Protocol Title:

A phase II, randomized, open-label study to assess the efficacy, safety, and pharmacokinetics (PK) of maintenance cabozantinib (XL184) plus best supportive care (BSC) versus BSC in children, adolescents and young adults (AYA) with unresectable residual osteosarcoma either at diagnosis or at first relapse after standard treatment.

Protocol Number: CLIN-60000-461

Compound: Cabozantinib

Study Name**:** CabOSTar

Short Title:

Effects of maintenance cabozantinib+BSC versus BSC in children and AYA with osteosarcoma.

Study Phase: Phase II

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Date: 20 January 2025
Version number: 4.2
Amendment: EU-2

Persons supplied with this information must understand that it is strictly confidential. Information contained herein cannot be disclosed, submitted for publication or used for any purpose other than that contemplated herein without the sponsor's prior written authorisation.

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Principal Investigator Signature Page

I have read and agree to Protocol CLIN-60000-461 Version 4.2 entitled "A phase II, randomized, open-label study to assess the efficacy, safety, and pharmacokinetics (PK) of maintenance cabozantinib (XL184) plus best supportive care (BSC) versus BSC in children, adolescents and young adults (AYA) with unresectable residual osteosarcoma either at diagnosis or at first relapse after standard treatment." I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:

TITLE: PRINCIPAL INVESTIGATOR SIGNATURE:

DATE:

OFFICE: [ ]
[ ]
[ ]
[ ]
[ ]

PROTOCOL AMENDMENT SUMMARY OF CHANGES

	DOCUMENT HISTORY		
Document	**Version**	**Date**	**Status**
Local Amendment EU-2	4.2	20 January 2025	Effective
Amendment 3	4.0	26 September 2024	Superseded
Local Amendment EU-1	3.2	07 May 2024	Superseded
Local Amendment GBR 1	3.1	28 March 2024	Superseded
Amendment 2	3.0	29 November 2023	Superseded
Amendment 1	2.0	07 November 2023	Superseded
Original Protocol	1.0	25 September 2023	Superseded

Amendment EU-2 (20 January 2025)

Overall Rationale for the Amendment:

Changes have been made to the protocol to remove the requirement for mandatory CT of the neck, leaving this optional and as per Investigator judgment.

Summary change table from previous version of the protocol

Any new or amended text in the protocol is indicated in bold (IS column). Deletions are marked in strikeout text (WAS column). Minor formatting and editing are not included.

Section	WAS (Version 4.0, 26 SEPTEMBER 2024)	IS (Version 4.2, 20 JANUARY 2025)	Rationale
8.2.1 Tumor Assessments	All CT/MRI (chest/abdomen/pelvis~~/neck~~ (CAP~~N~~) ~~and~~ Extremity (E) (~~if applicable)~~ (CAP~~N~~ ± E), brain) and technetium bone scan imaging studies are recommended to be performed using the study-specified imaging protocol (refer to the most recent version of the imaging manual).	All CT/MRI (chest/abdomen/pelvis (CAP) ± **neck/**extremity (**N**/E) (**as per Investigator's judgement**) (CAP ± **N**/E), brain) and technetium bone scan imaging studies are recommended to be performed using the study-specified imaging protocol (refer to the most recent version of the imaging manual).	To reduce radiation exposure in neck region of pediatric population.

Section	WAS (Version 4.0, 26 SEPTEMBER 2024)	IS (Version 4.2, 20 JANUARY 2025)	Rationale
	Radiographic tumor assessments will include the following: (1) CAP~~N and~~ E ~~(if applicable)~~: CT (or MRI) of CAP~~N~~ ± E will be performed in all participants at screening and every 8 weeks (± 7 days) after randomization during the course of the study. If MRI of the abdomen and pelvis is performed at screening, then a CT of the chest ~~and neck~~ must be performed as well.	Radiographic tumor assessments will include the following: (1) CAP ± **N**/E: CT (or MRI) of CAP ± **N**/E (**as per Investigator's judgment**) will be performed in all participants at screening and every 8 weeks (± 7 days) after randomization during the course of the study. If MRI of the abdomen and pelvis ± **N/E** (**as per Investigator's judgment**) is performed at screening, then a CT of the chest must be performed as well.	
	(2) Brain: MRI (or CT) of the brain will be performed in all participants at screening. After randomization, MRI (or CT) scans of the brain are only required in participants with known brain metastasis following the same post-baseline frequency as the imaging for CAP~~N and~~ E (~~if applicable~~).	(2) Brain: MRI (or CT) of the brain will be performed in all participants at screening. After randomization, MRI (or CT) scans of the brain are only required in participants with known brain metastasis following the same post-baseline frequency as the imaging for CAP ± **N**/E (**as per Investigator's judgement**).	
10.14.2 Exclusion Criteria	(23a)	(23b)	Typographical error in Version 4.0

Amendments to be implemented in the following documents:

Informed consent form	Yes ☐	No ☒
Case report form (CRF)	Yes ☒	No ☐
Statistical analysis plan (SAP)	Yes ☐	No ☒

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LIST OF ABBREVIATIONS

Abbreviation	Wording Definition
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
AMP	Auxiliary Medicinal Product
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AUC	Area under the plasma concentration time curve
AXL	GAS6 receptor
AYA	Adolescent and young adults
B/AKT	Protein kinase B or Akt (serine/threonine kinase)
BIRC	Blinded Independent Radiology Committee
BP	Blood pressure
BSA	Body surface area
BSC	Best supportive care
C1D1	Cycle 1 Day 1
CAP	Chest/abdomen/pelvis
CFR	Code of Federal Regulations (United States of America)
CI	Confidence interval
CIOMS	Council for International Organisations of Medical Sciences
ChT	Chemotherapy
C_{max}	Maximum observed plasma drug concentration
c-MET	Hepatocyte growth factor receptor protein
C_{min}	Minimum observed plasma drug concentration
COG	Children’s Oncology Group
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete remission
CRF	Case report form
CS	Clinically significant

Abbreviation	Wording Definition
CSR	Clinical study report
CT	Computerised tomography
CTOS	Connective Tissue Oncology Society
CTX	Cyclophosphamide
%CV	Coefficient of variation
DBL	Data base lock
DCR	Disease control rate
DICOM	Digital Imaging and Communications in Medicine
DLTs	Dose limiting toxicities
DNA	Deoxyribonucleic acid
DTC	Differentiated thyroid carcinoma
DVT	Deep vein thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EOSI	End of study intervention
ER	Exposure-response
ESMO	European Society for Medical Oncology
ETM	Events to monitor
Eto	etoposide
EU	European Union
EURACAN	European Canadian consortium
EWS	Ewing sarcoma
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase-3
FMS	Type 3 receptor tyrosine kinase that binds to macrophage or monocyte colony-stimulating factor (M-CSF or CSF-1)
FSG	French Sarcoma Group
GCP	Good Clinical Practice

Abbreviation	Wording Definition
G-CSF	Granulocyte colony-stimulating factors
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C virus
HD-MTX	High-dose methotrexate
HGBS	High grade bone sarcomas
HGF	Hepatocyte growth factor
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ifo	ifosfamide
IMP	Investigational Medicinal Product
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
KIT	Stem cell factor
LDH	Lactate dehydrogenase
Len	Lenvatinib
LMWH	Low molecular weight heparins
LR	Local recurrence
MAP	Methotrexate + Adriamycin® (doxorubicin) + platinol ® (cisplatin)
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Wording Definition
Mer	Receptor tyrosine kinase (a TAM receptor)
MET	Mesenchymal-epithelial transition
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MRP2	Multidrug resistance-associated protein 2
MTC	Medullary thyroid cancer
MWA	Microwave thermal ablation
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCCR	National Childhood Cancer Registry
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCI-CTEP	National Cancer Institute – Cancer Therapy Evaluation Program
NCS	Non-clinically significant
NCT	Identification number for ClinicalTrials.gov
N/E	Neck/Extremity
NIMP	Non-investigational medicinal product
NOS	Not otherwise specified
NPACT	Non protocol anticancer therapy
NRSTS	Non-rhabdomyosarcoma soft tissue sarcoma
ORR	Objective response rate
OS	Overall survival
P/C	Protein/creatinine
PD	Progressive disease
PDGFR-β	Platelet derived growth factor receptor beta
PE	Pulmonary embolism
PedsQL	Paediatric quality of life inventory
PEG	Percutaneous endoscopic gastrostomy
PET/CT	Positron emission tomography/computed tomography
PFS	Progression-free survival
PI	Package insert
PK	Pharmacokinetics
PPES	Palmar-plantar erythrodysaesthesia

Abbreviation	Wording Definition
PPI	Proton pump inhibitor
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once daily
QoL	Quality of life
QTc	Corrected QT interval
QTcF	Corrected QT interval calculated by the Fridericia formula
R	Randomization
RANK	Receptor activator of nuclear factor κB
RANKL	RANK ligand
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RET	Rearranged during transfection
RFA	Radiofrequency ablation
RIDA	Ridaforolimus
RMS	Rhabdomyosarcoma
RNA	Ribonucleic acid
ROS1	ROS Proto-Oncogene 1
RP2D	Recommended phase II dose
RPLS	Reversible posterior leukoencephalopathy syndrome
RTK	Receptor tyrosine kinase inhibitor
SAEs	Serious Adverse Events
SAP	Statistical analysis plan
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SoA	Schedule of activities
SoD	Sum of the diameters
StD	Standard deviation
STS	Soft tissue sarcoma

Abbreviation	Wording Definition
SUSAR	Suspected unexpected serious adverse reaction
TAM	TYRO3, AXL, and MER receptors
Tbili	Total bilirubin
TEAE	Treatment Emergent Adverse Event
TIA	Transient ischemic attack
TIE-2	Tunica interna endothelial cell kinase 2
TKIs	tyrosine kinase inhibitors
mTKIs	Multi-targeted kinase inhibitors
TRKA	Tropomyosin receptor kinase A
TRKB	Tropomyosin receptor kinase B
TSH	Thyroid stimulating hormone
TYRO3	TYRO3 protein tyrosine kinase
ULN	Upper limit of normal
UPCR	Urine protein/creatinine ratio
US(A)	United States (of America)
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptors
WBC	White blood cell(s)
WT	Wilms tumor
κB (RANK)	Receptor activator of nuclear factor κB (ligand)

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A phase II, randomized, open-label study to assess the efficacy, safety, and pharmacokinetics (PK) of maintenance cabozantinib (XL184) plus best supportive care (BSC) versus BSC in children, adolescents and young adults (AYA) with unresectable residual osteosarcoma either at diagnosis or at first relapse after standard treatment.

Short Title:

Effects of maintenance cabozantinib+BSC versus BSC in children and AYA with osteosarcoma.

Regulatory Authority Identifier Number(s)

EU CT: 2023-506229-12-00

Rationale:

There is a strong scientific rationale for targeting vascular endothelial growth factor (VEGF) and mesenchymal-epithelial transition (MET) in osteosarcoma (Assi et al 2021). Several therapeutically targetable tyrosine kinase receptors or their ligands are overexpressed in osteosarcoma, including KIT, vascular endothelial growth factor 2 (VEGFR 2), -3, PDGFR-β and MET (Czarnecka et al 2020; Tian et al 2020).

Cabozantinib as multi-tyrosine kinase inhibitor (mTKI) has been explored in several studies in children and adolescents and young adults (AYA) with solid tumors including patients with osteosarcoma. Study ADVL1622 showed that cabozantinib is active in patients with relapsed refractory osteosarcoma and deserves further study in this disease (Akshintala et al 2021). The CABONE trial also showed encouraging clinical results in osteosarcoma (Italiano et al 2020)

Based on the encouraging clinical results showed by cabozantinib in children and AYA with relapsed or refractory osteosarcoma, the aim of the study is to assess the role of cabozantinib as maintenance therapy in osteosarcoma. The study population consists of participants with unresectable residual osteosarcoma who achieved partial response (PR) or stable disease (SD) at the end of conventional chemotherapy either in first line at diagnosis or after first relapse treated with chemotherapy.

The study will evaluate the efficacy and safety of maintenance cabozantinib plus BSC versus BSC alone, and further characterize the PK parameters of cabozantinib in children and AYA with osteosarcoma.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the efficacy of maintenance cabozantinib plus BSC versus BSC in improving the PFS in participants with osteosarcoma	• Progression-free Survival: PFS by BIRC using RECIST version 1.1 *PFS is defined as the time from the date of randomization to the date of first documented disease*

Objectives	Endpoints
	progression (according to RECIST version 1.1) or the date of death due to any cause, whichever occurs first
Secondary	
• To assess the efficacy of maintenance cabozantinib plus BSC versus BSC in improving PFS rate at 4 months and 1 year, ORR and DCR	• PFS rate at 4 months and 1 year by BIRC using RECIST version 1.1 • ORR by BIRC *ORR is defined as the proportion of participants who have achieved CR or PR determined by BIRC using RECIST version 1.1.* • DCR by BIRC *DCR is defined as the proportion of participants who have achieved CR, PR, or SD determined by BIRC per RECIST version 1.1* • PFS, PFS rate at 4 months and 1 year, ORR and DCR as assessed by investigator using RECIST version 1.1
• To compare OS of maintenance cabozantinib plus BSC versus BSC	• OS • OS at 1 year *OS is defined as the time from date of randomization to the date of death, from any cause.*
• To assess the safety and tolerability of maintenance cabozantinib plus BSC in children and AYA	• Safety and tolerability of cabozantinib including TEAEs and SAEs • AESIs (ETMs), including growth plate thickening
• To evaluate the PK of cabozantinib in children and AYA and explore exposure/response relationship with efficacy and safety endpoints, if applicable	• To characterize the PK of cabozantinib in children and AYA, the inter-individual variability, and to identify the covariates which potentially impact the PK of cabozantinib • PK parameters, exposure-response relationship between selected PK measures of exposure and safety and efficacy endpoints, if applicable
• To assess the acceptability and palatability of cabozantinib tablets in children and adolescents	• Acceptability and palatability in children and adolescents will be assessed using a horizontal visual assessment scale.
• To compare the QoL with maintenance cabozantinib plus BSC versus BSC in children and AYA	• Change from baseline in score for all Paediatric QoL Inventory (PedsQL) Scales including Generic Core Scales and Cancer Modules. • For Adults: Change from baseline in EORTC QLQ-C30

AESI=adverse event of special interest, AYA=adolescents and young adults, BIRC=Blinded Independent Radiology Committee, BSC=best supportive care, CR=complete response, DCR=disease control rate, EORTC QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ETM=event to monitor, ORR=objective response rate, OS=overall survival, PedsQL=paediatric quality of life inventory, PFS=progression-free survival, PK=pharmacokinetic, PR=partial response, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, SD=stable disease, TEAE=treatment emergent adverse event

Overall Design:

This is a phase II, multicenter, randomized, open-label, two-arm, parallel-group study evaluating maintenance cabozantinib plus BSC versus BSC in children and AYA with

unresectable residual osteosarcoma, who achieved PR or SD at the end of conventional chemotherapy, either in first line at diagnosis or after first relapse treated with chemotherapy. Participants who have not received previous chemotherapy at the time of first relapse (who achieved surgical remission, or who were completely resected) are eligible at the time of the subsequent relapse if treated with chemotherapy. The last dose of chemotherapy must have been received at least 4 weeks, but not more than 2 months, before randomization.

Participants will be randomly assigned (1:1) to receive one of the following two study interventions:

- Arm A: Cabozantinib+BSC
- Arm B: BSC alone

The starting dose of cabozantinib for this trial will be 40 mg/m^2/day for children and adolescents (<18 years of age). Cabozantinib will be administered orally once daily (QD) on a continuous dosing schedule for cycles of 28 days. Dosing will be performed based on body surface area (BSA) and rounded to the nearest 20 mg using a dosing nomogram. The cumulative weekly dose of cabozantinib cannot exceed 420 mg.

The starting dose for participants ≥18 years of age will be 60 mg/day.

Dose reductions will be allowed for toxicities.

BSC will be administered in both arms per investigator's discretion and institutional guidelines. BSC includes antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including radiotherapy), etc. but does not include tumor specific therapy.

Switch after Disease Progression

As the selected population for the study has limited treatment options, the study will allow eligible participants randomized to the BSC arm to switch to the cabozantinib arm if they meet the following criteria and based on investigator's judgment, as applicable:

- Disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

  Note: Clinical deterioration or clinical progression determined by the investigator will not be considered radiographical progression events. If clinically indicated, radiologic tumor assessment will be scheduled in order to evaluate disease status according to RECIST v1.1. Disease progression, to allow switch, will be evaluated based on investigator's assessment. Blinded Independent Radiology Committee (BIRC) review will be utilized for the primary analysis
- No new systemic anticancer medication prior to switch
- All safety parameters listed in the inclusion criteria, and none of the safety parameters listed in the exclusion criteria
- The study is ongoing.

Participants who switch to cabozantinib during the course of the study will continue to receive cabozantinib until tumor progression, unacceptable toxicity, participant request, investigator's decision or study termination, whichever occurs first.

Local Therapy with Curative Intent during the Study

If after evaluation of the endpoint progression-free survival (PFS)-4 month, participants become suitable for surgery or any other therapy with curative intent, as per investigator judgement, and after discussion with the Sponsor, surgery or any other therapy with curative intent can be allowed, respecting the following criteria:

- Participants in the cabozantinib plus BSC arm: cabozantinib must be stopped at least 28 days prior to surgery. After consultation with the Sponsor, study participants will be allowed to restart cabozantinib, after complete wound healing (based on clinical judgment) and at least 28 days after the surgical procedure, unless it is safe and feasible to reintroduce it sooner as per investigator judgement.

  Hold and restart time of cabozantinib will be discussed with the Sponsor, on a case-by-case basis, prior to administration of any other therapy with curative intent.
- Participants in the BSC arm: participants receiving BSC will be managed as per investigator local site guidance.

Follow-up Period

Participants will be followed until death, participant request to discontinue from follow-up, or until the last participant to enter survival Follow-up period has been followed for 1 year, or the Sponsor decides to discontinue collection of these data in the study whichever occurs first.

Visit Frequency:

Every 2 weeks during Cycles 1 to 3 and every cycle (1 cycle=28 days) thereafter.

Study Participant Duration:

The average total study duration for each participant is estimated to be approximately 24 months (including Screening, Treatment and Follow-up period). However, a participant could remain in the study longer if demonstrating treatment benefit.

Statistical Methods:

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Primary Analysis

PFS will be compared between the study intervention arms at the interim and final analyses using stratified log-rank test. The stratification factor to be used in the analysis is disease setting (initial diagnosis or at first relapse after chemotherapy) and will be based on the stratification for randomization.

Secondary Analyses

Objective response rate (ORR) will be summarized descriptively with two-sided exact binomial 95% confidence intervals (CIs). The inference testing will be conducted with the stratified Cochran-Mantel-Haenszel test. The stratification factor will be the same as those used in the primary PFS analysis.

The overall survival (OS) will be compared between the study intervention arms using the same methods as for PFS. In addition, OS rates by intervention arm at 1 year will be presented along with their associated 95% CIs.

PFS rate at 4 months and 1 year will also be presented by intervention arm with corresponding 95% CIs. Other secondary efficacy endpoints, such as ORR per investigator, DCR per BIRC and investigator, will be computed along with exact two-sided 95% CIs.

The final analysis of ORR and OS will be performed at the time of the primary PFS analysis.

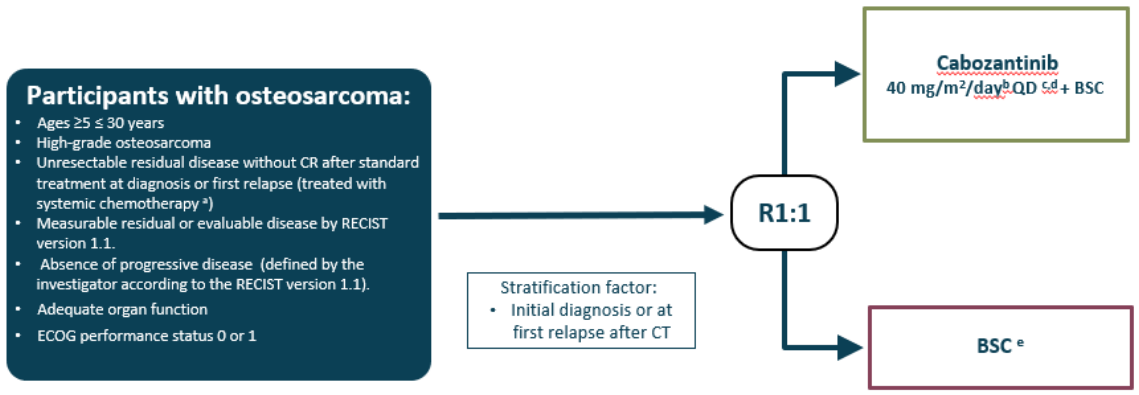
Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to monitor the safety of the study on a regular basis and review the results of the interim analysis. The membership and decision process of the IDMC are independent of the Sponsor and the study clinical investigators.

1.2 Schema

The study schema is shown in Figure 1.

Figure 1 Study Schema



BSC=best supportive care, CR=complete remission, CT=chemotherapy, ECOG=Eastern Cooperative Oncology Group, QD=daily, R=randomization, RECIST=response evaluation criteria in solid tumors

a Receipt of chemotherapy at least 4 weeks, but not more than 2 months before randomization.

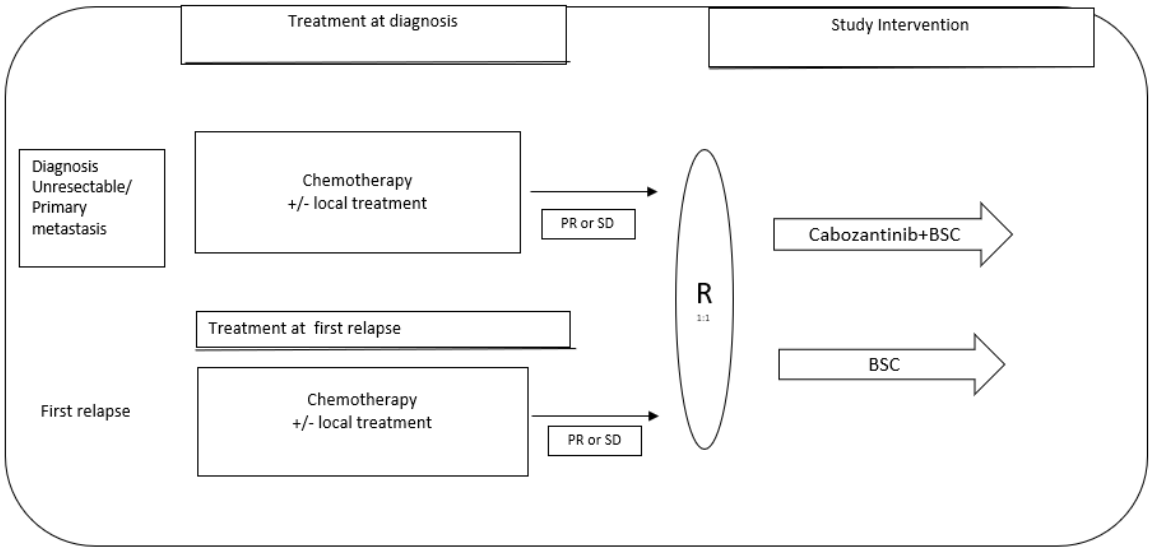
b Cabozantinib 40 mg/m^2/day will be given up to a maximum dose of 420 mg/week.

c Cabozantinib will be given on a continuous dosing schedule until disease progression or unacceptable toxicity. A cycle is 28 days.

d Adult participants (≥18 years) will receive cabozantinib at a starting dose of 60 mg.

e BSC excludes non-protocol anticancer therapy. Participants in BSC arm are allowed to switch to cabozantinib arm at disease progression. BSC includes antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy according with the timelines), etc. but does not include tumor specific therapy.

Figure 2 Study Population Based on Disease Setting



BSC=best supportive care, PR=partial response, SD=stable disease, R=randomization

1.3 Schedule of Activities (SoA)

If disruption of the clinical trial due to a regional or national emergency declared by a governmental agency prevents participants from coming to the site, participants can have their study visit assessments performed remotely (including laboratory assessments) as judged appropriate by the investigator. This must be discussed with the sponsor before being implemented. In such a case, the investigator will perform a telemedicine visit and will make every effort, where applicable, to contact the participant's general practitioner or specialist physician to ensure all important medical information and safety event(s) occurring since the last visit are collected. Guidance on how to collect protocol-planned assessments will be provided to the investigator in a separate document. Such document will be filed in the trial master file. Independent ethics committees (IECs)/institutional review boards (IRBs) will be notified of the changes as applicable locally. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations.

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before Day 1)	Treatment Period Cycle, Day 1 Each cycle=28 days (± 3 days[u])							EOSI (30 days after last dose ± 7 days)	Follow-up[a]
		C1		C2		C3		C4 and subsequent		
		W1 D1	W3 D1	W5 D1	W7 D1	W9D 1	W11 D1			
Informed consent	X									
Inclusion and exclusion criteria	X	X								
Demography	X									
Full physical examination including height and weight [b]	X	X	X	X	X	X	X	X	X	X
Vital signs	X (<7 days)	X	X	X	X	X	X	X	X	
Performance status	X (<7 days)	X	X	X	X	X	X	X	X	
Medical history (includes cancer history)	X									
Pregnancy test (WOCBP only) [c]	X (<7 days)	X		X		X		X	X	
HIV, Hepatitis B and C screening. HIV testing will be performed at screening if and as required by local regulation	X									
Laboratory tests [d, e, f,]	X (<7days)	X	X	X	X	X	X	X	X	
12-lead ECG [g, h, i]	X (<7 days)	X		X		X		X	X	
Randomization [j]		X								
Study intervention administration[k]		X	X	X	X	X	X	X		
Acceptability and palatability [l]		X								
Tumor material [m]	X									
Blood (plasma) biomarkers [n]		X		X		X		X (C7/W25D1 only)	X (At disease progression)	

Procedure	Screening (up to 28 days before Day 1)	Treatment Period Cycle, Day 1 Each cycle=28 days (± 3 days[u])							EOSI (30 days after last dose ± 7 days)	Follow-up[a]
		C1		C2		C3		C4 and subsequent		
		W1 D1	W3 D1	W5 D1	W7 D1	W9D 1	W11 D1			
Blood (ctDNA/RNA) biomarkers [n]		X						X (C4/W13D1 and C7/W25D1)	X (At disease progression)	
HRQoL PedsQL/ EORTC QLQ-C30 [o, p]	X	X		X		X		X	X	
AE review [q]	X	X								
SAE review [q]	X	X								X
X-ray growth plate [r]	X							X		X
Prior/Concomitant medication review	X	X								
Pharmacokinetics [s]		X		X						
Tumor disease evaluation [t]	X	X (Every 8 weeks (± 7 days) from the date of randomization regardless of treatment delays until evidence of PD)								
Dispense/return of cabozantinib and compliance accounting		X	X	X	X	X	X	X	X	
Survival, post study intervention										Participants will be contacted every 3 months (± 14 days) after follow-up visit until death

AE=adverse event, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BIRC= Blinded Independent Radiology Committee, BSC=best supportive care, C=cycle, CBC=complete blood count, CT=computerised tomography, ctDNA=circulating tumor DNA, D=day, ECG=electrocardiogram, EORTC QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EOSI=end of study intervention, FAS/VAS-5=facial hedonic scale with a correlated 100-point visual analog scale, HCG=human chorionic gonadotropin, HIV=human immunodeficiency virus, HRQoL=health-related quality of life, INR=international normalised ratio, MRI=magnetic resonance imaging, PedsQL=paediatric quality of life inventory, PTT=partial thromboplastin time, QTc=corrected QT interval, SAE=serious adverse event, SoA=schedule of activities, TSH=thyroid stimulating hormone, W=week, WOCBP=women of child-bearing potential

(a) Follow-up will continue until death, participant request to discontinue from follow-up, or until the last participant to enter survival Follow-up period has been followed for 1 year, or the Sponsor decides to discontinue collection of these data in the study whichever occurs first.

(b) For participants <18 years of age, weight and height measured on D1 (<7 days for C1) of each cycle should be used. Height and weight need not be repeated at C1D1 if therapy starts within 7 days of obtaining these data. Height, weight and BMI (including height, weight and BMI percentiles for pediatric participants) will be measured and recorded. After EOSI, 6-monthly height assessments will be performed. For adult participants, height will be measured at baseline and weight on D1 (<7 days for C1) of each cycle.

(c) β-HCG in serum at screening and in serum or urine after first dose of study intervention for females of childbearing potential. Female participants of childbearing potential require a negative pregnancy test prior to the start of each cycle. β-HCG in serum need not be repeated at C1D1 if performed within 7 days of randomization.

(d) CBC, differential, platelets, albumin, alkaline phosphatase, AST, ALT, bicarbonate, urea/blood urea nitrogen, calcium, chloride, creatinine, γ-glutamyl transferase, glucose, lactate dehydrogenase, magnesium, phosphate, potassium, sodium, total bilirubin, direct bilirubin, total protein, urinalysis, amylase, lipase, prothrombin/INR/PTT, TSH. Laboratory tests need not be repeated at C1D1 if therapy starts within seven (7) days of obtaining labs to assess eligibility.

(e) Laboratory assessments will be collected prior to dosing. If participants have Grade 4 neutropenia, then CBC should be checked at least every other day or at the investigator's discretion. If participants develop Grade 4 thrombocytopenia, then CBC should be checked every 3 to 4 days or at investigator's discretion.

(f) TSH: If TSH results are within the normal range, repeat testing at mid-cycle on C1D15, C2D15, and C3D15 is not required. However, if TSH levels are abnormal, thorough monitoring of TSH, T3, and T4 should be performed in accordance with the schedule of assessments, including mid-cycle evaluations, to ensure timely detection and management of any thyroid-related issues. Participants who enter the study on thyroid replacement should have their medication adjusted to maintain TSH in the normal range.

(g) Required in triplicate at baseline. Three ECGs should be obtained within 30 minutes but at least 3 minutes apart and including QTc interval. ECG will be performed prior to dosing at Cycles 1, 2, 3 and 4 and every other cycle thereafter, and at EOSI. Additional ECGs should be performed if clinically indicated.

(h) If the ECG has been performed during screening within 7 days prior to first dose of study intervention (C1D1), this assessment does not need to be performed on C1D1 unless the participants' clinical status has changed (e.g., onset of new symptoms indicative of clinical deterioration). If the assessment is performed on C1D1, the results must be available to and reviewed by the investigator prior to any study intervention being administered.

(i) Participants with prolonged QTc should have correctable causes of prolonged QTc addressed if possible, including medications and correction of electrolyte abnormalities (including calcium, potassium, and magnesium).

(j) Randomization should occur as close as possible prior to the planned start of study intervention (i.e., within 24 hours prior if practicable, but no more than 3 days).

(k) Cabozantinib will be given in clinic on C1D1 and taken at home thereafter until study intervention is discontinued. Cabozantinib will be administered orally, once daily, with a large glass of water on an empty stomach, and participant should not eat 2 hours before or 1 hour after each dose of study intervention. BSC will be administered per investigator's discretion and institutional guidelines.

(l) Acceptability and palatability will be assessed in participants <18 years of age, randomized to the cabozantinib+BSC arm using a 5-point FHS/VAS-5 for use in children aged 5 to 17. The questionnaire will be collected once only at C1D1.

(m) The most recent archival tumor material can be collected. Otherwise, tumor material should be collected at screening as optional fresh biopsy where feasible, at investigator discretion.

(n) Blood samples will be obtained pre-dose at the specified timepoints in the SoA. ctDNA genomic assessment is based on consent and could be optional for some study participants.

(o) PedsQL will be used to assess QoL in participants <18 years of age. EORTC QLQ-C30 will be used for participants ≥18 years of age. The PedsQL is a modular instrument designed to measure HRQoL in children and adolescents. The PedsQL 4.0 Generic Core Scales are multidimensional child self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL disease specific modules. The PedsQL 3.0 Cancer Module was designed to measure paediatric cancer specific HRQoL. For participants that are 17 years old at study entry both PedsQL and EORTC QLQ-C30 will be collected at baseline. For these participants, PedsQL will be collected until 18 years of age, following which the EORTC questionnaire will be used.

(p) These assessments are to be performed regardless of whether study intervention is given, reduced, held, or discontinued. HRQoL assessments will be discontinued for participants in the BSC arm who switch to cabozantinib.

(q) All AEs will be collected during study intervention. After EOSI, only SAEs (including deaths) that are attributed (related) to cabozantinib must be reported and followed-up until resolution or stabilization.

(r) X-ray growth plate. Prior to the start of study intervention in all participants ≤18 years of age at enrollment. For participants with open growth plates, radiographs must be monitored during protocol therapy for growth plate toxicity every 6 months until 1 year after last dose, and at any time as per clinical judgment.

(s) For participants in the cabozantinib arm only, blood samples will be obtained at the following time points: C1D1 prior to first dose (baseline) and 4h post-dose and C2D1 pre-dose and 4h post-dose. At Cycle 2, if no dose is planned to be taken based on dosing nomogram, samples must be taken 4 hours apart only.

(t) Radiological and clinical tumor assessment will be performed at baseline, every 8 weeks during the treatment period (every 3 months during the follow up period for participants who discontinue study intervention due to reasons other than radiological progression or consent withdrawal), regardless of treatment delays until evidence of disease progression or initiation of non-protocol anti-cancer therapy. The two most recent radiological evaluations (e.g. CT or MRI scan) including the one following completion of chemotherapy should be available later to facilitate BIRC review.

(u) This window also applies to each visit.

Table 2 Schedule of Activities (Participants who Switch to Cabozantinib+BSC)

This schedule is to be followed for participants who switch from the BSC arm to receive cabozantinib+BSC. C1D1 will be the first day of switch to cabozantinib +BSC.

