Amsterdam, 23 February 2023
EMA/CHMP/68009/2023
Committee for Medicinal Products for Human Use (CHMP)

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

Cometriq
Cabometyx

International non-proprietary name: cabozantinib

Procedure no.: EMA/H/C/002640/P46
EMA/H/C/004163/P46

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	23 May 2022	23 May 2022	☐
☐	CHMP Rapporteur Assessment Report	27 Jun 2022	28 Jun 2022	☐
☐	CHMP members comments	11 Jul 2022	11 Jul 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	14 Jul 2022	15 Jul 2022	☐
☐	CHMP adoption of conclusions:	21 Jul 2022	21 Jul 2022	☐
☐	Submission	24 Jan 2023	24 Jan 2023	☐
☐	Re-start	25 Jan 2023	25 Jan 2023	☐
☐	CHMP Rapporteur Assessment Report	08 Feb 2023	09 Feb 2023	☐
☐	CHMP members comments	13 Feb 2023	13 Feb 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	16 Feb 2023	16 Feb 2023	☐
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1. Introduction

On 22 April 2022 the MAH submitted a completed paediatric study for Cabozantinib, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

In this report the data from study ADVL1622 for Cometriq® (cabozantinib 20 mg, 80 mg hard capsules) and Cabometyx® (cabozantinib 20 mg, 40 mg and 60 mg film-coated tablets) is assessed.

ADVL1622, study 7 of the PIP (EMEA-001143-PIP01-11), is an open label two-stage phase 2 trial. The study includes cohorts of different tumour types i.e. Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) cohort, osteosarcoma, Wilms tumour and a rare solid tumour cohort including patients with metastatic medullary thyroid carcinoma (MTC), advanced renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), hepatoblastoma, adrenocortical carcinoma and other paediatric solid tumours (including central nervous system (CNS) tumours) with known molecular alterations in the targets of cabozantinib.

The MAH does not apply for a paediatric indication nor proposes to modify the SmPC within this procedure. Limited information on paediatric use of Cabometyx is included in section 5.2 of the SmPC based on the results of study ADVL1211 assessed during the P46 procedure EMEA/H/C/002640/II/036.

Cabozantinib is a small-molecule inhibitor of multiple tyrosine kinases including the hepatocyte growth factor (HGF) receptor protein (MET), vascular endothelial growth factor receptor 2 (VEGFR2), the GAS 6 receptor (AXL) and rearranged during transfection (RET). MET and its ligand hepatocyte growth factor (HGF) have been shown to be deregulated in many human cancers and correlate with poor prognosis. The tyrosine kinases inhibited by cabozantinib are potential therapeutic targets in many paediatric and adult solid tumours. Preclinical in vivo studies have shown that cabozantinib inhibits these kinases resulting in decreased tumour and endothelial cell proliferation, increased apoptosis, tumour growth inhibition, and tumour regression. In the Children's Oncology Group (COG)/pilot consortium paediatric phase 1 trial of cabozantinib, ADVL1211 (study 4 of cabozantinib Paediatric Investigation Plan (PIP)), partial responses (PRs) and prolonged disease stabilization were observed in several solid tumours at doses that were tolerable, in patients aged $\geqslant$ 2 years and $\leqslant$ 18 years. Study ADVL1622 assessed the activity of cabozantinib in selected paediatric solid tumours based on results of ADVL1211.

<u>Current indication</u>

The currently approved indications are:

Cabometyx (20, 40, 60 mg film-coated tablets):

Renal cell carcinoma (RCC)

Cabometyx is indicated as monotherapy for advanced renal cell carcinoma

- As first-line treatment of adult patients with intermediate or poor risk,
- In adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

Cabometyx, in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults

Hepatocellular carcinoma (HCC)

Cabometyx is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib

Differentiated thyroid carcinoma (DTC)

Cabometyx is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

Cometriq (20, 80 mg hard capsules):

Cometriq is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

For patients in whom rearranged during transfection (RET) mutation status is not known or is negative a possible lower benefit should be taken into account. For patients in whom rearranged during transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in section 5.1)"

Extract from Current posology

Cabometyx (20, 40, 60 mg film-coated tablets):

For RCC, HCC and DTC, the recommended dose of Cabometyx is 60 mg once daily.
The recommended dose of Cabometyx in combination with nivolumab in first line advanced RCC, is 40 mg once daily. Nivolumab should be administered intravenously at either 240 mg every 2 weeks or 480 mg every 4 weeks.

Cometriq (20, 80 mg hard capsules):

The recommended dose of Cometriq is 140 mg once daily, taken as one 80 mg orange capsule and three 20 mg grey capsules.

Currently the safety and efficacy of cabozantinib in children and adolescents aged <18 years have not yet been established. Available data for Cabometyx are included in section 5.2 of the SmPC.

2.2. Information on the pharmaceutical formulation used in the study

The tablet formulations of Cabometyx (cabozantinib 20 mg and 60 mg film-coated tablets) were used in the ADVL1622 study.

2.3. Clinical aspects

2.3.1. Introduction

This report concerns the Article 46 submission of study ADVL1622 for Cometriq and Cabometyx. No extension of the indication is applied, also no modifications of the SmPC are proposed.

ADVL1622

Study ADVL1622 is an intergroup study involving five participating organizations namely the COG, Alliance for Clinical Trials in Oncology, Eastern Cooperative Oncology Group (ECOG)-ACRIN cancer Research Group, NRG Oncology and SWOG Cancer Research Network. The study was performed as a multicentre study in the USA. Of the 186 sites initiated, 53 sites recruited at least one patient.

ADVL1622 is a multicentre, open label two stage phase 2 trial to assess the activity of cabozantinib in selected paediatric solid tumours. The study includes the following solid tumour strata; Ewing sarcoma, rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), osteosarcoma, Wilms tumour and other rare solid tumours. Cabozantinib was administered orally once daily in tablet strength of 20 mg and 60 mg, on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram). Patients were ≥2 and ≤30 years of age at the time of study entry for all strata, except for the MTC, RCC and HCC strata for which the upper age limit was 18 years.

Primary objectives of the study were**:**

- To determine the objective response rate (ORR; complete response (CR)+ partial response (PR)) of cabozantinib in children and young adults in the following disease strata;
    - Ewing sarcoma
    - RMS
    - NRSTS including microphthalmia, transcription factor associated soft tissue sarcomas (alveolar soft part sarcoma (ASPS) and clear cell sarcoma (CCS))
    - Wilms tumour (non-statistical cohort)
    - Rare tumours (non-statistical cohort)
        - MTC
        - RCC
        - HCC
        - Hepatoblastoma
        - Adrenocortical carcinoma
        - Paediatric solid tumours (including central nervous system (CNS) tumours) with known molecular alterations in the targets of cabozantinib (i.e. MET amplification, overexpression, activating mutation, MET translocation, MET exon skipping mutations, activating RET mutations, RET rearrangement, overexpression or activation of AXL).

- To estimate whether cabozantinib therapy either improves the disease control rate (DCR) at 4 months in patients with recurrent measurable osteosarcoma as compared to a historical COG experience or produces an ORR.

Secondary objectives of the study were**:**

- To further define cabozantinib related toxicities in paediatric, adolescent and young adult patients.
- To further define cabozantinib PK in paediatric and adolescent patients.
- To estimate 1-year time to progression (TTP), progression free survival (PFS) and overall survival (OS) for each stratum, and if feasible to compare to historical controls.

Exploratory objectives the study were**:**

- To assess the effect of cabozantinib on patients' immune cell subsets.

To obtain tumour tissue (snap frozen, formalin-fixed and paraffin-embedded (FFPE) blocks or unstained slides) from diagnosis, recurrence, or both, for possible future studies.

2.3.2. Pharmacokinetics

Bioanalytical method (AD20-1089, IPS000426)

The bioanalysis of study ADVL1622 was conducted by Alturas Analytics, Inc. (1324 Alturas Drive, Moscow). Acetonitrile precipitation followed by HPLC/MS/MS were used to determine the concentration of cabozantinib from human K_2EDTA plasma. The method was previously validated in another procedure (AV11XL18401).

Study samples were stored at nominal -70 ± 10 °C. Study samples were analysed within 993 days from collection. Long term stability for cabozantinib in human K_2EDTA plasma has been validated for up to 840 days at -70 °C. A total of 20 out of 20 samples passed the incurred sample reanalysis. As a criterion of acceptance two thirds of the repeat samples should have met the percent difference criteria of ≤20.0% between original and re-assayed concentrations. No reanalysed samples were reported.

Context of Use

In this procedure, one population pharmacokinetic model was submitted, which aimed:

- to develop a population pharmacokinetic (PopPK) model to describe the time course of cabozantinib concentrations in children and adolescent patients;
- to estimate between- and within-subject variability and explore and quantify the potential influence of covariates that contribute significantly to the between-subject differences in the pharmacokinetic (PK) parameters;
- to simulate concentration-time profiles associated with different dose regimens and BSA categories in the cabozantinib nomogram and derive exposure metrics over the first week of treatment and at steady-state.

Data

The population pharmacokinetic model was developed based on available data from two clinical trials (ADVL1211 and ADVL1622). In short, Study ADVL1211 was a phase 1 study of cabozantinib in children and adolescents with recurrent or refractory solid tumours, including CNS tumours. Patients received cabozantinib daily under fasted conditions to achieve a weekly cumulative dose equivalent to 210, 280 or 385 mg/m^2/day on a continuous dosing schedule in 28-day cycles. Study ADVL1622 was a phase 2 study of cabozantinib in children and young adults with refractory sarcomas, Wilms Tumour, and other rare tumours. Patients received a 40 mg/m^2/day dose cabozantinib daily (rounded to the nearest 20 mg and a cumulative weekly dose of 280 mg/m^2) under fasted conditions on a continuous dosing schedule in 28-day cycles. A dosing nomogram (see Table 1) was used in both studies. Pharmacokinetic sampling schemes of both trials are displayed in Table 2.

Table 1. Cabozantinib Dosing Nomogram

Dose Level 1 30 mg/m^2	Dose Level 2 40 mg/m^2	Dose Level 3 55 mg/m^2	
BSA (m^2)	BSA (m^2)	BSA (m^2)	Weekly Dose/Schedule for Initial Dosing
0.35 – 0.42			80 mg = 20 mg M, W, F, Sun
0.43 – 0.52	0.35 – 0.39		100 mg = 20 mg M, W, F, Sat, Sun
0.53 – 0.60	0.40 – 0.45		120 mg = 20 mg M, T, W, F, Sat, Sun
0.61 – 0.73	0.46 – 0.55	0.35 – 0.40	140 mg = 20 mg daily
0.74 – 0.85	0.56 – 0.64	0.41 – 0.46	160 mg = 40 mg M, W, F, Sun
0.86 – 1.04	0.65 – 0.78	0.47 – 0.57	200 mg = 40 mg M, W, Th, Sat, Sun
1.05 – 1.21	0.79 – 0.90	0.58 – 0.66	240 mg = 40 mg M, T, W, F, Sat, Sun
1.22 – 1.46	0.91 – 1.09	0.67 – 0.80	280 mg = 40 mg daily
1.47 – 1.57	1.10 – 1.17	0.81 – 0.85	300 mg = 60 mg M, W, Th, Sat, Sun
1.58 – 1.85	1.18 – 1.36	0.86 – 0.99	360 mg = 60 mg M, T, W, F, Sat, Sun
1.86 – 2.14	1.37 – 1.65	1.00 – 1.16	420 mg = 60 mg daily
≥ 2.15	1.66 – 1.85	1.17 – 1.35	480 mg = 80 mg M, T, W, F, Sat, Sun
	1.86 – 2.07	1.36 – 1.5	560 mg = 80 mg daily
	≥ 2.08	1.51 – 1.68	600 mg = 100 mg M, T, W, F, Sat, Sun
		1.69 – 2.00	700 mg = 100 mg daily
		≥ 2.01	840 mg = 120 mg daily

Table 2. Summary of Pharmacokinetic Assessments by Study (Cycle [C], Day [D])

Study	Planned PK Data[a]
ADVL1211	• C1D1: Pre-dose and 4 hr • C1D21: Pre-dose, 2, 4, 8 and 24 hr • C3D1: Pre-dose
ADVL1622	• C1D1: Pre-dose, 2, 4, 8 and 20-28 hr • C1D22: Pre-dose and 2-4 hr • C2D1 and C3D1: Pre-dose

A total of 398 observations in 56 subjects were collected. A total of 68 samples prior to the first recorded dose, of which 13 were quantifiable, were excluded from the dataset. An additional 3 samples, collected post-dose, were below the lower limit of quantification (<1%) and therefore also excluded from the analysis. After exclusion, 327 observations in 55 subjects were initially included in the population pharmacokinetic analysis (Table 3). Another 24 observations were excluded after evaluation of some initial models due to: uncertainty around unscheduled samples (n = 16), anomalous day 1 profile (n = 3), observations taken approximately two weeks after the last recorded dose (n = 2) and observations with absolute CWRES values > 3 (n = 3).

