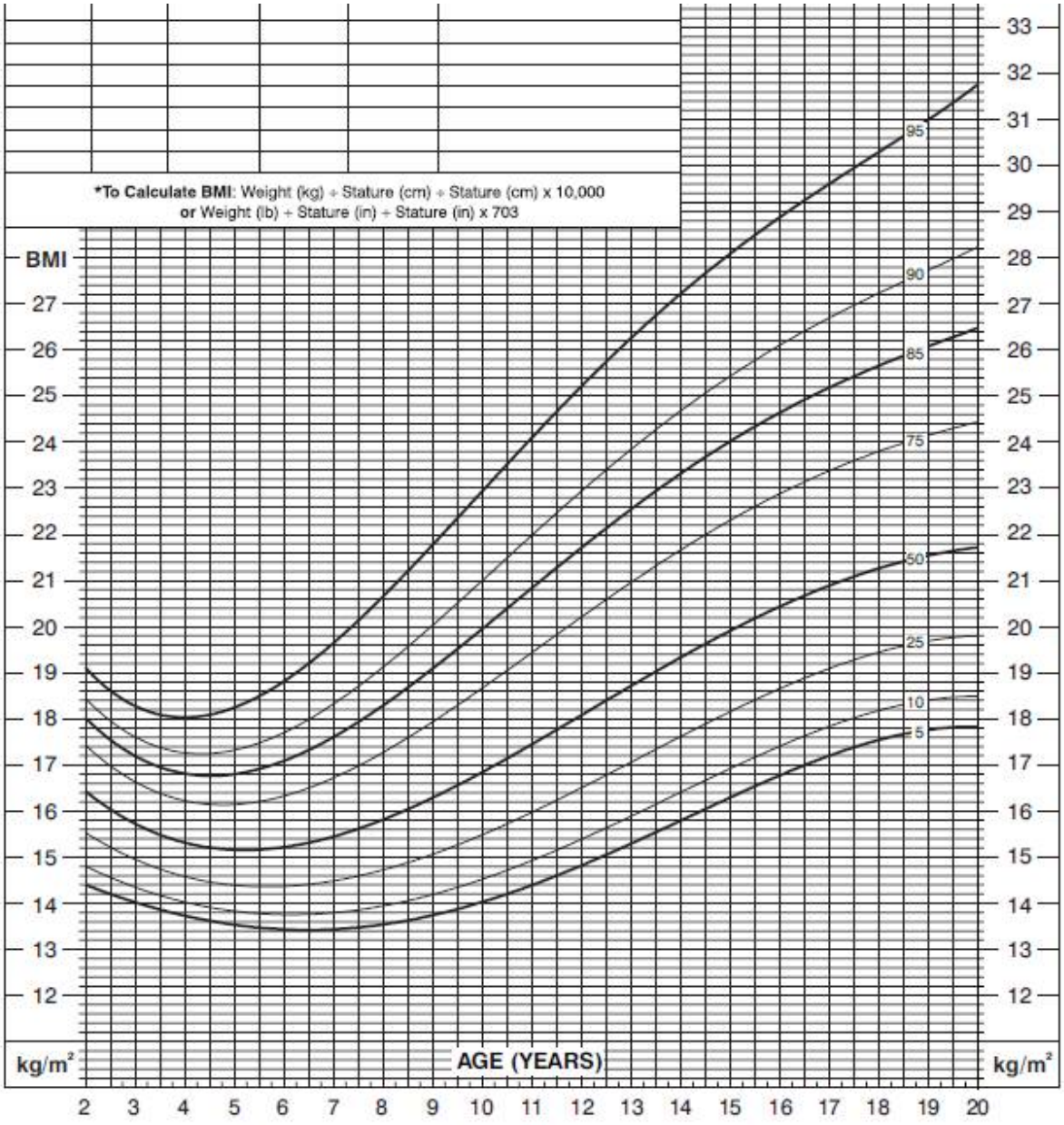
	BP	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
AGE	Percentile	Percentile of Height							Percentile of Height						
(Year)	Ð	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74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

Abbreviations: BP blood pressure; SD standard deviation.