Procedure	Switch screening (up to 28 days before switch) [a]	Treatment Period C1D1 Each cycle=28 days (± 3 days[m])							EOSI/ET (30 days after last dose ± 7 days)	Follow-up
		C1		C2		C3		C4 and subsequent		
		W1 D1	W3 D1	W5 D1	W7 D1	W9 D1	W11 D1			
Informed consent [b]	X									
Inclusion and exclusion criteria	X									
Full physical examination including height, weight [c]	X (<7 days)	X	X	X	X	X	X	X	X	X
Vital signs	X (<7 days)	X	X	X	X	X	X	X	X	
Performance status	X (<7 days)	X	X	X	X	X	X	X	X	
Interval medical history [d]	X									
Pregnancy test (WOCBP only) [e]	X (<7 days)	X		X		X		X	X	
Laboratory tests [f]	X (<7days)	X	X	X	X	X	X	X	X	
12-lead ECG [g]	X (<7 days)	X		X		X		X	X	
Cabozantinib+BSC [h]		X	X	X	X	X	X	X		
Pharmacokinetics [i]		X		X						
AE review [j]	X	X								
SAE review [j]	X	X								X
X-ray growth plate [k]	X							X		X
Concomitant medication review	X	X								
Tumor disease evaluation [l]	X	X (Every 8 weeks (± 7 days) from the date of randomization regardless of treatment delays until evidence of PD)								

Dispense/return of cabozantinib and compliance accounting		X	X	X	X	X	X	X	X	
Survival, post study intervention										Participants will be contacted every 3 months (± 14 days) after follow-up visit until death

AE=adverse event, BSC=best supportive care, C=cycle, CRF=case report form, D=day, ECG=electrocardiogram, EOSI=end of study intervention, ET=early termination, PD=progressive disease, QTc=corrected QT interval, SAE=serious adverse event, W=week, WOCBP=women of child-bearing potential

(a) Screening assessments must be reviewed by the investigator before switch to confirm that the participant meets the switch eligibility criteria. Only participants randomized to the BSC arm who opt to switch to receive cabozantinib will undergo switch screening. EOSI assessments can coincide with switch screening assessments.

(b) In addition to informed consent obtained for the main study, informed consent specific for the switch to cabozantinib+BSC must be obtained.

(c) For participants <18 years of age, weight and height measured on D1 (<7 days for C1) of each cycle should be used. Height and weight need not be repeated at C1D1 if therapy starts within 7 days of obtaining these data. Height, weight and BMI (including height, weight and BMI percentiles for pediatric participants) will be measured and recorded. After EOSI, 6-monthly height assessment will be performed. For adult participants height will be measured at baseline and weight on D1 (<7 days for C1) of each cycle.

(d) Interval medical history will be collected for participants randomized to the BSC arm who undergo screening for switch and who have discontinued study intervention >30 days prior to C1D1 of switch. For participants who switch within 30 days of EOSI, any relevant medical history should be recorded on the AE CRF page.

(e) Pregnancy testing to be performed at the timepoints listed. If a urine test cannot be confirmed as negative, a negative serum pregnancy test is required.

(f) Safety laboratory assessments to be obtained at the timepoints listed. CBC, differential, platelets, albumin, alkaline phosphatase, AST, ALT, bicarbonate, urea/blood urea nitrogen, calcium, chloride, creatinine, γ-glutamyl transferase, glucose, lactate dehydrogenase, magnesium, phosphate, potassium, sodium, total bilirubin, direct bilirubin, total protein, urinalysis, amylase, lipase, prothrombin/INR/PTT, TSH. Additional safety assessments should be performed if clinically needed. If TSH results are within the normal range, repeat testing at mid-cycle on C1D15, C2D15, and C3D15 is not required. However, if TSH levels are abnormal, thorough monitoring of TSH, T3, and T4 should be performed in accordance with the schedule of assessments, including mid-cycle evaluations, to ensure timely detection and management of any thyroid-related issues.

(g) ECGs to be obtained at the timepoints listed. Three ECG should be obtained within 30 minutes but at least 3 minutes apart and including QTc interval. ECG will be performed prior to dosing at Cycles 1, 2, 3 and 4 and every other cycle thereafter, and at EOSI. Additional ECGs should be performed if clinically needed.

(h) Cabozantinib will be given in clinic on C1D1 and taken at home thereafter until study intervention is discontinued. Cabozantinib will be administered orally, once daily, with a large glass of water on an empty stomach, and participant should not eat 2 hours before or 1 hour after each dose of study intervention.

(i) Blood samples will be obtained at the following time points: C1D1 prior to first dose (baseline) and 4h post-dose, and C2D1 pre-dose and 4h post-dose. At Cycle 2, if no dose is planned to be taken based on dosing nomogram, samples must be taken 4 hours apart only.

(j) All AEs will be collected during study intervention. After EOSI, only SAEs (including deaths) that are attributed (related) to cabozantinib must be reported and followed-up until resolution or stabilization.

(k) X-ray growth plate. Prior to the start of study intervention in all participants ≤18 years of age at enrollment. For participants with open growth plates, radiographs must be monitored during protocol therapy for growth plate toxicity every 6 months until 1 year after last dose, and at any time as per clinical judgment.

(l) Radiological and clinical tumor assessment will be performed at baseline, every 8 weeks during the treatment period (every 3 months during the follow up period for participants who discontinue the study intervention due to reasons other than radiological progression or consent withdrawal), regardless of treatment delays until evidence of disease progression or initiation of non-protocol anti-cancer therapy. If scans are >8 weeks prior to first switch dose, new scans are required to establish the switch baseline. Re-establish baseline based upon the most recent set of scans performed prior to switch; if these scans are >8 weeks prior to first switch dose, new scans are required to establish the switch baseline. For details of tumor assessments performed, see Section 8.2.1

(m) This window also applies to each visit

2 INTRODUCTION

Cabozantinib is a small molecule inhibitor of multiple tyrosine kinases including MET (half maximal inhibitory concentration (IC_{50}) 8nM), VEGFR2 (IC_{50} 2nM), rearranged during transfection (RET) (IC_{50} 85nM), stem cell factor (KIT) (IC_{50} 5nM), FMS-like tyrosine kinase-3 (FLT3) (IC_{50} 11 nM) and the tunica interna endothelial cell kinase 2 (TIE-2). Other recognized targets of cabozantinib include the GAS6 receptor (AXL), FMS tyrosine kinase (FMS), ROS proto-oncogene 1(ROS1), tropomyosin receptor kinase A (TRKA), tropomyosin receptor kinase B (TRKB), TYRO3 protein tyrosine kinase (TYRO3), MER, VEGFR1, and VEGFR3 (Yakes et al 2011, Cabozantinib Investigator's Brochure).

Several targets of cabozantinib play a role in immunosuppression, particularly VEGFR, MET, and the TYRO3, AXL, and MER receptors (TAM) kinases. Inhibition of these signaling molecules likely contributes to antitumor immunomodulatory effect of cabozantinib across various tumor indications (Bergerot et al 2019).

Cabozantinib has demonstrated pre-clinical activity in vitro and in vivo osteosarcoma and Ewing sarcoma (EWS) models consistent with its known anti-MET and anti-angiogenic activity (Smith et al 2013; Fioramonti et al 2018). Cabozantinib can decrease proliferation and migration of osteosarcoma cells by inhibiting c-MET activation and extracellular signal -regulated kinase and protein kinase B/AKT signaling pathways while also leading to inhibition of the proliferation of osteosarcoma cells expressing receptor activator of nuclear factor κB (RANK). Cabozantinib further impacts the bone microenvironment by decreasing RANK ligand (RANKL) production, while increasing the production of osteoprotegerin, a soluble receptor of RANKL, thus further reducing the stimulation of RANK-positive osteosarcoma cells. Cabozantinib might therefore represent a new potential treatment for osteosarcoma, affecting both osteosarcoma cells and their microenvironment (Fioramonti et al 2018).

Cabozantinib tablets (Cabometyx™) is approved in the European Union in the adult population as monotherapy for the treatment of advanced renal cell carcinoma (RCC), hepatocellular carcinoma (HCC) in patients who have previously been treated with sorafenib and locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine who have progressed during or after prior systemic therapy; and in combination with nivolumab, for the first line treatment of adult patients with advanced RCC (Cabometyx Summary of Product Characteristics 2023). In the United States, cabometyx is indicated for the treatment of patients with RCC, patients with advanced RCC, as a first-line treatment in combination with nivolumab, patients with HCC who have been previously treated with sorafenib, and adult and paediatric patients 12 years of age and older with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible (Cabometyx USPI).

2.1 Study Rationale

There is a strong scientific rationale for targeting VEGF and MET in osteosarcoma (Assi et al 2021). Several therapeutically targetable tyrosine kinase receptors or their ligands are overexpressed in osteosarcoma, including KIT, VEGFR 2, -3, platelet derived growth factor receptor beta (PDGFR-β) and MET (Czarnecka et al 2020; Tian et al 2020).

Cabozantinib as mTKI has been explored in several studies in children and AYA with solid tumors including patients with osteosarcoma. Study ADVL1622 showed that cabozantinib is active in patients with relapsed refractory osteosarcoma and deserves further study in this disease (Akshintala et al 2021). The CABONE trial also showed encouraging clinical results in osteosarcoma (Italiano et al 2020).

Based on the encouraging clinical results showed by cabozantinib in children and AYA with relapsed or refractory osteosarcoma, the aim of the study is to assess the role of cabozantinib as maintenance therapy in osteosarcoma. The study population consists of participants with unresectable residual osteosarcoma who achieved PR or SD at the end of conventional chemotherapy either in first line at diagnosis or after first relapse treated with chemotherapy.

The study will evaluate the efficacy and safety of maintenance cabozantinib plus BSC versus BSC alone, and further characterize the PK parameters of cabozantinib in children and AYA with osteosarcoma.

2.2 Background

There is a great need for the development of novel and effective therapies for paediatric patients and AYA with osteosarcoma, where limited treatment options exist.

Approximately 15% to 20% of patients with osteosarcoma present with metastatic disease at initial diagnosis (Salah et al 2014; Piperno-Neumann et al 2020).

Primary metastatic high grade bone sarcomas (HGBS) are treated with a curative intent following the same approach of non-metastatic ones, while treatment of recurrent HGBS is primarily surgical if there are isolated lung metastases. In some cases, complete removal of all metastases is not achievable, and the prognosis remains poor, with shorter PFS of 3 to 8 months (Brahmi et al 2022).

Traditionally, at an advanced stage, not amenable to curative-intent strategy, systemic treatment could be administered until severe toxicity, disease progression, or a cumulative dose has been reached (e.g., as in the case of doxorubicin) (Lebellec et al 2020).

In the metastatic setting there is a clinical need to prevent or delay progressive disease (PD).

After the administration of classical chemotherapy and in the absence of disease progression (including complete or partial response (PR) or stable disease (SD)), maintenance therapy can be considered by treating physician. Maintenance therapy aims to maintain response, prevent or delay PD, and improve quality of life (QoL) (Lebellec et al 2020). In this setting, there is no consensus on maintenance treatment.

2.2.1 Background Information on the Disease to be Treated

2.2.1.1 Epidemiology

Osteosarcoma, although identified as a rare disease, is the most common type of primary malignant bone tumor. Bone tumors make up about 3%–5% of childhood cancers and less than 1% of cancers in adults (Mirabello et al 2009). Osteosarcoma is defined by the presence of malignant mesenchymal cells producing osteoid or immature bone.

The population affected is primarily composed of children and AYA. Osteosarcoma incidence in childhood and adolescence is relatively consistent throughout the world. In the Mirabello et al (2009) study, overall worldwide osteosarcoma incidence rates were quite similar in the younger age groups. The greatest variation in incidence rates was observed in the elderly (Mirabello et al 2009). The first peak incidence is in the second decade of life during the adolescent growth spurt (13 to 17 years depending on patient gender with a median age of 13 years for females and 15 years for males). The second peak is in the seventh and eighth decades of life (Mirabello et al 2009; ESMO– PaedCan–EURACAN 2021). The predilection of osteosarcoma during the pubertal growth spurt and the sites of maximum growth suggest a correlation with rapid bone proliferation (Taran et al 2017). No cases of osteosarcoma or very low incidence rates were reported for children aged 0 to 4 years (Mirabello et al 2009; NCCR*Explorer Application (cancer.gov)), thus highlighting the rarity of osteosarcoma in young children and neonates.

2.2.1.2 Available Therapies in Osteosarcoma

Curative treatment of high-grade osteosarcoma consists of chemotherapy (ChT) and surgery [II, A] (ESMO-PaedCan–EURACAN 2021). The extent of histological response to preoperative ChT predicts survival. ESMO–PaedCan–EURACAN Clinical Practice Guidelines 2021 recommend doxorubicin, cisplatin, high-dose methotrexate (HD-MTX) and ifosfamide (Ifo) for their antitumor activity in osteosarcoma [I, A]. In patients aged >40, preferred regimens often combine doxorubicin, cisplatin and Ifo without HD-MTX [III, B] (

The National Comprehensive Cancer Network (NCCN) Bone Cancer guidelines recommend the backbone regimen consisting of cisplatin and doxorubicin, with or without high-dose methotrexate as preferred regimens (NCCN Bone Cancer 3.2023). Even if these therapies result in long-term survival rates of 60% to 70% in patients with localized disease, patients with metastatic or relapsed osteosarcoma have an overall 5-year survival rate of about 20% (Kansara et al 2014; Messerschmitt et al 2008).

For patients aged younger than 15 years, improvements in treatment over time have been achieved with an increase in 5-year overall survival (OS) from 40% (1975–1978) to 68% (1987–1990), with notably minimal improvements in 5-year OS in the last 3 decades. This plateau in patient survival is apparent in studies using longitudinal, multi-centre databases. However, there is a subset of patients for whom survival has continued to improve. A 2010 analysis of the Surveillance, Epidemiology, and End Results (SEER) program database of the National Cancer Institute identified improvements in survival for all patients with high-grade disease over the preceding 2 decades. The authors of the SEER study argue that this improved survival is owing to the use of more specific intensified ChT regimens for patients with an aggressive disease. Although survival has improved over previous decades, patients with metastatic and recurrent disease continue to have poor outcomes (Jawad et al 2011; Smith 2010; Mirabello et al 2009; Marina et al 2004).

Over half of patients with metastatic disease who relapse do so within the first year of diagnosis (53.0% v 29.6% of non-metastatic patients, $p<0.0001$) (Spraker-Perlman 2019).

Radiotherapy may be considered in osteosarcoma patients with unresectable primary tumors where surgery would be unacceptably morbid, or as adjuvant treatment of tumors at high risk of local recurrence (LR) and with limited option for further surgery [IV, B] (ESMO PaedCan-EURACAN 2021).

Primary metastatic osteosarcoma patients may be treated with a curative intent following the same principles as applied in non-metastatic osteosarcomas. Retrospective data suggest that there are subsets of patients who can have a very similar prognosis to that of localised disease, provided surgical removal of all known metastatic deposits is achievable [III, B] (ESMO PaedCan–EURACAN 2021).

The management of recurrent osteosarcoma needs to take into account the timing of recurrences and the number and sites of metastases. The treatment of recurrent osteosarcoma is primarily surgical in patients with isolated lung metastases or LR. Complete removal of all resectable metastases must be attempted [III, B], as more than one-third of patients with a complete second surgical remission survive for >5 years. Even patients with subsequent recurrences may be cured as long as recurrences are resectable, and repeated thoracotomies are often warranted. For lung metastases, stereotactic radiotherapy (RT), radiofrequency ablation (RFA) or cryotherapy might be used as alternative options in patients unfit for surgery [IV, B]. Some groups also consider RFA and stereotactic RT as potentially alternative local treatment options for bone metastases (ESMO PaedCan–EURACAN 2021).

In the European Society for Medical Oncology (ESMO) guidelines (ESMO–PaedCan–EURACAN 2021) second-line ChT for recurrent osteosarcoma includes Ifo or cyclophosphamide, possibly in association with etoposide (Eto) and/or carboplatin [III, B], and other active drugs including gemcitabine and docetaxel [IV, C]. Data on cabozantinib and regorafenib are reported in the ESMO PaedCan–EURACAN 2021 (Supplementary material). RT may have a role in palliation.

In general, despite second-line treatment, the prognosis of recurrent disease has remained poor, with a 5-year post relapse survival rate of <20% (ESMO PaedCan–EURACAN 2021).

In the NCCN guidelines (NCCN Bone Cancer 3.2023), this list includes high-dose Ifo with or without Eto, sorafenib, and regorafenib. Additional recommended regimens include gemcitabine with or without docetaxel, cabozantinib, ChT combination with cyclophosphamide (CTX) and topotecan and sorafenib with everolimus. There are other options defined Useful in Certain Circumstances (refer to NCCN v3.2023). For details on the category of recommendations, refer to the guidelines.

Tyrosine Kinase Inhibitors (TKI) in Osteosarcoma

Recent clinical trials have shown several mTKIs to be effective in the treatment of osteosarcoma: apatinib (Xie et al 2019), lenvatinib (Len) (Gaspar et al 2018; Gaspar et al 2021), sorafenib (Grignani et al 2012; Grignani et al 2015), regorafenib (Duffaud et al 2019; Davis al 2019) and cabozantinib (Italiano et al 2020). However, it is necessary to inhibit several key receptor tyrosine kinase inhibitors (RTKs) simultaneously in order to achieve a breakthrough in the treatment of osteosarcoma. For example, cabozantinib, which can simultaneously inhibit VEGFRs, KIT, RET, MET, and AXL has the best effect in the treatment of osteosarcoma, with a median PFS of 6.7 months, compared to other TKIs (Tian et al 2020; Italiano et al 2020).

A phase II study (NCT04154189) with Ifo and Eto with or without Len has been conducted in children and AYA with relapsed and refractory osteosarcoma (OLIE). The results of this trial have been presented at the Connective Tissue Oncology Society (CTOS) congress in Nov 2022 (Gaspar et al 2021; Gaspar et al 2022). As reported by the authors, the primary endpoint of PFS was not met, as the P-value was not below the boundary for significance (0.025). PFS per RECIST v1.1 by independent review was 6.5 months (95% CI: 5.7–8.2) in the Len + Ifo + Eto arm and 5.5 months (95% CI: 2.9–6.5) in the Ifo + Eto arm (hazard ratio [HR] 0.54 [95% CI: 0.27–1.08]; P = 0.0396. Median OS was 11.9 months (95% CI: 10.1–not estimable [NE]) in the Len + Ifo + Eto arm and 17.4 months (95% CI 14.2–NE) in the Ifo + Eto arm (HR 1.28 [95% CI 0.60–2.70]; P = 0.7451). Greater proportions of patients in the Ifo + Eto arm underwent surgery or received subsequent anticancer therapy than in the Len + Ifo + Eto arm this, along with patient crossover, may have impacted OS outcomes.

Overall, the safety profile of Len + Ifo + Eto was consistent with the known safety profiles of the individual agents; no new safety signals were detected. Pearson et al (2022) published the outcome of the ACCELERATE Paediatric Strategy Forum for medicinal product development of mTKIs in bone sarcomas. According to the authors, studies currently being planned or in progress, in frontline and relapsed setting may inform the further development of TKIs in bone sarcoma. They should address the question whether mTKIs should be included in the standard of care for patients with bone sarcoma. Specifically, data from the OLIE and Children's Oncology Group (COG) AOST2032 trial (NCT05691478; COG frontline study in patients with osteosarcoma randomising MAP (methotrexate + Adriamycin® (doxorubicin) + platinol® (cisplatin)) ChT with or without cabozantinib) can be used to inform the future direction of mTKIs in osteosarcoma and whether the next-generation mTKIs would be moved forward or

no further evaluation is required. Generally, current evidence suggests that mTKIs may be used in combination with ChT backbone at the recommended doses, with some exceptions. Evidence also suggests a possible role for maintenance therapy following the combination therapy, which is currently being investigated (Pearson et al 2022).

2.2.1.3 Available Data from Cabozantinib Studies Relevant to the Proposed Population

Several studies in children and AYA have been conducted in solid tumors including participants with osteosarcoma.

Study ADVL1211

A phase I study (ADVL1211) of cabozantinib in paediatric participants with solid tumors has been conducted by the COG (Chuk et al 2018). Cabozantinib was dosed based on BSA according to a dosing nomogram. Eligible participants were ≥2 years and ≤18 years. This study enrolled participants at 3 dose levels: 30 mg/m^2, 40 mg/m^2, and 55 mg/m^2 once daily on a continuous dosing schedule (weekly dosing by BSA and rounded to the nearest 20 mg).

The objective was to define dose limiting toxicities (DLTs), to determine the recommended phase II dose (RP2D), to obtain preliminary PK data in children and to explore efficacy in solid tumors. Forty-one participants were enrolled, of whom 36 were fully evaluable. Participants had a variety of solid tumors: medullary thyroid cancer (MTC) (n=5), osteosarcoma (n=2), EWS (n=4), rhabdomyosarcoma (RMS) (n=2), other soft tissue sarcoma (STS) (n=4), Wilms tumor (WT) (n=2), hepatoblastoma (n=2), HCC (n=2), RCC (n=3), central nervous system (CNS) tumors (n=9), and others (n=6).

Evidence of clinical activity of cabozantinib was seen in MTC and several sarcoma subtypes.

Of the 36 participants in the evaluable population, no participant had disease status complete response (CR), four participants (11.1%) had best overall response of PR and eight participants (22.2%) had SD. Of the 12 participants with PR or SD greater than or equal to 6 cycles, 10 participants were in the cabozantinib 40 mg/m^2 or 55 mg/m^2 groups (seven and three, respectively).

Of the five participants with MTC, two had disease status PR and two had SD with a long duration and one had PD, providing preliminary evidence that the activity of cabozantinib in MTC demonstrated in adults is also seen in children.

Given the safety profile (including the frequency, severity and duration of the TEAEs (including dose interruptions and reductions and actual dose administered)) and tumor response data across the dose levels, the dose of cabozantinib recommended for further evaluation in paediatric participants with solid tumors is 40 mg/m^2/day (tablets) orally.

Study ADVL1622

ADVL1622 (NCT02867592) was a phase II study, led by the COG with cabozantinib in children and young adults with refractory sarcomas, WT, and other rare tumors (Akshintala 2021). Participants aged 2-30 years old with selected relapsed or refractory cancer that was measurable (RECIST version 1.1) were eligible. Using a Simon minimax design, participants were enrolled to six strata: Osteosarcoma, EWS, RMS, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), WT, and rare tumor (a non-statistical stratum including tumors of specific histologies or molecular features). Cabozantinib (40 mg/m^2/day) was administered on a continuous schedule (1 cycle=28 days). For the osteosarcoma stratum, activity was determined based on ORR (CR + PR) or disease control success defined as at least SD for ≥4 months. For all other strata, the primary endpoint was ORR.

In this study 109 participants were enrolled (105 eligible, 104 evaluable for response and toxicity). Median age was 15.8 (range 5.6-27.1 years); 55 participants were male.

Results in the Osteosarcoma Cohort

A total of 29 participants were enrolled in the osteosarcoma stratum and received at least one dose of cabozantinib, including 17 children (age 9 to 17 years old) and 12 adults (age 18 to 22 years old). All 29 participants were evaluable for response. The majority of the participants were heavily pre-treated; 21/29 participants (72.4%) had received more than one line of therapy. A PR was observed in one adult and one child; the ORR was 6.9% (95% CI: 0.8, 22.8). The DCR was 34.5% (95% CI: 17.9, 54.3). DCR was higher in adults than in children (50% vs. 23.5%). The median duration of PFS was 4.6 months (95% CI: 2.1, 6.0) with a minimum duration of 0.95 months and a maximum duration of 25.56 months; the median OS was 9.3 months.

There were 2 participants with PRs, 8 participants with prolonged SD of at least 4 months. Six participants were not evaluable for response as follows: four participants had a first response of SD and no subsequent evaluations, and two participants had withdrawn from study treatment before the first evaluation.

A total of 21/29 participants (72.4%) had at least one Treatment Emergent Adverse Event (TEAE). The majority of participants (20 participants (69.0%)) had TEAEs that were evaluated as treatment-related TEAEs by investigator assessment.

There were eight participants (27.6%) who had treatment emergent SAEs, including five participants (17.2%) who had treatment related SAEs. One participant (3.4%) experienced a Grade 5 TEAE of death not otherwise specified (NOS) that occurred within 30 days following last dose of cabozantinib. The TEAEs with highest incidence (reported for ≥5% of participants) by decreasing frequency were AST increased (10.3%), lipase increased, neutrophil count decreased, weight decreased, hypokalaemia, wound dehiscence, pain in extremity, pneumothorax and hypertension (6.9% each). Two participants with pulmonary metastases at baseline had two events of pneumothorax each, during the treatment period. The most frequent TEAEs leading to DLT (reported for ≥5% participants) by PT were AST increased (10.3%), weight decreased, wound dehiscence and pneumothorax (6.9% each).

The most frequent Grade 3 TEAEs (≥5% incidence) reported for participants in osteosarcoma stratum in descending order of incidence were AST increased (10.3%), neutrophil count decreased, weight decreased, hypokalaemia, pain in extremity, pneumothorax, and hypertension (6.9% each). A Grade 4 TEAE of lipase increased was reported by one participant (3.4%).

A total of 20 deaths were reported as of the data cutoff date, of which one event occurred during the study treatment; the other events occurred during the follow-up period. Per investigator assessment, all deaths were attributed to disease progression.

Overall, the DCR indicates that cabozantinib monotherapy at a dose of 40 mg/m^2/day has clinical activity in children and young adults with relapsed or refractory osteosarcoma.

The authors concluded that cabozantinib is active in patients with relapsed or refractory osteosarcoma and deserves further study in this disease (Akshintala et al 2021).

The CABONE Study

In collaboration with the NCI-CTEP, the French Sarcoma Group (FSG) conducted a clinical phase II study of cabozantinib (CABONE trial; NCT02243605) in participants >12 years of age with advanced recurrent/relapsed osteosarcoma and EWS, who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and documented disease progression (according to RECIST version 1.1) before study entry. The number of previous lines of treatment was not limited. Participants received cabozantinib (adults 60 mg, children (<16 years) 40 mg/m²) orally once daily in 28-day cycles until disease progression, unacceptable toxicity, the investigator's decision to discontinue or participant withdrawal.

The primary endpoint for EWS was best objective response within 6 months of treatment onset. A dual primary endpoint of 6-month objective response and 6-month non progression was assessed in osteosarcoma.

This study enrolled 90 participants (45 with EWS and 45 with osteosarcoma), of which 2/45 (4%) in the EWS group and 6/45 (13%) in the osteosarcoma group were 12 to 18 years old. Median follow-up was 31.1 months (24.4–31.7) for participants with osteosarcoma. A total of 42 (93%) participants with osteosarcoma were assessable for efficacy after histological and radiological review.

Osteosarcoma Cohort Results

In participants with osteosarcoma, five (12%; 95% CI: 4, 26) of the 42 participants had an objective response (all PRs) and 14 (33%; 95% CI: 20, 50) had 6-months of non-progression. In the osteosarcoma group, median PFS was 6.7 months (95% CI: 5.4, 7.9) and median OS was 10.6 months (95% CI: 7.4, 12.5). PFS was 71% (95% CI: 55, 83) at 4 months, 52% (95% CI: 36, 66) at 6 months, 9% (95% CI: 3, 21) at 12 months, and 9% (95% CI: 3, 21) at 24 months. OS was 78% (95% CI: 62, 88) at 6 months, 38% (95% CI: 23, 53) at 12 months, and 23% (95% CI: 11, 38) at 24 months. One participant with a PR to cabozantinib had surgery for lung metastases. A histological assessment 3 weeks after completion of cycle 8 showed no residual tumor cells. The most common grade 3 or 4 AEs were hypophosphataemia (3 [7%]), AST increase (3 [7%]), PPES (2 [4%]), pneumothorax (4 [9%]), and neutropenia (4 [9%]). No participants died from drug-related toxic effect.

2.2.1.4 Maintenance Treatment in Osteosarcoma

As stated in the overview of available therapies for osteosarcoma, the current internationally recommended approach for high-grade osteosarcoma, following biopsy, is the use of neo-adjuvant ChT. Essential to the treatment is surgical resection of the primary tumor and metastases aiming for wide margins. Surgery is followed by further adjuvant ChT. With this approach the overall 5-year event-free survival (EFS) for resectable, non-metastatic osteosarcoma is approximately 60% and 30% for metastatic patients (Pearson et al 2022).

Although the survival of patients with primary localized disease has improved significantly since the 1970s, with the introduction of active multi-agent ChT, the outcomes of patients who present with metastatic disease remains poor. Approximately 15% of patients with osteosarcoma present with metastatic disease at initial diagnosis (Salah et al 2014; Kaste et al 1999).

Primary metastatic HGBS are treated with a curative intent following the same approach of non-metastatic ones, while treatment of recurrent HGBS is primarily surgical if there are isolated lung metastases. In some cases, complete removal of all metastases is not achievable, and the prognosis remains poor, with shorter PFS of 3 to 8 months (Brahmi et al 2022). Traditionally, at an advanced stage, not amenable to curative-intent strategy, systemic treatment

could be administered until severe toxicity, disease progression, or a cumulative dose has been reached (e.g., as in the case of doxorubicin) (Lebellec et al 2020).

In the metastatic setting there is a clinical need to prevent or delay progressive disease (PD).

After the administration of classical ChT and in the absence of disease progression (including CR or PR or SD), maintenance therapy can be considered by treating physician. Maintenance therapy aims to maintain response, prevent or delay PD, and improve quality of life (QoL) (Lebellec et al 2020). In this setting, there is no consensus on maintenance treatment.

The key-difference between maintenance therapy and further line is that maintenance therapy is given in patients experiencing non-PD and further line is given in those experiencing PD (Lebellec et al 2020).

In advanced stages of different clinico-pathological sarcoma entities, different maintenance therapies (e.g., metronomic ChT, antiangiogenic agents, and molecularly targeted therapies) have been explored. Most of the related trials have been phase I trials, with a few being phase III trials (Lebellec et al 2020).

In 2013, Demetri et al 2013 reported a large double-blind phase III trial assessing the clinical benefit of switch maintenance therapy with oral ridaforolimus (RIDA) in sarcoma patients showing SD or response after first-, second-, or third-line treatment for advanced disease (Kokkali-Zervos et al 2020). The study population was heterogeneous, including patients aged 13 years or higher, with soft-tissue (90%) and bone sarcoma (10%), regardless of histological subtype. The primary objective was median PFS by blinded central review. Overall, 711 patients were randomly assigned to receive placebo (364) or RIDA (347). RIDA treatment led to a modest, although significant, improvement in PFS per independent review compared with placebo (hazard ratio (HR), 0.72; 95% CI: 0.61, 0.85; p=0.001; median PFS of 17.7 vs 14.6 weeks). Median OS with RIDA was 90.6 weeks versus 85.3 weeks with placebo (HR, 0.93; 95% CI: 0.78, 1.12; p=0.46). Despite meeting the primary objective, the trial failed to support the approval of the study drug.

Maintenance therapy could be effective if the selected regimen provides clear evidence of activity at the metastatic stage. Furthermore, the toxicity profile must be carefully considered. In case of advanced disease, the maintenance therapy administered to delay disease progression must be well tolerated and must not alter the quality of life (QoL) (Lebellec et al 2020).

Currently there are few clinical trials ongoing in maintenance setting, including paediatric osteosarcoma patients:

- CaboMain: Phase II trial evaluating cabozantinib in patients with ultra-high risk paediatric solid tumors (NCT05135975; Shah et al 2022).
- REGOMAIN: A randomized, placebo-controlled, double-blinded, multicenter, comparative phase II study of the efficacy of regorafenib as maintenance treatment in patients (pts) with high-grade bone sarcomas (HGBS) at diagnosis or relapse and without complete remission after standard treatment (NCT04698785; Brahmi et al 2022).
- REGOSTA: A randomized, placebo-controlled, double-blinded, multicentre study evaluating the efficacy and safety of regorafenib as maintenance therapy after first-line treatment in patients with bone sarcomas (NCT04055220).

In conclusion, no current standard treatment is available in osteosarcoma maintenance in the advanced setting, creating a high unmet need in this patient population.

2.3 Benefit/Risk Assessment

Current clinical guidelines for the treatment of osteosarcoma have remained largely unchanged in the last decades and no current standard treatment is available in osteosarcoma maintenance in the advanced setting, creating a high unmet need in this patient population.

Therefore, the development of innovative medicinal products in osteosarcoma is of high priority to address this unmet need.

2.3.1 Risk Assessment

The risk assessment for this study is summarised in Appendix 10.7. The clinical data presented, apart from data on growth plate widening, are from adult studies.

Identified risks include:

- Gastrointestinal (GI) perforation and fistula (GI and non-GI)
- Thromboembolic Events
- Haemorrhage
- Wound complications
- Osteonecrosis
- Posterior reversible encephalopathy syndrome (PRES) also known as reversible posterior leukoencephalopathy syndrome (RPLS)

Potential risks include:

- Renal failure
- Hepatotoxicity
- Embryotoxicity (male and female participants should seek medical advice and consider fertility preservation before starting treatment; refer to Appendix 10.7)
- Carcinogenicity

Other Concerns for the Paediatric population include growth plate widening.

2.3.2 Benefit Assessment

This is a phase II study in osteosarcoma participants with unresectable residual osteosarcoma either at diagnosis or at first relapse after standard treatment. Maintenance therapy could be effective if the selected regimen provides clear evidence of activity at the metastatic stage.

Based on the encouraging clinical results showed by cabozantinib in children and AYA with relapsed or refractory osteosarcoma, supported by clinical data in the adult population, there is anticipated clinical benefit for the participants from receipt of the study intervention.

The primary endpoint is PFS by BIRC using RECIST version 1.1. Secondary endpoints include PFS rate at 4 months, ORR, DCR, OS, Safety and tolerability, PK, acceptability and palatability of cabozantinib, and QoL.

Altogether, these endpoints will provide data for an assessment of the overall benefit-to-risk profile of cabozantinib for participants in this setting.

2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants, the potential risks identified with cabozantinib are justified by the anticipated benefits that may be afforded to participants with osteosarcoma.

3 OBJECTIVES AND ENDPOINTS

Table 3 displays the objectives and corresponding endpoints. Other study aspects are described in other sections: population in Section 5, study intervention in Section 6, prohibited medications in Section 6.9.2, and analysis sets are defined in Section 9.3.