Table 3. Number of Subjects and Cabozantinib Concentrations included in population pharmacokinetic analysis

	Study		
	ADVL1211	**ADVL1622**	**Overall**
Number of Subjects (%)	37 (67)	18 (33)	55
Number of concentrations (%)	230 (70)	97 (30)	327
By Visit Day:			
Day 1	34	66	100
Day 21	151	0	151
Day 22	0	28	28
Day 29	0	2	2
Day 57	26	1	27
Day 85	3	0	3
Unscheduled	16	0	16
By Dose Level:			
30 mg/m²	41	-	41
40 mg/m²	117	97	214
55 mg/m²	72	-	72

Methodology

Development population pharmacokinetic model

Non-linear mixed-effects modelling and simulations were conducted using NONMEM (version 7.5) pre- and post-processing was done in R (version 3.6.2). Model parameters were estimated using Monte Carlo Importance Sampling Expectation Maximisation (EM) assisted by mode a posteriori (IMPMAP). Mu referencing was used to improve efficiency of the computations.

One- and two-compartment linear models with different absorption models (e.g. first-order absorption with lag-time, sequential zero-order and first-order absorption) were investigated. The effect of BSA (scaled to typical value of 1.73 m^2) on both clearance and volume of distribution terms were incorporated into the base model using estimated allometric exponents, respectively. Inter-individual variability was included on all structural parameters assuming a log-normal distribution. The influence of additional covariates (i.e. age, weight, body surface area, body mass index, creatinine clearance, bilirubin, aspartate aminotransferase, alanine aminotransferase, haemoglobin, sex, race, ethnicity, tumour type, renal impairment group, hepatic impairment group (NCI score)) was evaluated after. The full model with backwards deletion approach was utilized for covariate modelling. All covariate-parameter relationships of interest were entered in the model simultaneously. Highly correlated covariates were tested one at a time in order to avoid confounding in the estimation of covariate effects. A backwards deletion was carried out at the p=0.001 (increased objective function value [OFV] less than 10.83 points, degrees of freedom [d.f.]=1) significance level. A combined additive and proportional error model was used as starting point in the modelling.

The final model was considered a model in which: minimisation was successful, completion of covariance step without warnings, number of significant digits ≥ 3, robust final estimates, relative standard errors less than 20%, 95% confidence interval for estimated fixed effects that would effectively reduce the hierarchical structure of the model, relative standard errors of off-diagonal omegas less than 50%, no correlation (rho < 0.95) between individual etas for all parameter pairs, no bias in standard goodness-

of-fit plots. The predictive performance was evaluated using prediction-corrected visual predictive checks (pcVPCs) using n = 1000 simulations.

Estimation individual pharmacokinetic parameters

The final model was used to derive individual estimates of AUC, Cmax and Cmin over the first week following initiation of cabozantinib for the children and adolescent subjects in the PopPK analysis for the actual doses each subject received over that first week of treatment, rather than following the dosing nomogram for cabozantinib. The same dosing schedule was also used to derive individual estimates over a steady-state week. The individual estimates of all model parameters were obtained from the final model by an empirical Bayes estimation. Individual estimates of AUC, Cmax and Cmin were obtained by simulation of the concentration-time profiles (concentrations simulated at every 30 min over the first 8 hours and then hourly over each day) for respective individuals using their individual empirical Bayes estimates, and zero values for residual variability. The PK parameters AUC (linear up/log down trapezoidal rule), Cmax and Cmin were determined by non-compartmental methods.

Simulation of BSA-based cabozantinib nomogram

The final PopPK model was used to simulate AUC, Cmax and Cmin over both the first week following initiation of cabozantinib and at steady-state for a virtual population of 1000 children and adolescent subjects in the PopPK analysis based on the BSA-based dosing nomogram for cabozantinib that was used in the clinical studies. 1000 subjects were created with their individual BSA sampled from the distribution of BSA of the children and adolescent subjects included in the PopPK analysis. A lower limit of > 0.65 m^2 was applied. For each dose level (30, 40 and 55 mg/m^2), subjects were assigned to the specific BSA-defined weekly dosing schedule as per the nomogram.

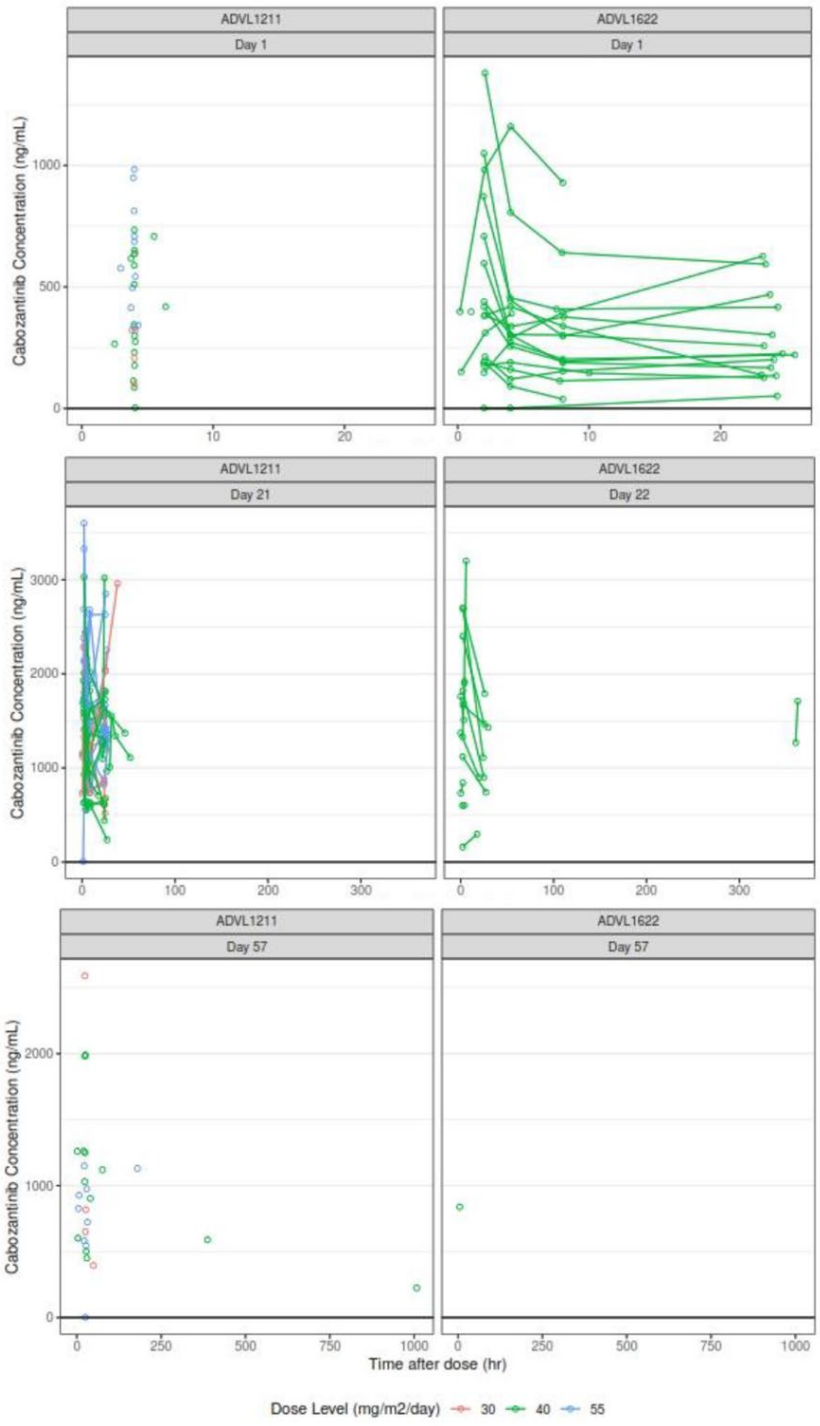
Final model

Population included and observed profiles

The observed pharmacokinetic profiles in both studies are displayed in

Figure **1**. The median age across the two studies was 13 years (min-max: 4-18) with median weight of 41.5 kg (min-max: 15.9-106) and median BSA of 1.34 m^2 (min-max: 0.670-2.31). There were a similar number of male and female subjects (53 and 47%, respectively). The majority of the subjects were White (69%), with 13% Black and only 5% Asian. Only one subject did not have normal renal status and the majority of subjects (73%) had normal hepatic status with the other 27% having mild hepatic impairment. Of the 55 subjects, 33% had sarcoma, with 16% having CNS tumour. The majority of subjects (67%) were assigned to the 40 mg/m^2 dose level, with only 11 and 22% assigned to either 30 or 55 mg/m^2 dose levels.

Figure 1. Observed Cabozantinib Concentrations versus Time after Dose by Study and Day



Description of the model

The final model was a two-compartment model with first-order absorption and first-order elimination. Body-surface area was the only included covariate in the model (Table 4). Between-subject variability was estimated on all model parameters using a full variance-covariance matrix and the residual error was described using a proportional error. An overview of the model parameters is provided in Table 4 and a pcVPC of the final model in Figure 2.

Table 4. Parameter Estimates of Final Cabozantinib PopPK Model (Run R0010)

$CL/F = 1.80 \times (BSA/1.73)^{0.618}$ L/hr; $Q/F = 23.9 \times (BSA/1.73)^{0.618}$ L/hr;
$Vc/F = 119 \times (BSA/1.73)^{1.86}$ L; $Vp/F = 153 \times (BSA/1.73)^{1.86}$ L;
$Ka = 1.94$ hr^{-1}.