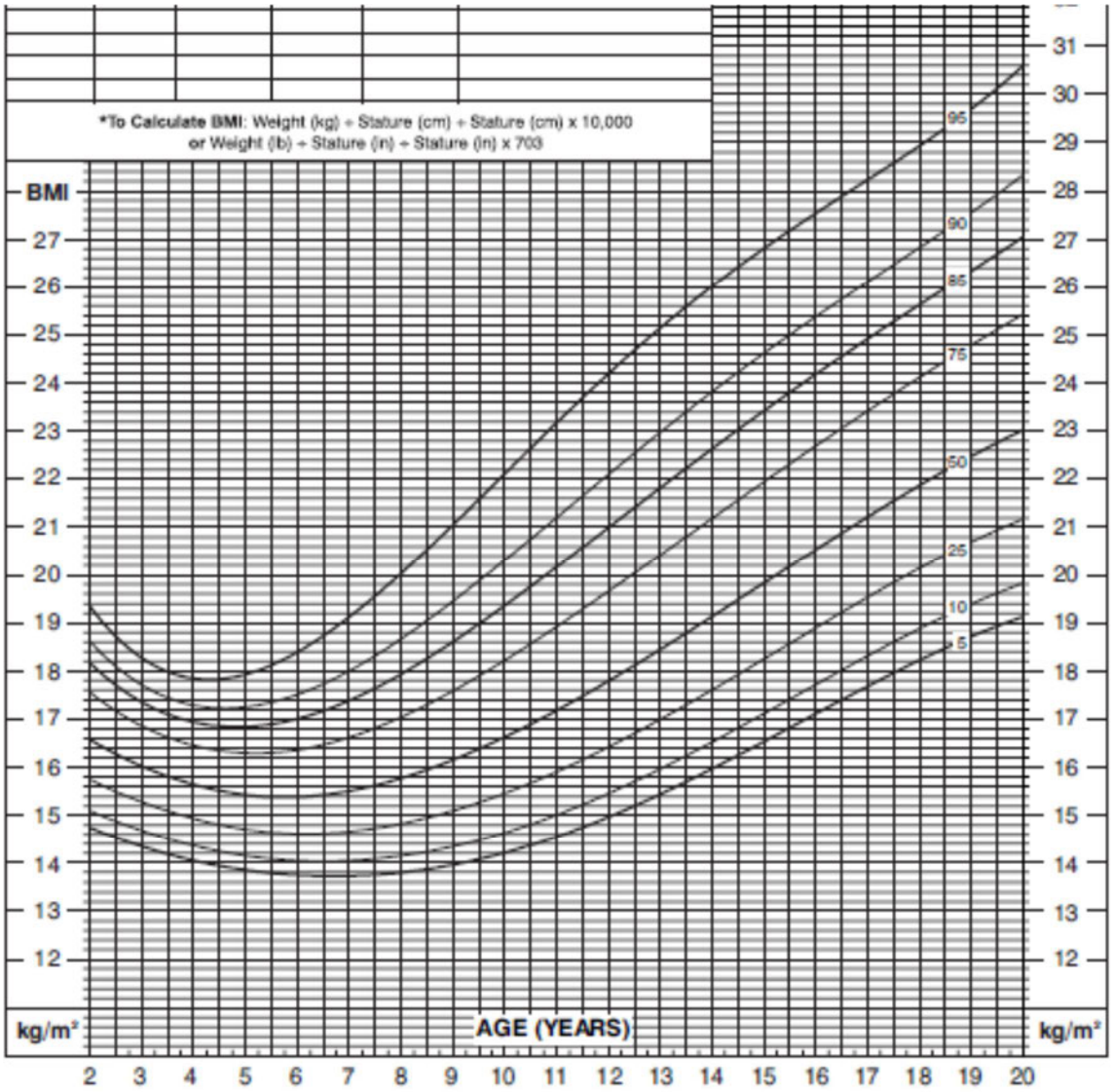
Note: The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

10.13 Appendix 13: Body Mass Index-For-Age Percentiles

2 to 20 years: Girls



2 to 20 years: Boys



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

http://www.cdc.gov/growthcharts

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

10.14 Appendix 14: Monoclonal Antibodies Half-Lives

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

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

10.15 Appendix 15: Abbreviations

Abbreviation	Expanded Term
ADL	activities of daily living
AE(s)	adverse event(s)
AFP	alpha fetoprotein
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Ang	angiopoietin
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
bFGF	basic fibroblast growth factor
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BOR	best overall response
BP	blood pressure
BSA	body surface area
BUN	Blood Urea Nitrogen
CBR	clinical benefit rate
CBTRUS	The Central Brain Tumor Registry of the United States
CDC	Centers for Disease Control
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
C[x]D[y]	Cycle [x] Week [y]
DCR	disease control rate
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DTC	differentiated thyroid carcinoma
EAS	Evaluable Analysis Set
ECG(s)	electrocardiogram(s)
ECHO	echocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOT	end of treatment
EWS	Ewing sarcoma
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendment Acts
FGF	fibroblast growth factor

Abbreviation	Expanded Term
FGFR	fibroblast growth factor receptor
FSH	follicle-stimulating hormone
FU	follow-up
G	gastrostomy
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GI	gastrointestinal
HBsAg	Hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	Hepatitis C Virus
HGF	hepatocyte growth factor
HGG	high-grade glioma
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
^{131}I-MIBG	radiolabeled antibody, iodine-131 metaiodobenzylguanidine
IFN-γ	interferon gamma
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IHC	immunohistochemistry
IMP	investigational medicinal product
INR	International Normalized Ratio
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVRS	interactive voice response system
KDR	kinase insert domain receptor
KPS	Karnofsky performance status
LAM	lactational amenorrhoea method
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MIBG	meta-iodobenzylguanidine scan
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MUGA	multiple gated acquisition scan
NCT	National Clinical Trial
NG	nasogastric
NHLBI	National Heart Lung and Blood Institute
ONJ	osteonecrosis of the jaw
OR	objective response
ORR	objective response rate
OS	overall survival
P/C	protein/creatinine
PD	disease progression
PDGF(R)	platelet-derived growth factor (receptor)

Abbreviation	Expanded Term
PFS	progression-free survival
PK	pharmacokinetic
PlGF	placental growth factor
po	orally
pPNET	peripheral primitive neuroectodermal tumor
PR	partial response
PRES/RPLS	Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome
PT	prothrombin time
QD	once daily
QT	Q wave T wave
QTcF	QT interval correction by Fridericia
Q[x]W	every [x] weeks
RANO	Response Assessment in Neuro-Oncology
RBC	red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1
RET/PTC	rearranged transformation/papillary thyroid carcinoma
RF	radiofrequency
RMS	rhabdomyosarcoma
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results (www.seer.cancer.gov)
SIM	Site Imaging Manual
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SPD	sum of product diameters
SPRT	sequential probability ratio testing
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
T4	thyroxine
TAMs	tumor-associated macrophages
TEAE	treatment-emergent adverse event
TiTE CRM	time-to-event continual reassessment method
TKI	tyrosine-kinase inhibitor
TME	tumor microenvironment
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WOCBP	woman/women of childbearing potential
XRT	radiotherapy

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