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of maintenance cabozantinib plus BSC versus BSC in improving the PFS in participants with osteosarcoma	• Progression-free Survival: PFS by BIRC using RECIST version 1.1 *PFS is defined as the time from the date of randomization to the date of first documented disease progression (according to RECIST version 1.1) or the date of death due to any cause, whichever occurs first*
Secondary	
• To assess the efficacy of maintenance cabozantinib plus BSC versus BSC in improving PFS rate at 4 months and 1 year, ORR and DCR	• PFS rate at 4 months and 1 year by BIRC using RECIST version 1.1 • ORR by BIRC *ORR is defined as the proportion of participants who have achieved CR or PR determined by BIRC using RECIST version 1.1.* • DCR by BIRC *DCR is defined as the proportion of participants who have achieved CR, PR, or SD determined by BIRC per RECIST version 1.1* • PFS, PFS rate at 4 months and 1 year, ORR and DCR as assessed by investigator using RECIST version 1.1
• To compare OS of maintenance cabozantinib plus BSC versus BSC	• OS • OS at 1 year *OS is defined as the time from date of randomization to the date of death, from any cause.*
• To assess the safety and tolerability of maintenance cabozantinib plus BSC in children and AYA	• Safety and tolerability of cabozantinib including TEAEs and SAEs • AESIs (ETMs), including growth plate thickening.
• To evaluate the PK of cabozantinib in children and AYA and explore exposure/response relationship with efficacy and safety endpoints, if applicable	• To characterize the PK of cabozantinib in children and AYA, the inter-individual variability, and to identify the covariates which potentially impact the PK of cabozantinib • PK parameters, exposure-response relationship between selected PK measures of exposure and safety and efficacy endpoints, if applicable
• To assess the acceptability and palatability of cabozantinib tablets in children and adolescents	• Acceptability and palatability in children and adolescents will be assessed using a horizontal visual assessment scale.
• To compare the QoL with maintenance cabozantinib plus BSC versus BSC in children and AYA	• Change from baseline in score for all Paediatric QoL Inventory (PedsQL) Scales including Generic Core Scales and Cancer Modules. • For Adults: Change from baseline in EORTC QLQ-C30
Exploratory	

Objectives	Endpoints
• To explore pharmacodynamic parameters associated with treatment in blood and potential predictive biomarkers of clinical response to maintenance cabozantinib in blood and/or tissue where feasible.	• Correlation of plasma proteins at baseline or plasma protein changes during treatment with clinical outcomes from maintenance cabozantinib initiation. • Correlation of genomic alterations and/or ctDNA concentration at baseline or changes during study intervention and at disease progression where applicable, with clinical outcomes. • Correlation of genomic alterations and/or protein expression in tumor tissue at baseline, with clinical outcomes from maintenance cabozantinib initiation.
• Impact of maintenance cabozantinib in participants experiencing surgery or any other therapy with curative intent	• Responses after surgery or any other therapy with curative intent and safety profile

AESI=adverse event of special interest, AYA=adolescents and young adults, BIRC=Blinded Independent Radiology Committee, BSC=best supportive care, CR=complete response, ctDNA=circulating tumor DNA, DCR=disease control rate, EORTC QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ETM=event to monitor, ORR=objective response rate, OS=overall survival, PedsQL=paediatric quality of life inventory, PFS=progression-free survival, PK=pharmacokinetic, PR=partial response, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, SD=stable disease, TEAE=treatment emergent adverse event

4 STUDY DESIGN

4.1 Overall Design

This is a phase II, multicenter, randomized, open-label, two arm, parallel-group study evaluating maintenance cabozantinib plus BSC versus BSC in children and AYA with unresectable residual osteosarcoma, who achieved PR or SD at the end of conventional chemotherapy, either in first line at diagnosis or after first relapse treated with chemotherapy (see Figure 1 for the study design). Participants who have not received previous chemotherapy at the time of first relapse (who achieved surgical remission, or who were completely resected) are eligible at the time of the subsequent relapse if treated with chemotherapy. The last dose of chemotherapy must have been received at least 4 weeks, but not more than 2 months, before randomization.

Participants will be randomly assigned (1:1) to receive one of the following two study interventions (Figure 1):

- Arm A: Cabozantinib+BSC
- Arm B: BSC alone

Randomization will be stratified according to the setting of the disease at screening: either initial diagnosis or at first relapse after chemotherapy.

The starting dose of cabozantinib for this trial will be 40 mg/m^2/day for children and adolescents (<18 years of age). Cabozantinib will be administered orally QD on a continuous dosing schedule for cycles of 28 days. Dosing will be performed based on BSA and rounded to the nearest 20 mg using the dosing nomogram (see Appendix 10.8). The cumulative weekly dose of cabozantinib cannot exceed 420 mg.

The starting dose for participants ≥18 years of age will be 60 mg/day.

Dose reductions will be allowed for toxicities as outlined in Section 6.6.

BSC will be administered in both arms per investigator's discretion and institutional guidelines. Per European Medicines Agency (EMA) guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev. 6), BSC includes antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy), etc. but does not include tumor specific therapy.

The estimated duration of study for participants including follow up is at least 24 months or until disease progression or death or unacceptable toxicity.

Switch after Disease Progression

As the selected population for the study has limited treatment options, the study will allow eligible participants (refer to Appendix 10.14 for specific eligibility section) randomized to the BSC arm to switch to the cabozantinib arm if they meet the following key eligibility criteria and based on investigator's judgment, as applicable:

- Disease progression per RECIST version 1.1

  Note: Clinical deterioration or clinical progression determined by the investigator will not be considered radiographical progression events. If clinically indicated, radiologic tumor assessment will be scheduled in order to evaluate disease status according to RECIST v1.1. Disease progression, to allow switch, will be evaluated based on investigator's assessment. BIRC review will be utilized for the primary analysis.
- No new systemic anticancer medication prior to switch

- All safety parameters listed in the inclusion criteria, and none of the safety parameters listed in the exclusion criteria
- The study is ongoing.

Participants who switch to cabozantinib during the course of the study will continue to receive cabozantinib+BSC until tumor progression, unacceptable toxicity, participant request, investigator's decision or study termination, whichever occurs first. Participants initiating cabozantinib+BSC from BSC arm will follow the schedule outlined in Section 1.3 (Table 2).

See Section 6.9.4 for information on local therapy with curative intent during the study.

Follow-up Period

Participants will be followed until death, participant request to discontinue from follow-up, or until the last participant to enter survival Follow-up period has been followed for 1 year, or the Sponsor decides to discontinue collection of these data in the study whichever occurs first.

4.2 Scientific Rationale for Study Design

This is a phase II, multicenter, randomized, open-label, two-arm, parallel-group study evaluating maintenance cabozantinib plus BSC versus BSC in children and AYA with unresectable residual osteosarcoma, who achieved PR or SD at the end of conventional chemotherapy, either in first line at diagnosis or after first relapse treated with chemotherapy.

As per current international guidelines, no treatment is considered standard of care in the context of maintenance in advanced setting (ESMO-PaedCan–EURACAN 2021; NCCN Bone Cancer 2.2023; see Section 2.2.1.4).

Based on the specific population of the trial (see Figure 2) and the need to not increase the burden of treatment and due to the absence of standard of care in maintenance in this setting, no placebo was considered; only BSC will be considered in the control arm.

BSC, excluding non-protocol anticancer therapy, as described in Section 4.1, will be administered in both arms per investigator's discretion and institutional guidelines.

The open-label study design enables appropriate monitoring of adverse events (AEs) in both study arms.

4.2.1 Participant Input into Design

Patient organisations and experts in sarcoma have been consulted in the design of this study and suggestions implemented.

4.3 Justification for Dose

Sparse pharmacokinetics (PK) data have been collected in two paediatric studies (ADVL1211 and ADVL1622) led by the COG, in children and AYA with refractory or recurrent solid tumors. A total of 327 quantifiable and evaluable cabozantinib concentrations from 55 participants were available (37 and 18 participants from ADVL1211 and ADVL1622 study, respectively), including the doses 30, 40 and 55 mg/m². Among the 55 participants, median age was 13 years (range: 4 to 18 years). A population PK analysis was performed on the data to characterize cabozantinib PK in children and AYA, to assess interindividual variability and which covariates could explain part of PK variability (Population Pharmacokinetic Analysis of Cabozantinib in Children and Adolescent Subjects Report).

The children, adolescent and adult population PK models were used to simulate and compare cabozantinib exposures (area under the plasma concentration time curve (AUC), maximum observed plasma drug concentration (C_{max}) and minimum observed plasma drug concentration (C_{min})) between these populations. Results indicated that exposures in children and adolescent patients following an administration of a BSA-based dose of cabozantinib of 40 mg/m² are similar to the exposures in adults who received a fixed dose of cabozantinib of 60 mg QD (the starting dose in adult patients in monotherapy (e.g. RCC, HCC patients)).

4.4 End of Study/Clinical Trial Definition

The average total study duration for each participant is estimated to be approximately 24 months (including Screening, Treatment and Follow-up period). However, a participant could remain in the study longer if demonstrating treatment benefit. For information on access to study intervention after study completion, see Section 6.7.

Participants are considered to have completed the study once they have PD, are off study intervention and have completed the end of study intervention (EOSI) visit or death has occurred, whichever occurs first. For participants who discontinued from study intervention without evidence of PD, tumor assessment will continue, and they will be considered as having completed the study once they have an assessment of PD, started new anti-cancer medication, died, are lost to follow-up, or withdrawn from the study, whichever occurs first. Note, for participants who switch to the cabozantinib + BSC arm, the study intervention completion will be considered at the EOSI according to the schedule of activities (SoA) (Section 1.3, Table 2).

The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last participant in the study globally.

The study will be considered complete if the Sponsor chooses to terminate the study early based on interim futility analysis for PFS, or after completion of the final PFS analysis.

Criteria for study intervention discontinuation and participant discontinuation/withdrawal from the study are described in Section 7.1 and Section 7.2, respectively. Lost to follow-up is described in Section 7.3.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

(1) Participants must be ≥5 and ≤30 years of age at the time of study entry.

Type of Participant and Disease Characteristics

(2) Histologically or cytologically confirmed diagnosis of high-grade osteosarcoma as defined by a local pathologist.

(3) Participants with unresectable residual disease after standard chemotherapy treatment at diagnosis or first relapse (treated with systemic chemotherapy). A minimum of 4 cycles of systemic chemotherapy (or minimum of 2 cycles if chemotherapy was stopped early due to toxicity) must have been received.

(4) Measurable residual or evaluable disease by RECIST version 1.1.

Participants will be considered with evaluable disease if they have only non-measurable disease as per RECIST version 1.1 criteria. Refer to Appendix 10.13 for more information.

(5) Absence of PD (defined by the investigator according to RECIST version 1.1) at study entry. Note, the two most recent radiological evaluations (e.g. computerised tomography (CT) or magnetic resonance imaging (MRI) scan) including the one following completion of chemotherapy should be available later to facilitate BIRC review.

(6) Chemotherapy must be the last anticancer treatment received by participants before study entry and must have been completed at least 4 weeks but no longer than 2 months before randomization.

(7) Participants must have recovered to Grade ≤1, except for alopecia, ototoxicity, and Grade ≤2 peripheral neuropathy, per Common Terminology Criteria for Adverse Events (CTCAE) version 5.0) from the acute toxic effects of all prior anticancer therapy at study entry, unless AEs are clinically nonsignificant and/or stable on supportive therapy, per investigator clinical judgment.

(8) Life expectancy >6 months.

(9) Performance level: participants must have a Lansky or Karnofsky performance status score of ≥70 corresponding to ECOG categories 0-1 (see Appendix 10.16).

Note: use Karnofsky for participants ≥16 years of age and Lansky for participants <16 years of age. Participants who are unable to walk because of paralysis, but who use a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

(10b) Adequate organ and marrow function. Organ Function Requirements, within 7 days before randomization are as follows:

- Adequate Bone Marrow Function Defined As:
  - Peripheral absolute neutrophil count (ANC) ≥1000/µL
  - Platelet count ≥100,000/µL
  - Hemoglobin ≥8.0 g/dL

- Transfusions are permitted to meet both the platelet and haemoglobin criteria if the transfusion is more than 7 days before screening laboratory sample collection. Participants must not be known to be refractory to red blood cell or platelet transfusions.

• Adequate Renal Function Defined As:
  - For participants below 18 years of age:

    Creatinine clearance GFR ≥70 mL/min/1.73 m^2 (using the revised bedside Schwartz formula ([(0.413 × Height (cm)) / Scr (mg/dL)]).
  - For participants ≥18 years of age: Serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥40 mL/min using the Cockcroft-Gault equation: (140 – age) × weight (kg) x [0.85 if female]/(serum creatinine [mg/dL] × 72).
  - Urine protein/creatinine ratio (UPCR) ≤1 mg/mg (≤113.1 mg/mmol) or 24-hour urine protein <1 g.
• Adequate Liver Function Defined As:
  - Total bilirubin ≤1.5 × ULN for age.

    Note: Participants with known Gilbert's disease or unconjugated hyperbilirubinemia who have serum bilirubin level ≤3 × ULN may be enrolled.
  - Alanine transaminase (ALT) and aspartate transaminase (AST) ≤3 × ULN in the absence of liver metastases or both ≤5.0 × ULN in the presence of liver metastases.
  - Alkaline phosphatase (ALP) ≤3 × ULN. ALP ≤5 × ULN if the participant has documented bone metastases.
  - Serum albumin ≥2.8 g/dL.
• Adequate Coagulation Status Defined As:
  - Partial thromboplastin time (PTT), prothrombin time (PT), and international normalized ratio (INR) ≤1.5 × ULN
• Adequate Pancreatic Function Defined As:
  - Serum amylase ≤1.5 × ULN.
  - Serum lipase ≤1.5 × ULN.

(11) Negative hepatitis B surface antigen (HBsAg) test within 28 days before randomization
  - Negative hepatitis C virus (HCV) antibody test, or positive HCV antibody test followed by a negative HCV RNA test and no ongoing anti-HCV therapy within 28 days before randomization.

Note: The HCV RNA test will be performed only for participants who have a positive HCV antibody test.

(12) Adequately controlled blood pressure (BP) with or without antihypertensive medications (refer to Appendix 10.9). A BP ≤the 95th percentile for age, height, and gender for pediatric participants <18 years old and ≤140/90 mmHg for participants ≥18 years old. Please note that 3 serial blood pressures should be obtained and averaged to determine baseline BP.

Weight

(13) Participants must have a BSA ≥0.65 m^2.

Sex and Contraception/Barrier Requirements

(14) Male and/or female (according to their reproductive organs and functions assigned by chromosomal complement) (FDA 2016)

(15a) Sexually active fertile participants and their partners must agree to use highly effective contraception as appropriate for their age and sexual activity, in combination with one acceptable barrier method, and as required by local regulations during the course of the study and for 4 months after the last dose of study intervention. Pregnancy testing is required as appropriate for the age and sexual activity of female participants and as required by local regulations during the course of the study (see Appendix 10.4).

(16) Female participants of childbearing potential must provide a negative pregnancy test within 7 days prior to the start of study intervention. If a urine test cannot be confirmed as negative, a negative serum pregnancy test is required.

Note: If the childbearing potential changes after start of the study (e.g., a premenarchal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the investigator must discuss this with the participant/legal guardian, who should determine if a female participant must begin a highly effective method of contraception, or a male participant must use a condom. If reproductive status is questionable, additional evaluation should be considered.

Informed Consent and Assent

(17) All participants (typically ≥18 years) and/or their parents or legal guardians must sign a written informed consent and assent must be obtained from minor participants according to local guidelines.

Note: The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant and/or their legal guardian (as defined in Appendix 10.1.3 and the participant's assent, when applicable, before any study-specific activity is performed unless a waiver of informed consent has been granted by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC). All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand.

Other

(18) Applicable for minor participants ONLY: A legal guardian or primary caregiver must be available to help the study-site personnel ensure follow up; accompany the participant to the study site on each assessment day according to the SoA (e.g., able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures); consistently and consecutively be available to provide information on the participant using the rating scales during the scheduled study visits; accurately and reliably dispense study intervention as directed.

A legal guardian or primary caregiver must be able to accurately maintain the child's take-home record, including items of general health.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

(1) Low grade osteosarcoma and periosteal osteosarcoma.

(2) Previous treatment with cabozantinib or another MET/hepatocyte growth factor (HGF) inhibitor (e.g., tivantinib, crizotinib).

(3) Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks or 5 half-lives of the agent, whichever is longer, before first dose of study intervention.

(4) Receipt of any type of cytotoxic, biologic or other systemic anticancer therapy (including investigational) within 4 weeks before first dose of study intervention (or washout of at least 5 half-lives, whichever is shorter).

(5) Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery or major surgery e.g., removal or biopsy of brain metastasis) and stable for at least 4 weeks prior to randomization. Eligible participants must be neurologically asymptomatic and without systemic corticosteroid treatment at the time of randomization.

Note: Participants with a known seizure disorder who are receiving non-enzyme inducing anticonvulsants and have well-controlled seizures on a stable dose of anti-convulsant may be enrolled. See Appendix 10.10 for a list of recommended non-enzyme inducing anticonvulsants.

(6) 'Deleted at Amendment 2'

(7) Ongoing Grade >2 peripheral neuropathy.

(8) Participants who have an uncontrolled/active infection requiring systemic therapy.

(9) Participants who are unable to swallow intact tablets.

(10) Acute or chronic hepatitis B or C infection, known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome-related illness where there is clinical or radiographic evidence of active mycobacterial infection. Note: HBV and HCV testing will be performed at screening. HIV testing will be performed at screening if and as required by local regulation.

(11) Participants with active bleeding. Specifically, clinically significant GI bleeding, GI perforation, intra-abdominal abscess or fistula for 6 months prior to enrollment, haemoptysis or other signs of pulmonary haemorrhage for 3 months prior to enrollment. Clinically significant hematuria, cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.

(12) Lesions invading or encasing any major blood vessels.

(13) Participants with evidence of an acute intracranial or intratumoral haemorrhage on CT or MRI.

(14) Participants with uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

(a) Cardiovascular disorders:

Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias. Uncontrolled hypertension defined as sustained BP >140 mm Hg systolic or >90 mm Hg diastolic or BP >the 95th percentile for age, height, and gender for pediatric participants <18 years old, despite optimal antihypertensive treatment. Stroke (including transient ischemic attack (TIA)), myocardial infarction (MI), or other ischemic event, or thromboembolic event (e.g., deep vein thrombosis (DVT), pulmonary embolism) within 6 months before first dose of study intervention.

- Corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms within 28 days before randomization. Note: If a single electrocardiogram (ECG) shows a QTcF with an absolute value >500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these 3 consecutive results for QTcF will be used to determine eligibility.

(b) Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation: The participant has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g., Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose of study intervention. Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose of study intervention. Other disorders associated with a high risk of fistula formation including percutaneous endoscopic gastrostomy (PEG) tube placement within 3 months before the first dose of study therapy.

(c) Other clinically significant disorders such as:

i. bone fracture within 28 days prior to randomization.

ii. history of solid organ transplantation.

iii. concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of study intervention.

(d) Participants with a diagnosis of incidental, subsegmental pulmonary embolism (PE) or DVT within 6 months are allowed if stable, asymptomatic, and treated with a stable dose of permitted anticoagulation for at least 1 week before first dose of study intervention

(e) Participants who have had significant traumatic injury within 28 days prior the enrollment are not eligible.

(f) Participants with any medical or surgical conditions that would interfere with GI absorption of the study drug are not eligible

(g) Other clinically significant disorders that would preclude safe study participation and preclude participants from receiving cabozantinib.

(h) Serious non-healing wound/ulcer/bone fracture.

(i) Moderate to severe hepatic impairment (Child-Pugh B or C).

(15) Previously identified allergy or hypersensitivity to components of the study treatment formulations.

(16) Any other active malignancy at time of first dose of study intervention or diagnosis of another malignancy within 3 years prior to first dose of study intervention that requires active treatment.

Prior/Concomitant Therapy

(17) Radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before first dose of study intervention. Systemic treatment with radionuclides within 6 weeks before first dose of study intervention. Participants with clinically relevant ongoing complications from prior radiation therapy are not eligible.

(18) Growth factor(s): Growth factors that support white cell number or function must not have been administered within the 7 days prior to enrollment (14 days if pegfilgrastim).

(19) Corticosteroids: Participants requiring corticosteroids who have not been on a stable or decreasing dose of corticosteroid for the 7 days prior to randomization are not eligible (not applicable for participants with brain metastasis). If used to modify immune AEs related to prior therapy, ≥14 days must have elapsed since last dose of corticosteroid.

(20a) Investigational Drugs: Participants who are currently receiving another investigational drug or who participated in any other clinical trial involving an investigational study treatment with the last administration of treatment within the last 28 days (4 weeks), or 5 half-lives (whichever is longer) prior to first dose of study intervention are not eligible.

(21) Anti-cancer Agents: Participants who are currently receiving other anticancer agents are not eligible.

(22) Participants who are receiving cyclosporine, tacrolimus, or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial.

(23a) Cytochrome P450 Family 3 Subfamily A Member 4 (CYP3A4) active agents: Participants must not be receiving any of the following potent CYP3A4 inducers or inhibitors: erythromycin, clarithromycin, ketoconazole, azithromycin, itraconazole, grapefruit juice or St. John's wort. A list of other known CYP3A4 inducers and inhibitors that should be discontinued prior to initiation of protocol therapy and should be avoided during study therapy if reasonable alternatives exist is provided in Appendix 10.12.

(24a) Concomitant anticoagulation with oral anticoagulants including, but not limited to, platelet inhibitors (eg, clopidogrel or ticagrelor), warfarin, dabigatran, and betrixaban, except for those specified below.

- Allowed anticoagulants are:
  - (a) Prophylactic use of low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH).
  - (b) Therapeutic doses of LMWH or the direct factor Xa inhibitors rivaroxaban, edoxaban, in participants without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before randomization and without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

(25) Enzyme-inducing Anticonvulsants: Participants must not have received enzyme-inducing anticonvulsants within 14 days prior to enrollment.

(26) Corrected QT interval (QTc) Agents: Participants who are receiving drugs that prolong QTc are not eligible.

Other Exclusions

(27) Pregnancy or breast-feeding.

Pregnant or breast-feeding women will not be enrolled in this study (see also Appendix 10.4).

(28) Participants who in the opinion of the investigator may not be able to comply with the requirements of the study are not eligible.

(29) Major surgery (eg, orthopaedic surgery, removal or biopsy of brain metastasis) within 8 weeks before randomization. Complete wound healing from major surgery must have occurred 4 weeks before randomization and from minor surgery (eg, simple excision, tooth extraction) at least 10 days before randomization. Participants with clinically relevant ongoing complications from prior surgery are not eligible.

(30) Participants who have received any local anticancer therapy including radiofrequency ablation (RFA), microwave thermal ablation (MWA) or cryotherapy within 28 days prior to randomization.

5.3 Lifestyle Considerations

The lifestyle considerations discussed below are required for this study.

5.3.1 Meals and Dietary Restrictions

Refrain from consumption of Seville oranges, grapefruit or grapefruit juice while being treated with cabozantinib.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical trial is 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 Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Mandatory information includes date of informed consent signature, demography, reason for screen failure and date of screen failure, eligibility criteria and any serious adverse event (SAE).

Participants may be re-screened once if they fail screening, per investigator decision. After screen failure, if participants are eligible for second screening and have met eligibility criteria, they will be marked as screen failure for the first screening and re-screened with a new participant number and sign another Informed Consent Form (ICF) (see Section 10.1.3). Former participant number of the first screening will be noted on the new case report form (CRF) case with the new participant number.

5.5 Criteria for Temporarily Delaying Randomization/Administration of Cycle 1 Day 1 Study Intervention

The following conditions may allow a participant to be randomized/administered study intervention once the conditions have resolved and the participant is otherwise well per investigator clinical judgement: current febrile illness (temperature 38.0°C (100.4°F)) or other acute illness within 48 hours eg, vomiting, diarrhoea, before study intervention administration.

Participant is less than 5 days into a course of systemic antibiotic therapy. Note: Participants receiving oral (including prophylactic) antibiotics with no symptoms of infection at randomization or oral valacyclovir (valaciclovir) are eligible.

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

Study interventions are all prespecified, investigational and non-investigational medicinal products intended to be administered to the study participants during the study conduct.

6.1 Study Interventions

Cabozantinib will be self-administered by the participant (for participants ≥18 years) or administered to the participant by a legal guardian or caregiver (for participants <18 years of age).

Study personnel should review dose administration requirements with the participant, as appropriate, and with the delegated caregiver(s) before administration and throughout the study as necessary.

Cabozantinib tablets and cabozantinib capsules are not bioequivalent and should not be used interchangeably.

Best supportive care includes antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including radiotherapy according to the timelines provided in the Section 5.2), etc. but does not include tumor specific therapy. BSC will be administered in both arms per investigator's discretion and institutional guidelines.

6.1.1 Study Intervention(s) Administered

Table 4 Study interventions administered

Intervention Name	Cabozantinib	BSC
Intervention Description	Tablet containing Cabozantinib (S)-malate	NA, product dependent
Type	Drug	NA, product dependent
Dose Formulation	Film-coated tablet	NA, product dependent
Unit Dose Strength(s)	20 mg and 60 mg	NA, product dependent
Dosage Level(s)	60 mg starting dose for participants ≥18 years. For participants <18 years of age, refer to dosing nomogram (Appendix 10.8)	NA, product dependent
Route of Administration	oral	NA, product dependent
Use	Experimental	Background intervention
IMP and NIMP/AMP.	IMP	NIMP/AMP
Sourcing	Provided centrally by the sponsor	Provided locally by the study site.
Packaging and Labelling	Study intervention will be provided in container. Each container will be labelled as required per country requirement.	NA, provided locally by the study site per patient need and investigator decision.
Storage requirements	To be stored as required by product label	To be stored as required by product label

AMP=auxiliary investigational product, BSC=Best supportive care, IMP=investigational medicinal product, NA=not applicable, NIMP=non-investigational medicinal product.

Table 5 Study Arm(s)

Arm Title	Arm A: Cabozantinib + BSC	Arm B: BSC alone
Arm Type	Experimental	Control
Arm Description	Participants will receive cabozantinib and BSC. The starting dose of cabozantinib for this trial will be 40 mg/m^2/day for children and adolescents (<18 years of age). Cabozantinib will be administered orally QD on a continuous dosing schedule for cycles of 28 days. Dosing will be performed based on BSA and rounded to the nearest 20 mg using the dosing nomogram (see Appendix 10.8). The cumulative weekly dose of cabozantinib cannot exceed 420 mg (maximum dose is 60 mg/day). The starting dose for participants ≥18 years of age will be 60 mg/day. Treatment will continue until tumor progression, unacceptable toxicity, withdrawal of consent, investigator's decision to discontinue or study termination, whichever occurs first. BSC will be administered per investigator's discretion and institutional guidelines. BSC excludes non-protocol anticancer therapy.	Participants will receive BSC alone administered per investigator's discretion and institutional guidelines. BSC excludes non-protocol anticancer therapy

BSA=body surface area, BSC=Best supportive care, QD=once daily.

6.1.2 Timing of Cabozantinib Dose for Each Participant

Cabozantinib tablets will be administered orally at approximately the same time, preferably at bedtime. Only the first dose will be given in the clinic (first dose to occur ≤3 days after randomization).

Drug doses should be adjusted based on the BSA calculated from height and actual body weight measured within 7 days prior to the beginning of each cycle, and according to the dosing nomogram (see Appendix 10.8). Mosteller's equation will be used to calculate BSA. Sites will fill out the number of prescribed tablets per day in the participant diary.

Participants must complete the diary with the date, time and number of cabozantinib tablets taken each day. The participant diary should be reviewed after completion of each treatment cycle.

If a participant vomits after the dose of cabozantinib is administered, the dose should not be repeated. The tablet should be taken with a large glass of water on an empty stomach, and participant should not eat 2 hours before or 1 hour after each dose of cabozantinib. The tablet should not be crushed or broken but be swallowed whole. Furthermore, a missed dose should not be taken within 12 hours of the next dose.

6.2 Preparation, Handling, Storage and Accountability (Applicable for Cabozantinib)

The excipients used in the investigational medicinal product formulations are safe for administration in the paediatric population participating in the study. Further guidance and information for the receipt, preparation, management, and disposal/return of the study intervention are provided in the "Investigational Medicinal Product Handling Manual".

- Only participants screened in the study and who meet the eligibility criteria may receive study intervention and only authorised site staff may supply or administer study intervention.
- Cabozantinib must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution or the head of the medical institution (where applicable) is responsible for cabozantinib accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- The sponsor will provide guidance on the destruction of unused cabozantinib. If destruction is authorised to take place at the investigational site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy and any special instructions provided by the sponsor. All destruction must be adequately documented.
- Further guidance and information for the receipt, preparation, management and disposal/return of the study intervention are provided in the "Investigational Medicinal Product Handling Manual".

6.3 Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention using an interactive web response system (IWRS). Before the study is initiated at each site, the log-in information and directions for the IWRS will be provided to each site.

Cabozantinib will be dispensed at the study visits as summarized in the SoA (Section 1.3). BSC will be administered per local guidance by the investigator.

Returned study intervention should not be redispensed to the participants.

6.4 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; there is no blinding. Although this is an open-label study, the study team will be blinded to the randomized treatment assignment by the IWRS. The study team will not be allowed to perform analyses or summaries based on the randomized or actual treatment assignment before the randomized treatment assignment for all randomized participants is unblinded to the study team for any pre-specified analyses. Additionally, blinded image reviewers are also blinded to treatment assignment to mitigate bias in determining disease response.

6.4.1 Randomization

This is an open-label study; no blinding applies to this study.

The sponsor's randomization manager will supervise the preparation of a list of randomization numbers. It will be produced in blocks, on a balanced ratio 1:1 (1 cabozantinib plus BSC: 1 BSC). The randomization will be stratified by the setting of the disease at screening: Initial diagnosis *versus* 1st relapse (after chemotherapy).

The randomization and intervention arm assignation will be managed by IWRS. After eligibility is confirmed, at Cycle 1 Day 1 (C1D1), participants will be assigned a randomization number and will be randomized to the corresponding intervention arm in sequential order within each level of strata.

For participants who are randomized to cabozantinib plus BSC, the first dose of study intervention should be administered on the day of randomization, if possible. Where this is not possible, the first dose should occur within 3 days after randomization.

Of note, in case of disease progression for participants randomized in Arm B (BSC only), the participant may be allowed to switch to cabozantinib arm after a switch screening visit to assess eligibility for switch (refer to Appendix 10.14).

The IWRS will also manage all the logistical aspects of intervention (e.g. intervention supplies, replacement of lost, damaged, quarantined, and expired kits).

This service provides investigators, site coordinators and project team members with a 24-hour per day, 7-day per week service (additional details may be found in the IWRS reference manual provided to each site). In case of medical or technical randomization or dispensation queries, a 24-hour helpline is available – see supporting information in the IWRS manual.

Recruitment will stop once approximately 90 participants have been randomized (with at least 45 paediatric participants, <18 years of age, evaluable for the primary analysis). Participants may be randomized and decide to withdraw early without providing sufficient information. These participants will not be replaced.

Randomized participants who terminate their study participation for any reason before their first intervention will retain their randomization number (i.e. this number will not be reused). The next participant will be assigned another randomization number, even if he/she should receive the same intervention. Participants who leave the study early will not be replaced.

The sponsor's randomization manager will keep the master randomization list. A copy of this list will also be provided to the Service Provider in charge of IWRS. The master list and the copy supplied to the service provider in charge of IWRS will be kept confidential in a secure location. Access to the randomization list must be restricted until authorisation is given to release it for planned analysis.

6.4.2 Maintenance of Blinding

This is an open-label study, therefore no procedures for blinding are applicable.

Note: the independent central reviewers making tumor assessments will be blinded to certain participant baseline and response information (see Section 8.2.1).

6.5 Study Intervention Compliance

Participants will self-administer (for participants ≥18 years) or be administered study intervention(s) by a legal guardian or caregiver (participants <18 years of age) at home. Except for Cycle 1 Day 1, the first dose of study intervention for participants randomized to cabozantinib+BSC will be administered at the site.

For participants aged 5 to 17, assessment for acceptability and palatability will be performed on Cycle 1 Day 1 (refer to Appendix 10.15 for instructions and the facial hedonic scale).

Compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets, and participant diaries during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the quantity of cabozantinib dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention, holds and/or dose reductions, will also be recorded in the CRF.

6.6 Dose Modification

6.6.1 Reductions and Interruptions

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruptions):

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity. Should this be ineffective, dose reductions or interruptions should be considered to prevent worsening of toxicity.
- Dose reduction will be allowed for the management of AEs associated with cabozantinib (see dose modification criteria, Table 6).

If dose reduction is necessary, cabozantinib will be administered as follows:



Two dose reduction levels of cabozantinib are permitted in the cabozantinib+ BSC arm. If a participant experiences a toxicity after two dose reductions, they must be removed from protocol therapy.

In order to improve treatment compliance, PK simulations were performed to optimize the dose reduction strategy for children and adolescents with BSA range CCI, and CCI up to CCI. The children and adolescents Population PK model built from the CCI and CCI studies was used to simulate cabozantinib exposure (CCI) after CCI using the CCI approach and the fixed dose approach employed in adults.

Results indicated that, after first dose reduction, cabozantinib exposures, especially the AUC, are CCI. For the second dose reduction, exposure is slightly CCI using the fixed dose approach, but the difference is not clinically relevant given the variability.

Therefore, children and adolescents with BSA range CCI and CCI up to CCI will follow the same dosing strategy as adults.

Cabozantinib Dose Reductions Table (Participants ≥18 Years of Age)

The assigned dose for cabozantinib is 60 mg QD. Two dose reductions will be permitted (Table 7):

- 60 mg QD to 40 mg QD (first level dose reduction)
- 40 mg QD to 20 mg QD (second level dose reduction)

Study intervention must be discontinued if a QD dose of 20 mg cabozantinib is not tolerated.

Table 7 Cabozantinib Dose Reductions Table (Participants ≥18 Years of Age)

Assigned Dose	First Dose Level Reduction	Second Dose Level Reduction
60 mg of cabozantinib oral QD	40 mg of cabozantinib oral QD	20 mg of cabozantinib oral QD

QD=once daily

Table 8 General Dose Modification Criteria

Toxicity Criteria	Recommended for Management
Grade 1 AEs	Add supportive care as indicated. Continue study intervention at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue study intervention at the current dose level with supportive care.
Grade 2 AEs which are **intolerable** and **cannot be adequately managed**	Study intervention should be dose reduced or interrupted. Note: It is recommended that dose interruptions be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Study intervention should be interrupted unless the toxicity can be easily managed with a dose reduction of study intervention and optimal medical care. Note: It is recommended that dose interruptions be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Study intervention must be interrupted immediately. In general, study intervention should be discontinued unless the following criteria are met: • Participant is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor • Toxicity can be managed with a dose reduction of study intervention following recovery to Grade 1 (or baseline) and optimal medical care Sponsor must be contacted to discuss continuation of study intervention upon resolution of AEs.

AE=adverse event.

Dose interruptions of study treatment due to AEs management are allowed for up to 8 weeks.

Restarting treatment after interruptions longer than 8 weeks may be allowed, only if participants is clinical benefitting as per investigator decision and is on the best interest of the participants to restart, with approval of the Sponsor.

Refer to Appendix 10.6 for guidance for specific AE management.

6.7 Continued Access to Study Intervention after the End of the Study

After study completion (see Section 4.4), participants who continue to demonstrate clinical benefit may be eligible to receive Sponsor-supplied study intervention.

The Sponsor will follow local regulations and will work with study investigators to act in the best interest of the study participants.

6.8 Treatment of Overdose

Study-site personnel should instruct the legal guardian and caregivers to store the study intervention out of reach of pediatric participants to avoid accidental overdose.