Parameter [Units]	NONMEM Estimates			
	Point Estimate[a]	%RSE[b]	95% CI[a]	
CL/F [L/hr]	1.80	12.7	1.40 - 2.31	
Vc/F [L]	119	28.1	68.6 - 207	
Q/F [L/hr]	23.9	25.4	14.5 - 39.3	
Vp/F [L]	153	38.9	71.1 - 327	
Ka [hr^{-1}]	1.94	48.0	0.758 - 4.98	
CL/F,Q/F~BSA [unitless]	0.618	47.8	0.0394 - 1.20	
Vc/F, Vp/F~ BSA [unitless]	1.86	17.7	1.22 - 2.51	
Inter-individual variability				**CV%[c]**
$\omega^2_{CL/F}$	0.193	31.1	0.0755 - 0.311	46.2
$\omega^2_{Vc/F}$	0.464	62.1	-0.101 - 1.03	76.8
$\omega^2_{Q/F}$	0.166	93.9	-0.139 - 0.471	42.5
$\omega^2_{Vp/F}$	1.26	45.0	0.148 - 2.38	159
ω^2_{Ka}	0.256	75.6	-0.123 - 0.636	54.1
Residual variability				**CV% or SD**
σ^2_{prop}	0.0882	10.6	0.0699 - 0.107	CV%=29.7%

[a] Back-transformed from natural log scale (except for σ^2, CL/F~ BSA, Vc/F~ BSA, Q/F~ BSA, Vp/F~ BSA)

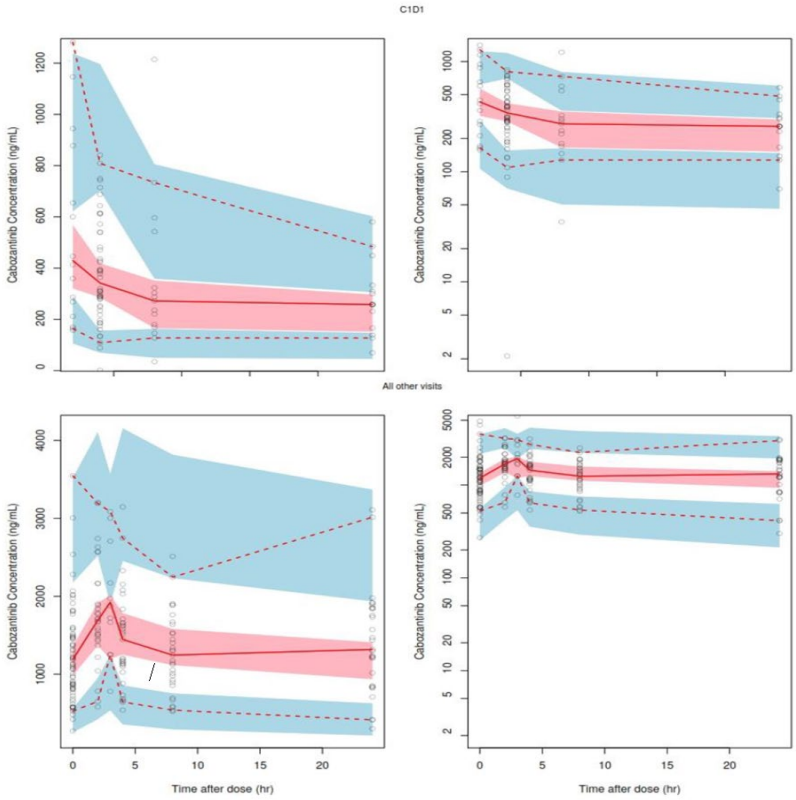
[b] RSE=SE.100 (except for σ^2). RSE for σ^2, CL/F~ BSA, Vc/F~ BSA, Q/F~ BSA, Vp/F~~ BSA =SE(θ)/θ.100

[c] CV for IIV calculated as $CV_{TVP}=\sqrt{e^{\omega^2_P}}$ .100 if $\omega^2_P \leq 0.15$, else $CV_{TV_P} = \sqrt{e^{\omega^2_P} - 1}$ .100

Abbreviations: CL/F = apparent total clearance, Vc/F = apparent volume of central compartment, Vp/F = apparent volume of peripheral compartment, Q/F = inter compartment clearance between central and peripheral compartments, Ka=first-order absorption, $\omega^2_{CL/F}$, $\omega^2_{Vc/F}$, $\omega^2_{Q/F}$, $\omega^2_{Vp/F}$, and ω^2_{Ka} =variance of random effect of CL/F, V_c/F, Q/F, V_p/F, and Ka, respectively; CI=confidence interval, RSE=relative standard error, CV=coefficient of variation, σ^2_{prop} = proportional residual error

The reference population is a 1.73 m^2 subject.

Figure 2. Prediction-Corrected Visual Predictive Check for the Final Cabozantinib



Application

Estimation individual pharmacokinetic parameters

The individual estimates of cabozantinib exposure (AUC, Cmax and Cmin) are summarised in Table 5 by dose level.

Table 5. Summary of Cabozantinib pharmacokinetic parameters by dose level

Dose	Dose Level	n	Statistic	AUC (ng*hr/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
First Week	30 mg/m^2	6	GeoMean (CV)	103064 (34.5)	1184 (25.6)	756 (30.7)
		6	Mean (CV)	108000 (29.1)	1220 (24.1)	783 (28.3)
		6	Median (90% PI)	111000 (65900-143000)	1250 (849-1580)	770 (521-1060)
	40 mg/m^2	35	GeoMean (CV)	98956 (51.1)	1178 (39.3)	672 (58.7)
		35	Mean (CV)	108000 (37.2)	1250 (33.0)	756 (42.1)
		35	Median (90% PI)	103000 (35700-171000)	1260 (573-1960)	782 (190-1220)
	55 mg/m^2	12	GeoMean (CV)	165249 (22.2)	1937 (16.9)	1065 (40.9)
		12	Mean (CV)	169000 (20.1)	1960 (16.2)	1130 (29.7)
		12	Median (90% PI)	170000 (117000-215000)	1930 (1540-2360)	1200 (550-1490)
Steady-State	30 mg/m^2	6	GeoMean (CV)	236811 (43.8)	1819 (30.2)	1216 (55.0)
		6	Mean (CV)	256000 (44.1)	1890 (29.6)	1360 (53.4)
		6	Median (90% PI)	210000 (161000-412000)	1820 (1280-2630)	1090 (750-2360)
	40 mg/m^2	35	GeoMean (CV)	209919 (46.5)	1728 (33.3)	1048 (60.2)
		35	Mean (CV)	230000 (44.1)	1820 (31.2)	1200 (52.2)
		35	Median (90% PI)	209000 (103000-445000)	1770 (889-2770)	1100 (381-2540)
	55 mg/m^2	12	GeoMean (CV)	271407 (34.7)	2364 (20.3)	1295 (54.2)
		12	Mean (CV)	285000 (30.5)	2410 (18.4)	1430 (41.4)
		12	Median (90% PI)	296000 (148000-405000)	2440 (1660-2970)	1500 (580-2240)

Simulation of BSA-based cabozantinib nomogram

To assess the impact of BSA on the derived cabozantinib exposures at steady-state, tertiles of BSA were created and each subject assigned to their appropriate tertile (0.67 – 1.16, 1.16 – 1.51 and 1.51 – 2.31 m^2). Given the low number of subjects for both the 30 and 55 mg/m^2 dose levels, this assessment was done for the 40 mg/m^2 dose level only (Table 6).

Table 6. Summary of Steady-State Cabozantinib PK Parameters for 40 mg/m^2 Dose Level

BSA (m^2)	n	Statistic	AUC (ng*hr/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
0.67 – 1.16	13	GeoMean (CV)	168180 (44.9)	1587 (33.2)	788 (65.1)
	13	Mean (CV)	182000 (40.4)	1660 (30.0)	914 (51.9)
	13	Median (90% PI)	196000 (90200-291000)	1720 (887-2400)	953 (333-1530)
1.16 – 1.51	10	GeoMean (CV)	221593 (32.3)	1765 (26.3)	1124 (37.0)
	10	Mean (CV)	232000 (32.3)	1820 (25.7)	1190 (38.0)
	10	Median (90% PI)	214000 (145000-349000)	1810 (1260-2530)	1060 (738-1930)
1.51 – 2.31	12	GeoMean (CV)	255133 (49.6)	1862 (38.8)	1347 (58.6)
	12	Mean (CV)	281000 (44.7)	1980 (35.2)	1530 (49.9)
	12	Median (90% PI)	246000 (132000-469000)	1930 (1120-3040)	1320 (582-2640)

The BSA-based dosing nomogram was supported by simulations in a virtual population (as described above). For the 1000 subjects included in this virtual population simulation dataset, the median BSA was 1.35 m^2, with individual values ranging from 0.66 to 2.31 m^2. The results at steady state are summarised in table 7 to 9.

Table 7. Summary of predicted cabozantinib exposures at steady-state of treatment for 30 mg/m² dose level

BSA (m^2)	Weekly Dosing Schedule	n	Statistic	AUC (ng*hr/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
0.61-0.73	140 mg = 20 mg daily	23	GeoMean (CV)	106125 (40.8)	939 (26.8)	488 (54.6)
		23	Mean (CV)	115000 (47.7)	973 (29.8)	558 (61.5)
		23	Median (90% PI)	104000 (55200-218000)	956 (622-1410)	480 (220-1210)
0.74-0.85	160 mg = 40 mg M, W, F, Sun	46	GeoMean (CV)	119334 (42.6)	1262 (27.4)	621 (50.4)
		46	Mean (CV)	129000 (42.7)	1310 (26.5)	689 (47.3)
		46	Median (90% PI)	120000 (61000-212000)	1320 (806-1830)	629 (274-1140)
0.86-1.04	200 mg = 40 mg M, W, Th, Sat, Sun	119	GeoMean (CV)	133640 (51.3)	1236 (29.4)	721 (58.3)
		119	Mean (CV)	149000 (47.6)	1290 (30.7)	825 (51.5)
		119	Median (90% PI)	136000 (60000-279000)	1200 (835-1970)	746 (267-1560)
1.05-1.21	240 mg = 40 mg M, T, W, F, Sat, Sun	144	GeoMean (CV)	145722 (49.4)	1197 (32.2)	774 (56.1)
		144	Mean (CV)	162000 (46.8)	1260 (33.2)	880 (51.3)
		144	Median (90% PI)	148000 (66200-324000)	1170 (776-2040)	791 (308-1840)
1.22-1.46	280 mg = 40 mg daily	272	GeoMean (CV)	156006 (48.6)	1139 (37.5)	817 (57.3)
		272	Mean (CV)	174000 (54.7)	1220 (44.3)	943 (60.8)
		272	Median (90% PI)	149000 (79700-324000)	1100 (656-2090)	788 (349-1840)
1.47-1.57	300 mg = 60 mg M, W, Th, Sat, Sun	104	GeoMean (CV)	161174 (46.9)	1300 (34.2)	893 (51.3)
		104	Mean (CV)	178000 (47.5)	1370 (34.2)	1000 (51.1)
		104	Median (90% PI)	157000 (82600-344000)	1320 (727-2190)	876 (412-2000)
1.58-1.85	360 mg = 60 mg M, T, W, F, Sat, Sun	187	GeoMean (CV)	170569 (46.7)	1267 (35.6)	930 (53.0)
		187	Mean (CV)	188000 (48.0)	1350 (38.0)	1050 (51.5)
		187	Median (90% PI)	172000 (83800-364000)	1250 (703-2300)	950 (433-2110)
1.86-2.14	420 mg = 60 mg daily	84	GeoMean (CV)	178032 (44.1)	1230 (36.1)	981 (48.3)
		84	Mean (CV)	195000 (45.8)	1310 (38.1)	1090 (49.4)
		84	Median (90% PI)	178000 (101000-373000)	1220 (729-2300)	977 (488-2190)
>=2.15	480 mg = 80 mg M, T, W, F, Sat, Sun	21	GeoMean (CV)	203651 (59.3)	1452 (44.7)	1128 (64.8)
		21	Mean (CV)	232000 (48.2)	1580 (39.2)	1310 (51.3)
		21	Median (90% PI)	232000 (96500-405000)	1610 (782-2570)	1300 (477-2340)