For this study, any dose of cabozantinib greater than the daily dose recommended in Section 4.1 will be considered an overdose. The sponsor does not recommend specific treatment for an overdose. Participants should be medically supervised, and supportive treatment initiated as applicable.

In the event of an overdose, the investigator/treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities (as medically appropriate and until the next scheduled follow-up).
- Document the quantity of the excess dose as well as the duration of the overdose. See Appendix 10.3.1 for reporting requirements concerning overdose.

6.9 Prior and Concomitant Therapy

All concurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the investigator according to acceptable local standards of medical care. Participants should receive analgesics, antiemetics, antibiotics, anti-pyretics, and blood products as necessary.

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving during the period from 28 days before randomization (screening period) through 30 days after the date of the decision to permanently discontinue study intervention must be recorded in source documents and the CRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Paracetamol/Acetaminophen, at doses allowed as per label, according to different age criteria and as per investigator's judgment, is permitted for use. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

6.9.1 Permitted During Study

Vaccines used in the event of a disease outbreak or pandemic are allowed. However, while prioritizing standard clinical care, efforts should be made not to administer non-study vaccines within 14 days (for non-live vaccines) or 28 days (for live vaccines) prior to randomization.

The following concomitant medications are permitted during this study, but they must be closely monitored and every effort should be made to keep their dose and dose regimen constant throughout the course of the study:

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated;
- Granulocyte colony-stimulating factors (G-CSF) or granulocyte macrophage (GM)-CSF are allowed if used per clinical guidelines (e.g. American Society of Clinical Oncology (ASCO) or ESMO guidelines);
- Drugs used to control bone loss (e.g. bisphosphonates and denosumab) are allowed if started prior to screening activities and can be used to control bone loss or hypercalcemia if the benefit outweighs the risk per the investigator's discretion.
  - Note: osteonecrosis of the jaw has been reported in participants using bisphosphonates or denosumab. Oral examinations are recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the investigator. Frequent monitoring for potentially overlapping toxicities with study intervention is recommended.
- Transfusions, hormone replacement (including thyroid stimulating hormone (TSH)-suppressive thyroid hormone therapy), and short-term higher doses of corticosteroids should be utilised as indicated by standard clinical practice;
- Oral contraceptives with a failure rate of <1% per year
- Individualised anticoagulation therapy is allowed if it can be provided safely and effectively under the following circumstances:
  - Prophylactic use of low dose aspirin for cardioprotection (per local applicable guidelines), and low dose of LMWH are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion;
  - Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, or edoxaban, are allowed in participants without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before baseline without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor;
  - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy must be followed. This includes, but is not limited to, participant education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (e.g. due to kidney dysfunction);
  - For restrictions on oral anticoagulants see Section 6.9.2.

Potential drug interactions with cabozantinib are summarized in Section 6.9.3. Additional details regarding potential drug interactions with cabozantinib can be found in the investigator's Brochure.

Other

Use of medication (e.g., Adderall™ or Ritalin™) is allowed for treatment of those participants with attention deficit hyperactivity disorder (ADHD) who are otherwise deemed eligible.

Any potential additive, potentiation or antagonistic effects of the concomitant compounds when used together with cabozantinib should be considered by the investigator.

6.9.2 Prohibited or Restricted Therapies

The following therapies are prohibited while the participant is receiving study intervention:

- Any other investigational agent or investigational medical device;

- Any nonprotocol systemic anticancer treatment (eg, chemotherapy, immunotherapy, radionuclides, drug or herbal product used specifically for the treatment of osteosarcoma);
- Any other local treatment including surgery, ablation, or embolization or radiation (except as reported below for palliative external radiation for pain management). Note: for Local Therapy with Curative Intent during the Study please refers to Section 6.9.4.
- For participants on cabozantinib treatment, any coumarin agents (e.g. warfarin), direct thrombin inhibitor including but not limited to dabigatran, platelet inhibitors (e.g. clopidogrel) or direct Factor Xa inhibitors except rivaroxaban, or edoxaban (see Section 5.2, Section 6.9.1 and Section 10.14.2).

The following therapies should be avoided while the participant is receiving study intervention:

- Palliative external radiation for pain management should not be performed while on study except if it is clinically unavoidable and after exclusion of disease progression as per RECIST 1.1. Participants who have such an intervention may be considered not evaluable on and after receiving radiation (and may be assigned a censoring or progression date) for certain efficacy endpoints; if clinically unavoidable the investigator should consult the sponsor prior to the procedure for safety guidance.

The following therapies should be avoided while the participant is on cabozantinib treatment:

- Erythropoietic stimulating agents (e.g. epoetin alfa and darbepoetin alfa): when deemed necessary use is allowed if used per clinical guidelines (e.g. ASCO or ESMO guidelines); Note: Frequent monitoring for potentially overlapping toxicities with study intervention is recommended;
- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended (refer to Appendix 10.12);
- Caution must be used when discontinuing study intervention with a strong CYP3A4 inducer in a participant who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib (refer to Appendix 10.12);
- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g. ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations and should be avoided (refer to Appendix 10.12);
- Concomitant medications known to prolong the QTc interval should be avoided in participants who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to Appendix 10.11 for a list of drugs which have the potential to prolong the QTc interval).

Additional details regarding potential drug interactions with cabozantinib can be found in the Investigator's Brochure.

6.9.3 Potential Interactions with Cabozantinib

CYP450: Data from a clinical drug interaction study (Study XL184-008) showed that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the

AUC of co-administered rosiglitazone, a CYP450 Family 2 Subfamily C Member 8 (CYP2C8) substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared to CYP2C8 (i.e. CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). *In vitro* data indicate that cabozantinib is unlikely to induce CYP450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 µM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, cytochrome P450 Family 2 Subfamily B Member 6 (CYP2B6), or CYP1A2 substrate), based on data from *in vitro* studies.

Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g. ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways. Drug Development and Drug Interactions, FDA.

Protein Binding: Cabozantinib is highly bound (≥99.7%) to human plasma proteins (for details see the SmPC (Cabometyx Summary of Product Characteristics 2023; Section 5.2) and the cabozantinib Investigator's Brochure). Therefore, highly protein-bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. Therefore, concomitant medications that are highly protein bound (eg, diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of oral anticoagulants is not allowed in participants receiving cabozantinib due to the potential for a protein binding displacement interaction.

Multidrug resistance-associated protein 2 (MRP2) inhibitors: *In vitro* data demonstrate that cabozantinib is a substrate of MRP2. Therefore, administration of MRP2 inhibitors may lead to

increased plasma concentration of cabozantinib. Use caution and monitor adverse events when MRP2 inhibitors are co administered with cabozantinib.

Bile salt-sequestering agents: Bile salt-sequestering agents such as cholestyramine and cholestagel may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure (for details see the SmPC (Cabometyx Summary of Product Characteristics 2023; Section 5.2)). The clinical significance of these potential interactions is unknown.

Effect of cabozantinib on other medicinal products: The effect of cabozantinib on the PK of contraceptive steroids has not been investigated. As unchanged contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended (see Appendix 10.4).

Other Interactions: Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. *In vitro* data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein. Participants should be cautioned regarding taking a P-glycoprotein substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib. Monitoring of adverse events when P-gp substrates are co-administered with cabozantinib is recommended. Additional details related to these overall conclusions can be found in the Investigator's Brochure.

Concomitant administration of proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy subjects. Therefore, concomitant use of gastric pH modifying agents (i.e., PPIs, H2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib.

Additional details regarding potential drug interactions with cabozantinib can be found in the Investigator's Brochure.

6.9.4 Local Therapy with Curative Intent during the Study

If after evaluation of the endpoint PFS-4 month, participants become suitable for surgery or any other therapy with curative intent, as per investigator judgement, and after discussion with the Sponsor, surgery or any other therapy with curative intent can be allowed, respecting the following criteria:

- Participants in the cabozantinib plus BSC arm: cabozantinib must be stopped at least 28 days prior to surgery. After consultation with the Sponsor, study participants will be allowed to restart cabozantinib, after complete wound healing (based on clinical judgment) and at least 28 days after the surgical procedure, unless it is safe and feasible to reintroduce it sooner as per investigator judgement.

  Hold and restart time of cabozantinib will be discussed with the Sponsor, on a case-by-case basis.
- Participants in the BSC arm: participants receiving BSC will be managed as per investigator local site guidance.

6.9.4.1 Surgical Procedures

Participants should not have elective surgical procedures while on therapy, except for the aforementioned case. For participants who require emergent or urgent procedures, therapy may not be restarted until 28 days after major procedures and 7 days after minor procedures such as central venous line replacement (3 days for external lines (e.g. Hickman or Broviac)) and only after complete wound healing (based on clinical judgment).

6.9.5 Rescue Medicine

No rescue medicine is included in this protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 10.1.9.

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention OR the participant may request to discontinue the study intervention.

If study intervention is permanently discontinued, the participant should remain in the study to be evaluated as per the assessments in Section 1.3. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Participants who discontinue study intervention will remain in the study and must be followed for survival data until death or end of the study (unless the participant has specifically withdrawn consent for any further contact).

If participants are lost to follow-up, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Reasons for Discontinuing Study Intervention

A participant will be discontinued from protocol therapy under the following circumstances:

- If there is evidence of radiological PD.
- The investigator feels it is not in the best interest of the participant to continue on study intervention.
- Participation in another clinical study using an investigational agent or investigational medical device.
- Necessity for treatment with non-protocol systemic anticancer therapy.
- Unacceptable side effects the investigator feels may be due to study intervention.
- If a participant becomes pregnant or is unwilling to use appropriate birth control techniques as outlined in the inclusion criteria.
- Necessity for withholding study intervention for greater than 8 weeks for AEs, unless continuation of treatment is approved by the Sponsor.
- Request by the Sponsor.
- Participant request to discontinue study intervention.
- Significant noncompliance with the protocol schedule in the opinion of the investigator or the Sponsor.

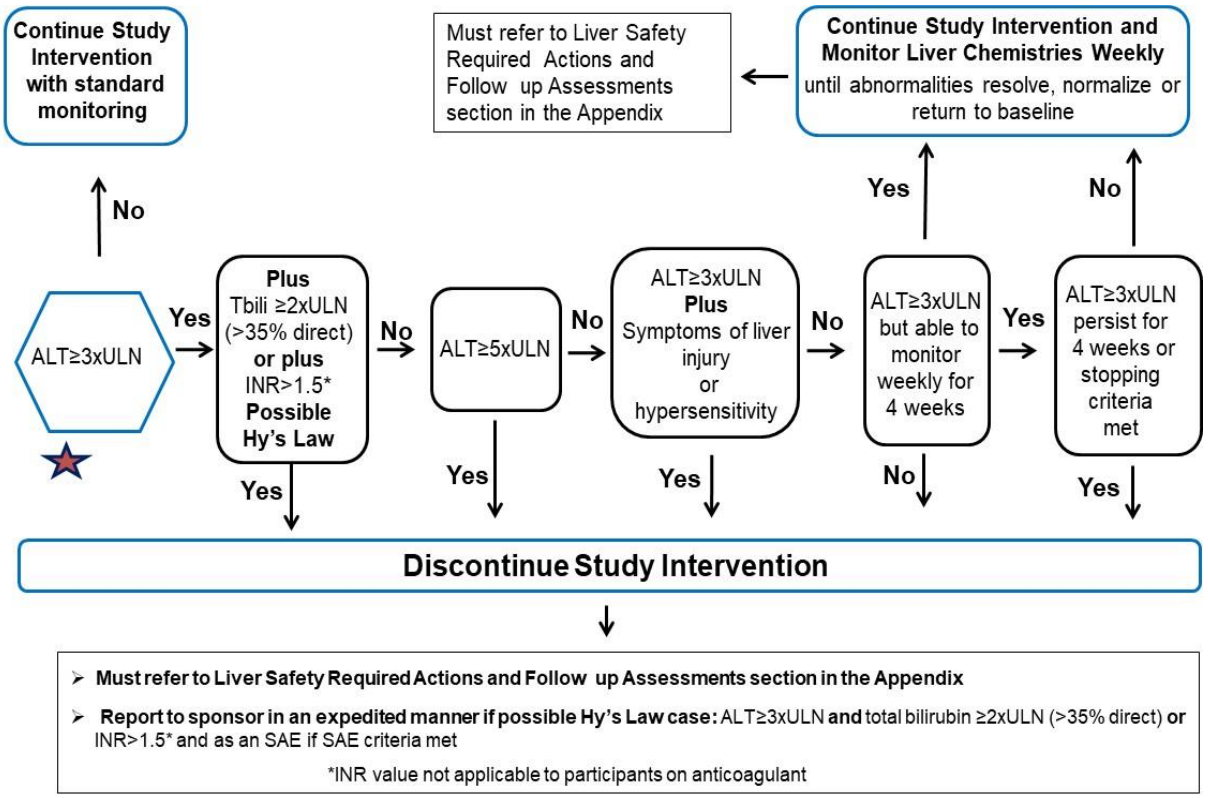
Participants can stop participating at any time. However, if participants stop study intervention due to reasons other than consent withdrawal or radiographic progression, they will continue to be followed for disease progression and survival.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in the algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

Study intervention will be discontinued **for a participant** if liver chemistry stopping criteria are met.

Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin

Liver Safety: Suggested Actions and Follow-up Assessments can be found in Appendix 10.6.

7.1.2 QTc Stopping Criteria

If the average QTcF from the three ECGs is >500 ms, the following actions must be taken:

- Interrupt study intervention and refer to Appendix 10.6 for the appropriate management.

7.1.3 Temporary Discontinuation

In case of clinical trial disruption due to a regional or national emergency declared by a governmental agency, the intervention administration may be temporarily discontinued depending on the participant clinical presentation. In some cases, the investigator may request a participant be retested before the intervention administration is resumed.

For all temporary intervention discontinuations, duration should be recorded by the investigator in the appropriate pages of the CRF.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request for any reason (or without providing any reason).

For participants <18 years of age, the legal guardian and the pediatric participant have the right to withdraw permission (consent or assent, respectively) at any time during the study. If the

study staff identifies any reluctance in the legal guardian or pediatric participant (e.g., signs of verbal or physical dissent) about continued participation in the study, the pediatric participant's continuation in the study should be re-evaluated. The same principles that govern permission/assent/consent also govern its withdrawal.

A participant will be withdrawn from the study for any of the following reasons:

- Withdrawal of consent or assent if applicable (a paediatric participant's dissent should be respected).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioural or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The reason for discontinuation will be recorded in the CRF.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent.
- If the participant withdraws consent for any further contact, the investigator will explain in the medical records as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or post-study intervention follow-up. This information must be entered in the CRF.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Participants in the optional research biobanking have the right to withdraw their consent at any time and for any reason during the study or during the period of sample storage (i.e. the entire 15 years during which samples are kept).
- If a participant wishes to withdraw their consent for optional biobanking and the samples are still at the investigator site or at the central laboratory at the time, the investigator must inform the study monitor in writing of the participant's decision and destroy the samples.
- If the samples are at the sponsor's repository (biobanking vendor), the investigator must inform the sponsor directly using the e-mail address: IpsenBiobanking@ipsen.com, mentioning only the participant ID in this e-mail. The sponsor will ensure destruction of the samples and all corresponding aliquots and issue confirmation of the destruction, which will be forwarded to the investigator. Analyses conducted before the withdrawal will not be affected.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site until the end of the study.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The site should counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, attempts to make contact should continue until study closure and participant might be confirmed as lost to follow up at time of study closure.
- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not receive study intervention. All sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 1.3). Protocol waivers and exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- 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 (e.g. blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- The maximum amount of blood collected from each participant per day will be approximately 36 mL and maximum per cycle will be approximately 55 mL. For paediatric participants, study-related blood loss will not exceed 3% of a participant's total blood volume during a period of 4 weeks AND should not exceed 1% at any single time (maximum blood volume in children is 80 to 90 mL/kg (ethical considerations.doc (europa.eu)), then blood draw should be adapted for participants with weight less than 28 kg or as per local guidelines and as per local capabilities for testing and blood draw. If the total required blood volume would exceed the limits established by the clinical site for paediatric subjects, then priority should be given to the key safety laboratory tests. This will ensure that the total blood volume drawn is within the established limits.
- Repeat or unscheduled samples may be taken for safety reasons or in case of technical issues with the samples.

8.1 Administrative and General/Baseline Procedures

Administrative and general/baseline procedures e.g. medical history are outlined in the SoA (see Section 1.3).

8.1.1 Demography

Age, sex, year of birth and, according to individual country regulations/requirements and if authorised in the country, race/ethnicity will be collected. The collection of these data is needed to establish if there are potential clinically important sex- or racial/ethnic-based differences in the anticipated effects of the intervention.

8.2 Efficacy Assessments

For the timing of efficacy assessments in this study, please refer to the SoA (Section 1.3).

8.2.1 Tumor Assessments

Response and progression will be evaluated in this study using the revised RECIST guideline (version 1.1) (Eisenhauer et al 2009) (Appendix 10.13). For the purpose of determining the study primary endpoints of PFS, response rates, central review of radiographic images will be conducted by a BIRC. All radiographic tumor assessments (both scheduled and unscheduled) will be sent to the BIRC, which also will review prior radiation history data for the purpose of

selection of target lesions. Independent oncologists will be part of BIRC to assist assessment of clinical information to be evaluated along with radiology images.

All CT/MRI (chest/abdomen/pelvis (CAP) ± neck/extremity (N/E) (as per Investigator's judgement) (CAP ± N/E), brain) and technetium bone scan imaging studies are recommended to be performed using the study-specified imaging protocol (refer to the most recent version of the imaging manual). To ensure image consistency, the same imaging modalities and acquisition protocols used at screening should be used for subsequent tumor assessments. All imaging must be acquired and transmitted for central review in original Digital Imaging and Communications in Medicine (DICOM) format (not a secondary capture). Low dose non-contrast CT images from combined positron emission tomography/computed tomography (PET/CT) imaging cannot be used for tumor evaluations in this study.

Radiographic tumor assessments will include the following:

(1) **CAP ± N/E**: CT (or MRI) of CAP ± N/E (as per Investigator's judgement) will be performed in all participants at screening and every 8 weeks (± 7 days) after randomization during the course of the study. If MRI of the abdomen and pelvis ± N/E (as per Investigator's judgement) is performed at screening, then a CT of the chest must be performed as well. Additional imaging of potential disease sites is to be performed whenever radiographic PD is suspected.

(2) **Brain**: MRI (or CT) of the brain will be performed in all participants at screening. After randomization, MRI (or CT) scans of the brain are only required in participants with known brain metastasis following the same post-baseline frequency as the imaging for CAP ± N/E (as per Investigator's judgement). MRI is the preferred imaging method for brain. If CT of the brain is performed instead of MRI, ambiguous results must be confirmed by MRI. (Note: In order to meet the eligibility requirements of the study, brain metastasis must have been treated and stable for at least 4 weeks before randomization). Participants without documented brain metastasis during the screening assessment are not required to undergo post-randomization brain imaging unless clinically indicated.

(3) **Bone scans:** Technetium bone scans will be performed at screening in all participants and after randomization only in participants with known bone metastasis every 24 weeks (± 14 days). Technetium bone scans are also to be performed for clinical symptoms indicative of new bone metastases. Bone scan findings alone cannot be used for the determination of progression or response per RECIST version 1.1 and need to be corroborated by CT or MRI. Tumor assessments are to continue on the protocol-defined schedule (see SoA, Section 1.3, Table 1) relative to the date of randomization regardless of whether study intervention is given, reduced, held, or discontinued, including for participants randomized to BSC who switch over to receive cabozantinib (see SoA, Section 1.3, Table 2). The same imaging modalities used at screening will be used for subsequent tumor assessments after randomization.

Radiographic tumor assessments are to continue until study intervention discontinuation for reasons other than radiological progression or consent withdrawal; however, radiographic tumor assessments may cease at the time of first systemic non protocol anticancer therapy (NPACT), if given before these milestones occur. Bone scan evaluations will end on the date of last CT/MRI scan. If the bone scan schedule does not coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI scan has been performed.

8.2.1.1 Switch Over

Participants randomized to BSC who switch over to receive cabozantinib+BSC will have baseline re-established and will re-start the tumor assessment schedule. The new baseline is to be based upon the most recent set of scans performed prior to the first cabozantinib dose received date during the switch over period. If available scans were performed >8 weeks prior to first switch over dose, new scans are required to establish the new baseline. Radiographic studies performed after switch over will not be submitted to the BIRC. After switch over, radiographic tumor assessments are to continue until the later of: (a) investigator-assessed radiographic disease progression per RECIST 1.1 (relative to the new baseline), or (b) the date of the decision to permanently discontinue study intervention.

However, radiographic tumor assessments may cease at the time of first systemic NPACT, if given before these milestones occur. Bone scan evaluations will end on the date of last CT/MRI scan. If the bone scan schedule does not coincide with the last CT/MRI scan, no additional bone scan is needed after the last CT/MRI scan has been performed (see SoA, Section 1.3, Table 2).

8.2.1.2 Confirmation of Tumor Response

For participants with an overall response of PR or CR per RECIST 1.1 by investigator at a given time point, a repeat assessment is to be performed no fewer than 4 weeks after the criteria for response are first met.

8.2.1.3 Confirmation of Tumor Progression by BIRC

At the time of investigator-determined radiographic progression per RECIST 1.1, and only in case of presence of clinical benefit, investigators may request from the Sponsor's medical monitor (or designee) confirmation of BIRC-determined radiographic PD.

8.2.1.4 Quantification of Disease Burden

The sum of the diameters (longest for non-nodal target lesions, short axis for nodal target lesion) will be calculated and reported as the disease measurement.

8.2.1.5 Time Point Response per RECIST 1.1

See Appendix 10.13 for information on time point assessments.

8.2.2 Overall Survival

OS will be assessed at the end of study intervention visit and every 3 months (± 14 days) after last dose of study intervention. Participants, including participants that will switch over, will be followed until death or Sponsor decision to no longer collect these data. Receipt of NPACT and subsequent progression status will also be collected during follow-up contacts. If a participant withdraws consent for non-interventional study assessments, information regarding survival status may be obtained from public records such as government vital statistics or obituaries, as permitted by local regulations.

8.2.3 Patient-reported Outcome (PRO) Measures

The Paediatric QoL Inventory (PedsQL) will be used to assess QoL in participants <18 years of age while the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) will be used for participants ≥18 years of age. For participants that are 17 years old at study entry both PedsQL and EORTC will be administered at baseline. For these participants, PedsQL will be collected until 18 years of age, following which the EORTC questionnaire will be used.

PedsQL

The PedsQL is a modular instrument designed to measure health-related quality of life (HRQoL) in children and adolescents. The PedsQL 4.0 Generic Core Scales are multidimensional child self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL disease specific modules. The PedsQL 3.0 Cancer Module was designed to measure paediatric cancer specific HRQoL.

EORTC QLQ-C30

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group to assess HRQoL, functioning, and symptoms in cancer clinical trials. It has undergone extensive testing and validation as well as detailed cross-cultural testing and validation (Aaronson et al 1993). It is a 30-item self-administered questionnaire for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), a 2-item global QoL scale, 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and 1 item on the financial impact of the disease. All but 2 questions have 4-point scales: "Not at All," "A Little," "Quite a Bit," and "Very Much." The 2 questions concerning global health status and QoL have 7-point scales with responses ranging from "Very poor" to "Excellent." For each of the 15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate better functioning, better HRQoL, or greater level of symptoms (Aaronson et al 1993).

Patient reported outcome (PRO) assessments will be performed according to the SoA (Section 1.3).

Participants should complete questionnaires on the day of the visit prior to seeing study site personnel. Participants should not receive any information on their most recent medical results prior to completing the questionnaires in order to not influence their reporting. At clinic visits, completed questionnaires should be carefully reviewed for completeness by study site personnel.

PRO assessments will be discontinued for BSC participants who switch to cabozantinib +BSC.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.3).

Clinically significant abnormal laboratory results, physical examination findings, ECG and vital signs will be recorded as an AE in the case that there is an increase in severity or new abnormality.

AEs should include the reporting of any observed effects on organ maturation and growth and development, including fertility.

8.3.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. Height, weight and BMI (including height, weight and BMI percentiles for pediatric participants) will be measured and recorded. Height and weight will be measured using a calibrated stadiometer appropriate for the participant's age and plotted on age and gender appropriate charts e.g., Center for Disease Control, World Health Organization so that a visual assessment can be performed relative to normative standards for height and weight and change in height and weight over time. For height and weight measurements, the participant is allowed to wear indoor, daytime clothing with no shoes.

- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Tanner Staging for puberty development will be conducted at Screening, every 6 months during the study intervention period and at EOSI until 1 year after last dose. Tanner Staging is not required once pubertal development is complete (i.e. Tanner Stage 5).
- Linear growth, weight gain, and sexual development (see Section 8.3.1.1 Assessment of Sexual Maturity) will be monitored to determine if there are any adverse effects on growth or development. The anthropomorphic examination can provide information about short- and long-term growth. Comparison of this information to reference data will help in monitoring growth status over time. Percentiles or z-scores are used to express growth status in children as they take into consideration age and gender.

8.3.1.1 Assessment of Sexual Maturity

- Tanner Sexual Maturity Rating Scale will be performed and used to assess changes related to puberty.
- Assess for changes in onset of menses (female participants) or sexual activity (male or female participants). Determine if there is a need for contraception or barrier use.

8.3.2 Vital Signs

- Temperature (taken via oral, axillary, rectal or tympanic methods or from skin surface or temporal artery), heart rate, respiratory rate, and BP will be recorded (before blood collection for laboratory tests).
- BP and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones). BP will be measured using an appropriate size cuff.
- For blood pressure measurements (three consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the three BP readings will be recorded in the CRF.

8.3.3 Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures intervals in the heart's electrical cycle. ECGs will be taken following resting in the supine position for at least 10 minutes in a quiet environment and at least 5 minutes prior to PK blood sampling.
- ECGs will be reviewed and signed and dated by the investigator or designee. The ECGs will be classified as normal, having a non-clinically significant abnormality, or having a clinically significant abnormality. In addition, ECG parameters of ventricular rate, RR and PR interval, QRS complex, and QT interval (corrected and uncorrected) will be noted on the CRF. All clinically significant findings will be recorded as AEs.
- At each time point at which triplicate ECGs are required (see also Section 10.6), three individual ECG tracings should be obtained as closely as possible in succession within 30 minutes but at least 3 minutes apart.

8.3.4 Tibial Radiographs

Given the antiangiogenic targeting of cabozantinib and concern for possible impact on growth in children, linear growth will be determined at baseline based on a tibial X-ray for all

participants ≤18 years of age. For participants with open growth plates, radiographs must be monitored during protocol therapy for growth plate toxicity every 6 months until 1 year after last dose, and at any time as per clinical judgment, as outlined in the SoA (Section 1.3). Any abnormal finding should be reported as an AE. Further details about handling participants with evidence of growth plate thickening or other changes are described in Appendix 10.7.

8.3.5 Clinical Safety Laboratory Tests/Assessments

- See Appendix 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. All protocol-required laboratory tests must be conducted in accordance with the laboratory manual and the SoA.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If clinically significant/any values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the sponsor notified.
    - If laboratory values from non-protocol specified laboratory tests performed at the study site laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3.6 Pregnancy Testing

Female participants of childbearing potential require a negative pregnancy test prior to the start of each cycle; see Section 1.3 (SoA). Sexually active participants must use an acceptable method of birth control.

Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria. The assessment will be performed locally.

Any positive urine pregnancy test must be confirmed via serum β-human chorionic gonadotropin.

Any participant becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study are to be reported as described in Section 8.4.5.

Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure plus an additional 30 days and correspond with the time frame for female participant contraception in Section 5.1, Inclusion Criteria.

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 participant's participation in the study.

8.4 Adverse Events (AEs) and Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs or SAEs, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE section of the CRF.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of awareness of the event, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

Clinical Presentation of Adverse Events (for Participants <18 years of age)

Study-site staff should instruct the legal guardians and caregivers on how to report signs and symptoms (e.g., crying and pain) in the individual pediatric participant. They will be instructed to report both specific and non-specific symptoms (including vomiting, diarrhea, sleepiness, variation in the intensity and pattern of crying, etc.). These non-specific symptoms may be the only manifestations of some adverse reactions observed in children and AYA. Care should be taken that the clinical presentation of adverse reactions is not misinterpreted as the manifestation of a pre-existing or unrelated condition.

Moreover, symptoms that are dependent on participant communication ability (e.g., nausea, pain, mood alterations) in younger or mentally disabled children could potentially be at risk for under- or mis-reporting.

These events may or may not have been noted in the participant diary.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed up until resolution or stabilisation or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an 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 relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the IB/package insert/Summary of Product Characteristics (SmPC) and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor's policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

- For a female participant (<18 years of age) who becomes pregnant, this information will be shared with the study participant's legal guardian as required by local regulations.
- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected from the signing of the ICF and for at least 4 months after the last dose of cabozantinib (see Section 5.1).
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant /pregnant female partner will be followed up through the end of her pregnancy and the infant should have a follow-up at least 6 months after birth. If a female partner of a male participant becomes pregnant during the study, the pregnant female partner will be asked to consent to be followed through the end of her pregnancy and the infant should have a follow-up for at least 6 months after birth. The investigator must inform the Sponsor of the pregnancy. Forms for reporting pregnancies will be provided to the study sites upon request. The investigator will collect follow-up information on the participant /pregnant female partner and the offspring and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants' pregnant female partners, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

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

Natural progression or deterioration of the disease under study will be recorded as part of the efficacy evaluation and should not be recorded as an AE/SAE. Death due to the progression of the disease under study is not to be reported as an SAE.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a disease related event):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

  OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.4.7 Adverse Events of Special Interest

Adverse events of special interest (AESI) (events to monitor (ETM)) are AEs that may not be serious but are of special importance to a particular drug or class of drugs.

ETM for this study include:

- Growth plate thickening
- Hepatobiliary disorders
- Decreased lymphocyte count
- Decreased neutrophil count
- Hair color changes
- Skin hypopigmentation
- GI perforation
- Abscess
- Intra-abdominal and pelvic abscess
- Fistula
- Wound complication
- Osteonecrosis
- Haemorrhage
- Hypertension
- Proteinuria
- PPES
- PRES (RPLS)
- Arterial thromboembolic events
- Venous/Mixed thromboembolic events
- QT prolongation
- Renal failure
- Hepatotoxicity
- Embryotoxicity
- Carcinogenicity (Confirmed secondary malignancy post cabozantinib exposure)

These events must be collected on the AE form of the CRF according to the completion guideline and using the specific AESI reporting option within 24 hours of investigator's or qualified designees' awareness.

If they meet the seriousness criteria, they should also be reported as SAEs (refer to Appendix 10.3).

8.4.8 Reporting of Study Intervention Errors Including Misuse/Abuse

- Medication errors are unintentional errors in the prescribing, storing, dispensing, preparing or administering of a study intervention (medicinal product) while under the control of a healthcare professional, participant or consumer.
- Misuse refers to situations where the study intervention is intentionally and inappropriately used not in accordance with the protocol.
- Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- Study intervention errors and uses outside of what is foreseen in the protocol, such as misuse, abuse or overdose, will be recorded on the appropriate CRF page irrespective of whether associated with an AE/SAE or not, within 24 hours of investigator's or qualified designees' awareness. If an AE/SAE is associated with this study intervention error, it should be documented in the AE/SAE section of the CRF. Please refer to Section 6.8 and 10.3.1 for more details about overdose.

8.5 Pharmacokinetics

- PK samples of approximately 2 mL of blood will be collected for measurement of plasma concentrations of cabozantinib as specified in the SoA (Section 1.3).
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection, handling and shipment of biological samples will be provided in the PK Sample Management Plan by the Sponsor or designee. The accurate date and time (24-hour clock time) of each sample collection must be recorded.
- Samples will be used to evaluate the PK of cabozantinib. Each plasma sample will be divided into 2 aliquots (one each for PK, and a back-up for PK sample re-analysis or other analyses). Samples collected for analyses of cabozantinib plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Residual PK plasma samples used for cabozantinib analysis may also be used for exploratory analysis. This could include using leftover PK plasma samples for protein binding analysis, metabolite profiling or analysis of excipients. PK plasma samples remaining from the analysis may be retained by the sponsor for additional investigations (i.e. long-term stability, reproducibility, bioanalytical method cross-validation).
- Genetic analyses will not be performed on these blood samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained. At visits during which plasma samples for the determination of multiple aspects of cabozantinib will be taken, one sample of sufficient volume can be used.

8.6 Pharmacodynamics

- Blood samples will be collected for pharmacodynamic assessments as specified in the SoA (Section 1.3).
  a) One 4 mL blood sample to investigate plasma biomarkers, which may include, but are not limited to, protein biomarkers such as angiogenic, hypoxia-related or other microenvironment markers, receptor-ligand pairs for cabozantinib targets, inflammation-related markers and/or osteosarcoma- or bone-related-markers.
  b) One 10 mL blood sample to investigate pharmacodynamic biomarkers in circulating tumor DNA (ctDNA)/RNA. ctDNA genomic assessment is based on consent and is optional for some study participants.
- Instruction for the collection, handling and shipment of biological samples will be provided in the laboratory manual.
- Residual blood samples may be used for exploratory analysis, or future research, of additional plasma components.

8.7 Genetics and/or Pharmacogenomics

The following biological samples will be collected as specified in the SoA from all participants for analysis of gene mutations, genomic alterations or gene expression, impacting prognosis and efficacy to cabozantinib.

- Blood sample for ctDNA/RNA collected as part of pharmacodynamics assessment.
- Fresh or archived tumor biopsy collected prior to treatment, collected as part of biomarkers assessment.

Genomic alterations will be assessed to explore biomarkers that may be associated with efficacy, prognosis, and tumor biology.

See Appendix 10.5 Genetics for information regarding genetic research.

Details on processes for collection, storage shipment and destruction of these samples can be found in the laboratory manual AND/OR Sample Management Plan.

8.8 Biomarkers

Archived or fresh tumor biopsy samples will be collected during this study prior to treatment for correlating with clinical outcome to evaluate biomarkers representing relevant targets for cabozantinib. Analysis may also include, but not be limited to, analysis of markers for osteosarcoma tumor biology. Relevant cabozantinib targets may include but are not limited to:

- c-MET, VEGFR2 or AXL

Samples will be collected at the timepoints indicated in the SoA.

- Any residual samples may be retained for future research.
- Details on processes for collection, storage, shipment, and destruction of biomarker samples can be found in laboratory manual AND/OR Sample Management Plan.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary objective is to assess the efficacy of maintenance cabozantinib plus BSC versus BSC in improving the PFS in participants with osteosarcoma. The primary analysis for this study will be the comparison of the distribution of PFS as assessed by BIRC using RECIST version 1.1 in the intent-to-treat (ITT) population. Assuming proportional hazard for PFS, the hypothesis to be tested for PFS HR is as follows:

Null hypothesis: HR ≥1 vs. Alternative hypothesis: HR <1

9.1.1 Multiplicity Adjustment

A fixed-sequence testing procedure will be implemented to control the family-wise type I error at 5% for the primary endpoint of PFS and the key secondary efficacy endpoint of ORR per BIRC. The primary efficacy endpoint of PFS will be tested first. If the superiority of cabozantinib plus BSC over BSC is established, the treatment effect in the ORR will be tested subsequently. Any endpoint which is not formally tested for significance (per the hierarchy) will be regarded as descriptive and exploratory.

9.2 CCI

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9.3 Analysis Sets

For the purposes of analysis, the analysis sets are defined in Table 9.

Table 9 Analysis Sets

Participant Analysis Set	Description
Screened	All participants who signed an ICF
Randomized	The randomized set will contain all participants who were randomized to study treatment. A participant will be considered as randomized if a treatment group has been assigned by the IWRS. For analyses and displays, participants will be classified according to randomized treatment.
Safety	The safety set will contain all participants who receive at least one dose of study treatment. For analyses on the safety set, participants will be classified according to treatment received. If there is any doubt whether a participant was treated or not, he/she will be assumed treated for the purposes of analysis.
Intent-to-treat (ITT)	The ITT analysis set will contain all participants from the randomized analysis set.
Pharmacokinetic population	All participants who receive at least one dose of cabozantinib dose at Cycle 1 Day 1 and have at least one plasma concentration higher than the limit of quantitation.

ICF=informed consent form, ITT=intent-to-treat, IVRS=Interactive Web Response System

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalised prior to data base lock (DBL), and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Other endpoints as well as demographic, baseline characteristics and disposition will be detailed in the SAP.

The cabozantinib concentration data obtained in this study will be combined with data from other studies in the clinical development program to develop a population PK model. In addition, exposure-response (ER) analyses with selected efficacy and safety endpoints will be conducted. A separate dedicated detailed analysis plan will be developed for Population PK and ER analysis.

9.4.1 General considerations

Descriptive statistics will be used to summarize the study endpoints. Categorical variables will be summarized by number and percentage. Continuous variables will be summarized using n (number of participants with available data), mean, standard deviation (StD), median, and range (minimum and maximum) unless otherwise specified. Cabozantinib concentration data will be summarized using n, mean, StD, coefficient of variation (%CV), geometric mean, median, minimum, and maximum. Survival data (PFS and OS) will be estimated using the Kaplan-Meier method.

Efficacy will be evaluated based on the ITT population. Safety data will be evaluated using the safety population. PK data will be evaluated using the PK population. All primary and supplementary analyses will be performed based on EudraCT age category cutoff: children (5-11 years), adolescents (12-17 years), and adults (≥18 years).

9.4.2 Analysis of Primary endpoint

The primary endpoint is PFS, defined as the time from the date of randomization to the date of first documented disease progression based on BIRC assessment per RECIST v1.1 or the date of death due to any cause, whichever occurs first. PFS will be censored at the date of the last adequate disease assessment for participants who do not have disease progression and are alive at clinical cut-off date. Participants without any post-randomization tumor assessment and who are alive will be censored on their date of randomization. The detailed censoring rules will be specified in the SAP.

PFS will be compared between the treatment arms at the interim and final analyses using stratified log-rank test. The stratification factor to be used in the analysis is disease setting (initial diagnosis or at first relapse after chemotherapy) and will be based on the stratification for randomization.

The interim futility analysis of PFS will be conducted when at least 20 events have occurred. Details are provided in Section 9.5. The final analysis will be performed after at least 67 events have been observed in the ITT population.

The PFS distribution and median PFS along with a 95% CI will be estimated using the Kaplan-Meier product-limit method in each treatment arm. The HR for cabozantinib plus BSC relative to BSC and its associated 95% CI will be calculated based on the stratified Cox proportional hazards model by the stratification factor.

9.4.3 Analysis of Secondary endpoints

9.4.3.1 Objective Response Rate

The secondary endpoint of ORR is defined as the proportion of participants who have achieved CR or PR. Participants with missing post-randomization disease assessment data are considered as non-responders.

The primary ORR analysis will be based on BIRC assessment using RECIST v1.1. Estimates of ORR, along with its exact two-sided 95% CI by Clopper and Pearson method will be presented by treatment arm. Additionally, ORR will be tested using the Cochran-Mantel-Haenszel test with stratification factor for randomization at the 2-sided 0.05 level of significance in the ITT population if the null hypothesis for final PFS analysis is rejected. Similar descriptive analyses will be repeated for ORR based on the investigator's assessment.

9.4.3.2 Progression-Free Survival Rate

PFS rates at 4 months and 1 year will be derived from the Kaplan-Meier estimates and corresponding 95% CIs will be provided based on Greenwood formula for variance derivation and on log-log transformation applied on the PFS distribution. The analyses will be performed based on BIRC assessment and repeated for PFS based on investigator's assessment.

9.4.3.3 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of participants who have achieved CR, PR, or SD. Similar descriptive analyses for ORR will be presented for DCR based on the BIRC and the investigator's assessments.

9.4.3.4 Overall Survival

OS is defined as the time from date of randomization to the date of death from any cause. For participants who are alive, their survival time will be censored at the date of last contact date or last known alive date. OS will be censored at the date of randomization for participants who were randomized but had no follow-up.

OS will be analyzed using similar methods as PFS. OS at 1 year will be presented along with their associated 95% CIs for each treatment arm.

9.4.3.5 Patient-reported Outcome

In participants <18 years of age, comparison of the QoL in the two arms will be based on change from baseline in scores for all PedsQL scales, including generic core scales and cancer modules.

In participants >18 years of age, the main PRO endpoints of the EORTC QLQ-C30, including symptoms, functioning and HRQoL will be assessed. The analyses will include change from baseline in EORTC QLQ-C30 scores, and time to deterioration in selected scales of the EORTC QLQ-C30, including global health status/QoL, physical functioning, role functioning and pain.

Further details of the PedsQL and EORTC QLQ-C30 analyses will be described in the SAP.

9.4.4 Analysis of Exploratory Endpoints

Analyses for exploratory endpoints will be detailed in the SAP.

9.4.5 Safety Analyses

All safety analyses will be based on the safety population.

9.4.5.1 Adverse Events

AEs reported by investigators using the National Cancer Institute – Common Toxicity Criteria for Adverse Events (NCI-CTCAE) classification (version 5.0; CTCAE v5.0) will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

A TEAE is defined as any AE that occurs or worsens on or after date of first dose of study intervention and through the 30-day post-treatment follow-up period. Only TEAEs will be tabulated in summary tables.

Summary incidence tables will be provided, classified by body system, preferred term, and associated CTCAE worst grade by treatment arm for TEAE, treatment-related TEAE, serious TEAE, and AESI. Summaries of events that resulted in dose modifications and treatment discontinuation will also be provided.

9.4.5.2 Laboratory Data

Haematological and biochemical toxicities will be recorded and graded according to the CTCAE v5.0 criteria, where available. Laboratory assessment data will be analyzed for on-treatment evaluation by worst CTCAE grade, and shift tables.

9.4.6 Other Analyses

9.4.6.1 Pharmacokinetic Analysis

Population PK analysis will be performed to characterize the PK of cabozantinib in osteosarcoma participants (children and AYA), the inter-individual variability, and to identify the covariates which potentially impact the PK of cabozantinib.

Graphical exploratory analysis will be performed to assess any relationship between PK metric(s) (e.g. Concentrations, AUC, average concentration, C_{min}, C_{max}) and PD endpoint(s) for efficacy and/or safety. If a trend is shown, an attempt to build an ER model using a population approach will be performed. Those analyses (population PK and ER) will be described in a separate data analysis plan and reported in a standalone report.

9.5 Interim Analyses

An interim non-binding futility analysis for the primary endpoint of PFS will occur at approximately CCI from the date of first participant randomized in the study. It will be performed by an independent statistical group who has no direct contact with study team. The interim analysis results will be reviewed by the IDMC, consisting of 2 clinicians and 1 statistician who are independent experts not otherwise involved in the study when at least 20 events have occurred.

The analysis method for the primary efficacy endpoint described in Section 9.4.2 will be used for the interim analysis. Based on the group sequential design with the Lan-DeMets (O'Brien Fleming) beta spending approach, the HR needs to be CCI
CCI
CCI.

The interim analysis will be conducted such that the ongoing study integrity is maintained. Only the independent statistical support group, who is responsible for providing the interim analysis results to the IDMC, will be unblinded to the individual treatment group assignments. Interim analysis results will not be shared with investigators, participants, or the study team who are involved in the conduct of the study before the final database lock.

The SAP will describe the planned interim analyses in greater detail.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations such as Regulation EU 536/2014.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g. any participant recruitment materials) must be approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The protocol and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Notifying immediately your site monitor or the contact(s) provided by the sponsor or designee of (suspected) serious breach.
  - In that perspective, a serious breach is a breach likely to affect to a significant degree the safety and rights of the participant or the reliability and robustness of the data generated in the clinical trial.
  - Providing oversight of the conduct of the study at the site and adherence to applicable local regulations, ICH guidelines and the IRB/IEC requirements/procedures.
  - The investigator will be responsible for reporting cases of suspected child abuse and/or neglect according to local regulations including local medical association (e.g., American Academy of Pediatrics (AAP), EU Academy of Pediatrics (EAP)) or Health Department guidelines.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

10.1.3 Informed Consent Process

- The ICF and any participant/assent recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws. They must be approved prior to use as described in Appendix 10.1.1

Adult Participant Consent Process

- The investigator or the investigator's authorised representative will explain to the potential participant the nature and objectives of the study and possible risks and benefits associated with the participation. They will answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary.
- The investigator or the investigator's authorised representative will obtain written informed consent from each participant before any study-specific procedure is performed. The investigator will retain the original of each participant's signed ICF.
- A copy of the signed ICF(s) must be provided to the participant.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. If changes to the ICF do not apply to all participants, this will be communicated to the IRB/IEC with a rationale. IRB/IEC approval must be received before implementation as required by local regulations.
- The ICF will contain a separate section that addresses the use of all data for optional future research. These data and biosamples may only be used for future research and analysis to advance science and public health, including in order to:
  - understand and evaluate the study drug and/or other drugs,
  - better understand the studied disease and associated health problems,
  - develop new drugs and find new ways to detect, treat, prevent or cure health problems,
- Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. A specific consent will be required to document a participant's agreement to allow any data to be used for future research.
- If a pregnancy is reported for a female partner of a male participant during the study, the partner will be asked to sign appropriate consent for the sponsor to follow the outcome of the pregnancy.
- When permitted by local regulation, the ICF will contain a separate section that addresses the remote access by the study monitors to source documents/data for the purpose of source data verification. A specific consent will be required to document a participant's agreement.
- For withdrawal of consent from optional biobanking programme, refer to Section 7.2.

Legal Guardian Consent and Pediatric Participant Assent Processes:

- The investigator, or a person designated by the investigator, will provide the legal guardian (refer to the list of Abbreviations and Definitions) with the written Informed Consent Form (ICF) and the participant with the assent if applicable. They must be

informed that participation is voluntary. The legal guardian will be required to sign written consent, and the participant if applicable will be required to sign written assent, that meets the requirements of 21 CFR 50, local regulations, International Conference on Harmonisation (ICH) guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center after the nature of the study has been fully explained and before performance of any study-related activity.

- Assent requirements for pediatric participants may vary across regions and countries; local regulations should be followed as appropriate.
- The medical record must include a statement that written informed consent from the legal guardian and assent from the pediatric participant (if deemed appropriate by local ethics review or local regulations) were obtained before the participant was enrolled in the study and the date the written consent and assent were obtained. The medical record should describe how the clinical investigator determined that the person signing the ICF was the participant's legal guardian. The authorized person obtaining the informed consent must also sign the ICF and assent form attesting that the pediatric participant did not show signs of dissent particularly in those studies including toddlers and small children; it should be written in language appropriate to the child's developmental and functional status.
- Participants and their legal guardian (where applicable) must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study.
- Minor participants who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their legal guardian still wants them to participate.
- Minor participants must be re-consented if they reach the age of maturity during the course of the study, in order to continue participating.
- A copy of the informed consent and assent forms must be provided to the participant and the participant's legal guardian.
- As appropriate, participants may be given the opportunity to meet privately with a member of the site staff to ask confidential questions and to decline assent for confidential reasons, which, at their request, would not be shared with their legal guardian, unless required by local law.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- There will be no attempt to recontact participants <18 years of age at adulthood. However, the participant retains the right to withdraw assent/consent for storage of samples unless specified.
- Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent/assent for their samples to be stored for research.

10.1.4 Data Protection

- 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 which would make the participant identifiable will not be transferred.

- The participant or participant's legal guardian (as appropriate) must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant or participant's legal guardian (as appropriate) who will be required to give consent for their data to be used as described in the informed consent.
- The participant or participant's legal guardian (as appropriate) must be informed that his/her medical records may be examined by the sponsor's auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants or participant's legal guardian (as appropriate) must be informed that their study-related data will be used for the whole drug development program, i.e., for this study as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.
- The sponsor will ensure that appropriate organisational and technical arrangements are implemented to comply with the applicable rules on the protection of personal data. Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- In the event of a potential data security breach concerning personal data processed on behalf of the sponsor, the data protection officer must be informed without undue delay and no later than 24 hours from the discovery of the event. The data protection officer will evaluate the event and notify the Data Protection Authorities within 72 hours, if required. Corrective actions and preventive actions will be implemented to mitigate the possible adverse effects. Affected study participants will be informed accordingly. Ipsen Data Protection Officer can be contacted by email: dataprivacy@ipsen.com.

10.1.5 Committees Structure

10.1.5.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to monitor the safety of the study on a regular basis. In addition, IDMC will also review the interim analysis for PFS. The membership and decision process of the IDMC are independent of the Sponsor and the study clinical investigators. Detailed IDMC roles and responsibilities will be outlined in the IDMC charter.

Unblinded safety data will be reviewed by IDMC on a periodic basis. Depending on the actual enrollment, the safety review may initiate 6 months after the first participant randomized and take place every 6-month or as needed. The interim PFS analysis review may be combined with periodic safety review into one single review meeting if deemed sufficiently close. All analyses for IDMC review will be prepared by external group not affiliating with the study team.

The IDMC will provide a recommendation to the Sponsor per IDMC charter after each review. For interim PFS futility analysis, the IDMC will recommend the Sponsor to continue or stop the study. However, the final decision will remain with the Sponsor. Details will be specified in the IDMC charter.

10.1.5.2 Blinded Independent Radiology Committee

A BIRC will be established to evaluate tumor scans and prior radiation history data of study

participants in a central, blinded, and independent fashion.

The BIRC will comprise of board-certified radiologists who will determine radiographic response and progression following randomization. Independent oncologists will be part of BIRC to assist assessment of clinical information to be evaluated along with radiology images. Additional imaging results may be requested by the Sponsor for BIRC review.

Primary analyses of radiographic study endpoints will be based on BIRC assessments.

10.1.6 Dissemination of Clinical Trial Data

- Protocol information and study results will be made publicly available on the US website (www.clinicaltrials.gov) and for studies run in the EU/EEA on the EU Clinical Trials Portal (https://euclinicaltrials.eu/home). Where applicable, the sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation.
- A lay protocol synopsis and a summary of the study will be made available on the EU Clinical Trials Portal (https://euclinicaltrials.eu/home) and on the sponsor website (https://www.ipsen.com/patients/lay-summaries/).
- A clinical study report will be prepared if at least one participant has signed informed consent and received intervention, regardless of whether the study is completed or prematurely terminated. The clinical study report may be disclosed according to regulatory requirements.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded in the CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by signing the CRF.
- All entries in the CRF will be made under the e-signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorised users will have access to the CRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the CRF.
- Guidance on completion of CRFs will be provided in CRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections, and provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing, and inspection by domestic and foreign regulatory authorities.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organisations).

- Records and documents, including signed ICFs, pertaining to the conduct of this study should be retained by the investigator according to the ICH-GCP guidelines, to local regulations, or as specified in the study agreement, whichever is longer. 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.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source documents/data and their location will be documented in a specific form.
- The investigator must maintain accurate documentation that supports the information entered in the CRF. Source data must be attributable, legible, contemporaneous, original, accurate and complete.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorised 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. When permitted by local regulation and guidance, study monitors will access remotely to source documents/data to conduct source data verification, while maintaining appropriate security measures and ensuring the protection of the data. This will be described in the monitoring plan or equivalent.

10.1.9 Study and Site Start and Closure

First Act of Recruitment

The trial start date is the date on which the clinical trial will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development
- The study is terminated due to safety concerns

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. Should this be necessary, the Sponsor and the investigator will arrange the procedures on an individual basis after review and consultation. In terminating the study, the Sponsor and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

10.1.10 Publication Policy

- The sponsor seeks to publish the results of its clinical trials in biomedical journals, whatever the outcome. Clinical trial results may also be presented at international congresses as posters or oral presentations.
- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator should discuss specific publication concepts, including data to be covered, target congress/journal and proposed authors, with the Sponsor for agreement before initiation. 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.
- 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 multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix: Clinical Laboratory Tests

- Refer to SoA (Section 1.3) for details of visits.
- The tests detailed in Table 10 will be performed by the study site laboratory.
- The study site laboratory results are used to make either a study intervention decision or response evaluation; results must be recorded. Results or status from routine (dipstick) analysis and microscopic urine examination tests will be recorded on CRFs but will not be submitted to the study local laboratory management vendor.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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.
- Investigators must document their review of each laboratory safety report.

Table 10 Protocol-Required Safety Laboratory Tests

Parameters	Screening	Intervention Period	EOS/Discontinuation
Haematology			
Platelet count	X	X	X

Parameters	Screening	Intervention Period	EOS/Discontinuation
Red blood cell (erythrocyte) count	X	X	X
Haemoglobin	X	X	X
Haematocrit	X	X	X
Mean corpuscular volume	X	X	X
Mean corpuscular haemoglobin	X	X	X
Mean corpuscular haemoglobin concentration	X	X	X
White blood cell count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	X	X	X
Clinical Chemistry[a]			
Urea or blood urea nitrogen (BUN)	X	X	X
Creatinine	X	X	X
Glucose (fasting)	X	X	X
Potassium	X	X	X
Sodium	X	X	X
Calcium	X	X	X
Aspartate Aminotransferase (AST)	X	X	X
Alanine Aminotransferase (ALT)	X	X	X
Total Alkaline phosphatase	X	X	X
Total bilirubin	X	X	X
Direct (conjugated) bilirubin	X	X	X
Chloride	X	X	X
Bicarbonate	X	X	X
Phosphate	X	X	X
Magnesium	X	X	X
Gamma glutamyl transferase	X	X	X
Amylase	X	X	X
Lipase	X	X	X
Albumin	X	X	X
Total Protein	X	X	X
LDH	X	X	X
Coagulation			
PT, PTT and INR	X	X	X
Urinalysis			
• Specific gravity • pH, specific gravity, glucose, protein, blood, ketones, bilirubin or urobilinogen , nitrite, leukocyte esterase by dipstick or routine • Protein (spot urine; fully quantitative) • Urine protein/creatinine ratio (UPCR; spot urine) [b] • Microscopic examination (e.g. epithelial cells, bacteria, crystals, casts, WBC, RBC), as clinically indicated	X	X	X

Parameters	Screening	Intervention Period	EOS/Discontinuation
Pregnancy testing			
Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c]	X	X	X
Thyroid function			
Thyroid stimulating hormone (TSH), free T4 (fT4), free T3 (fT3) [d]	X	X	X
Other Screening Tests			
Serology (HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody) if applicable	X		

[a] Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 Liver Chemistry Stopping Criteria and- Appendix 10.6 Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines. All events of ALT or AST ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT or AST ≥3 × ULN and international normalized ratio (INR) >1.5, (if INR measured) which may indicate severe liver injury (possible Hy's Law), must be reported to the Sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

[b] When UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm results

[c] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

[d] If TSH results are within the normal range, repeat testing at mid-cycle on C1D15, C2D15, and C3D15 is not required. However, if TSH levels are abnormal, thorough monitoring of TSH, T3, and T4 should be performed in accordance with the schedule of assessments, including mid-cycle evaluations, to ensure timely detection and management of any thyroid-related issues.

Abnormalities in any clinical laboratory test (including tests not required per protocol), that leads to a change in participant management (eg, dose interrupted or reduced, treatment discontinued, requirement for additional medication or monitoring) or suggest a disease and/or organ toxicity that is new or has worsened from baseline are considered clinically significant for the purposes of this study and should be reported as AEs. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (with associated laboratory values) needs to be reported as an SAE (see Section 10.3.4).

10.3 Appendix: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence (including an abnormal laboratory finding, symptom, or disease) in a clinical study participant to whom a medicinal product is administered and which does not necessarily have a causal relationship with the treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition 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 intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, including death due to disease progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g. 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.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:	
(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 hospitalisation or prolongation of existing hospitalisation** In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline and for diagnostic work-up with no accompanying AE are not considered an AE.
(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, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
(e)	**Is a congenital abnormality/birth defect**
(f)	**Other medically important situations:** Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one 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 for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse, even if they do not result in inpatient hospitalization.
(g)	Is a suspected transmission of any infectious agent via an authorised medicinal product

Seriousness criteria are applied by the investigator to each AE as specifically defined within above criteria used to determine whether an AE is serious or non-serious, the assessment is made independently of severity assessment, based on investigator clinical judgement.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- 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 required forms.
- 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 redacted 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. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- All fatal outcomes should be considered AEs, even if the fatal outcome is not considered to be related to the medicinal product. The convention for recording death which is not related to disease progression is as follows:
  - AE term that led to death (e.g. multiple organ failure, pneumonia, myocardial infarction etc.); outcome: fatal;
  - If cause of death is unknown (i.e. sudden or unexplained death), the AE term may be 'death' or 'sudden death'.
- Death due to the progression of the disease under study is not to be reported as a SAE; see Section 8.4.6.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study using the National Cancer Institute - Common Toxicity Criteria for AEs (NCI-CTCAE) version 5.0 or higher.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine whether an adverse event is considered to be related to study intervention, indicating "yes" or "no" accordingly.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the 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 or qualified designee will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE in English language to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours of awareness of the event.
- 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 electronic data collection 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 electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).

SAE Reporting to sponsor via paper data collection tool

- The site will scan and email the SAE paper form to the sponsor if the electronic data collection tool is unavailable. It must be retrospectively recorded as soon as the electronic data collection tool becomes available.
- SAE report should be sent by email to adverse.events@ipsen.com.

10.4 Appendix: Contraceptive and Barrier Guidance

In inclusion criterion 15a (Section 5.1), sexually active fertile participants and their partners must agree to use highly effective contraception as appropriate for their age and sexual activity, in combination with an additional acceptable barrier method, and as required by local regulations during the course of the study and for 4 months after the last dose of study intervention. Pregnancy testing is required as appropriate for the age and sexual activity of female participants and as required by local regulations during the course of the study.

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

(1) Following menarche

(2) From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal 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.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), 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.

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

10.4.2 Contraception Guidance

Contraception Guidance for WOCBP

One of the highly effective methods of contraception listed in the table below, in combination with an additional acceptable barrier method listed in the table below, is required during the course of the study and for 4 months after the last dose of study intervention. Local laws and regulations may require use of alternative and/or additional contraception methods.

Contraception Guidance for Male Participants with Partners of Childbearing Potential

Male participants with female partners of childbearing potential are eligible if they agree to the following during the course of the study and for 4 months after the last dose of study intervention.

- Inform any and all partners of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom during the course of study and for 4 months after the last dose of study intervention.
- Female partners of male participants in the study to consider use of effective methods of contraception during the course of study and for 4 months after the last dose of study intervention in the male participant.

Male participants 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 penetration during the course of study and for 4 months after the last dose of study intervention. Refrain from donating sperm during the course of study and for 4 months after the last dose of study intervention.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• 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 during the course of the study and for 4 months after the last dose of study intervention should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c.) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, tumor and blood samples will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to cabozantinib or tumors and related diseases. They may also be used to develop tests/assays including diagnostic tests related to cabozantinib and/or interventions of this drug class and indication. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analysed for exploring genomic alterations in tumor tissue and blood samples. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to cabozantinib or study interventions of this class to understand the study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on cabozantinib or study interventions of this class or indication continues but no longer than 15 years or other period as per local requirements.

10.6 Appendix: Guidance for Specific AE Management and Dose Modifications

General

The most frequent AEs experienced by ≥20% of subjects treated with cabozantinib in descending order of frequency were diarrhea, fatigue, decreased appetite, nausea, weight decreased, PPES, vomiting, constipation, hypertension, dysgeusia, dysphonia, asthenia, and dyspnea. For a full description of the safety profile of cabozantinib, refer to the Cabozantinib Investigator's Brochure.

Other medically important but less frequent AEs including arterial thrombotic AEs (eg, TIA, and MI) and venous thrombotic AEs (eg, DVT and pulmonary embolism), severe hemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS; also known as PRES).

AEs associated with laboratory abnormalities experienced by ≥5% of subjects treated with cabozantinib in descending order of frequency were anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, lactate dehydrogenase (LDH) increased, lipase increased, neutropenia, hyponatremia, ALP increased, leukopenia, and hyperglycemia.

AEs may occur within the first few weeks in the course of treatment, as cabozantinib is expected to reach steady-state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting.

Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (Table 8).

Study intervention should be discontinued for the following AEs: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, and RPLS.

Please refer to Table 8 for general toxicity management.

Gastrointestinal Disorders

GI perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatment, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula (Turnage and Badgwell 2016) are present. Discontinue study intervention and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Guidelines for the evaluation and management of diarrhea are shown in Table 11. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study intervention should be temporarily interrupted, or dose reduced. When the diarrhea is controlled, retreatment with study intervention may be acceptable per investigator decision. In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

Recurrent or prolonged diarrhea can be associated with anal or perianal skin erosions which increase the risk for anal abscesses, fistulas, or proctitis. Good personal hygiene should be emphasized. Regular examinations of the perianal region should be performed whenever diarrhea has occurred during treatment. Infections of the perianal region should be treated per local guidelines.

Table 11 Management of Diarrhea with Cabozantinib

Status	Management
Tolerable Grade 1-2 (duration <48 h)	Continue with study intervention and consider dose reduction. Initiate treatment with an antidiarrheal agent (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea (maximum: 16 mg loperamide per day)) For participants below 12 years of age, please follow the standard local clinical practice and appropriate clinical guidelines. Dietary modifications (eg, small lactose-free meals, bananas and rice) Intake of isotonic fluids as appropriate Re-assess after 24 hours: Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval Diarrhea not resolving: Continue/resume antidiarrheal treatment
Intolerable Grade 2, Grade 2 >48 h, or ≥Grade 3	Interrupt study intervention Ask subject to attend clinic Rule out infection (eg, stool sample for culture) Administer antibiotics as needed (eg, if fever or Grade 3-4 neutropenia persists >24 h) Administer fluids orally or intravenously, as appropriate, for hydration or to correct electrolyte abnormalities. For Grade 3-4 or complicated lower grade diarrhea consider hospitalization and IV hydration. Re-assess after 24 h Diarrhea resolving to baseline bowel habits or Grade ≤1: consider restarting study intervention at reduced dose Diarrhea not resolving: Start and/or continue antidiarrheal treatment (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea (maximum: 16 mg loperamide per day)). Consider starting second line antidiarrheal or referral to gastroenterologist. For participants below 12 years of age, please follow the standard local clinical practice and appropriate clinical guidelines.

H=hour, IV=intravenous

Hypertension

The table below provides treatment guidelines for hypertension deemed related to cabozantinib for adults and paediatric participants. BP should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. Decisions to reduce or interrupt the dose of study intervention must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.

Study intervention should be discontinued in subjects with hypertensive emergency.

Management of Hypertension Associated with Cabozantinib

For adult participants

Criteria for Dose Modifications	Treatment Dose Modification
>140 mm Hg (systolic)[a] and <160 mm Hg OR >90 mm Hg (diastolic) and <100 mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. If antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic reduce study treatment by one dose level if optimal. • If subject is symptomatic interrupt study treatment and only restart once symptoms have resolved and BP is <140 mm Hg systolic and <90 mm Hg diastolic.
≥160 mm Hg (systolic) OR ≥ 100 mm Hg (diastolic)	• Reduce study treatment by one dose level[b] or interrupt study treatment per investigator discretion. • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic, study treatment should be dose reduced further or interrupted. • Study treatment should be dose interrupted if upper limits of systolic BP (≥160 mm Hg) are sustained and not adequately manageable or if systolic BP is >180 mm Hg or diastolic BP >110 mm Hg, or if subject is symptomatic. • Re-start study treatment at a reduced dose.
Hypertensive emergency[c]	• Discontinue study treatment • Initiate appropriate medical management

BP, blood pressure.

[a] The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP >140 or diastolic BP >90 based on their clinical judgment and assessment of the individual subject.

[b] Permitted dose levels are defined by individual protocols.

[c] Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (eg, myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).

In paediatric participants

Refer to Appendix 10.9 for BP levels for children by age and height percentile.

- If BP ≤ULN, continue cabozantinib at the same dose.
- If BP ≤10 mm Hg above the ULN, continue cabozantinib at the same dose and recheck the BP within 72 hours.
- If the BP is ≤ULN on recheck, continue cabozantinib at the same dose.
- If the BP remains above the ULN on recheck, then start antihypertensive.
- If BP is 11 to 25 mm Hg above the ULN on ≥2 of 3 measurements or >35 mmHg above baseline on ≥2 of 3 measurements, start anti-hypertensive therapy, continue cabozantinib at the same dose, and monitor BP at least twice weekly.
- If the BP returns to ≤ULN within 14 days, continue cabozantinib at the same dose and continue anti-hypertensive therapy.
- If the BP remains elevated ≤25 mm Hg above the ULN or >35 mm Hg above baseline for more than 14 days after the institution of anti-hypertensive therapy, hold cabozantinib, monitor BP at least every 3 days, and antihypertensive therapy should be continued until the BP is less than the ULN. If the BP returns to ≤ULN within 14 days, restart cabozantinib at a reduced dose. If the BP remains elevated above 25 mm Hg above the ULN for more than 14 days, cabozantinib should be discontinued.
- If the BP increases to >25 mm Hg above the ULN despite anti-hypertensive therapy, hold cabozantinib, but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated.
- If the B P is ≤U LN within 14 days, cabozantinib may be restarted at a reduced dose.
- If the BP is >ULN for >14 days, the patient is Off Protocol Therapy.
- If the participant develops Grade 4 hypertension, discontinue cabozantinib, monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient is Off Protocol Therapy.

Corrected QT Prolongation

Concomitant treatment with strong CYP3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value >500 ms or an increase of >60 ms above baseline, 2 additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is >500 ms, the following actions must be taken:

- Interrupt study treatment.
- Immediately notify the Sponsor and submit ECGs to the Sponsor for independent review.
- Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management.
- Consider cardiology consultation for asymptomatic subjects for evaluation and management.
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated.
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (see Appendix 10.11)

- Repeat ECG triplicates hourly until the average QTcF is ≤500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.
- Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Study treatment may be restarted at a reduced dose level if all of the following conditions are met:
  - Symptoms are determined to be unrelated to the QT interval prolongation.
  - The QTcF value >500 ms is not confirmed.
  - Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤500 ms.
  - QT prolongation can be unequivocally associated with an event other than study treatment administration and is treatable/has been resolved.
  - Sponsor has reviewed all available information and has agreed to the continuation of study treatment.

Study treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation.

Dose Modifications for Proteinuria

In pediatric participants

Proteinuria has been reported with cabozantinib in adult studies and pediatric studies

- If urinalysis shows ≥trace protein then obtain UPCR.
- If the UPCR is ≤1.9 continue cabozantinib. If patient has Grade 3 proteinuria (UPCR >1.9), a second measurement should be obtained within 72 hours. A second confirmation of Grade 3 proteinuria will be considered a DLT.
- If the second measurement confirms Grade 3 proteinuria (UPCR >1.9), then interrupt cabozantinib treatment and re-assess weekly.
- If cabozantinib is held for ≥21 days then remove from protocol therapy. If the UPCR decreases to ≤1.9 in <21 days then resume cabozantinib with reduced dose.
- Monitor the UPCR weekly for 2 consecutive weeks once protocol therapy resumes.
- Nephrotic syndrome - Discontinue study treatment.

In adult participants

Severity of Proteinuria (UPCR)	Action To Be Taken
≤1 mg/mg	• No change in study treatment or monitoring (≤13.1 mg/mmol)
>1 and <3.5 mg/mg	• Consider confirming with a 24-hour protein assessment within 7 days (>113.1 and <395.9 mg/mmol) • No change in study treatment required if UPCR ≤2 mg/mg or urine protein ≤2 g/24 hours on 24-hour urine collection. • Dose reduce or interrupt study treatment if UPCR >2 mg/mg on repeat UPCR testing or urine protein >2 g/24 hours on 24-hour urine collection. Continue study treatment on a reduced dose if UPCR decreases to <2

Severity of Proteinuria (UPCR)	Action To Be Taken
	mg/mg. Consider holding study treatment if UPCR remains >2 mg/mg despite a dose reduction until UPCR decreases to <2 mg/mg. Restart study treatment at a reduced dose after a dose hold unless otherwise approved by sponsor. • Repeat UPCR within 7 days and once per week. If UPCR <1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.) If UPCR remains >1 mg/mg and <2 mg/mg for 1 month or is determined to be stable (<20% change) for 1 month, check urine protein/ creatinine per protocol or as clinically indicated.
≥3.5 mg/mg	• Hold study treatment pending repeat UPCR within 7 days and/or 24-hour (≥395.9 mg/mmol) • If ≥3.5 on repeat UPCR, continue to hold study treatment and check UPCR every 7 days. If UPCR decreases to <2 mg/mg, restart study treatment at a reduced dose, and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to <1 mg/mg. If UPCR remains >1 mg/mg and <2 mg/mg for 1 month or is determined to be stable (<20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
Nephrotic syndrome	• Discontinue study treatment

UPCR, urine protein/creatinine ratio

Palmar-plantar erythrodysesthesia Syndrome

PPES (also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with cabozantinib. All subjects on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry.

Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPES are summarized in the table below.

Management of hand-foot syndrome (PPES) associated with cabozantinib

CTCAE v5 Grade	Action To Be Taken
Grade 1	Study treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, study treatment should be reduced to the next lower dose level.[a] Start urea 20% cream twice daily AND clobetasol 0.05%

CTCAE v5 Grade	Action To Be Taken
	cream once daily. Reassess at least weekly; if PPES worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Study treatment may be continued if PPES is tolerated. Study treatment should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (eg, clobetasol 0.05%) once daily and add analgesics (eg, NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPES worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (eg, clobetasol 0.05%) twice daily AND analgesics. Resume study treatment at a reduced dose if PPES recovers to Grade ≤1. Discontinue subject from study treatment if PPES does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; NSAID, non-steroidal anti-inflammatory drug; PPES, palmar plantar erythrodysesthesia syndrome.