Table 8. Summary of predicted cabozantinib exposures at steady-state of treatment for 40 mg/m² dose level

BSA (m^2)	Weekly Dosing Schedule	n	Statistic	AUC (ng*hr/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
0.65-0.78	200 mg = 40 mg M, W, Th, Sat, Sun	42	GeoMean (CV)	150222 (37.3)	1569 (25.9)	788 (42.2)
		42	Mean (CV)	161000 (42.0)	1620 (26.5)	858 (47.3)
		42	Median (90% PI)	148000 (82300-299000)	1640 (1120-2530)	770 (408-1660)
0.79-0.90	240 mg = 40 mg M, T, W, F, Sat, Sun	54	GeoMean (CV)	180118 (50.1)	1571 (33.3)	924 (61.6)
		54	Mean (CV)	201000 (49.5)	1660 (34.6)	1070 (55.4)
		54	Median (90% PI)	181000 (88800-393000)	1480 (1010-2770)	948 (334-2230)
0.91-1.09	280 mg = 40 mg daily	123	GeoMean (CV)	177910 (46.5)	1408 (29.1)	896 (58.4)
		123	Mean (CV)	195000 (42.3)	1470 (29.5)	1020 (49.2)
		123	Median (90% PI)	183000 (81200-337000)	1360 (901-2190)	941 (302-1900)
1.10-1.17	300 mg = 60 mg M, W, Th, Sat, Sun	67	GeoMean (CV)	178497 (55.3)	1540 (32.9)	981 (61.2)
		67	Mean (CV)	202000 (50.3)	1620 (33.2)	1140 (53.2)
		67	Median (90% PI)	178000 (80100-376000)	1510 (963-2520)	989 (408-2180)
1.18-1.36	360 mg = 60 mg M, T, W, F, Sat, Sun	227	GeoMean (CV)	203255 (47.4)	1626 (33.9)	1080 (53.8)
		227	Mean (CV)	225000 (49.7)	1720 (37.4)	1230 (54.2)
		227	Median (90% PI)	200000 (102000-435000)	1590 (947-2890)	1070 (477-2420)
1.37-1.65	420 mg = 60 mg daily	262	GeoMean (CV)	227585 (49.6)	1619 (39.5)	1217 (57.5)
		262	Mean (CV)	255000 (54.7)	1750 (45.2)	1400 (60.2)
		262	Median (90% PI)	220000 (116000-486000)	1570 (892-3100)	1210 (492-2820)
1.66-1.85	480 mg = 80 mg M, T, W, F, Sat, Sun	120	GeoMean (CV)	218056 (45.5)	1623 (34.8)	1185 (52.4)
		120	Mean (CV)	240000 (46.7)	1720 (36.9)	1330 (50.8)
		120	Median (90% PI)	222000 (112000-414000)	1640 (915-2780)	1230 (574-2360)
1.86-2.07	560 mg = 80 mg daily	70	GeoMean (CV)	240369 (46.8)	1671 (37.4)	1324 (51.3)
		70	Mean (CV)	265000 (47.8)	1790 (39.2)	1490 (51.3)
		70	Median (90% PI)	245000 (126000-515000)	1640 (972-3180)	1330 (640-3000)
>=2.08	600 mg = 100 mg M, T, W, F, Sat, Sun	35	GeoMean (CV)	248172 (48.2)	1767 (37.9)	1375 (52.3)
		35	Mean (CV)	273000 (43.2)	1880 (35.3)	1540 (45.9)
		35	Median (90% PI)	261000 (122000-494000)	1920 (980-3070)	1440 (638-2880)

Table 9. Summary of predicted cabozantinib exposures at steady-state of treatment for 55 mg/m² dose level

BSA (m^2)	Weekly Dosing Schedule	n	Statistic	AUC (ng*hr/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
0.58-0.66	240 mg = 40 mg M, T, W, F, Sat, Sun	4	GeoMean (CV)	149562 (60.4)	1770 (34.0)	623 (64.0)
0.58-0.66		4	Mean (CV)	167000 (51.9)	1840 (32.6)	709 (58.0)
0.58-0.66		4	Median (90% PI)	167000 (91500-244000)	1790 (1260-2500)	618 (368-1180)
0.67-0.80	280 mg = 40 mg daily	44	GeoMean (CV)	213141 (35.9)	1781 (27.4)	1039 (46.0)
0.67-0.80		44	Mean (CV)	227000 (40.9)	1850 (28.9)	1150 (49.9)
0.67-0.80		44	Median (90% PI)	207000 (123000-412000)	1850 (1240-2780)	978 (511-2210)
0.81-0.85	300 mg = 60 mg M, W, Th, Sat, Sun	21	GeoMean (CV)	225827 (51.0)	2151 (31.0)	1192 (64.3)
0.81-0.85		21	Mean (CV)	252000 (50.0)	2250 (30.7)	1380 (55.5)
0.81-0.85		21	Median (90% PI)	226000 (113000-409000)	2150 (1390-3270)	1230 (402-2260)
0.86-0.99	360 mg = 60 mg M, T, W, F, Sat, Sun	80	GeoMean (CV)	247430 (50.6)	2126 (32.6)	1284 (58.9)
0.86-0.99		80	Mean (CV)	276000 (47.2)	2240 (33.8)	1470 (52.6)
0.86-0.99		80	Median (90% PI)	252000 (110000-512000)	2070 (1350-3770)	1340 (454-2840)
1.00-1.16	420 mg = 60 mg daily	131	GeoMean (CV)	253341 (50.3)	1971 (33.1)	1295 (61.4)
1.00-1.16		131	Mean (CV)	282000 (46.6)	2080 (33.6)	1500 (52.7)
1.00-1.16		131	Median (90% PI)	261000 (115000-512000)	1960 (1190-3280)	1350 (467-2920)
1.17-1.35	480 mg = 80 mg M, T, W, F, Sat, Sun	224	GeoMean (CV)	273840 (46.9)	2185 (34.0)	1456 (53.2)
1.17-1.35		224	Mean (CV)	303000 (49.0)	2310 (37.2)	1650 (53.5)
1.17-1.35		224	Median (90% PI)	269000 (138000-575000)	2140 (1260-3780)	1450 (643-3240)
1.36-1.50	560 mg = 80 mg daily	133	GeoMean (CV)	311984 (51.1)	2270 (38.5)	1645 (60.8)
1.36-1.50		133	Mean (CV)	353000 (59.0)	2450 (47.5)	1930 (65.5)
1.36-1.50		133	Median (90% PI)	296000 (160000-688000)	2170 (1420-4250)	1600 (646-3960)
1.51-1.68	600 mg = 100 mg M, T, W, F, Sat, Sun	151	GeoMean (CV)	311565 (47.6)	2326 (37.4)	1702 (52.5)
1.51-1.68		151	Mean (CV)	345000 (48.6)	2490 (38.5)	1920 (52.3)
1.51-1.68		151	Median (90% PI)	311000 (148000-686000)	2390 (1340-4390)	1730 (747-3950)
1.69-2.00	700 mg = 100 mg daily	165	GeoMean (CV)	312301 (47.3)	2184 (37.2)	1692 (54.8)
1.69-2.00		165	Mean (CV)	346000 (48.5)	2340 (40.0)	1920 (52.8)
1.69-2.00		165	Median (90% PI)	317000 (163000-678000)	2210 (1220-4160)	1740 (778-3920)
>=2.01	840 mg = 120 mg daily	47	GeoMean (CV)	347804 (44.9)	2346 (37.8)	1914 (49.3)
>=2.01		47	Mean (CV)	380000 (41.9)	2500 (36.2)	2120 (45.3)
>=2.01		47	Median (90% PI)	366000 (172000-702000)	2490 (1300-4310)	2020 (922-4060)

Discussion on pharmacokinetics

The validation of the bioanalytical method of cabozantinib has been assessed previously (see EMEA/H/C/4163). Some samples were analysed after the confirmed long-term stability period. The

applicant was requested to justify how many samples were analysed after the long-term stability period, confirm this stability period and discuss clinical implications.

The applicant characterised the pharmacokinetics of cabozantinib in the paediatric age range using a population pharmacokinetic model, which was based on data collected in studies ADVL1211 and ADVL1622. The paediatric population included in the analysis had a median age of 13 years (min-max: 4-18), median weight of 41.5 kg (min-max: 15.9-106) and median BSA of 1.34 m^2 (min-max: 0.670-2.31).

The dose in adolescents was based on a comparable exposure to adults (See also, EMEA/H/C/004163/II/0023). It is important to note that no adult patients were included in the analysis submitted in this procedure and therefore no pharmacokinetic comparison with adults can be performed. It is unclear how the adult dose (Cometriq dose is administered as 140 mg once daily and Cabometyx is administered as 60 mg once daily) compares to the BSA-based dosing schedule in the paediatric population. BSA was implemented in the model using power functions on clearance and volume of distribution terms and, if BSA adequately scales exposure, these terms were expected to be close to 1 (instead of 0.6 and 1.9). The applicant is requested to discuss and to clarify whether the plasma exposure in adolescent and paediatric patients included in studies ADVL1211 and ADVL1622 can be considered similar to adult patients (and a justification for clinically relevant exposure metric should be provided). It should also be noted that the Cometriq and Cabometyx formulations are not bioequivalent in the adult population and should not be used interchangeably. This further complicates the comparison with adult data. Nonetheless, the applicant is requested to clarify whether the plasma exposure in adolescent and paediatric patients included in studies ADVL1211 and ADVL1622 can be considered similar to adult patients (and a justification for clinically relevant exposure metric should be provided). No extrapolation approach is pursued for this indication, therefore these issues will be raised as other concern. The paediatric exposure in different age ranges and a comparison with adults should be reflected in section 5.2 of the SmPC or it should be justified that the current statement is still appropriate.

In the population pharmacokinetic model, some samples were excluded after initial model fitting. This is not considered an ideal approach without any sensitivity analysis, but as the number of samples excluded was less than 10% and the model parameters only changed slightly, this issue is not pursued. No estimates of the covariance matrix were tabulated (only in NONMEM output). These should be provided in the parameter table (and ideally converted to correlation coefficients) in future reports.

2.3.3. Clinical study

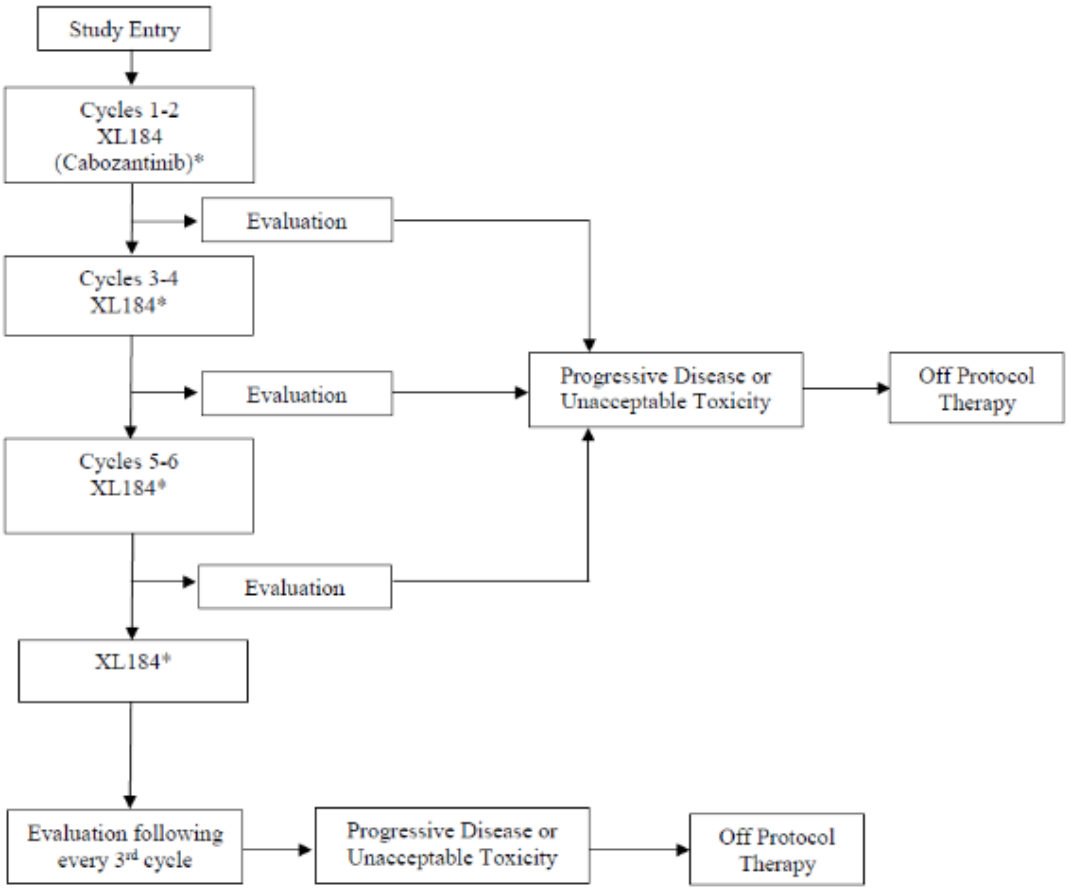
Description

Methods

- **Overall Study Design and Plan**

ADVL1622 was an open label, multicentre, two-stage phase 2 trial in the following solid tumour strata: Ewing sarcoma, RMS, NRSTS, osteosarcoma, Wilms tumour and other rare solid tumours.

Figure 3 Study Design



XL184=cabozantinib
Source: Appendix 16.1.1.
* Cabozantinib was administered on a continuous dosing schedule. A cycle was 28 days.

- The cabozantinib dose for this trial was 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram; see Table 1). This was the recommended phase 2 dose determined from the phase 1 study ADVL1211. ADVL1211 trial enrolled 41 patients at three dose levels; 30 mg/m^2, 40 mg/m^2 and 55 mg/m^2 once daily on a continuous dosing schedule. Based on dose-limiting toxicity (DLTs) in Cycle 1 and in later cycles requiring dose reductions, the 40 mg/m^2/day on continuous schedules (one cycle=28 days) determined to be the recommended phase 2 dose.

- Dosing was performed based on body surface area (BSA) and rounded to the nearest 20 mg using a dosing nomogram as used in ADVL1211. Treatment continued until tumour progression or unacceptable toxicity.

Study participants

The study population consisted of patients aged 2 to ≤ 30 years of age.

Main inclusion criteria

1. Patients aged 2 to ≤ 30 years, for the strata MTC, RCC and HCC the upper age limit was 18 years.

2. Patients had to have a BSA ≥0.35 m^2.

3. Patients had to have recurrent or refractory disease, or newly diagnosed disease with no known curative therapy or therapy proven to prolong survival with an acceptable quality of life. Patients had to

have had histologic verification of one of the malignancies listed below at original diagnosis or at relapse:

- Ewing sarcoma
- RMS
- NRSTS including microphthalmia transcription factor associated NRSTS (ASPS and CCS)
- Osteosarcoma
- Wilms tumour
- Rare tumours
    - MTC
    - RCC
    - HCC
    - Hepatoblastoma
    - Adrenocortical carcinoma
    - Paediatric solid tumours (including CNS tumours) with known molecular alterations in the targets of cabozantinib

4. Patients had to have radiographically measurable disease.

5. Patients had to have a Lansky or Karnofsky performance status score of ≥50, corresponding to ECOG categories 0, 1 or 2.

6. Patients had to have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering the study.

7. Patients much have adequate bone marrow-, renal-, liver-, cardiac-, pancreatic- and central nervous system function, and adequate blood pressure control and coagulation according to predefined criteria.

Main exclusion Criteria

Patients were excluded from the study if they met the following criteria:

1. Pregnancy or breast feeding
2. Concomitant medications including growth factors, corticosteroids, previous treatment with cabozantinib or another MET/HGF inhibitor (tivantinib, crizotinib), investigational drugs, anti-cancer agents, anti-graft versus host disease of agents to prevent organ rejection post-transplant, cytochrome P450 3A4 active agents, concomitant anticoagulation with oral anticoagulants, enzyme inducing anticonvulsants and QTc agents
3. Patients who were unable to swallow intact tablets
4. Patients who had an uncontrolled infection
5. Patients with active bleeding
6. Patients who had had or were planning to have one of the predefined invasive procedures (for instance major surgical procedure).
7. Patients who had significant traumatic injury within 28 days prior to enrolment.
8. Patients with any medical or surgical condition that could interfere with GI absorption.

9. Patients who in the opinion of the investigator were unable to comply with the safety monitoring requirements of the study.

Treatments

Cabozantinib was administered at 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2) on a continuous dosing schedule (one cycle=28 days). A cycle could be repeated every 28 days if the patient had at least SD and had met laboratory parameters as defined in the eligibility. Based on patients' BSA, there could be days where dose was not administered. Dosing was performed based on BSA and rounded to the nearest 20 mg.

Dose reductions were allowed for toxicities as outlined in Table 10. Patients who experienced a DLT after two dose reductions were removed from the protocol.

Table 10 Dose Reduction

Cabozantinib 40 mg/m^2/day		
BSA (m^2)	**Weekly dose/Schedule for 1st dose reduction due to toxicity**	**Weekly dose/Schedule for 2nd dose reduction due to toxicity**
0.35 – 0.39	60 mg=20 mg M, W, F (or Day 1, 3, 5 of each week)	Off therapy
0.40 – 0.45	80 mg=20 mg M, W, F, Sun (or Day 1, 3, 5, 7 of each week)	60 mg=20 mg M, W, F (or Day 1, 3, 5 of each week)
0.46 – 0.55	100 mg=20 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)	60 mg=20 mg M, W, F (or Day 1, 3, 5 of each week)
0.56 – 0.64	120 mg = 20 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)	80 mg=20 mg M, W, F, Sun (or Day 1, 3, 5, 7 of each week)
0.65 – 0.78	140 mg=20 mg Daily	100 mg=20 mg M, W, Th, Sat, Sun (or Day 1,3, 4, 6, 7 of each week)
0.79 – 0.90	160 mg=40 mg M, W, F, Sun (or Day 1, 3, 5, 7 of each week)	120 mg=20 mg M, T, W, F, Sat, Sun (or Day 1, 2,3, 5, 6, 7 of each week)
0.91 – 1.09	200 mg=40 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)	140 mg=20 mg Daily
1.10 – 1.17	200 mg=40 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)	140 mg=20 mg Daily
1.18 – 1.36	240 mg = 40 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)	160 mg=40 mg M, W, F, Sun (or Day 1, 3, 5, 7 of each week)
1.37 – 1.65	300 mg=60 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)	200 mg=40 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)
1.66 – 1.85	360 mg=60 mg M, T, W, F, Sat, Sun (or Day 1, 2, 3, 5, 6, 7 of each week)	240 mg = 40 mg M, T, W, F, Sat, Sun (or Day 1, 2,3, 5, 6, 7 of each week)
1.86 – 2.07	420 mg=60 mg Daily	300 mg=60 mg M, W, Th, Sat, Sun (or Day 1, 3, 4, 6, 7 of each week)
≥2.08	420 mg=60 mg Daily	300 mg = 60 mg M, W, Th, Sat, Sun (or Day 1, 3,4, 6, 7 of each week)

BSA=body surface area, F=Friday, M=Monday, Sat=Saturday, Sun=Sunday, T=Tuesday, Th=Thursday, W=Wednesday

Study therapy was stopped when the patient met any of the following criteria;

1. Progressive disease (PD)
2. AEs requiring removal from the therapy
3. Start of concurrent anti-cancer or investigational therapy
4. Refusal of further protocol therapy by patient/parent/guardian

5. Physician determined it was in patient's best interest
6. Repeat eligibility studies were outside the parameters required for eligibility
7. Non-compliance that in the opinion of the investigator did not allow for ongoing participations
8. Development of a second malignant neoplasm
9. Pregnancy
10. Study was terminated by the sponsor

Patients who were removed from protocol therapy were followed until they met the criteria for off study (i.e. death, lost to follow up, entry into another COG study, not receiving any protocol treatment after study enrolment, withdrawal of consent, fifth anniversary).

Outcomes/endpoints

Primary Efficacy Measurement

The primary aim of ADVL1622 study was to evaluate the ORR (CR+PR) in all strata and DCR in the osteosarcoma stratum only. The DCR was defined as the rate of patients with disease control success (CR or PR or SD after 4 months of treatment or at the end of the sixth cycle, whichever occurred first). Any evaluable patient with osteosarcoma who died because of treatment-related toxicity during the first six cycles of therapy and/or within the first 4 months since starting treatment was considered not to have experienced disease control success. Also, any patient who was eligible, received one dose of cabozantinib and was lost to follow-up at (for example) the end of Cycle 2 was not considered a disease control success.

Disease response was assessed using the revised RECIST version 1.1 (Eisenhauer 2009).

Tumour disease evaluations were conducted on all patients pre-study and were repeated at the end of cycle 2, prior to cycles 5 and 7 and then every 3rd cycle.

The pertinent imaging studies (CT, MRI etc) of those patients who responded, based on investigator's/institutional review, to therapy or had long term SD on protocol therapy were centrally reviewed.

For the non-osteosarcoma strata, ORR was assessed within 6 months of the first dose of cabozantinib. For the osteosarcoma stratum ORR was assessed if the patients performed at least six treatment cycles, between the date of the first dose of cabozantinib and the date of the sixth cycle. Otherwise, ORR was assessed within 4 months of the first dose of cabozantinib.

Secondary Endpoints

- Best overall response
- Time to Progression
- Progression Free survival
- Overall Survival
- Time to Response
- Duration of Response

Safety Measurements

For the extent of exposure, the following parameters were measured for the study; duration of exposure (weeks), total exposure at cycle i (where i ≥1), BSA at Cycle 1, duration of each cycle, average weekly dose at each cycle, average daily dose during the study.

AEs were monitored from the time the patients gave informed consent and throughout the study. AEs were reported in a routine manner at scheduled times.

Given the antiangiogenic targeting of cabozantinib and concern for possible impact on growth in children, linear growth was 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 were required. For patients with an open tibial growth plate, plain anteroposterior radiographs of the same tibial growth plates were repeated before Cycle 2, 5 and every 6 months until off protocol therapy.

Biological Markers assessment

The association between host immune system and response to cabozantinib were to be assessed in an exploratory manner.

These biological markers were considered to potentially give important insights into the mechanism of action of cabozantinib.

Submission of tumour tissue to be banked for future research studies was strongly encouraged. Tumour tissue obtained as result of biopsy or resection at initial diagnosis, and/or of a suspected disease recurrence site prior to therapy, and/or of a suspected disease recurrence during the first 12 months from the time of enrolment was requested for banking (snap frozen, FFPE blocks or unstained slides).

Analysis

Data analysis was performed for all patients enrolled in osteosarcoma stratum and non-osteosarcoma strata (including the non-statistical rare tumour cohort).