[a] See Section 6.6 for dose modification.

Hepatocellular Toxicity

Evaluations of aminotransferases (ALT and AST) and bilirubin have been observed during treatment with cabozantinib. It is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin, and other causes (eg, cancer related) should be evaluated.

Management of Hepatotoxicity Associated with Cabozantinib

Severity of ALT, AST, total bilirubin Elevations by CTCAE	Treatment Dose Modification
Grade 1	• Dose adjustment is usually not required. • Consider discontinuing concomitant hepatotoxic medications and add supportive care as indicated.
Grade 2	• Interrupt study treatment if lasting longer than 1 week. • Restart study treatment after lab abnormalities have resolved to at least CTCAE Grade ≤1 or baseline.
Grade ≥3	• Interrupt study treatment and consider more frequent monitoring of ALT, AST, and bilirubin. • Restart study treatment at a reduced dose after lab abnormalities have resolved to at least CTCAE Grade ≤1 or baseline. • Discontinue if lab abnormalities cannot be reversed despite interruption of study treatment.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events

The following conditions require discontinuation of study treatment unless these laboratory abnormalities have recovered to Grade 1 or baseline level after an interruption and the sponsor has approved reinstitution of study treatment:

- Drug-related ALT or AST >8 × ULN.
- Drug-related ALT or AST >3 × ULN in combination with total bilirubin >2 × ULN without reasonable other explanation, consistent with drug-induced liver injury.

Elevations of aminotransferases when hepatic metastases are present may not require dose modifications if there are no progressive changes in the aminotransferases (less than a doubling) and if there are no progressive elevations in serum bilirubin concentration or coagulation factors.

10.7 Appendix: Study Risk Assessment

Risk	Non-clinical Data	Clinical Data	Actions
Identified Risk: Gastrointestinal (GI) Perforation and Fistula (GI and Non-GI).	GI tract toxicity at systemically toxic doses in rats (CCI mg/kg qd x CCI) and dogs (CCI mg/kg qd x CCI)	Gastrointestinal perforation and fistulas (GI and non-GI) have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. • **Monotherapy Studies**[a]: *GI Perforation*: CCI% cabozantinib arm, CCI% comparator arm *Non-GI Fistula*: CCI% cabozantinib arm, CCI% comparator arm *GI Fistula*: CCI% cabozantinib arm, none in comparator arm	Ongoing studies exclude enrollment of subjects with the following conditions: • GI disorders associated with risks for GI perforation or fistula • Incomplete healing following abdominal surgery or incomplete resolution of intra-abdominal abscess confirmed prior to initiation with cabozantinib. • Risk for non-GI fistula formation. • Radiation therapy within 4 weeks (2 weeks for bone metastases) prior to randomization, subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible. Investigator Brochure: monitor for early signs of GI perforation, and discontinuation of cabozantinib in subjects who develop GI perforation or fistula (GI or non-GI).
Identified Risk: Thromboembolic Events	No findings.	Arterial thrombotic events (ie, TIA, MI) and venous thromboembolic events (deep vein thrombosis, pulmonary embolism) have been observed across studies with cabozantinib. • **Monotherapy Studies**[a]: *Arterial Thrombotic Events*: CCI% cabozantinib arm, CCI% comparator arm *Venous and Mixed Thrombotic Events*: CCI% cabozantinib arm, CCI% comparator arm	Ongoing studies exclude enrollment of subjects with the following conditions: • History of stroke (including TIA or other ischemic event), myocardial infarction, or thromboembolic event within 6 months of randomization. Investigator Brochure: hold cabozantinib treatment for PE or DVT until therapeutic anticoagulation is established, resume if benefits outweigh risks associated with anticoagulation. Discontinue for clinically significant arterial thromboembolic complication. Subjects should be evaluated for history of thromboembolic events/complications.
Identified Risk: Haemorrhage	No findings.	Hemorrhagic events are a known toxicity of VEGF inhibitor drugs. Serious (≥G3) and sometimes fatal events of hemorrhage have	Ongoing studies:

Risk	Non-clinical Data	Clinical Data	Actions
		been observed in clinical studies with cabozantinib. • **Monotherapy Studies[a]:** CCI% cabozantinib arm, CCI% comparator **arm**	• Inclusion criteria: platelet and hemoglobin count above a minimum value at enrollment • Exclusion criteria • Subjects with a history of clinically significant hematemesis / hemoptysis or other signs of pulmonary hemorrhage, active peptic ulcer disease, or inflammatory GI diseases. • Concomitant treatment with therapeutic doses of anticoagulants or anti-platelet agents • Subjects with cavitating pulmonary lesion(s) or a lesion invading or encasing a major blood vessel Investigator Brochure: evaluate for potential risk factors for bleeding before starting treatment. Monitor for bleeding with CBC and physical examination. Discontinuation of cabozantinib for serious and/or life-threatening bleeding events or recent hemoptysis (≥2.5 mL of red blood).
Identified Risk: Wound Complications	No findings.	Inhibitors of VEGF pathways can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. • **Monotherapy Studies[a]:** CCI% cabozantinib arm, CCI% comparator **arm**	Ongoing studies exclude enrollment of subjects with the following conditions: • Major surgery within 4 weeks and minor surgery within 10 days before enrollment, both with and without wound healing complications. Any surgeries before those times must have complete wound healing before enrollment • Any ongoing, serious non-healing wounds/ulcers/injuries Investigator Brochure: monitor any surgical and traumatic wounds for wound dehiscence, wound infections, and other signs of impaired wound healing while on cabozantinib. Stopping of cabozantinib at least four weeks

Risk	Non-clinical Data	Clinical Data	Actions
			prior to scheduled surgery and resuming based on clinical judgment of adequate wound healing.
Identified Risk: Osteonecrosis	No osteonecrosis observed; bone microscopic changes present in rats ([redacted] mg/kg qd x [redacted]) and dogs ([redacted] mg/kg qd x [redacted]). Teeth changes (missing, extremely white, excessively long, cut or curved) in subchronic and chronic rat toxicity studies ([redacted] mg/kg/day)	Osteonecrosis of the jaw (ONJ) has been reported in subjects receiving VEGF inhibitors including cabozantinib. • **Monotherapy Studies**[a]: [redacted]% cabozantinib arm, [redacted]% comparator arm	Ongoing studies: • Exclusion criteria: major surgeries within 4 weeks (including invasive dental procedures) and minor surgeries within 10 days before enrollment, or any ongoing complications from prior surgery. • Radiation therapy within 4 weeks (2 weeks for bone metastases) before enrollment or any ongoing clinically relevant complications from prior radiation therapy. • Any use of systemic steroids within 14 days before enrollment. Concurrent use of bisphosphonates, denosumab, and anti-angiogenic drugs should also be evaluated prior to enrollment. Investigator Brochure: oral examinations prior to initiation of cabozantinib and periodically during therapy; stopping cabozantinib at least four weeks prior to invasive dental procedures (or orofacial surgeries) and resume based on clinical judgment of adequate wound healing. Caution should be used for concurrent use of bisphosphonates, denosumab, corticosteroids, radiotherapy, other chemotherapy, and anti-angiogenic drugs prior to enrollment.
Identified Risk: Posterior Reversible Encephalopathy Syndrome (PRES) also known as Reversible Posterior leuko-encephalopathy Syndrome (RPLS)	Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical toxicology studies.	PRES has been reported in patients receiving VEGF inhibitors including cabozantinib. • **Monotherapy Studies**[a]: [redacted]% cabozantinib arm, [redacted]% comparator arm	Investigator Brochure: assess any new or progressive, unexplained neurological symptoms for underlying causes; RPLS should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinuation is recommended in subjects diagnosed with PRES.

Risk	Non-clinical Data	Clinical Data	Actions
Potential Risk: Renal Failure	Dose-related effects on kidney weights, urine volume, and urine specific gravity; microscopic changes in rats included reversible minimal moderate glomerular basement membrane thickening, tubular degeneration and a slight increase in the severity and/or incidence of chronic progressive nephropathy (CPN).	Renal failure has been reported in subjects receiving VEGF inhibitors including cabozantinib. • **Monotherapy Studies[a]:** CCI% cabozantinib, CCI% comparator	Ongoing studies: • Inclusion criteria: • serum creatinine ≤1.5 x ULN or calculated creatinine clearance ≥40 ml//min • urine protein to creatinine ratio (UPCR) ≤1 mg/ml (≤113.1 mg/mmol) creatinine or 24 h urine protein <1 g. • Exclusion criteria: • Requirements for dialysis Investigator Brochure: use with caution in subjects with mild or moderate renal impairment; there is no experience with cabozantinib in subjects with severe renal impairment.
Potential Risk: Hepatotoxicity	Dose-related liver transaminase elevations in rats (CCI mg/kg qd x CCI); only non-specific liver microscopic changes in rats and dogs given cabozantinib	Elevations of liver enzymes were frequently reported in clinical studies with a higher frequency of Grade 3-4 events observed in IO combination study CA2099ER; however, no confirmed cases of drug- induced liver injury: • **Monotherapy Studies[a]:** CCI% cabozantinib arm, CCI% comparator arm	Ongoing studies: Inclusion criteria: • ALT, AST, and bilirubin below a maximum value. • Negative HBsAg and HCV antibody tests • Liver function tests are routinely evaluated at study visits. Exclusion criteria: • Moderate to severe hepatic impairment or known cirrhosis • Any active hepatic infection requiring treatment, such as hepatitis B or hepatitis C Investigator Brochure: Interrupt for related CTCAE Grade 3 or higher hepatic injury, and when transaminase increases are accompanied by progressive elevations of total bilirubin and/or elevations of coagulation tests. Discontinuation of cabozantinib is recommended if hepatic dysfunction is not reversed despite interruption of study treatment. Discontinue other hepatotoxic concurrent

Risk	Non-clinical Data	Clinical Data	Actions
			medications when ALT, AST, or bilirubin levels are increased.
Potential Risk: Embryotoxicity	In rats, cabozantinib caused post-implantation loss, foetal oedema, cleft palate/lip, dermal aplasia and kinked or rudimentary tail. In rabbits, cabozantinib produced foetal soft tissue changes (reduced spleen size, small or missing intermediate lung lobe) and increased foetal incidence of total malformations. Cabozantinib was negative in in vivo mouse bone marrow micronucleus genotoxicity bioassays.	Limited clinical data on embryo-foetal toxicities exist as pregnancy should be avoided during cabozantinib treatment. Across the cabozantinib Phase 3 studies one pregnancy was documented in a partner of a subject with MTC (enrolled in study XL184-301) and exposed to cabozantinib. The baby was evaluated as healthy at approximately 5 months of age.	Before starting cabozantinib (as applicable): Male and female participants should be advised to seek medical advice and consider fertility preservation before starting treatment. The National Institute for Health and Care Excellence (NICE) recommend that doctors should offer sperm banking to any man having cancer treatment that may affect their fertility. Teenage boys who have been through puberty can also collect and store sperm; refer to Sperm collection and storage | Cancer Research UK For male participants, consider sperm cryopreservation for males and adolescent boys who are preparing for medical treatment with cabozantinib. For female participants who are preparing for medical treatment with cabozantinib, consider oocyte or embryo cryopreservation as appropriate to females of reproductive age (including adolescent girls). Refer to NICE guidance and Coping with losing your fertility for women | Cancer Research UK Ongoing studies: • Inclusion criteria: • sexually active fertile participants and their partners must use contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 3 - 6 months (depending on protocol) after the last dose of study treatment.

Risk	Non-clinical Data	Clinical Data	Actions
			• female participants of childbearing potential must not be pregnant at screening.
Potential Risk: Carcinogenicity	In a 2-year rat carcinogenicity study, administration of cabozantinib resulted in benign and malignant pheochromocytoma in males and females at doses equivalent to doses less than the 60 mg human dose in RCC and HCC patients.	Pheochromocytomas have not been reported in the clinical development program.	
Other Concerns Specific for the Paediatric Population			
Growth Plate Widening	In a pre-clinical setting, a 2-week repeat-dose toxicity study in young adult rats (XL184-NC-014) showed bone lesion (thickened physis in the femur) at [redacted] mg/kg/day for [redacted] days. In another 2-week repeat-dose toxicity study in young-adult dogs (XL184-NC-006) results indicated cessation of growth associated with atrophy of the primary spongiosa of the distal metaphysis manifest at systemically toxic doses ([redacted] mg/kg/day for [redacted] days). Further preclinical fertility studies conducted in rats (XL184-NC-020) showed tooth appearance (extremely white, missing, excessively long, malocclusion, cut or curved upward) and primarily in males dosed at systemically toxic doses ([redacted] mg/kg/day) comparable teeth changes were noted in the	Study 4 of the PIP (NCI-CTEP study ADVL1211) is a Phase 1 study of cabozantinib in subjects (n = 41) between 4 and 18 years of age (median: 13 years) with relapsed or refractory solid tumors, including CNS tumors (Chuk et al 2018). Cabozantinib was administered at dose levels of 30, 40, and 55 mg/m^2 /day (tablet formulation), and the recommended Phase 2 dose was determined to be 40 mg/m^2/day. This study observed tibial radiographic growth plate thickening in 5/23 subjects with open physes at baseline. Longitudinal growth occurred in all 5 subjects, including those with a duration of treatment greater than 12 months (Chuk et al 2018). No clinical implications emerged from this trial, and subjects continued to receive treatment. Study 7 of the PIP (NCI-CTEP study ADVL1622) is a Phase 2 study of the safety and efficacy of 40 mg/m2 /day (tablet formulation) cabozantinib in subjects with refractory sarcoma, Wilms tumor, and other rare tumors (Akshintala et al 2021). The safety population	Given the antiangiogenic targeting of cabozantinib and concern for possible impact on growth in children, linear growth is determined at baseline based on a tibial X-ray for patients ≤18 years of age. For patients with a closed tibial growth plate, no further radiographs are required. For patients with an open tibial growth plate, plain anteroposterior radiographs of the same tibial growth plates are repeated every 6 months until off protocol therapy. Physeal and longitudinal growth monitoring is recommended in children with open growth plates. Investigator Brochure: In subjects with evidence of growth plate thickening or other changes, a knee MRI without contrast may be needed as indicated clinically. In subjects with growth plate changes, the benefits and risks of continuing treatment with cabozantinib should be evaluated in an individualized manner.

Risk	Non-clinical Data	Clinical Data	Actions
	juvenile rat toxicity studies (XL184-NC-032, -040). In reproductive toxicity studies in pregnant rats or rabbits (184-NC-022 and -024) there was no evidence in foetal skeletal malformations at top systemic exposures CCI -fold those at steady state in subjects with RCC treated with CCI mg cabozantinib daily (clinical AUC ~48,000 ng.hr/mL) and exposures were low in order to minimize potential maternal toxicity (max AUC ~ 4,000 ng.hr/mL). Juvenile toxicity studies in rats (XL184-NC-032 and -040) showed physeal hypertrophy and decreased cortical bone in the femur in PND; in total 12 rats were dosed at CCI mg/kg daily until PND35 (AUC 37-CCI ng.hr/mL at 2MKD). Results showed decreased bone (femur) mineral density in PND 12 or PND 21 rats dosed at CCI mg/kg daily until PND 35 or PND 70, however, this was not present in recovery cohorts, suggesting reversibility upon discontinuation of dosing.	(n=108) included 70 children, including 27 children <12 years of age. In this study, 17 subjects had an open tibial growth plate at baseline. None of the 17 subjects showed evidence of growth plate thickening during the study, and no associated TEAEs were reported. Growth plate toxicity was an area of close monitoring, however none of the subjects reported TEAEs related to growth plate toxicity (tibial thickening) during the study.	

ALT=alanine aminotransferase, AST=aspartate aminotransferase, AUC=area under curve, CBC=complete blood count, CNS=central nervous system, CPN=chronic progressive nephropathy, CTCAE=Common Terminology Criteria for Adverse Events, DVT=deep vein thrombosis, GI=gastrointestinal, HBsAg=hepatitis B surface antigen, HCC=hepatocellular carcinoma, HCV=hepatitis C virus, IO=immuno-oncology, MI=myocardial infarction, MTC=medullary thyroid cancer, NCI-CTEP=National Cancer Institute – Cancer Therapy Evaluation Program, ONJ=osteonecrosis of the jaw, PE=pulmonary embolism, PIP=Paediatric Investigation Plan, PND=post-natal day, PRES=posterior reversible encephalopathy syndrome, qd=once daily dosing, RCC=renal cell carcinoma, RPLS=reversible posterior leukoencephalopathy syndrome, TEAE=treatment emergent adverse event, TIA=transient ischaemic attack, ULN=upper limit of normal, UPCR=urine protein to creatinine ratio, VEGF=vascular endothelial growth factor.
a Monotherapy studies include: XL184-301, 306, 307, 308, 309, 311, 401, and A031203 (Cabosun)

10.8 Appendix: Cabozantinib Dosing Nomogram



10.9 Appendix: Blood Pressure Levels for Children by Age and Height Percentile

Blood Pressure (BP) Levels **For BOYS**

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (in)	30.4	30.8	31.6	32.4	33.3	34.1	34.6	30.4	30.8	31.6	32.4	33.3	34.1	34.6
	Height (cm)	77.2	78.3	80.2	82.4	84.6	86.7	87.9	77.2	78.3	80.2	82.4	84.6	86.7	87.9
	50th	85	85	86	86	87	88	88	40	40	40	41	41	42	42
	90th	98	99	99	100	100	101	101	52	52	53	53	54	54	54
	95th	102	102	103	103	104	105	105	54	54	55	55	56	57	57
	95th + 12 mm Hg	114	114	115	115	116	117	117	66	66	67	67	68	69	69
2	Height (in)	33.9	34.4	35.3	36.3	37.3	38.2	38.8	33.9	34.4	35.3	36.3	37.3	38.2	38.8
	Height (cm)	86.1	87.4	89.6	92.1	94.7	97.1	98.5	86.1	87.4	89.6	92.1	94.7	97.1	98.5
	50th	87	87	88	89	89	90	91	43	43	44	44	45	46	46
	90th	100	100	101	102	103	103	104	55	55	56	56	57	58	58
	95th	104	105	105	106	107	107	108	57	58	58	59	60	61	61
	95th + 12 mm Hg	116	117	117	118	119	119	120	69	70	70	71	72	73	73
3	Height (in)	36.4	37	37.9	39	40.1	41.1	41.7	36.4	37	37.9	39	40.1	41.1	41.7
	Height (cm)	92.5	93.9	96.3	99	101.8	104.3	105.8	92.5	93.9	96.3	99	101.8	104.3	105.8
	50th	88	89	89	90	91	92	92	45	46	46	47	48	49	49
	90th	101	102	102	103	104	105	105	58	58	59	59	60	61	61
	95th	106	106	107	107	108	109	109	60	61	61	62	63	64	64
	95th + 12 mm Hg	118	118	119	119	120	121	121	72	73	73	74	75	76	76
4	Height (in)	38.8	39.4	40.5	41.7	42.9	43.9	44.5	38.8	39.4	40.5	41.7	42.9	43.9	44.5
	Height (cm)	98.5	100.2	102.9	105.9	108.9	111.5	113.2	98.5	100.2	102.9	105.9	108.9	111.5	113.2
	50th	90	90	91	92	93	94	94	48	49	49	50	51	52	52
	90th	102	103	104	105	105	106	107	60	61	62	62	63	64	64
	95th	107	107	108	108	109	110	110	63	64	65	66	67	67	68
	95th + 12 mm Hg	119	119	120	120	121	122	122	75	76	77	78	79	79	80
5	Height (in)	41.1	41.8	43.0	44.3	45.5	46.7	47.4	41.1	41.8	43.0	44.3	45.5	46.7	47.4
	Height (cm)	104.4	106.2	109.1	112.4	115.7	118.6	120.3	104.4	106.2	109.1	112.4	115.7	118.6	120.3
	50th	91	92	93	94	95	96	96	51	51	52	53	54	55	55
	90th	103	104	105	106	107	108	108	63	64	65	65	66	67	67
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th + 12 mm Hg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
6	Height (in)	43.4	44.2	45.4	46.8	48.2	49.4	50.2	43.4	44.2	45.4	46.8	48.2	49.4	50.2
	Height (cm)	110.3	112.2	115.3	118.9	122.4	125.6	127.5	110.3	112.2	115.3	118.9	122.4	125.6	127.5
	50th	93	93	94	95	96	97	98	54	54	55	56	57	57	58
	90th	105	105	106	107	109	110	110	66	66	67	68	68	69	69
	95th	108	109	110	111	112	113	114	69	70	70	71	72	72	73
	95th + 12 mm Hg	120	121	122	123	124	125	126	81	82	82	83	84	84	85
7	Height (in)	45.7	46.5	47.8	49.3	50.8	52.1	52.9	45.7	46.5	47.8	49.3	50.8	52.1	52.9
	Height (cm)	116.1	118	121.4	125.1	128.9	132.4	134.5	116.1	118	121.4	125.1	128.9	132.4	134.5
	50th	94	94	95	97	98	98	99	56	56	57	58	58	59	59
	90th	106	107	108	109	110	111	111	68	68	69	70	70	71	71
	95th	110	110	111	112	114	115	116	71	71	72	73	73	74	74
	95th + 12 mm Hg	122	122	123	124	126	127	128	83	83	84	85	85	86	86

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
8	Height (in)	47.8	48.6	50	51.6	53.2	54.6	55.5	47.8	48.6	50	51.6	53.2	54.6	55.5
	Height (cm)	121.4	123.5	127	131	135.1	138.8	141	121.4	123.5	127	131	135.1	138.8	141
	50th	95	96	97	98	99	99	100	57	57	58	59	59	60	60
	90th	107	108	109	110	111	112	112	69	70	70	71	72	72	73
	95th	111	112	112	114	115	116	117	72	73	73	74	75	75	75
	95th + 12 mm Hg	123	124	124	126	127	128	129	84	85	85	86	87	87	87
9	Height (in)	49.6	50.5	52	53.7	55.4	56.9	57.9	49.6	50.5	52	53.7	55.4	56.9	57.9
	Height (cm)	126	128.3	132.1	136.3	140.7	144.7	147.1	126	128.3	132.1	136.3	140.7	144.7	147.1
	50th	96	97	98	99	100	101	101	57	58	59	60	61	62	62
	90th	107	108	109	110	112	113	114	70	71	72	73	74	74	74
	95th	112	112	113	115	116	118	119	74	74	75	76	76	77	77
	95th + 12 mm Hg	124	124	125	127	128	130	131	86	86	87	88	88	89	89
10	Height (in)	51.3	52.2	53.8	55.6	57.4	59.1	60.1	51.3	52.2	53.8	55.6	57.4	59.1	60.1
	Height (cm)	130.2	132.7	136.7	141.3	145.9	150.1	152.7	130.2	132.7	136.7	141.3	145.9	150.1	152.7
	50th	97	98	99	100	101	102	103	59	60	61	62	63	63	64
	90th	108	109	111	112	113	115	116	72	73	74	74	75	75	76
	95th	112	113	114	116	118	120	121	76	76	77	77	78	78	78
	95th + 12 mm Hg	124	125	126	128	130	132	133	88	88	89	89	90	90	90
11	Height (in)	53	54	55.7	57.6	59.6	61.3	62.4	53	54	55.7	57.6	59.6	61.3	62.4
	Height (cm)	134.7	137.3	141.5	146.4	151.3	155.8	158.6	134.7	137.3	141.5	146.4	151.3	155.8	158.6
	50th	99	99	101	102	103	104	106	61	61	62	63	63	63	63
	90th	110	111	112	114	116	117	118	74	74	75	75	75	76	76
	95th	114	114	116	118	120	123	124	77	78	78	78	78	78	78
	95th + 12 mm Hg	126	126	128	130	132	135	136	89	90	90	90	90	90	90
12	Height (in)	55.2	56.3	58.1	60.1	62.2	64	65.2	55.2	56.3	58.1	60.1	62.2	64	65.2
	Height (cm)	140.3	143	147.5	152.7	157.9	162.6	165.5	140.3	143	147.5	152.7	157.9	162.6	165.5
	50th	101	101	102	104	106	108	109	61	62	62	62	62	63	63
	90th	113	114	115	117	119	121	122	75	75	75	75	75	76	76
	95th	116	117	118	121	124	126	128	78	78	78	78	78	79	79
	95th + 12 mm Hg	128	129	130	133	136	138	140	90	90	90	90	90	91	91
13	Height (in)	57.9	59.1	61	63.1	65.2	67.1	68.3	57.9	59.1	61	63.1	65.2	67.1	68.3
	Height (cm)	147	150	154.9	160.3	165.7	170.5	173.4	147	150	154.9	160.3	165.7	170.5	173.4
	50th	103	104	105	108	110	111	112	61	60	61	62	63	64	65
	90th	115	116	118	121	124	126	126	74	74	74	75	76	77	77
	95th	119	120	122	125	128	130	131	78	78	78	78	80	81	81
	95th + 12 mm Hg	131	132	134	137	140	142	143	90	90	90	90	92	93	93
14	Height (in)	60.6	61.8	63.8	65.9	68.0	69.8	70.9	60.6	61.8	63.8	65.9	68.0	69.8	70.9
	Height (cm)	153.8	156.9	162	167.5	172.7	177.4	180.1	153.8	156.9	162	167.5	172.7	177.4	180.1
	50th	105	106	109	111	112	113	113	60	60	62	64	65	66	67
	90th	119	120	123	126	127	128	129	74	74	75	77	78	79	80
	95th	123	125	127	130	132	133	134	77	78	79	81	82	83	84
	95th + 12 mm Hg	135	137	139	142	144	145	146	89	90	91	93	94	95	96

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
15	Height (in)	62.6	63.8	65.7	67.8	69.8	71.5	72.5	62.6	63.8	65.7	67.8	69.8	71.5	72.5
	Height (cm)	159	162	166.9	172.2	177.2	181.6	184.2	159	162	166.9	172.2	177.2	181.6	184.2
	50th	108	110	112	113	114	114	114	61	62	64	65	66	67	68
	90th	123	124	126	128	129	130	130	75	76	78	79	80	81	81
	95th	127	129	131	132	134	135	135	78	79	81	83	84	85	85
	95th + 12 mm Hg	139	141	143	144	146	147	147	90	91	93	95	96	97	97
16	Height (in)	63.8	64.9	66.8	68.8	70.7	72.4	73.4	63.8	64.9	66.8	68.8	70.7	72.4	73.4
	Height (cm)	162.1	165	169.6	174.6	179.5	183.8	186.4	162.1	165	169.6	174.6	179.5	183.8	186.4
	50th	111	112	114	115	115	116	116	63	64	66	67	68	69	69
	90th	126	127	128	129	131	131	132	77	78	79	80	81	82	82
	95th	130	131	133	134	135	136	137	80	81	83	84	85	86	86
	95th + 12 mm Hg	142	143	145	146	147	148	149	92	93	95	96	97	98	98
17	Height (in)	64.5	65.5	67.3	69.2	71.1	72.8	73.8	64.5	65.5	67.3	69.2	71.1	72.8	73.8
	Height (cm)	163.8	166.5	170.9	175.8	180.7	184.9	187.5	163.8	166.5	170.9	175.8	180.7	184.9	187.5
	50th	114	115	116	117	117	118	118	65	66	67	68	69	70	70
	90th	128	129	130	131	132	133	134	78	79	80	81	82	82	83
	95th	132	133	134	135	137	138	138	81	82	84	85	86	86	87
	95th + 12 mm Hg	144	145	146	147	149	150	150	93	94	96	97	98	98	99

Use percentile values to stage BP readings according to the scheme in Table 3 (elevated BP: ≥90th percentile; stage 1 HTN: ≥95th percentile; and stage 2 HTN: ≥95th percentile + 12 mm Hg). The 50th, 90th, and 95th percentiles were derived by using quantile regression on the basis of normal-weight children (BMI <85th percentile).[77]

Source: Flynn et al 2017

Blood Pressure (BP) Levels **For GIRLS**

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (in)	29.7	30.2	30.9	31.8	32.7	33.4	33.9	29.7	30.2	30.9	31.8	32.7	33.4	33.9
	Height (cm)	75.4	76.6	78.6	80.8	83	84.9	86.1	75.4	76.6	78.6	80.8	83	84.9	86.1
	50th	84	85	86	86	87	88	88	41	42	42	43	44	45	46
	90th	98	99	99	100	101	102	102	54	55	56	56	57	58	58
	95th	101	102	102	103	104	105	105	59	59	60	60	61	62	62
	95th + 12 mm Hg	113	114	114	115	116	117	117	71	71	72	72	73	74	74
2	Height (in)	33.4	34	34.9	35.9	36.9	37.8	38.4	33.4	34	34.9	35.9	36.9	37.8	38.4
	Height (cm)	84.9	86.3	88.6	91.1	93.7	96	97.4	84.9	86.3	88.6	91.1	93.7	96	97.4
	50th	87	87	88	89	90	91	91	45	46	47	48	49	50	51
	90th	101	101	102	103	104	105	106	58	58	59	60	61	62	62
	95th	104	105	106	106	107	108	109	62	63	63	64	65	66	66
	95th + 12 mm Hg	116	117	118	118	119	120	121	74	75	75	76	77	78	78
3	Height (in)	35.8	36.4	37.3	38.4	39.6	40.6	41.2	35.8	36.4	37.3	38.4	39.6	40.6	41.2
	Height (cm)	91	92.4	94.9	97.6	100.5	103.1	104.6	91	92.4	94.9	97.6	100.5	103.1	104.6
	50th	88	89	89	90	91	92	93	48	48	49	50	51	53	53
	90th	102	103	104	104	105	106	107	60	61	61	62	63	64	65
	95th	106	106	107	108	109	110	110	64	65	65	66	67	68	69
	95th + 12 mm Hg	118	118	119	120	121	122	122	76	77	77	78	79	80	81
4	Height (in)	38.3	38.9	39.9	41.1	42.4	43.5	44.2	38.3	38.9	39.9	41.1	42.4	43.5	44.2
	Height (cm)	97.2	98.8	101.4	104.5	107.6	110.5	112.2	97.2	98.8	101.4	104.5	107.6	110.5	112.2
	50th	89	90	91	92	93	94	94	50	51	51	53	54	55	55
	90th	103	104	105	106	107	108	108	62	63	64	65	66	67	67
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th + 12 mm Hg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
5	Height (in)	40.8	41.5	42.6	43.9	45.2	46.5	47.3	40.8	41.5	42.6	43.9	45.2	46.5	47.3
	Height (cm)	103.6	105.3	108.2	111.5	114.9	118.1	120	103.6	105.3	108.2	111.5	114.9	118.1	120
	50th	90	91	92	93	94	95	96	52	52	53	55	56	57	57
	90th	104	105	106	107	108	109	110	64	65	66	67	68	69	70
	95th	108	109	109	110	111	112	113	68	69	70	71	72	73	73
	95th + 12 mm Hg	120	121	121	122	123	124	125	80	81	82	83	84	85	85
6	Height (in)	43.3	44	45.2	46.6	48.1	49.4	50.3	43.3	44	45.2	46.6	48.1	49.4	50.3
	Height (cm)	110	111.8	114.9	118.4	122.1	125.6	127.7	110	111.8	114.9	118.4	122.1	125.6	127.7
	50th	92	92	93	94	96	97	97	54	54	55	56	57	58	59
	90th	105	106	107	108	109	110	111	67	67	68	69	70	71	71
	95th	109	109	110	111	112	113	114	70	71	72	72	73	74	74
	95th + 12 mm Hg	121	121	122	123	124	125	126	82	83	84	84	85	86	86
7	Height (in)	45.6	46.4	47.7	49.2	50.7	52.1	53	45.6	46.4	47.7	49.2	50.7	52.1	53
	Height (cm)	115.9	117.8	121.1	124.9	128.8	132.5	134.7	115.9	117.8	121.1	124.9	128.8	132.5	134.7
	50th	92	93	94	95	97	98	99	55	55	56	57	58	59	60
	90th	106	106	107	109	110	111	112	68	68	69	70	71	72	72
	95th	109	110	111	112	113	114	115	72	72	73	73	74	74	75
	95th + 12 mm Hg	121	122	123	124	125	126	127	84	84	85	85	86	86	87

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
8	Height (in)	47.6	48.4	49.8	51.4	53	54.5	55.5	47.6	48.4	49.8	51.4	53	54.5	55.5
	Height (cm)	121	123	126.5	130.6	134.7	138.5	140.9	121	123	126.5	130.6	134.7	138.5	140.9
	50th	93	94	95	97	98	99	100	56	56	57	59	60	61	61
	90th	107	107	108	110	111	112	113	69	70	71	72	72	73	73
	95th	110	111	112	113	115	116	117	72	73	74	74	75	75	75
	95th + 12 mm Hg	122	123	124	125	127	128	129	84	85	86	86	87	87	87
9	Height (in)	49.3	50.2	51.7	53.4	55.1	56.7	57.7	49.3	50.2	51.7	53.4	55.1	56.7	57.7
	Height (cm)	125.3	127.6	131.3	135.6	140.1	144.1	146.6	125.3	127.6	131.3	135.6	140.1	144.1	146.6
	50th	95	95	97	98	99	100	101	57	58	59	60	60	61	61
	90th	108	108	109	111	112	113	114	71	71	72	73	73	73	73
	95th	112	112	113	114	116	117	118	74	74	75	75	75	75	75
	95th + 12 mm Hg	124	124	125	126	128	129	130	86	86	87	87	87	87	87
10	Height (in)	51.1	52	53.7	55.5	57.4	59.1	60.2	51.1	52	53.7	55.5	57.4	59.1	60.2
	Height (cm)	129.7	132.2	136.3	141	145.8	150.2	152.8	129.7	132.2	136.3	141	145.8	150.2	152.8
	50th	96	97	98	99	101	102	103	58	59	59	60	61	61	62
	90th	109	110	111	112	113	115	116	72	73	73	73	73	73	73
	95th	113	114	114	116	117	119	120	75	75	76	76	76	76	76
	95th + 12 mm Hg	125	126	126	128	129	131	132	87	87	88	88	88	88	88
11	Height (in)	53.4	54.5	56.2	58.2	60.2	61.9	63	53.4	54.5	56.2	58.2	60.2	61.9	63
	Height (cm)	135.6	138.3	142.8	147.8	152.8	157.3	160	135.6	138.3	142.8	147.8	152.8	157.3	160
	50th	98	99	101	102	104	105	106	60	60	60	61	62	63	64
	90th	111	112	113	114	116	118	120	74	74	74	74	74	75	75
	95th	115	116	117	118	120	123	124	76	77	77	77	77	77	77
	95th + 12 mm Hg	127	128	129	130	132	135	136	88	89	89	89	89	89	89
12	Height (in)	56.2	57.3	59	60.9	62.8	64.5	65.5	56.2	57.3	59	60.9	62.8	64.5	65.5
	Height (cm)	142.8	145.5	149.9	154.8	159.6	163.8	166.4	142.8	145.5	149.9	154.8	159.6	163.8	166.4
	50th	102	102	104	105	107	108	108	61	61	61	62	64	65	65
	90th	114	115	116	118	120	122	122	75	75	75	75	76	76	76
	95th	118	119	120	122	124	125	126	78	78	78	78	79	79	79
	95th + 12 mm Hg	130	131	132	134	136	137	138	90	90	90	90	91	91	91
13	Height (in)	58.3	59.3	60.9	62.7	64.5	66.1	67	58.3	59.3	60.9	62.7	64.5	66.1	67
	Height (cm)	148.1	150.6	154.7	159.2	163.7	167.8	170.2	148.1	150.6	154.7	159.2	163.7	167.8	170.2
	50th	104	105	106	107	108	108	109	62	62	63	64	65	65	66
	90th	116	117	119	121	122	123	123	75	75	75	76	76	76	76
	95th	121	122	123	124	126	126	127	79	79	79	79	80	80	81
	95th + 12 mm Hg	133	134	135	136	138	138	139	91	91	91	91	92	92	93
14	Height (in)	59.3	60.2	61.8	63.5	65.2	66.8	67.7	59.3	60.2	61.8	63.5	65.2	66.8	67.7
	Height (cm)	150.6	153	156.9	161.3	165.7	169.7	172.1	150.6	153	156.9	161.3	165.7	169.7	172.1
	50th	105	106	107	108	109	109	109	63	63	64	65	66	66	66
	90th	118	118	120	122	123	123	123	76	76	76	76	77	77	77
	95th	123	123	124	125	126	127	127	80	80	80	80	81	81	82
	95th + 12 mm Hg	135	135	136	137	138	139	139	92	92	92	92	93	93	94

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
15	Height (in)	59.7	60.6	62.2	63.9	65.6	67.2	68.1	59.7	60.6	62.2	63.9	65.6	67.2	68.1
	Height (cm)	151.7	154	157.9	162.3	166.7	170.6	173	151.7	154	157.9	162.3	166.7	170.6	173
	50th	105	106	107	108	109	109	109	64	64	64	65	66	67	67
	90th	118	119	121	122	123	123	124	76	76	76	77	77	78	78
	95th	124	124	125	126	127	127	128	80	80	80	81	82	82	82
	95th + 12 mm Hg	136	136	137	138	139	139	140	92	92	92	93	94	94	94
16	Height (in)	59.9	60.8	62.4	64.1	65.8	67.3	68.3	59.9	60.8	62.4	64.1	65.8	67.3	68.3
	Height (cm)	152.1	154.5	158.4	162.8	167.1	171.1	173.4	152.1	154.5	158.4	162.8	167.1	171.1	173.4
	50th	106	107	108	109	109	110	110	64	64	65	66	66	67	67
	90th	119	120	122	123	124	124	124	76	76	76	77	78	78	78
	95th	124	125	125	127	127	128	128	80	80	80	81	82	82	82
	95th + 12 mm Hg	136	137	137	139	139	140	140	92	92	92	93	94	94	94
17	Height (in)	60.0	60.9	62.5	64.2	65.9	67.4	68.4	60.0	60.9	62.5	64.2	65.9	67.4	68.4
	Height (cm)	152.4	154.7	158.7	163.0	167.4	171.3	173.7	152.4	154.7	158.7	163.0	167.4	171.3	173.7
	50th	107	108	109	110	110	110	111	64	64	65	66	66	66	67
	90th	120	121	123	124	124	125	125	76	76	77	77	78	78	78
	95th	125	125	126	127	128	128	128	80	80	80	81	82	82	82
	95th + 12 mm Hg	137	137	138	139	140	140	140	92	92	92	93	94	94	94

Use percentile values to stage BP readings according to the scheme in Table 3 (elevated BP: ≥90th percentile; stage 1 HTN: ≥95th percentile; and stage 2 HTN: ≥95th percentile + 12 mm Hg). The 50th, 90th, and 95th percentiles were derived by using quantile regression on the basis of normal-weight children (BMI <85th percentile).[77]

Source: Flynn et al 2017

10.10 Appendix: Unacceptable Enzyme Inducing and Recommended Non-Enzyme Inducing Anticonvulsants

The list below is not exhaustive; please refer to https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Recommended Non-enzyme inducing anticonvulsants
Clonazepam
Diazepam
Ethosuximide
Ezogabine
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Lorazepam
Perampanel
Tiagabine
Topiramate
Valproic Acid
Zonisamide
Unacceptable Enzyme inducing anticonvulsants
Carbamazepine
Felbamate
Phenobarbital
Fosphenytoin
Phenytoin
Primidone
Oxcarbazepine

10.11 Appendix: Medications Associated with Prolonged QTc

Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (Crediblemeds).