Five analysis sets were defined for this study;

- Enrolled population; all patients who signed the informed consent for the study
- Eligible population; all patients who fulfilled all inclusion and none of the exclusion criteria
- Safety population; all patients in the enrolled population who received at least one dose of cabozantinib
- Evaluable population for response; all eligible patients who had an answer equal to "Yes: at the question "Is the patients evaluable for response assessment" from the "study Chair Eligibility Review"
- Evaluable population for PK; any patient who was eligible and consented to participate in the PK portion of the study and who received cabozantinib on cycle 1 day 1 and had at least one plasma cabozantinib concentration

According to the distribution of patients in subgroups, efficacy and safety analyses were repeated using the following age groups:

- < 18, ≥18 years
- < 12 years, ≥12 years and <18, ≥18 years

Determination of sample size

Table 11 Two stage study design

In all the non-osteosarcoma strata, Simon's minimax two-stage design have been planned:

	Cumulative number of responses	Decision
Stage 1: Enter 13 patients	0	Terminate the trial early: agent ineffective
	1 or more RECIST* response (Partial Response (PR) or Complete Response (CR) as best overall response)	Inconclusive results, continue trial (proceed Stage 2)
Stage 2: Enter 7 additional patients	2 or fewer RECIST response (Partial Response (PR) or Complete Response (CR) as best overall response)	Terminate the trial early: agent ineffective
	3 or more RECIST response (Partial Response (PR) or Complete Response (CR) as best overall response)	Terminate the trial: agent effective

* RECIST: Response Evaluation Criteria In Solid Tumors

In the osteosarcoma stratum, the below two-stage design has been planned:

	Cumulative responses results	Decision
Stage 1: Enter 19 patients	≤4 disease control successes AND ≤1 RECIST responders (Partial Response (PR) or Complete Response (CR) as best overall response)	Terminate the trial early: agent ineffective
	≥5 disease control successes OR ≥2 RECIST responders (Partial Response (PR) or Complete Response (CR) as best overall response)	Inconclusive results, continue trial (proceed Stage 2)

	Cumulative responses results	Decision
Stage 2: Enter 10 additional patients	≤8 disease control successes AND ≤4 RECIST responders (PR or CR as best overall response)	Terminate the trial early: agent ineffective
	≥9 disease control successes OR ≥5 RECIST responders among stage 1 and stage 2 (PR or CR as best overall response)	Terminate the trial: agent effective

Non-osteosarcoma strata: The goal of non-osteosarcoma strata was enrolment of at least 39 patients and a maximum of 110 patients to ensure 13 or 20 patients were evaluated for response in each statistical stratum.

Wilms tumour and rare tumours disease groups were planned per protocol as non-statistical cohorts. Wilms tumour was updated in the SAP to be a statistical cohort. The reason for this change was the

enrolment of 13 response-evaluable patients; therefore, a two-stage design was applied to Wilms tumour disease group.

Osteosarcoma stratum: The goal of osteosarcoma stratum was enrolment of at least 19 patients and a maximum of 36 patients to ensure either 19 or 29 evaluable for response patients in this group.
A sample sizes of evaluable patients permitted the estimation of response rates with a CI that was no more than 20 percentage points wide.

Changes in the conduct of the study

There were three protocol amendments during the conduct of the study. The original protocol d.d. 09 February 2017. Substantive protocol changes are summarized below.

Protocol Amendment 1, 26 January 2018 main changes:

- Osteosarcoma was included in the list of solid tumour strata being studied.
- RET rearrangement mutation was added to the list of rare tumour molecular alterations.
- A primary aim to estimate whether cabozantinib therapy improves the DCR at 4 months in patients with recurrent measurable osteosarcoma compared to a historical COG experience or produces an ORR was added to reflect the addition of the osteosarcoma stratum.
- A secondary aim to estimate 1-year TTP, PFS and OS for each stratum, and if feasible to compare to historical controls was added.
- The rationale for adding the osteosarcoma stratum was added.
- Osteosarcoma was added to the list of eligible diagnoses for enrolment into the study.
- The eligibility criteria regarding anti-cancer agents, antibody doses, ALT, BP control were updated.
- A recommendation to use caution and monitor AE when administering cabozantinib with MRP2 inhibitors was added.
- Guidelines to monitor QTc after taking concomitant medications with risk of prolonged QTc were added.
- The cumulative weekly dose was set at 280 mg/m^2.
- Dose-limiting hypertension definition was revised.
- An adult BP criterion for hypertension was added.
- Consent to PK collection, additional PK, defining PK evaluability and evaluation of PK parameters sampling was added.
- Long term SD was defined.
- Patient not receiving protocol treatment after study enrolment was added as an off-study criterion.
- Sample size, stratum-specific study design and study duration estimates for the osteosarcoma stratum were added.
- New disease control response criteria specifically for the osteosarcoma were added.

Protocol Amendment 2, 18 July 2018 main changes were:

- The version number of CTCAE was updated from version 4 to version 5.

- Definition of CNS function inclusion criterion was updated.
- Non-haematological DLT was updated to clarify the ULN for AST, dosing tables were clarified to account for a different start day other than Monday.
- Definition of neonatal death was updated.
- Expediting reporting was updated to include pregnancy loss.

Protocol Amendment 3, 16 April 2019

Main change was the update of cabozantinib Comprehensive Adverse Events and Potential Risks per the guidelines in the Rapid Request for Amendment.

The SAP was finalized on 03-Feb-2022, no changes to the planned analyses were made after the SAP was finalized.

Results

Study population

A total of 109 patients were enrolled into the study at 53 study centres, of whom 108 patients (99.1%) received at least one dose of cabozantinib. All 108 patients received study treatment in cycle 1, 86 patients (79.6%) in cycle 2, 51 patients (47.2%) in cycle 3 and one patient (0.9%) in cycle 29.

Of the 109 enrolled patients, 105 patients (96.3%) were eligible and 104 patients (95.4%) were evaluable for response.

Four ineligible patients were treated in the study and therefore included in the safety population.

Efficacy analyses were performed using the evaluable population for response and include all patients in the osteosarcoma stratum, 94.5% of the patients in the non-osteosarcoma strata and 92.0% of the patients in the rare tumours strata (Table 12).

Safety analysis was performed using the safety population and included all patients in the osteosarcoma and rare tumours strata, and 98.2% of the patients in the non-osteosarcoma strata.

Table 12 Summary of Patient populations-All tumour types (enrolled Population)

Population n (%)	Osteosarcoma N=29	Non-osteosarcoma [a] N=55	All rare tumors N=25	Overall N=109
Eligible population	29 (100.0)	53 (96.4)	23 (92.0)	105 (96.3)
Safety population	29 (100.0)	54 (98.2)	25 (100.0)	108 (99.1)
Evaluable population for response	29 (100.0)	52 (94.5)	23 (92.0)	104 (95.4)
Evaluable population for PK	1 (3.4)	12 (21.8)	5 (20.0)	18 (16.5)

BP=blood pressure, BSA=body surface area, CNS=central nervous system, CSI=craniospinal irradiation, ECG=electrocardiogram, N=total number of subjects, n=number of subjects with data, PK=pharmacokinetic, RMS=rhabdomyosarcoma

Ninety-two of the 108 treated patients (85.2%) entered the follow-up period and had a minimum follow-up time after the last dose of cabozantinib of 29 days. Sixteen out of 108 treated patients (14.8%) did not enter the follow-up period as follows:

• Seven patients died during study treatment period.

• Three patients were enrolled onto another COG study with tumour therapeutic intent.

• Two patients withdrew consent for any further data submissions.

• Four patients had missing information on the vital status .

One patient with MTC in the rare tumours strata, remained on long-term study treatment at the data cut-off date.

Overall the withdrawal rate during treatment period was 98.1%. The most frequent reasons for discontinuation of study treatment were PD (65/104 patients (62.5%)), and AEs (12/104 patients (11.5%)) (**Table 13**). One patient with MTC in the rare tumour strata was ongoing in the study (8 cycles of treatment) at data cut-off date. The mean duration of patients participation in the study was 46.94 (±40.99) weeks (min: 0.3 weeks and max:192 weeks).

Data through the data cut-off date (30 June 2021) were used to analyse the primary endpoints.

Table 13 Patient Disposition - All Tumour Types (Safety Population)

	Osteosarcoma N=29	Non-osteosarcoma [a] N=54	All rare tumors N=25	Overall N=108
Treated subjects (n (%))	29 (100.0)	54 (100.0)	25 (100.0)	108 (100.0) [b]
Subjects withdrawn from cabozantinib during the protocol therapy (n (%)) [c]	28 (96.6)	54 (100.0)	24 (96.0)	106 (98.1)
Primary reason for withdrawal from cabozantinib therapy	27	53	24	104
Missing information	1	1	0	2
Progressive disease [d]	17 (63.0)	35 (66.0)	13 (54.2)	65 (62.5)
Adverse events requiring removal from protocol therapy [d]	5 (18.5)	6 (11.3)	1 (4.2)	12 (11.5)
Subject received concurrent anti-cancer or investigational therapy [d]	1 (3.7)	0	0	1 (1.0)
Refusal of further protocol therapy by subject/parent/guardian [d]	2 (7.4)	2 (3.8)	4 (16.7)	8 (7.7)
Physician determines it is in subject's best interest [d]	1 (3.7)	5 (9.4)	5 (20.8)	11 (10.6)
Repeat eligibility studies (if required) are outside the parameters required for eligibility [d]	0	5 (9.4)	0	5 (4.8)
Non-compliance that in the opinion of the investigator does not allow for ongoing participation [d]	1 (3.7)	0	1 (4.2)	2 (1.9)
Subjects off-study (n (%)) [d]	23 (79.3)	42 (77.8)	20 (80.0)	85 (78.7)
Death [e]	20 (87.0)	40 (95.2)	20 (100.0)	80 (94.1)
Subject enrollment onto another COG study with tumor therapeutic intent (e.g. at recurrence) [e]	2 (8.7)	1 (2.4)	0	3 (3.5)

	Osteosarcoma N=29	Non-osteosarcoma [a] N=54	All rare tumors N=25	Overall N=108
Withdrawal of consent for any further data submissions [e]	1 (4.3)	1 (2.4)	0	2 (2.4)

COG=Children's Oncology Group, N=total number of subjects, n=number of subjects with data
Source: Table 14.1.1.8. Data cutoff date was 30 June 2021.
[a] All non-osteosarcoma strata without rare tumors are presented.
[b] Four ineligible subjects were treated in the study and therefore included in the safety population. See Section 10.
[c] The denominator is the number of subjects in the given column (N).
[d] The number of subjects withdrawn from cabozantinib **for whom the reason of withdrawal from treatment is provided** is the denominator used for the calculation of percentages.
[e] The number of subjects off-study is the denominator used for the calculation of percentages.

Demographic Characteristics

Table 14 Demographics - All tumour types (Safety Population)

Parameters	Statistics	Osteosarcoma N=29	Non-osteosarcoma [a] N=54	All rare tumors N=25	Overall N=108
Age (years)	Mean (StD)	15.8 (3.6)	16.6 (5.9)	12.9 (3.7)	15.5 (5.1)
	Median	16	16	13	15
	Min, Max	9, 22	5, 27	5, 19	5, 27
Age subgroup 1 (n (%))	<18 years	17 (58.6)	31 (57.4)	22 (88.0)	70 (64.8)
	≥18 years	12 (41.4)	23 (42.6)	3 (12.0)	38 (35.2)
Age subgroup 2 (n (%))	<12 years	5 (17.2)	12 (22.2)	10 (40.0)	27 (25.0)
	≥12 years to <18 years	12 (41.4)	19 (35.2)	12 (48.0)	43 (39.8)
	≥18 years	12 (41.4)	23 (42.6)	3 (12.0)	38 (35.2)
Weight (kg)	Mean (StD)	54.36 (19.92)	56.87 (23.61)	50.70 (24.96)	54.77 (22.93)
	Median	55.9	54.9	45.0	53.3
	Min, Max	20.6, 111.8	16.9, 121.6	20.4, 141.2	16.9, 141.2
Height (cm)	Mean (StD)	162.58 (18.35)	159.10 (20.04)	149.23 (17.08)	157.75 (19.41)
	Median	165.0	161.3	152.9	161.3
	Min, Max	125.6, 188.0	106.3, 193.0	115.0, 183.9	106.3, 193.0
Body surface area (m^2) [b]	Mean (StD)	1.561 (0.338)	1.564 (0.400)	1.415 (0.359)	1.529 (0.377)
	Median	1.63	1.60	1.37	1.57
	Min, Max	0.86, 2.27	0.70, 2.46	0.86, 2.43	0.70, 2.46
Sex (n (%))	Female	10 (34.5)	27 (50.0)	15 (60.0)	52 (48.1)
	Male	19 (65.5)	27 (50.0)	10 (40.0)	56 (51.9)

Parameters	Statistics	Osteosarcoma N=29	Non-osteosarcoma [a] N=54	All rare tumors N=25	Overall N=108
Race (n (%))	Asian	1 (3.4)	5 (9.3)	2 (8.0)	8 (7.4)
	Black or African American	6 (20.7)	6 (11.1)	2 (8.0)	14 (13.0)
	Multiple	0	1 (1.9)	0	1 (0.9)
	Native Hawaiian or other pacific islander	1 (3.4)	0	1 (4.0)	2 (1.9)
	Not reported	2 (6.9)	2 (3.7)	2 (8.0)	6 (5.6)
	Unknown	3 (10.3)	5 (9.3)	4 (16.0)	12 (11.1)
	White	16 (55.2)	35 (64.8)	14 (56.0)	65 (60.2)
Ethnicity (n (%))	Hispanic or Latino	8 (27.6)	5 (9.3)	8 (32.0)	21 (19.4)
	Not Hispanic or Latino	20 (69.0)	47 (87.0)	15 (60.0)	82 (75.9)
	Not reported	1 (3.4)	1 (1.9)	1 (4.0)	3 (2.8)
	Unknown	0	1 (1.9)	1 (4.0)	2 (1.9)

BSA=body surface area, Max=maximum, Min=minimum, N=total number of subjects, n=number of subjects with data, StD=standard deviation
Source: Table 14.1.2.4. Data cutoff date was 30 June 2021.
The denominator is the number of subjects in the given column (N).
[a] All non-osteosarcoma strata without rare tumors are presented.
[b] BSA (m^2) as reported by the investigator.

Baseline Disease Characteristics

At baseline, most patients (44/107 patients (41.1%)) had one measurable target lesion to be followed for response. The most frequent target lesion site was the lower lobe of the lung (33/108 patients (30.6%)).

Across strata, the majority of patients (93/107 patients (86.9%)) had no lymph nodes to be measured as target lesions.

Overall, there were 5/25 patients (20.0%) in the rare tumours strata and 2/54 patients (3.7%) in non-osteosarcoma strata with CNS tumour at baseline.

Growth plate assessments were conducted in patients who were skeletally immature (open growth plate).
Overall, there were 78 patients ≤18 years of age with 21 patients in osteosarcoma stratum, 33 patients in non-osteosarcoma strata and 24 patients in rare tumours strata. Twenty-seven of 78 patients (34.6%) aged ≤18 years had a plain anteroposterior radiograph of a single proximal tibial growth plate obtained prior to the first dose of cabozantinib, 17 of whom (63.0%) had an open tibial growth plate.

Overall, the majority of patients (104/108 (96.3%)) had received at least one anti-cancer therapy prior to baseline (Table 15). The most frequent prior therapies were chemotherapy with multiple agents

(93/104 patients (89.4%)), surgery (76/104 (73.1%)) and radiation therapy (57/104 patients (54.8%)).

Table 15 Prior Anti-cancer Therapies by Type of Therapy - All Tumour Types (Safety Population)

	Osteosarcoma N=29	Non-osteosarcoma [a] N=54	All rare tumors N=25	Overall N=108
Subjects with at least one prior therapy (n (%)) [b]	29 (100.0)	53 (98.1)	22 (88.0)	104 (96.3)
Subjects with at least one (n (%)) [c]				
Anti-retroviral	0	0	0	0
Antisense	0	0	0	0
Bone marrow transplant	1 (3.4)	1 (1.9)	0	2 (1.9)
Chemotherapy single agent	6 (20.7)	9 (17.0)	2 (9.1)	17 (16.3)
Chemotherapy multiple agents	28 (96.6)	49 (92.5)	16 (72.7)	93 (89.4)
Chemotherapy non-cytotoxic	2 (6.9)	2 (3.8)	0	4 (3.8)
Chemotherapy NOS	3 (10.3)	3 (5.7)	3 (13.6)	9 (8.7)
Drug and/or immunotherapy	4 (13.8)	10 (18.9)	3 (13.6)	17 (16.3)
Gene transfer	0	0	0	0
Hematopoietic stem cell	0	2 (3.8)	0	2 (1.9)
Hormonal therapy	0	0	0	0
Image directed local	0	0	1 (4.5)	1 (1.0)
Oncolytic virotherapy	0	0	0	0
Radiation therapy	3 (10.3)	45 (84.9)	9 (40.9)	57 (54.8)
Surgery	29 (100.0)	31 (58.5)	16 (72.7)	76 (73.1)
Vaccine and/or therapy NOS	1 (3.4)	6 (11.3)	4 (18.2)	11 (10.6)
Subjects with at least one prior chemotherapy (n (%)) [b]	29 (100.0)	51 (94.4)	17 (68.0)	97 (89.8)

N=total number of subjects, n=number of subjects with data, NOS=not otherwise specified
Source: Table 14.1.3.4. Data cutoff date was 30 June 2021.
[a] All non-osteosarcoma strata without rare tumors are presented.
[b] The denominator is the number of subjects in the given column (N).
[c] The number of subjects with at least one prior therapy is the denominator used for the calculation of percentages.

Osteosarcoma stratum

At baseline, most patients (12/29 subjects (41.4%)) had one measurable target lesions to be followed for response. The most frequent target lesion sites were the lower lobe of the lung (41.4%), the upper lobe of the lung (24.1%) and lung lesions (17.2%).

The majority of patients (89.7%) had no lymph nodes to be measured as target lesions.

Table 16 Lesion Assessment at Baseline - Osteosarcoma Stratum (Safety Population)

Parameters	**Statistics**	**Osteosarcoma N=29**
Number of lesions (n (%))	1	12 (41.4)
	2	11 (37.9)
	3	2 (6.9)
	4	2 (6.9)
	5	2 (6.9)
Method of evaluation (n (%)) [a]	N	29
	Subjects with at least one CT scan	25 (86.21)
	Subjects with at least one MRI	8 (27.59)
Time (in days) between evaluation of the target lesion and the first dose of cabozantinib	Mean (StD)	8.1 (4.45)
	Median	8
	Min, Max	2; 15
Target lesion sites (ICD-O) (n (%))	Lung, lower lobe	12 (41.38)
	Lung, upper lobe	7 (24.14)
	Lung	5 (17.24)
	Pleura	4 (13.79)
	Long bones, upper limb scapula and associated joints	3 (10.34)
	Intrathoracic lymph node	2 (6.90)
	Soft tissue, lower limb and hip	2 (6.90)
	Limb, bones	1 (3.45)
	Long bones, lower limb and associated joints	1 (3.45)
	Lymph node	1 (3.45)
	Mediastinum	1 (3.45)
	Occipital lobe	1 (3.45)
	Pelvis	1 (3.45)
	Respiratory system and intrathoracic organs, overlapping lesion	1 (3.45)
	Rib, sternum, clavicle and associated joints	1 (3.45)
	Soft tissue, pelvis	1 (3.45)

Parameters	Statistics	Osteosarcoma N=29
Combination of target lesion sites (ICD-O) (n (%))	Lung, lower lobe	5 (17.24)
	Lung + lung	3 (10.34)
	Lung, lower lobe + lung, lower lobe	2 (6.90)
	Lung, lower lobe + lung, upper lobe	2 (6.90)
	Pleura	2 (6.90)
	Intrathoracic lymph node	1 (3.45)
	Intrathoracic lymph node + long bones, lower limb and associated joints + long bones, upper limb scapula and associated joints + pelvis + soft tissues, pelvis	1 (3.45)
	Limb, bones + limb, bones + lung + lung	1 (3.45)
	Long bones, upper limb scapula and associated joints	1 (3.45)
	Long bones, upper limb scapula and associated joints + lung, upper lobe + lung, upper lobe + occipital lobe	1 (3.45)
	Lung	1 (3.45)
	Lung, lower lobe + lung, lower lobe + lung, lower lobe + lung, upper lobe + lung, upper lobe	1 (3.45)
	Lung, lower lobe + lung, Lung, upper lobe + rib sternum clavicle and associated joints	1 (3.45)
	Lung, lower lobe + mediastinum + respiratory system and intrathoracic organs, overlapping lesion	1 (3.45)
	Lung, upper lobe	1 (3.45)
	Lung, upper lobe + lung, upper lobe	1 (3.45)
	Lymph node	1 (3.45)
	Pleura + pleura	1 (3.45)
	Pleura + soft tissue, lower limb and hip	1 (3.45)
	Soft tissue, lower limb and hip + soft tissue, lower limb and hip	1 (3.45)
Number of lymph nodes target lesions (n (%))	0	26 (89.66)
	1	3 (10.34)
Subjects with at least one nontarget lesion (n (%))	Yes	16 (55.2)
	No	13 (44.8)

CT=computerized tomography, ICD-O=International Classification of Diseases for Oncology, Max=maximum, Min=minimum, MRI=magnetic resonance imaging, N=total number of subjects, n=number of subjects with data, StD=standard deviation

Source: Table 14.1.2.9 add 1 Data cutoff date was 30 June 2021.

[a] Method of evaluation summarizes the number and percentages of subjects with at least one target lesion by the method of assessment.

The denominator is the number of subjects in the given column (N).

There were no patients with CNS tumour at baseline in the osteosarcoma stratum.

Non-osteosarcoma strata

Of the non-osteosarcoma strata (including Ewing sarcoma, RMS, NRSTS and Wilms tumour), at baseline, 5/14 patients (35.7%) in the Ewing sarcoma disease group had one measurable target lesion to be followed for response, and three patients each (21.4%) had three and four lesions. The most frequent target lesion site was the lower lobe of the lung (35.7%).

Seven of 14 patients (50%) in the RMS disease group had one measurable target lesion to be followed for response, and two patients each (14.23%) had three and four lesions. The most frequent target lesion sites were the lower lobe of the lung, nasopharynx, and head and neck (14.3% each).

At baseline, 6/13 patients (46.2%) in the NRSTS disease group had one measurable target lesion to be followed for response, and two patients each (15.4%) had two, three and four lesions. The most frequent target lesion site was the lower lobe of the lung (30.8%).

Six of 13 patients (46.2%) with Wilms tumour had one measurable target lesion to be followed for response, and three patients (23.1%) had five lesions and two patient each (15.4%) had two and three lesions. The most frequent target lesion sites were the lower lobe of the lung, and pelvis (23.1% each).