10.12 Appendix: List of Substrates, Inducers, and Inhibitors of Selected CYP450 Isozymes

Strong Inhibitors of CYP3A4	Strong Inducers of CYP3A4
Antivirals Boceprevir Cobicistat Conivaptan Danoprevir Dasabuvir Elvitegravir Indinavir Lopinavir Nelfinavir Ombitasvir Paritaprevir Ritonavir Saquinavir Telaprevir Tipranavir **Anti-Fungals** Itraconazole Ketoconazole Posaconazole Voriconazole **Antibiotics** Clarithromycin Telithromycin Troleandomycin Conivaptan Diltiazem Grapefruit juice/star fruit/Seville oranges Idelalisib Nefazodone	Carbamazepine Efavirenz Enzalutamide Erythromycin Mitotane Modafinil Nevirapine Oxcarbazepine Phenytoin Rifampin St. John's Wort **CYP3A4 Substrates with Narrow Therapeutic Index** Alfentanil Cyclosporine Dihydroergotamine Ergotamine Fentanyl Pimozide Quinidine Sirolimus Tacrolimus
Strong CYP2C8 Inhibitors	
Gemfibrozil	
CYP2D6 Substrates with Narrow Therapeutic Index	
Thioridazine	
CYP2C9 Substrates with Narrow Therapeutic Index	
Phenytoin	
CYP2C19 Substrates with Narrow Therapeutic Index	
S-mephenytoin	

This table is not all-inclusive. Please refer to the FDA website for the most updated lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

10.13 Appendix: Response Evaluation Criteria

Adapted from Eisenhauer et al 2009

Definitions

Baseline: Baseline is defined as the most recent assessment performed prior to randomization. Baseline assessments must be performed within the period defined in the protocol eligibility criteria.

Measurable lesions: Except for lymph nodes as described below, measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥10 mm with CT scan (if CT scans have slice thickness greater than 5 mm the minimum size for a measurable lesion is twice the slice thickness).

- To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and recorded.
- MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Nonmeasurable lesions: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered nonmeasurable. Lymph nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/ pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as nonmeasurable.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as **target lesions** and measured and recorded at baseline. Target lesions are to be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. Target lesions will be measured at each assessment (longest axis for nonnodal lesions, shortest axis for measurable malignant nodal lesions).

Nontarget lesions: All other lesions (or sites of disease) including all non-measurable lesions (including pathological lymph nodes with ≥10 to <15 mm short axis) and all measurable lesions over and above the 5 target lesions are to be identified as **non-target lesions** and recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each is to be recorded throughout follow-up. Lymph nodes that have a short axis <10 mm are considered non-pathological and are not to be recorded or followed.

To be considered progression of non-target lesions in the presence of measurable disease, unequivocal progression is defined as substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of the therapy.

Special Consideration

Lesions by clinical examination will not be used for response in this study.

Cystic lesions

- Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Bone lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. CT or MRI must be used to corroborate findings by these modalities.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Lesions with prior local treatment

- Lesions situated in a previously irradiated area are not considered measurable, unless lesion progressed after radiotherapy and prior to the last chemotherapy at screening and meeting measurable lesion definition.

Imaging Methods

The same method of assessment and the same technique used to characterize each identified and reported lesions at baseline should be used during each follow-up assessment. All measurements should be taken and recorded in metric notation using a ruler or calipers. Imaging based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but assessed by clinical examination (referring to biopsy-proven visible lesion(s) on the chest).

Chest x-ray: Chest x-ray will not be used for response assessment in this study.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion is twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scan) except for lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease.

Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET will not be used for response assessment in this study.

Ultrasound: Ultrasound will not be used for response assessment in this study.

Bone scans: CT or MRI scan will be used to confirm results of bone scans. Preferred method for confirmation is MRI.

Tumor Markers: Tumor markers may be evaluated for changes but will not be used to determine PD in this study.

Cytology, Histology: The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD will be considered malignant unless cytologically confirmed negative.

Time Point Assessments

The frequency and schedule of tumor assessments is defined in the protocol. The schedule is to be maintained regardless of whether study intervention is given, reduced, held, or discontinued, including for participants randomized to BSC who switch to receive cabozantinib+BSC (Appendix 10.14).

At baseline, tumors and lymph nodes are classified and documented as target or nontarget lesions per the definitions provided above. It is possible to record multiple nontarget lesions involving the same organ as a single item (eg, ‘multiple liver metastases’). At all postbaseline (follow-up) evaluations the baseline classification (target, nontarget) is to be maintained and lesions are to be documented and described in a consistent fashion over time (eg, recorded in the same order on source documents).

At each assessment, a sum of the diameters (longest for nonnodal lesions, short axis for nodal lesions) for all target lesions will be calculated and included in source documents. The *baseline sum of the diameters* (SoD) will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. The lowest SoD (nadir) since (and including) the baseline value will be used as reference for evaluating progression.

After baseline, target lesions should have the actual size documented, if possible, even if the lesions become very small. If in the opinion of the radiologist the lesion has likely disappeared, 0 mm should be recorded. If the lesion is present but too small to measure, an indicator for 'too small to measure' should be included in source documents.

Nontarget lesions are to be assessed qualitatively (present, absent, or unequivocal progression) and new lesions, if any, are to be documented separately.

At each evaluation, progression status is to be determined based upon the time point status for target lesions, nontarget lesions, and new lesions.

Finding of new lesions should not be attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. Necrosis of pre-existing lesions as part of a response to treatment should be excluded before defining a 'new' cystic lesion. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion. If a new lesion is equivocal because of its small size, repeat scans need to confirm there is definitely a new lesion, and progression should be declared using the date of the initial scan.

RESPONSE CRITERIA

Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in SoD of target lesions, taking as a reference the baseline SoD
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the SoD of target lesions, taking as a reference the smallest (nadir) SoD since (and including) baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.
Not Applicable (NA)	No target lesion identified at baseline.
Unable to Evaluate (UE)/Not evaluable (NE)	One or more target lesions are not imaged, and the remainder of the SoD compared with the nadir SoD does not meet the criterion for PD.

SoD=baseline sum of diameters (longest for non-nodal lesions; short axis for nodal lesions)

If the target lesion for a subject meets the criteria for both PR and PD at a given time point, the target lesion response is PD.

If the nadir of SoD is 0 (ie, the subject had a prior target lesion CR), the reappearance of any prior target lesion to any degree constitutes PD.

Non-Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis)
Non-CR / Non-PD	Persistence of one or more non-target lesion(s)
Progressive Disease (PD)	Unequivocal progression of non-target lesions. Unequivocal progression should normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase
Not Applicable (NA)	No non-target lesions identified at screening
Unable to Evaluate (UE or NE)	One or more non-target lesions are not imaged, and the remaining non-target lesions do not meet the criterion for PD.

New Lesion Time Point Response (TPR)	
Yes	Lesion present at follow-up visit either for the very first time or re-appearing (ie, lesion was present at baseline, disappeared at a follow-up visit and re-appeared later). Confirmation of bone scan findings must be obtained by performing CT or MRI of the area of concern. Preferred method for confirmation is MRI.
No	No new lesions present at follow-up.

CT=computed tomography, MRI=magnetic resonance imaging.

Evaluation of Overall Time Point Response (TPR)			
Target Lesion TPR	Non-target lesion TPR	New lesion TPR	Overall TPR
CR	CR or NA	No	CR*
CR	Non-CR/non-PD	No	PR*
CR	UE/NE	No	PR*
PR	Non-PD or NA or UE/NE	No	PR*
SD	Non-PD or NA or UE/NE	No	SD
UE	Non-PD	No	UE
PD	Any	No or Yes	PD
Any	PD	No or Yes	PD
Any	Any	Yes	PD
NA	CR	No	CR*
NA	Non-CR/Non-PD	No	Non-CR/non-PD
NA	UE/NE	No	UE/NE

CR=complete response, NA=not applicable (no such lesions at screening), NE=not evaluable, PR=partial response, PD=progressive disease, SD=stable disease, UE=unable to evaluate.

Any = CR, PR, SD, PD, NA, or UE.

The overall response at a given time point does not depend upon the overall response assigned at any prior time point.

* Participants with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met. However, the presence or absence of confirmation is not considered when assigning a time point response.

Confirmation

For subjects with an overall response of PR or CR at a given time point, a repeat assessment should be performed no less than 4 weeks after the criteria for response are first met. However, the presence or absence of confirmation is not considered when assigning a time point response.

10.14 Appendix: Eligibility Criteria for Switch

At the time of investigator-determined radiographic progression per RECIST 1.1, optional switch to cabozantinib will be allowed if the below criteria are fulfilled:

- Disease progression per RECIST version 1.1

Note: Clinical deterioration or clinical progression determined by the investigator will not be considered radiographical progression events. If clinically indicated, radiologic tumor assessment will be scheduled in order to evaluate disease status according to RECIST v1.1. Disease progression, to allow switch, will be evaluated based on investigator's assessment. BIRC review will be utilized for the primary analysis.

Note that the numbering of the criteria is maintained from the start of the study (Section 5.1 Inclusion Criteria and Section 5.2 Exclusion Criteria). "Not applicable" rows below refer to eligibility criteria from the start of the study that are not relevant for the Switch Phase as these participants have either already fulfilled the criteria upon study entry, or the criteria are not a requirement for the Switch Phase.

10.14.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

(1) Not applicable.

Type of Participant and Disease Characteristics

(2) Not applicable.

(3) Not applicable.

(4) Not Applicable.

(5) Not applicable.

(6) Not applicable.

(7b) Participants must have recovered to Grade ≤1, except for alopecia, ototoxicity, and Grade ≤2 peripheral neuropathy, per CTCAE version 5.0) from the acute toxic effects of all prior anticancer therapy at switch screening, unless AEs are clinically nonsignificant and/or stable on supportive therapy, per investigator clinical judgment.

(8) Life expectancy >6 months.

(9) Performance level: participants must have a Lansky or Karnofsky performance status score of ≥70, corresponding to ECOG categories 0-1 (see Appendix 10.16).

Note: use Karnofsky for participants ≥16 years of age and Lansky for participants <16 years of age. Participants who are unable to walk because of paralysis, but who use a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

(10b) Adequate organ and marrow function. Organ Function Requirements, within 7 days before switch, are as follows:

- Adequate Bone Marrow Function Defined As:
  - Peripheral ANC ≥1000/µL
  - Platelet count ≥100,000/µL

- Hemoglobin ≥8.0 g/dL
- Transfusions are permitted to meet both the platelet and haemoglobin criteria if the transfusion is more than 7 days before switch screening laboratory sample collection. Participants must not be known to be refractory to red blood cell or platelet transfusions.

• Adequate Renal Function Defined As:
- For participants below 18 years of age:

  Creatinine clearance GFR ≥70 mL/min/1.73 m^2 (using the revised bedside Schwartz formula ([(0.413 × Height (cm)) / Scr (mg/dL)]).
- For participants ≥18 years of age: Serum creatinine ≤1.5 × ULN or calculated creatinine clearance ≥40 mL/min using the Cockcroft-Gault equation: (140 – age) × weight (kg) x [0.85 if female]/(serum creatinine (mg/dL) × 72).
- UPCR ≤1 mg/mg (≤113.1 mg/mmol) or 24-hour urine protein <1 g.

• Adequate Liver Function Defined As:
- Total bilirubin ≤1.5 × ULN for age.

  Note: Participants with known Gilbert's disease or unconjugated hyperbilirubinemia who have serum bilirubin level ≤3 × ULN may be switched.
- ALT and AST ≤3 × ULN in the absence of liver metastases or both ≤5.0 x ULN in the presence of liver metastases.
- ALP ≤3 × ULN. ALP ≤5 × ULN if the participant has documented bone metastases
- Serum albumin ≥2.8 g/dL.

• Adequate Coagulation Status Defined As:
- PTT, PT, and INR ≤1.5 × ULN.

• Adequate Pancreatic Function Defined As:
- Serum amylase ≤1.5 × ULN.
- Serum lipase ≤1.5 × ULN.

(11) Not applicable

(12) Adequately controlled BP with or without antihypertensive medications (refer to Appendix 10.9). A BP ≤the 95th percentile for age, height, and gender for pediatric participants <18 years old and ≤140/90 mmHg for participants ≥18 years old. Please note that 3 serial BPs should be obtained and averaged to determine baseline BP.

Weight

(13) Participants must have a BSA ≥0.65 m^2.

Sex and Contraception/Barrier Requirements

(14) Male and/or female (according to their reproductive organs and functions assigned by chromosomal complement) (FDA 2016)

(15a) Sexually active fertile participants and their partners must agree to use highly effective contraception as appropriate for their age and sexual activity, in combination with one acceptable barrier method, and as required by local regulations during the course of the study and for 4 months after the last dose of study intervention. Pregnancy testing is

required as appropriate for the age and sexual activity of female participants and as required by local regulations during the course of the study (see Appendix 10.4).

(16) Female participants of childbearing potential must provide a negative pregnancy test within 7 days prior to the start of study treatment. If a urine test cannot be confirmed as negative, a negative serum pregnancy test is required.

Note: If the childbearing potential changes after start of the study (e.g., a premenarchal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the investigator must discuss this with the participant/legal guardian, who should determine if a female participant must begin a highly effective method of contraception, or a male participant must use a condom. If reproductive status is questionable, additional evaluation should be considered.

Informed Consent and Assent

(17) All participants (typically ≥18 years) and/or their parents or legal guardians must sign a written informed consent and assent must be obtained from minor participants according to local guidelines.

Note: The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant and/or their legal guardian (as defined in Appendix 10.1.3 and the participant's assent, when applicable, before any study-specific activity is performed unless a waiver of informed consent has been granted by an IRB/IEC. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand.

Other

(18) Applicable for minor participants ONLY: A legal guardian or primary caregiver must be available to help the study-site personnel ensure follow up; accompany the participant to the study site on each assessment day according to the SoA (e.g., able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures); consistently and consecutively be available to provide information on the participant using the rating scales during the scheduled study visits; accurately and reliably dispense study intervention as directed.

A legal guardian or primary caregiver must be able to accurately maintain the child's take-home record, including items of general health.

10.14.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

(1) Not applicable.

(2) Not applicable.

(3) Not applicable.

(4) Receipt of any type of cytotoxic, biologic or other systemic anticancer therapy (including investigational) between the end of BSC and the first dose of cabozantinib.

(5) 'Deleted at Amendment 3' Not applicable.

(6) 'Deleted at Amendment 2'

(7) Ongoing Grade >2 peripheral neuropathy.

(8) Participants who have an uncontrolled/active infection requiring systemic therapy.

(9) Participants who are unable to swallow intact tablets.

(10) Not Applicable.

(11a) Participants with active bleeding. Specifically, clinically significant GI bleeding, GI perforation, intra-abdominal abscess or fistula for 6 months prior to switch screening, haemoptysis or other signs of pulmonary haemorrhage for 3 months prior to switch screening. Clinically significant hematuria, cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.

(12) Lesions invading or encasing any major blood vessels.

(13) Participants with evidence of an acute intracranial or intratumoral haemorrhage on CT or MRI

(14a) Participants with uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

(a) Cardiovascular disorders:

Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias. Uncontrolled hypertension defined as sustained BP >140 mm Hg systolic or >90 mm Hg diastolic or BP >the 95th percentile for age, height, and gender for pediatric participants <18 years old, despite optimal antihypertensive treatment. Stroke (including TIA), MI, or other ischemic event, or thromboembolic event (e.g., DVT, PE) within 6 months before first dose of switch study intervention.

- Corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms within 28 days before switch. Note: If a single ECG shows a QTcF with an absolute value >500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these 3 consecutive results for QTcF will be used to determine eligibility.

(b) GI disorders including those associated with a high risk of perforation or fistula formation: The participant has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g., Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose of switch study intervention. Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose of study treatment. Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of switch study intervention.

(c) Other clinically significant disorders such as:

i. bone fracture within 28 days prior to switch.

ii. history of solid organ transplantation.

iii. concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of switch study intervention.

(d) Participants with a diagnosis of incidental, subsegmental PE or DVT within 6 months are allowed if stable, asymptomatic, and treated with a stable dose of permitted anticoagulation for at least 1 week before first dose of switch study intervention.

(e) Participants who have had significant traumatic injury within 28 days prior the switch are not eligible.

(f) Participants with any medical or surgical conditions that would interfere with GI absorption of the study intervention are not eligible.

(g) Other clinically significant disorders that would preclude safe study participation and preclude participants from receiving cabozantinib.

(h) Serious non-healing wound/ulcer/bone fracture.

(i) Moderate to severe hepatic impairment (Child-Pugh B or C).

(15a) Previously identified allergy or hypersensitivity to components of the study intervention formulations.

(16) Not applicable

Prior/Concomitant Therapy

(17a) Radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before first dose of study treatment. Systemic treatment with radionuclides within 6 weeks before first dose of switch study intervention. Participants with clinically relevant ongoing complications from prior radiation therapy are not eligible.

(18) Growth factor(s): Growth factors that support white cell number or function must not have been administered within the 7 days prior to switch (14 days if pegfilgrastim).

(19) Corticosteroids: Participants requiring corticosteroids who have not been on a stable or decreasing dose of corticosteroid for the 7 days prior to switch are not eligible (not applicable for participants with brain metastasis). If used to modify immune AEs related to prior therapy, ≥14 days must have elapsed since last dose of corticosteroid.

(20b) Investigational Drugs: Participants who are currently receiving another investigational drug or who participated in any other clinical trial involving an investigational study treatment with the last administration of treatment within the last 28 days (4 weeks), or 5 half-lives (whichever is longer) prior to first dose of switch study intervention are not eligible.

(21) Anti-cancer Agents: Participants who are currently receiving other anticancer agents are not eligible.

(22) Participants who are receiving cyclosporine, tacrolimus, or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial.

(23b) CYP3A4 active agents: Participants must not be receiving any of the following potent CYP3A4 inducers or inhibitors: erythromycin, clarithromycin, ketoconazole, azithromycin, itraconazole, grapefruit juice or St. John's wort. A list of other known CYP3A4 inducers and inhibitors that should be discontinued prior to initiation of switch study intervention and should be avoided during study intervention if reasonable alternatives exist is provided in Appendix 10.12.

(24a) Concomitant anticoagulation with oral anticoagulants including, but not limited to, platelet inhibitors (eg, clopidogrel or ticagrelor), warfarin, dabigatran, and betrixaban, except for those specified below.

- Allowed anticoagulants are:

  (a) Prophylactic use of low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH)

(b) Therapeutic doses of LMWH or the direct factor Xa inhibitors rivaroxaban, or edoxaban in participants without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before switch and without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

(25) Enzyme-inducing Anticonvulsants: Participants must not have received enzyme inducing anticonvulsants within 14 days prior to switch.

(26) QTc Agents: Participants who are receiving drugs that prolong QTc are not eligible.

Other Exclusions

(27) Pregnancy or breast-feeding.

Pregnant or breast-feeding women will not be entered on this study (see also Appendix 10.4).

(28) Participants who in the opinion of the investigator may not be able to comply with the requirements of the study are not eligible.

(29) Major surgery (eg, orthopaedic surgery, removal or biopsy of brain metastasis) within 8 weeks before switch. Complete wound healing from major surgery must have occurred 4 weeks before switch and from minor surgery (eg, simple excision, tooth extraction) at least 10 days before switch. Participants with clinically relevant ongoing complications from prior surgery are not eligible.

(30) Participants who have received any local anticancer therapy including radiofrequency ablation (RFA), microwave thermal ablation (MWA) or cryotherapy within 28 days prior to switch.

10.15 Appendix: Process for the Assessment of Palatability and Acceptability and the Facial Hedonic Scale

Process for the Assessment Adapted from Thompson et al 2015

Step 1. Assessment of palatability using cabozantinib tablet

- Day 1, time=1 minute, palate is cleansed with a glass of water
- Day 1, time=5 minutes, participant is dosed with test dosage form and a glass of water
- Day 1, time=6 minutes, participant identifies appropriate facial hedonic, with the use of verbal cues only if the participant is unable to make an immediate correlation
- Day 1, time=6 minutes, participant makes a selection on the 100-point visual analog scale that most closely aligns with their assessment of palatability
- Day 1, time=7 minutes, palate is cleansed with a glass of water

Step 2. Evaluation of AEs related to cabozantinib tablet intake

- Day 1, time=9 minutes, participant is evaluated for AEs

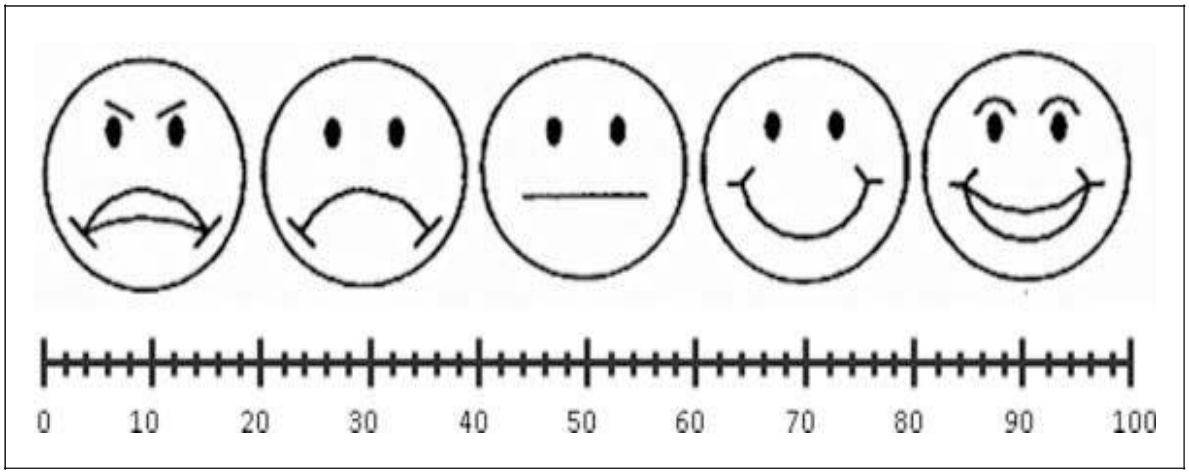
Step 3. Participant release

- Day 1, time=15 minutes, participant is released with follow-up paperwork to be completed

Step 4. Participant follow-up

- Day 3, participant is contacted by study investigator/support staff to ensure return of AE form and assess overall participant well-being

Facial Hedonic Scale



Five-point facial hedonic scale with a correlated 100-point visual analog scale (FHS/VAS-5) for use in children aged 4 to 18 years (Thompson et al 2015).

10.16 Appendix: Performance Scales

Performance Status Criteria

ECOG		Karnofsky		Lansky[a]	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs, or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort, some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of, and less time spent in, active play.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most of his/her personal needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
		30	Severely disabled, hospital admission is indicated, although death not imminent.	30	In bed, needs assistance even for quiet play.
	Completely disabled. Cannot carry on any selfcare. Totally confined to a bed or chair.	20	Very sick, hospital admission necessary; active supportive treatment necessary ..	20	Often sleeping, play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.
5	Dead	0	Dead	0	unresponsive

ECOG= Eastern Cooperative Oncology Group

a Lansky Play-Performance Scale for Children (LPPS)©

Source: CIBTMR (Karnofsky/Lansky Performance Status (docplayer.net)

10.17 Appendix: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.17.1 Amendment 3: (26 September 2024)

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
1.1 Synopsis (Independent Data Monitoring Committee)	An Independent Data Monitoring Committee (IDMC) will be established to monitor the safety of the study on a regular basis.	An Independent Data Monitoring Committee (IDMC) will be established to monitor the safety of the study on a regular basis **and review the results of the interim analysis**.	To fully reflect the role of the IDMC
1.3 Schedule of Activities (Table 1)	12-lead ECG: Screening: X (<~~14~~ days)	12-lead ECG: Screening: X (<7 days)	Revised to align with the corresponding footnote 'h'
1.3 Schedule of Activities (Table 1)	Footnotes: (b)…..After EOSI, 6-monthly height assessments will be performed. For adult participants, height will be measured at baseline and weight on D1 (<7 days for C1) of each cycle.	(b)…. **Height and weight need not be repeated at C1D1 if therapy starts within 7 days of obtaining these data. Height, weight and BMI (including height, weight and BMI percentiles for pediatric participants) will be measured and recorded.** After EOSI, 6-monthly height assessments will be performed. For adult participants, height will be measured at baseline and weight on D1 (<7 days for C1) of each cycle.	To improve clarity
	(c) β-HCG in serum at screening ~~and within 7 days prior to randomization~~ and in serum or urine after first dose of study intervention for females of childbearing potential. Female participants of childbearing potential require a negative pregnancy test prior to the start of each cycle.	(c) β-HCG in serum at screening and in serum or urine after first dose of study intervention for females of childbearing potential. Female participants of childbearing potential require a negative pregnancy test prior to the start of each cycle. **β-HCG in serum need not be repeated at C1D1 if performed within 7 days of randomization.**	
	(e)…. If participants have Grade 4 neutropenia, then CBC should be checked at least every other day. If participants develop Grade 4 thrombocytopenia, then CBC should be checked every 3 to 4 days.	(e)…… If participants have Grade 4 neutropenia, then CBC should be checked at least every other day **or at the investigator's discretion.** If participants develop Grade 4 thrombocytopenia, then CBC should be checked every 3 to 4 days **or at investigator's discretion**.	

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
	(f) TSH: Participants who enter the study on thyroid replacement should have their medication adjusted to maintain TSH in the normal range.	(f) TSH: **If TSH results are within the normal range, repeat testing at mid-cycle on C1D15, C2D15, and C3D15 is not required. However, if TSH levels are abnormal, thorough monitoring of TSH, T3, and T4 should be performed in accordance with the schedule of assessments, including mid-cycle evaluations, to ensure timely detection and management of any thyroid-related issues.** Participants who enter the study on thyroid replacement should have their medication adjusted to maintain TSH in the normal range.	
	(m) Tumor material should be collected at screening as optional fresh biopsy where feasible, at ~~the PI~~ discretion. Otherwise, the most recent archival tumor material can be collected.	(m) The most recent archival tumor material can be collected. Otherwise, tumor material should be collected at screening as optional fresh biopsy where feasible, at **investigator** discretion.	
	(n) Blood samples will be obtained pre-dose at the specified timepoints in the SoA.	(n) Blood samples will be obtained pre-dose at the specified timepoints in the SoA. **ctDNA genomic assessment is based on consent and is optional for some study participants.**	
	(s)… blood samples will be obtained at the following time points: C1D1 prior to first dose (baseline) and 4h post-dose and C2D1 pre-dose and 4h post-dose.	(s)… blood samples will be obtained at the following time points: C1D1 prior to first dose (baseline) and 4h post-dose and C2D1 pre-dose and 4h post-dose. **At Cycle 2, if no dose is planned to be taken based on dosing nomogram, samples must be taken 4 hours apart only.**	
1.3 Schedule of Activities (Table 2)	Switch screening (before switch)	Switch screening (**up to 28 days** before switch)	To add a window for the screening visit at switch

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
	Footnotes: (c)…. After EOSI, 6-monthly height assessment will be performed. For adult participants height will be measured at baseline and weight on D1 (<7 days for C1) of each cycle.	(c)…. **Height and weight need not be repeated at C1D1 if therapy starts within 7 days of obtaining these data. Height, weight and BMI (including height, weight and BMI percentiles for pediatric participants) will be measured and recorded**. After EOSI, 6-monthly height assessment will be performed. For adult participants height will be measured at baseline and weight on D1 (<7 days for C1) of each cycle.	To improve clarity
	(f)…. Additional safety assessments should be performed if clinically needed.	(f)…. **CBC, differential, platelets, albumin, alkaline phosphatase, AST, ALT, bicarbonate, urea/blood urea nitrogen, calcium, chloride, creatinine, γ-glutamyl transferase, glucose, lactate dehydrogenase, magnesium, phosphate, potassium, sodium, total bilirubin, direct bilirubin, total protein, urinalysis, amylase, lipase, prothrombin/INR/PTT, TSH.** Additional safety assessments should be performed if clinically needed. **If TSH results are within the normal range, repeat testing at mid-cycle on C1D15, C2D15, and C3D15 is not required. However, if TSH levels are abnormal, thorough monitoring of TSH, T3, and T4 should be performed in accordance with the schedule of assessments, including mid-cycle evaluations, to ensure timely detection and management of any thyroid-related issues.**	
	(i)…. C1D1 prior to first dose (baseline) and 4h post-dose, and C2D1 pre-dose and 4h post dose.	(i)…. C1D1 prior to first dose (baseline) and 4h post-dose, and C2D1 pre-dose and 4h post dose. **At Cycle 2, if no dose is planned to be taken based on dosing nomogram, samples must be taken 4 hours apart only**.	

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
	(j)… After EOSI, only SAEs (including deaths) that are attributed (~~possibly, probably, or definitely~~) to cabozantinib must be reported and followed-up until resolution or stabilization.	(j)… After EOSI, only SAEs (including deaths) that are attributed (**related**) to cabozantinib must be reported and followed-up until resolution or stabilization.	
2.3.1 Risk Assessment	Potential risks include: • Renal failure • Hepatoxicity • Embryotoxicity	Potential risks include: • Renal failure • Hepatotoxicity • Embryotoxicity **(male and female participants should seek medical advice and consider fertility preservation before starting treatment; refer to Appendix 10.7)**	Updated to include advice on gamete preservation based on Health Authority feedback
4.1 Overall Design 1.1 Synopsis Table 5	…..until tumor progression, unacceptable toxicity, participant request, investigator's decision or study termination.	……until tumor progression, unacceptable toxicity, participant request, investigator's decision or study termination, **whichever occurs first.**	To improve clarity
5.1 Inclusion Criteria	10. - Transfusions are permitted to meet both the platelet and haemoglobin criteria if the transfusion is more than 7 days before ~~randomization~~.	10**b**. - Transfusions are permitted to meet both the platelet and haemoglobin criteria if the transfusion is more than 7 days before **screening laboratory sample collection.**	To improve clarity
5.1 Inclusion Criteria 10.14.1 Inclusion Criteria	10. - Alanine transaminase (ALT)~~/~~aspartate transaminase (AST) ≤3 × ULN in the absence of liver metastases or both ≤5.0 × ULN in the presence of liver metastases.	- Alanine transaminase (ALT) **and** aspartate transaminase (AST) ≤3 × ULN in the absence of liver metastases or both ≤5.0 × ULN in the presence of liver metastases.	

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
5.1 Inclusion Criteria 10.14.1 Inclusion Criteria	Sex and Contraception/Barrier Requirements 15. Contraception ~~and barriers as well as pregnancy testing is required~~ as appropriate for their age and sexual activity of ~~pediatric participants~~ and as required by local regulations (see also Appendix 10.4)	Sex and Contraception/Barrier Requirements 15**a. Sexually active fertile participants and their partners must agree to use highly effective** contraception as appropriate for their age and sexual activity, **in combination with one acceptable barrier method,** and as required by local regulations **during the course of the study and for 4 months after the last dose of study intervention. Pregnancy testing is required as appropriate for the age and sexual activity of female participants and as required by local regulations during the course of the study** (see Appendix 10.4)**.**	Clarify contraception requirement based on Health Authority request
5.2 Exclusion Criteria 10.14.2 Exclusion Criteria	24 (b) Therapeutic doses of LMWH or the direct factor Xa inhibitors rivaroxaban, or edoxaban, ~~or apixaban~~ in participants without known brain metastases…..	24**a** (b) Therapeutic doses of LMWH or the direct factor Xa inhibitors rivaroxaban, or edoxaban in participants without known brain metastases…..	Removed for better alignment with guidance in the Investigator's Brochure
6.9.1 Permitted During Study	- Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban ~~or apixaban~~, are allowed in participants without known brain metastases	- Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, or edoxaban, are allowed in participants without known brain metastases	Removed for better alignment with guidance in the Investigator's Brochure
6.9.2 Prohibited or Restricted Therapies	The following therapies are prohibited while the participant is ~~on cabozantinib treatment~~: • Any other local ~~therapy such as~~ surgery, ablation, or embolization.	The following therapies are prohibited while the participant is **receiving study intervention**: • Any other local **treatment including** surgery, ablation, or embolization **or radiation (except as reported below for palliative external radiation for pain management)**.	To improve clarity

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
	• Any coumarin agents (e.g. warfarin), direct thrombin inhibitor dabigatran, direct Factor Xa inhibitors ~~**betrixaban**~~ or platelet inhibitors (e.g. clopidogrel);	• **For participants on cabozantinib treatment,** any coumarin agents (e.g. warfarin), direct thrombin inhibitor **including but not limited to** dabigatran, platelet inhibitors (e.g. clopidogrel) or direct Factor Xa inhibitors **except rivaroxaban, or edoxaban (see Section 5.2, Section 6.9.1 and Section 10.14.2**)	
		The following therapies should be avoided while the participant is **receiving study intervention:** • **Palliative external radiation for pain management** should not be performed while on study except if it is clinically unavoidable **and after exclusion of disease progression as per RECIST 1.1**. Participants who have such an intervention may be considered not evaluable on and after receiving radiation (and may be assigned a censoring or progression date) for certain efficacy endpoints; **if clinically unavoidable the investigator should consult the sponsor prior to the procedure for safety guidance.**	

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
	The following therapies should be avoided while the participant is ~~on cabozantinib treatment~~: • ~~Palliative external radiation to bone metastasis for bone pain should not be performed while on study except if it is clinically unavoidable. Participants who have such an intervention may be considered not evaluable on and after receiving radiation (and may be assigned a censoring or progression date) for certain efficacy endpoints~~;		

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
6.9.2 Prohibited or Restricted Therapies	• Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended; • Caution must be used when discontinuing study intervention with a strong CYP3A4 inducer in a participant who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib; • Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g. ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations and should be avoided;	• Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended **(refer to Appendix 10.12)**; • Caution must be used when discontinuing study intervention with a strong CYP3A4 inducer in a participant who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib **(refer to Appendix 10.12)**; • Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g. ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations and should be avoided **(refer to Appendix 10.12)**;	Added reference to list of substrates, inducers, and inhibitors of selected CYP450 isozymes, based on Health Authority request

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
7.2 Participant Discontinuation/ Withdrawal from the Study	Participants ~~to~~ the optional research biobanking ~~programme~~ have the right to withdraw their consent at any time and for any reason during the study or during the period of sample storage (i.e. The entire 15 years during which samples are kept).	Participants **in** the optional research biobanking have the right to withdraw their consent at any time and for any reason during the study or during the period of sample storage (i.e. The entire 15 years during which samples are kept).	Updated in response to Health Authority feedback
8 Study Assessments and Procedures	• The maximum amount of blood collected from each participant per day will be ~~19~~ mL and maximum per cycle will be ~~43~~ mL….. If the total ~~drawn~~ blood volume exceeds the limits established by the clinical site for paediatric subjects, then priority ~~will~~ be given to the key safety laboratory tests.	• The maximum amount of blood collected from each participant per day will be **approximately 36** mL and maximum per cycle will be **approximately 55** mL….. If the total **required** blood volume **would** exceed the limits established by the clinical site for paediatric subjects, then priority **should** be given to the key safety laboratory tests.	To provide maximum amount for all participants, not just paediatric participants
8.2.1 Tumor Assessments	All radiographic tumor assessments (both scheduled and unscheduled) will be sent to the BIRC, which also will review prior radiation history data for the purpose of selection of target lesions.	All radiographic tumor assessments (both scheduled and unscheduled) will be sent to the BIRC, which also will review prior radiation history data for the purpose of selection of target lesions. **Independent oncologists will be part of BIRC to assist assessment of clinical information to be evaluated along with radiology images.**	To provide more context on the composition of the BIRC
Section 8.3.1 Physical Examinations	• A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems.	• A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. **Height, weight and BMI (including height, weight and BMI percentiles for pediatric participants) will be measured and recorded**.	To improve clarity
8.3.3 Electrocardiograms	• ECGs will be ~~interpreted~~ and signed and dated by the investigator or designee.	• ECGs will be **reviewed** and signed and dated by the investigator or designee.	Revised for clarity

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
8.3.6 Pregnancy Testing	Female participants of childbearing potential require a negative pregnancy test prior to the start of each cycle; see Section 1.3 (SoA) ……. ~~Female participants of childbearing potential require a negative pregnancy test prior to the start of each cycle;~~ sexually active participants must use an acceptable method of birth control.	Female participants of childbearing potential require a negative pregnancy test prior to the start of each cycle; see Section 1.3 (SoA) Sexually active participants must use an acceptable method of birth control.	Deleted redundant text
8.6 Pharmacodynamics	(b) One 10 mL blood sample to investigate pharmacodynamic biomarkers in circulating tumor DNA (ctDNA)/RNA.	(b) One 10 mL blood sample to investigate pharmacodynamic biomarkers in circulating tumor DNA (ctDNA)/RNA. **ctDNA genomic assessment is based on consent and is optional for some study participants.**	To improve clarity
8.8 Biomarkers	• Any residual samples may be retained for future research ~~programmes~~.	• Any residual samples may be retained for future research.	Updated in response to Health Authority feedback
9.5 Interim Analyses	…. It will be performed by the IDMC, consisting of 2 clinicians and 1 statistician who are independent experts not otherwise involved in the study when at least 20 events have occurred.	…. It will be performed **by an independent statistical group who has no direct contact with study team. The interim analysis results will be reviewed** by the IDMC, consisting of 2 clinicians and 1 statistician who are independent experts not otherwise involved in the study when at least 20 events have occurred.	To clarify the role of the IDMC related to interim analyses
10.1.1. Regulatory and Ethical Considerations		• **Notifying immediately your site monitor or the contact(s) provided by the sponsor or designee of (suspected) serious breach.** • **In that perspective, a serious breach is a breach likely to affect to a significant degree the safety and rights of the participant or the reliability and robustness of the data generated in the clinical trial.**	Added in line with the protocol template

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
10.1.5.2 Blinded Independent Radiology Committee	The BIRC will comprise of board-certified radiologists who will determine radiographic response and progression following randomization.	The BIRC will comprise of board-certified radiologists who will determine radiographic response and progression following randomization. **Independent oncologists will be part of BIRC to assist assessment of clinical information to be evaluated along with radiology images.**	To clarify that BIRC will include independent oncologists to assess clinical information alongside radiology images
10.2 Appendix: Clinical Laboratory Tests (Table 10)		Footnote: (d) **If TSH results are within the normal range, repeat testing at mid-cycle on C1D15, C2D15, and C3D15 is not required. However, if TSH levels are abnormal, thorough monitoring of TSH, T3, and T4 should be performed in accordance with the schedule of assessments, including mid-cycle evaluations, to ensure timely detection and management of any thyroid-related issues.**	To clarify TSH assessments
10.3.1 Definition of AE	• 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 unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.**~~	An AE is any untoward medical occurrence **(including an abnormal laboratory finding, symptom, or disease)** in a clinical study participant **to whom a medicinal product is administered and which does not necessarily have a causal relationship with the treatment**.	Health Authority requested change
10.3.2 Definition of SAE	(f) Other situations:	(f) Other **medically important** situations:	Revised for clarity

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
10.3.4 Reporting of SAEs	• The site will email the SAE paper form ~~or fax the cover sheet and SAE form~~ to the sponsor if the electronic data collection tool is unavailable.	• The site will **scan** and email the SAE paper form to the sponsor if the electronic data collection tool is unavailable.	Revised to reflect the process
10.4 Appendix: Contraceptive and Barrier Guidance		**In inclusion criterion 15a (Section 5.1), sexually active fertile participants and their partners must agree to use highly effective contraception as appropriate for their age and sexual activity, in combination with an additional acceptable barrier method, and as required by local regulations during the course of the study and for 4 months after the last dose of study intervention. Pregnancy testing is required as appropriate for the age and sexual activity of female participants and as required by local regulations during the course of the study.**	Clarify contraception requirement based on Health Authority request

10.4.2 Contraception Guidance		**Contraception Guidance for WOCBP** **One of the highly effective methods of contraception listed in the table below, in combination with an additional acceptable barrier method listed in the table below, is required during the course of the study and for 4 months after the last dose of study intervention. Local laws and regulations may require use of alternative and/or additional contraception methods.** **Contraception Guidance for Male Participants with Partners of Childbearing Potential** **Male participants with female partners of childbearing potential are eligible if they agree to the following during the course of the study and for 4 months after the last dose of study intervention.** • **Inform any and all partners of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.** • **Male participants are required to use a condom during the course of study and for 4 months after the last dose of study intervention.** • **Female partners of male participants in the study to consider use of effective methods of contraception during the course of study and for 4 months after the last dose of study intervention in the male participant.** **Male participants 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 penetration during the course of study and for 4 months after the last dose of study intervention. Refrain**	Clarify contraception requirement based on Health Authority request

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
		from donating sperm during the course of study and for 4 months after the last dose of study intervention.	
10.4.2 Appendix: Contraception and Guidance (Table: contraceptives allowed during the study…)	Table footnote: a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.	Table footnote: a) Contraceptive use by men or women **during the course of the study and for 4 months after the last dose of study intervention** should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.	Clarify contraception requirement based on Health Authority request
10.6 Appendix: Guidance for Specific AE Management and Dose Modifications (Table: Management of Hypertension Associated with Cabozantinib)	• ……Antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic. • Reduce study treatment by one dose level if optimal	• …... **If** antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic reduce study treatment by one dose level if optimal.	Revised for clarification
	Footnote a The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP >1~~5~~0 or diastolic BP >1~~0~~0 based on their clinical judgment and assessment of the individual subject.	Footnote a The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP >140 or diastolic BP >90 based on their clinical judgment and assessment of the individual subject.	Revised to correct BP values

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
10.7 Appendix: Study Risk Assessment Potential Risk: Embryotoxicity	Actions Ongoing studies: • Inclusion criteria: • sexually active fertile subjects and their partners must use contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 3 - 6 months (depending on protocol) after the last dose of study treatment. • female subjects of childbearing potential must not be pregnant at screening.	Actions **Before starting cabozantinib (as applicable):** **Male and female participants should be advised to seek medical advice and consider fertility preservation before starting treatment. The National Institute for Health and Care Excellence (NICE) recommend that doctors should offer sperm banking to any man having cancer treatment that may affect their fertility. Teenage boys who have been through puberty can also collect and store sperm; refer to Sperm collection and storage | Cancer Research UK** **For male participants, consider sperm cryopreservation for males and adolescent boys who are preparing for medical treatment with cabozantinib.** **For female participants who are preparing for medical treatment with cabozantinib, consider oocyte or embryo cryopreservation as appropriate to females of reproductive age (including adolescent girls). Refer to NICE guidance and Coping with losing your fertility for women | Cancer Research UK** Ongoing studies: • Inclusion criteria: • sexually active fertile **participants** and their partners must use contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 3 - 6 months (depending on protocol) after the last dose of study treatment. • female **participants** of childbearing potential must not be pregnant at screening.	Updated to include advice on gamete preservation based on Health Authority feedback

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
10.13 Appendix: Response Evaluation Criteria	*Lesions with prior local treatment* • Lesions situated in a previously irradiated area are not considered measurable	*Lesions with prior local treatment* Lesions situated in a previously irradiated area are not considered measurable, **unless lesion progressed after radiotherapy and prior to the last chemotherapy at screening and meeting measurable lesion definition.**	To improve clarity
	Cytology, Histology: …..when the measurable tumor has met criteria for response or SD will be considered malignant unless cytologically confirmed.	Cytology, Histology: …..when the measurable tumor has met criteria for response or SD will be considered malignant unless cytologically confirmed **negative**.	
10.14.1 Inclusion Criteria (Switch)	(7a)…. from the acute toxic effects of all prior anticancer therapy at ~~study entry~~, unless AEs…….	(**7b**)…. from the acute toxic effects of all prior anticancer therapy at **switch screening**, unless AEs…….	To clarify
	(10) - Transfusions are permitted to meet both the platelet and haemoglobin criteria if the transfusion is more than 7 days before switch.	(10**b**) - Transfusions are permitted to meet both the platelet and haemoglobin criteria if the transfusion is more than 7 days before switch **screening laboratory sample collection**	
10.14.2 Exclusion Criteria	(5) ~~Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery or major surgery e.g., removal or biopsy of brain metastasis) and stable for at least 4 weeks prior to randomization. Eligible participants must be neurologically asymptomatic and without systemic corticosteroid treatment at the time of randomization. Note: Participants with a known seizure disorder who are receiving non-enzyme inducing anticonvulsants and have well-controlled seizures on a stable dose of anti-convulsant may be enrolled. See Appendix 10.10 for a list of recommended non-enzyme inducing anticonvulsants~~.	(5) **'Deleted at Amendment 3' Not applicable**.	Not applicable

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
	(11)… Specifically, clinically significant GI bleeding, GI perforation, intra-abdominal abscess or fistula for 6 months prior to ~~enrollment~~, haemoptysis or other signs of pulmonary haemorrhage for 3 months prior to ~~enrolment~~.	(11**a**)… Specifically, clinically significant GI bleeding, GI perforation, intra-abdominal abscess or fistula for 6 months prior to **switch screening**, haemoptysis or other signs of pulmonary haemorrhage for 3 months prior to **switch screening**	To clarify
	(14) (a) Cardiovascular disorders: …… Stroke (including TIA), MI, or other ischemic event, or thromboembolic event (e.g., DVT, PE) within 6 months before first dose of study ~~treatment~~.	(14**a**) (a) Cardiovascular disorders: …… Stroke (including TIA), MI, or other ischemic event, or thromboembolic event (e.g., DVT, PE) within 6 months before first dose of **switch** study **intervention**.	
	(b)…. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose of study ~~treatment~~….. Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of study ~~therapy~~.	(b)…. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose of **switch** study **intervention**…. Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of **switch** study **intervention**.	
	(c) iii concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of study treatment.	(c) iii concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of **switch** study **intervention**.	
	(d)….., and treated with a stable dose of permitted anticoagulation for at least 1 week before first dose of study ~~treatment~~.	(d)….., and treated with a stable dose of permitted anticoagulation for at least 1 week before first dose of **switch** study **intervention**.	
	(f) Participants with any medical or surgical conditions that would interfere with GI absorption of the study ~~drug~~ are not eligible.	(f) Participants with any medical or surgical conditions that would interfere with GI absorption of the study **intervention** are not eligible.	
	(15) Previously identified allergy or hypersensitivity to components of the study treatments formulations.	(15**a** Previously identified allergy or hypersensitivity to components of the study **intervention** formulations	

Section	WAS (Version 3.0, 29 NOVEMBER 2023)	IS (Version 4.0, 26 SEPTEMBER 2024)	Rationale
	(17) Systemic treatment with radionuclides within 6 weeks before first dose of study ~~treatment~~	(17**a**) Systemic treatment with radionuclides within 6 weeks before first dose of **switch** study **intervention**	
	(20a)….. or 5 half-lives (whichever is longer) prior to first dose of study intervention are not eligible.	(20**b**)….. or 5 half-lives (whichever is longer) prior to first dose of **switch** study intervention are not eligible.	
	(23a) ….A list of other known CYP3A4 inducers and inhibitors that should be discontinued prior to initiation of ~~protocol therapy~~ and should be avoided during study ~~therapy~~ ……	(23**b**) ….A list of other known CYP3A4 inducers and inhibitors that should be discontinued prior to initiation of **switch study intervention** and should be avoided during study **intervention** ……	
10:16 Appendix: Performance Scales (Performance Status Criteria)	Lansky 70 Both greater restriction of, and less time spent in, ~~play activity~~. 0 ~~Dead~~	Lansky 70 Both greater restriction of, and less time spent in, **active play**. 0 **unresponsive** **[a] Lansky Play-Performance Scale for Children (LPPS)©**	Amended to align with source reference used in EDC
	Kanofsky 60 Requires occasional assistance but is able to care for most of his/her needs. 30 Severely disabled, ~~hospitalization~~ indicated. Death not imminent. 20 Very sick, ~~hospitalization indicated~~. ~~Death not imminent~~	Kanofsky 60 Requires occasional assistance but is able to care for most of his/her **personal** needs. 30 Severely disabled, **hospital admission is** indicated, **although** death not imminent. 20 Very sick, **hospital admission necessary**; **active supportive treatment necessary**.	

10.17.2 Amendment 2: (29 November 2023)

Section	WAS (Version 2.0, 07 NOVEMBER 2023)	IS (Version 3.0, 29 NOVEMBER 2023)	Rationale
1.1 Synopsis/4.1 Overall Design	…cabozantinib plus BSC versus BSC in children and AYA with unresectable residual osteosarcoma, who achieved PR or SD at the end of conventional chemotherapy, either in first line at diagnosis or after first relapse treated with chemotherapy.	…cabozantinib plus BSC versus BSC in children and AYA with unresectable residual osteosarcoma, who achieved PR or SD at the end of conventional chemotherapy, either in first line at diagnosis or after first relapse treated with chemotherapy. **Participants who have not received previous chemotherapy at the time of first relapse (who achieved surgical remission, or who were completely resected) are eligible at the time of the subsequent relapse if treated with chemotherapy.**	Clarify patient population
1.3 Schedule of Activities (SoA)	Follow-up for survival ~~Every 3 months ±14 days after the last dose~~ Each cycle=28 days (± 3 days)	Follow-up Each cycle=28 days (± 3 days[u]) (Table 1) **[u] This window also applies to each visit** (Table 2) **[m] This window also applies to each visit**	For clarity
4.1 Study Design/1.1 Synopsis		**Follow-up Period** **Participants will be followed until death, participant request to discontinue from follow-up, or until the last participant to enter survival Follow-up period has been followed for 1 year, or the Sponsor decides to discontinue collection of these data in the study whichever occurs first.**	Update to include information on the Follow-up period in a dedicated subsection
Schedule of Activities(Table 1 – Footnote d)	CBC, differential, platelets, albumin, alkaline phosphatase, AST, ALT, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, γ-glutamyl transferase, glucose, lactate dehydrogenase, ~~lipase~~, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, urinalysis, amylase, lipase, prothrombin/INR/PTT, TSH. Laboratory tests need not be repeated at C1D1 if therapy starts within seven (7) days of obtaining labs to assess eligibility.	CBC, differential, platelets, albumin, alkaline phosphatase, AST, ALT, bicarbonate, **urea**/blood urea nitrogen, calcium, chloride, creatinine, γ-glutamyl transferase, glucose, lactate dehydrogenase, magnesium, phosph**ate**, potassium, sodium, **direct bilirubin,** total bilirubin, total protein, urinalysis, amylase, lipase, prothrombin/INR/PTT, TSH. Laboratory tests need not be repeated at C1D1 if therapy starts within seven (7) days of obtaining labs to assess eligibility.	Addition and for clarity

Section	WAS (Version 2.0, 07 NOVEMBER 2023)	IS (Version 3.0, 29 NOVEMBER 2023)	Rationale
Schedule of Activities (Table 1 and Table 2)	X-ray growth plate. Prior to the start of study intervention in all participants ≤18 years of age at enrollment, ~~every 6 months until 1 year after last dose, and at any time until 1 year after last dose, and at any time as per clinical judgment.~~	X-ray growth plate. Prior to the start of study intervention in all participants ≤18 years of age at enrollment. **For participants with open growth plates, radiographs must be monitored during protocol therapy for growth plate toxicity every 6 months until 1 year after last dose, and at any time as per clinical judgment.**	Updates to clarify frequency of growth plate assessment
Schedule of Activities (Table 1)	The two most recent radiological evaluations (e.g. CT or MRI scan) including the one following completion of chemotherapy should be available later to facilitate BIRC review. ~~For participants with evaluable disease only (see Section 5.1) additional 7 days for the screening period will be allowed for BIRC eligibility confirmation.~~	The two most recent radiological evaluations (e.g. CT or MRI scan) including the one following completion of chemotherapy should be available later to facilitate BIRC review.	Minor updates for clarification
4.4 End of Study/Clinical Trial Definition	However, a participant could remain in the study longer if demonstrating treatment benefit. For information on access to study after study completion, see Section 6.7. Note, for participants who switch to the cabozantinib + BSC arm, the study completion…	However, a participant could remain in the study longer if demonstrating treatment benefit. For information on access to study **intervention** after study completion, see Section 6.7. Note, for participants who switch to the cabozantinib + BSC arm, the study **intervention** completion…	Minor updates for clarification and/or not considered applicable
5.2 Exclusion Criteria/10.14.2 Exclusion Criteria	~~6. History of Ifo-related Grade ≥3 nephrotoxicity or encephalopathy~~		Removed criterion as no longer considered applicable
5.2 Exclusion Criteria/10.14.2 Exclusion Criteria	14 (g) Other clinically significant disorders that would preclude safe study participation	14 (g) Other clinically significant disorders that would preclude safe study participation **and preclude participants from receiving cabozantinib**	For clarity
5.2 Exclusion Criteria/10.14.2 Exclusion Criteria	20. Investigational Drugs: Participants who are currently receiving another investigational drug ~~are not eligible~~	20**a**. Investigational Drugs: Participants who are currently receiving another investigational drug **or who participated in any other clinical trial involving an investigational study treatment with the last administration of treatment within the last 28 days (4 weeks), or 5 half-lives (whichever is longer) prior to first dose of study intervention are not eligible.**	Minor updates for clarification

Section	WAS (Version 2.0, 07 NOVEMBER 2023)	IS (Version 3.0, 29 NOVEMBER 2023)	Rationale
	23 prior to initiation of protocol therapy and should be avoided during study therapy if reasonable alternatives exist	23a prior to initiation of protocol therapy and should be avoided during study therapy if reasonable alternatives exist **is provided in Appendix 10.12**	For clarity
		30. Participants who have received any local anticancer therapy including RFA, MWA or cryotherapy within 28 days prior to randomization/switch.	Added new criterion
6.1.1 Study intervention(s) Administered (Table 4: Sourcing (Cabozantinib))	Provided centrally by the sponsor ~~or locally by the study site, subsidiary, or designee~~	Provided centrally by the sponsor	Updates to clarify that cabozantinib will be provided centrally by the sponsor
6.1.2 Timing of Cabozantinib Dose for Each Participant	Mosteller's equation will be used to calculate BSA. ~~If height is not available, the single Mosteh-type equation will be used (Akkawi El Edelbi et al 2021)~~	Mosteller's equation will be used to calculate BSA.	Deleted for clarification
6.9.1 Permitted During Study	Other Use of medication (e.g., Adderall™ or Ritalin™) is allowed for treatment of those participants with attention deficit hyperactivity disorder (ADHD) who are otherwise deemed eligible.	Other Use of medication (e.g., Adderall™ or Ritalin™) is allowed for treatment of those participants with attention deficit hyperactivity disorder (ADHD) who are otherwise deemed eligible. **Any potential additive, potentiation or antagonistic effects of the concomitant compounds when used together with cabozantinib should be considered by the investigator.**	Text added as a safety consideration.
6.9.3 Potential Interactions with Cabozantinib	…selected CYP450 isozyme pathways: ~~https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactionstable-substrates-inhibitors-and-inducers~~.	… selected CYP450 isozyme pathways: **Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers | FDA**	Clear reference added
8.3.2 Vital Signs	~~For height and weight measurements, the participant is allowed to wear indoor, daytime clothing with no shoes~~		Deleted as text is also included under physical examinations
8.3.3 Electrocardiograms	At each time point at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession, ~~but no more than 2 minutes apart~~.	At each time point at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession, **within 30 minutes but at least 3 minutes apart**.	Included to increase ECG window

Section	WAS (Version 2.0, 07 NOVEMBER 2023)	IS (Version 3.0, 29 NOVEMBER 2023)	Rationale
8.3.4 Tibial Radiographs	…linear growth will be determined at baseline based on a tibial X-ray for all participants ≤18 years of age, ~~and every 6 months until 1 year after last dose, and at any time as per clinical judgment as outlined in the SoA (Section 1.3)~~	linear growth will be determined at baseline based on a tibial X-ray for all participants ≤18 years of age. **For participants with open growth plates, radiographs must be monitored during protocol therapy for growth plate toxicity every 6 months until 1 year after last dose, and at any time as per clinical judgment, as outlined in the SoA (Section 1.3).**	Updates to clarify frequency of growth plate assessment
10.1.6 Dissemination of Clinical Trial Data	• Protocol information and (~~final/interim~~) study results will be made publicly available on the US website (www.clinicaltrials.gov) and for studies run in the EU/EEA on the ~~EU Clinical Trials Register (www.clinicaltrialsregister.eu) or~~ EU Clinical Trials Portal (https://euclinicaltrials.eu/home). The sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation. • A lay ~~language~~ protocol synopsis and a summary of the study will be made available on the EU Clinical Trials Portal (https://euclinicaltrials.eu/home) and~~/or~~ Sponsor website.	• Protocol information and study results will be made publicly available on the US website (www.clinicaltrials.gov) and for studies run in the EU/EEA on the EU Clinical Trials Portal (https://euclinicaltrials.eu/home). **Where applicable,** the sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation. • A lay protocol synopsis and a summary of the study will be made available on the EU Clinical Trials Portal (https://euclinicaltrials.eu/home) and **on the** Sponsor website **(https://www.ipsen.com/patients/lay-summaries/).**	For clarity

Section	WAS (Version 2.0, 07 NOVEMBER 2023)	IS (Version 3.0, 29 NOVEMBER 2023)	Rationale
10.2 Appendix: Clinical Laboratory Tests (Table 10)	Haematology (others) Clinical Chemistry (Alkaline phosphatase[b]) Urinalysis • pH, glucose, protein, blood, ketones, total bilirubin, urobilinogen, nitrite, leukocyte by dipstick • Microscopic examination (e.g. epithelial cells, bacteria, crystals, casts, WBC, RBC)	Haematology (~~others~~) Clinical Chemistry (**Total** Alkaline phosphatase, **Magnesium**) Urinalysis • pH, **specific gravity**, glucose, protein, blood, ketones, ~~total~~ bilirubin or urobilinogen, nitrite, leukocyte **esterase** by dipstick **or routine** • Microscopic examination (e.g. epithelial cells, bacteria, crystals, casts, WBC, RBC) as clinically indicated	Assessments added; others clarified
	~~b If alkaline phosphatase is elevated, consider fractionating.~~		Not relevant
10.2 Appendix: Clinical Laboratory Tests	Abnormalities in any clinical laboratory test (including tests not required per protocol), that leads to a change in participant management (eg, dose interrupted or reduced, treatment discontinued, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and should be reported as AEs	Abnormalities in any clinical laboratory test (including tests not required per protocol), that leads to a change in participant management (eg, dose interrupted or reduced, treatment discontinued, requirement for additional medication or monitoring) **or suggest a disease and/or organ toxicity that is new or has worsened from baseline** are considered clinically significant for the purposes of this study and should be reported as AEs	Added for clarity
10.6 Appendix: Guidance for Specific AE Management and Dose Modifications General (Table 11 - Diarrhea)	Initiate treatment with an antidiarrheal agent (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea (maximum: 16 mg loperamide per day))	Initiate treatment with an antidiarrheal agent (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea (maximum: 16 mg loperamide per day)). **For participants below 12 years of age, please follow the standard local clinical practice and appropriate clinical guidelines.**	Corrections and additions to provide clear guidance
	Intake of isotonic fluids ~~(1 1.5L/day)~~ as appropriate	Intake of isotonic fluids as appropriate	
	Administer fluids ~~(1 1.5L/day)~~ orally or intravenously, as appropriate) for hydration or to correct electrolyte abnormalities.	Administer fluids orally or intravenously, as appropriate) for hydration or to correct electrolyte abnormalities.	

Section	WAS (Version 2.0, 07 NOVEMBER 2023)	IS (Version 3.0, 29 NOVEMBER 2023)	Rationale
	Consider starting second line antidiarrheal or referral to gastroenterologist.	Consider starting second line antidiarrheal or referral to gastroenterologist. **For participants below 12 years of age, please follow the standard local clinical practice and appropriate clinical guidelines.**	
10.6 Appendix: Guidance for Specific AE Management and Dose Modifications General (Hypertension)	The table below provides treatment guidelines for hypertension deemed related to cabozantinib ~~in~~ adults and ~~adolescents~~.	The table below provides treatment guidelines for hypertension deemed related to cabozantinib **for** adults and **paediatric participants.**	Corrections and additions to provide clear guidance
	>1~~5~~0 mm Hg (systolic)a and <160 mm Hg OR >~~10~~0 mm Hg (diastolic) and <1~~1~~0 mm Hg	>140 mm Hg (systolic)a and <160 mm Hg OR >90 mm Hg (diastolic) and <**100** mm Hg	
	If subject is symptomatic interrupt study treatment	If subject is symptomatic interrupt study treatment **and only restart once symptoms have resolved and BP is < 140 mm Hg systolic and < 90 mm Hg diastolic.**	
	≥160 mm Hg (systolic) OR	≥160 mm Hg (systolic) OR **≥ 100 mm Hg (diastolic)**	Added missing text
	Re-start study treatment at ~~the most tolerable dose and re-escalate only if BP falls to and is sustained at <150 mm Hg systolic and <100 mm Hg diastolic~~	Re-start study treatment at **a reduced dose**.	Corrections to align guidance with the Investigator's brochure
	Discontinue study treatment	Discontinue study treatment **Initiate appropriate medical management**	
10.6 Appendix: Guidance for Specific AE Management and Dose Modifications General (QTc Prolongation)	If at any time on study there is an increase in QTcF to an absolute value >500 ms, 2 additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG	If at any time on study there is an increase in QTcF to an absolute value >500 ms **or an increase of >60 ms above baseline**, 2 additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG	
10.7 Appendix: Study Risk Assessment (Growth Plate Widening)	Investigator Brochure: In subjects with growth plate changes, the benefits and risks of continuing treatment with cabozantinib should be evaluated in an individualized manner.	Investigator Brochure: In subjects with **evidence of growth plate thickening or other changes, a knee MRI without contrast may be needed as indicated clinically**. **In subjects with** growth plate changes, the benefits and risks of continuing treatment with cabozantinib should be evaluated in an individualized manner.	
10.14.1 Inclusion Criteria	7 …of all prior anticancer therapy ~~before switch~~, unless AEs are clinically nonsignificant and/or stable on supportive therapy, per investigator clinical judgment	7a … of all prior anticancer therapy **at study entry**, unless AEs are clinically nonsignificant and/or stable on supportive therapy, per investigator clinical judgment	Correction

Section	WAS (Version 2.0, 07 NOVEMBER 2023)	IS (Version 3.0, 29 NOVEMBER 2023)	Rationale
10.14.2 Exclusion Criteria	14. (g) Other clinically significant disorders that would preclude safe study participation.	13. (g) Other clinically significant disorders that would preclude safe study participation and preclude participants receiving cabozantinib.	Added for clarity
10.16 Appendix: Performance Scales	Karnofsky and ECOG Scales Karnofsky and Lansky Scales	Performance Status Criteria (ECOG, Karnofsky and Lansky)	Tables replaced with one that calibrates across the 3 scales

10.17.3 Amendment 1: (07 November 2023)

Section	WAS (Version 1.0, 25 SEPTEMBER 2023)	IS (Version 2.0, 07 NOVEMBER 2023)	Rationale
6.1 Study Interventions	Study personnel should review dose administration requirements with the participant, as appropriate, and with the delegated caregiver(s) before administration and throughout the study as necessary.	Study personnel should review dose administration requirements with the participant, as appropriate, and with the delegated caregiver(s) before administration and throughout the study as necessary. **Cabozantinib tablets and cabozantinib capsules are not bioequivalent and should not be used interchangeably.**	Health Authority requested change
6.9.3 Potential Interactions with Cabozantinib	Multidrug resistance-associated protein 2 (MRP2) inhibitors: In vitro data demonstrate that cabozantinib is a substrate of MRP2. Therefore, administration of MRP2 inhibitors may lead to increased plasma concentration of cabozantinib.	Multidrug resistance-associated protein 2 (MRP2) inhibitors: In vitro data demonstrate that cabozantinib is a substrate of MRP2. Therefore, administration of MRP2 inhibitors may lead to increased plasma concentration of cabozantinib. **Use caution and monitor adverse events when MRP2 inhibitors are co administered with cabozantinib.**	Health Authority requested change
	Participants should be cautioned regarding taking a P-glycoprotein substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib.	Participants should be cautioned regarding taking a P-glycoprotein substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib. **Monitoring of adverse events when P-gp substrates are co-administered with cabozantinib is recommended.**	Health Authority requested change

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