All patients in the NRSTS disease group and the majority of patients in the Ewing sarcoma and RMS disease groups (85.71% each), and the Wilms tumour disease group (84.6 %) had no lymph nodes to be measured as target lesions.

One patient each in the Ewing sarcoma (7.1%) and NRSTS (7.7%) disease groups had CNS tumour at baseline.

Rare tumours strata

A total of 25 patients were enrolled in the rare tumour disease group (2 patients with MTC, 4 patients with RCC, 8 patients with HCC, 2 patients with hepatoblastoma, 3 patients with adrenocortical carcinoma and 6 patients with other solid tumours (1 DTC and 5 CNS tumours).

The two patients with MTC had one target lesion each to be followed for response. The target lesion sites were the liver and the thyroid gland.

Two of four patients with RCC had two measurable target lesions to be followed for response and one patient each had three and five lesions. The target lesion sites were the lower lobe and the middle lobe of the lung, lymph node, retroperitoneum, head, face neck lymph node, intrathorarcic lymph node, mediastinum, pelvic bones, sacrum, coccyx and associated joints, renal pelvis and skull face and associated joints, bones.

At baseline, 4/8 patients with HCC had two measurable target lesions to be followed for response. The most frequent target lesion site was the liver.

The two patients with hepatoblastoma had one or three measurable target lesions to be followed for response. The target lesion sites were the liver, middle lobe of the lung, kidney and retroperitoneum.

Two of three patients with adrenocortical carcinoma had two measurable target lesions to be followed for response. The most frequent target lesion site was the lower lobe of the lung.

In other solid tumours disease group, five of six patients had one measurable target lesion to be followed for response. On patient who had only CNS target lesions at baseline was accounted for as missing in the data analysis.

All patients in the MTC, hepatoblastoma, adrenocortical carcinoma and other solid tumours disease groups, and the majority of patients in HCC disease group had no lymph nodes to be measured as target lesions. All patients with RCC had one or two lymph nodes to be measured as target lesions.

Efficacy results

According to the study protocol, the data cut-off date for the analysis was the primary completion date, which was the date when all patients in the statistical cohorts had reached 6 months of follow-up (30 June 2021).

Efficacy results Osteosarcoma Stratum

Primary Efficacy Endpoints: Objective Response Rate and Disease Control Rate

The primary endpoints for the osteosarcoma stratum were ORR and DCR. The ORR was 6.9% (95% CI: 0.8, 22.8) and the two objective responses were PRs. SD was the best overall response for 31.0% (95% CI: 15.3, 50.8) of patients. The DCR was 34.5% (95% CI: 17.9, 54.3) (Table 17).

Six patients (20.7%) were not evaluable for response as follows: four patients had a first response of SD and no subsequent evaluations and two patients had withdrawn from study treatment before the first evaluation.

Table 17 Objective Response Rate and Disease Control Rate - Osteosarcoma Stratum (Evaluable Population for Response)

	Osteosarcoma N=29
Best overall response	
PR (n (%))	2 (6.9)
95% CI	0.8; 22.8
SD (n (%))	9 (31.0)
95% CI	15.3; 50.8
PD (n (%))	12 (41.4)
95% CI	23.5; 61.1
Unable to evaluate (n (%)) [a]	6 (20.7)
95% CI	8.0; 39.7
Objective response rate (ORR) (CR + PR) (n (%)) [b]	2 (6.9)
95% CI	0.8; 22.8
Disease control rate (n (%)) [c]	10 (34.5)
95% CI	17.9; 54.3
Long term stable disease (n (%))	7 (24.1)
95% CI	10.3; 43.5

CI=confidence interval, CR=complete response, N=total number of subjects, n=number of subjects with data, ORR=objective response rate, PD=progressive disease, PR=partial response, SD=stable disease
Source: Table 14.2.1.1.1. Data cutoff date was 30 June 2021.
[a] Unable to evaluate corresponds to subjects who stopped study treatment before the first evaluation (N=2) and subjects with a first response SD and no other evaluation (N=4).
[b] ORR was assessed within 6 months of the first dose of cabozantinib (first intake date + 365.25/2).
[c] Disease control rate is the rate of subjects with disease control success defined as subjects with a best overall CR, PR or SD after 4 months of therapy (- 14 days) [≥ 4*30.4475 - 14] or at the end of the sixth treatment cycle, whichever occurred first.

Response data by age group are summarized in the Table 18.

Table 18 Objective Response Rate in Patients <12 Years of Age, ≥12 to <18 Years of Age and ≥18 Years of Age - Osteosarcoma Stratum (Evaluable Population for Response)

	<12 years N=5	≥12 years to <18 years N=12	≥18 years N=12
Best overall response			
PR (n (%))		1 (8.3)	1 (8.3)
95% CI		0.2; 38.5	0.2; 38.5
SD (n (%))	1 (20.0)	3 (25.0)	5 (41.7)
95% CI	0.5; 71.6	5.5; 57.2	15.2; 72.3
PD (n (%))	3 (60.0)	5 (41.7)	4 (33.3)
95% CI	14.7; 94.7	15.2; 72.3	9.9; 65.1
Unable to evaluate (n (%)) [a]	1 (20.0)	3 (25.0)	2 (16.7)
95% CI	0.5; 71.6	5.5; 57.2	2.1; 48.4
Objective response rate (ORR) (CR + PR) [b]	0	1 (8.3)	1 (8.3)
95% CI	0.0; 52.2	0.2; 38.5	0.2; 38.5
Disease control rate [c]	1 (20.0)	3 (25.0)	6 (50.0)
95% CI	0.5; 71.6	5.5; 57.2	21.1; 78.9
Long term stable disease (n (%))	1 (20.0)	1 (8.3)	5 (41.7)
95% CI	0.5; 71.6	0.2; 38.5	15.2; 72.3

CI=confidence interval, CR=complete response, N=total number of subjects, n=number of subjects with data, ORR=objective response rate, PD=progressive disease, PR=partial response, SD=stable disease
Source: Table 14.2.1.2.5. Data cutoff date was 30 June 2021.
[a] Unable to evaluate corresponds to subjects who stopped study treatment before the first evaluation (N=2) and subjects with a first response SD and no other evaluation (N=4).
[b] ORR was assessed within 6 months of the first dose of cabozantinib (first intake date + 365.25/2).
[c] Disease control rate is the rate of subjects with disease control success defined as subjects with a best overall CR, PR or SD after 4 months of therapy (- 14 days) [≥ 4*30.4475 - 14] or at the end of the sixth cycle, whichever occurred first.

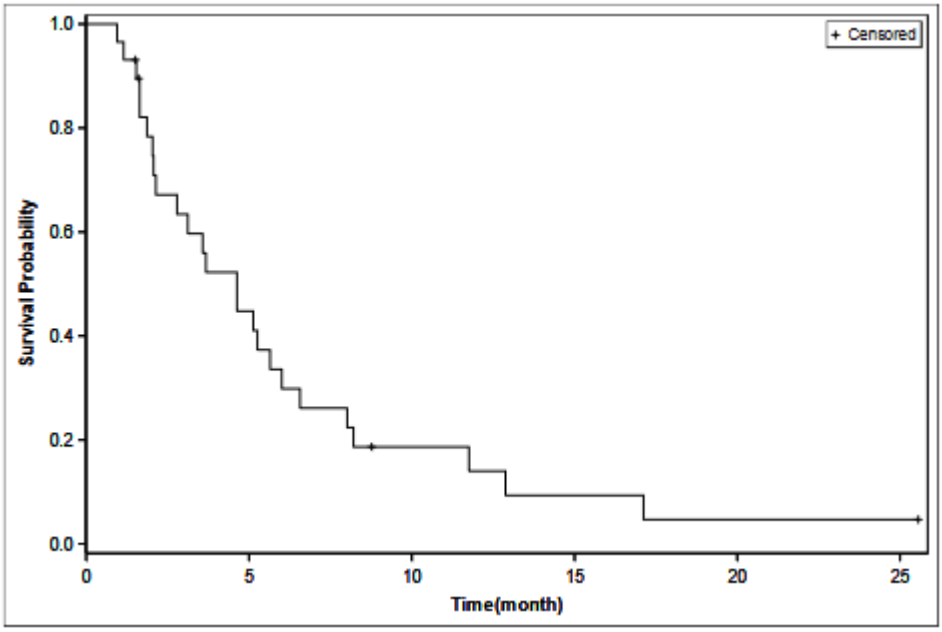
Secondary efficacy endpoints

The median TTP for patients with osteosarcoma was 4.6 months (95% CI: 2.1, 6.6) with a minimum duration of 0.95 months and a maximum duration of 26.45 months.

The median TTP was 3.1 months (95% CI: 1.6, 8.0) in children and 5.7 months (95% CI: 2.2, 6.6) in adults. The majority of children (8/17 patients (5.7%)) and adults (9/12 patients (83.3%)) had no tumour progression within 3 months after start of cabozantinib.

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 (Figure **4**).

Figure 4 Progression Free Survival - Survival Curves (Kaplan-Meier Method) – Osteosarcoma Stratum (Evaluable Population for Response)



The median duration of PFS was 3.1 months (95% CI: 1.6, 8.0) in children and 5.3 months (95% CI: 2.1, 6.6) in adults.

At the cut-off date, 20/29 patients with osteosarcoma had a documented death, 3/29 patients were alive and 6/29 patients had an unknown vital status. The median OS was 9.3 months (95% CI; 6.3, 12.2). Twenty-five patients (86.2%) were alive at 3 months, at 6, 9 and 12 months, 76.0%, 56.0% and 35.2% of the patients, respectively were alive.

Fourteen children (100% of the children for which survival was estimated) were alive at 3 months, at 6, 9 and 12 months, 71.4%, 57.1% and 34.3% of patients, respectively, were alive. Eleven adults (100% of the adults for which survival was estimated) were alive at 3 months, at 6, 9 and 12 months, 81.8%, 54.5% and 36.4% of patients, respectively, were alive.

The single child with a response maintained the response for 23.72 months and the single adult with a response maintained the response for 6.90 months. Among the four children with disease control, the median duration of disease control was 6.4 months (95% CI: 2.7, NC) and disease control was maintained for a minimum duration of 2.73 months and a maximum duration of 23.72 months. In the six adults with disease control, the median duration of disease control was 4.1 months (95% CI: 3.2, NC) and disease control was maintained for a minimum duration of 3.22 months and a maximum duration of 6.9 months.

A PR was observed in one child and one adult; the time to response was 3.71 months for the child and 1.91 months for the adult.

Four patients had tumour shrinkage ≥30% (the minimum tumour shrinkage for a PR).

Efficacy results Non-osteosarcoma Strata

Primary Efficacy Endpoints: Objective Response Rate

The non-osteosarcoma disease groups were not expanded beyond the initial 13 patients.

Following administration of cabozantinib, CRs or PRs were not observed in patients with Ewing sarcoma (Table 19). Two of 13 patients (15.4%) had SD and 8/13 patients (61.5%) had PD. Three patients were not evaluable for response due to discontinuation of study treatment before the first evaluation.

The RMS disease group, CRs or PRs were not observed. Stable disease was the best overall response for 1/13 patients (7.7%) and 10/13 patients (76.9%) had PD. Two of 13 patients (15.4%) were not evaluable for response because; one patient had a first response of SD and no subsequent evaluation and another patient had discontinued cabozantinib before the first evaluation.

In the NRSTS disease group, CRs or PRs were not observed, 6 of 13 patients (46.2%) had SD and 5/13 patients (38.5%) had PD. Two patients were not evaluable for response because one patient had first response of SD and no subsequent evaluations and another patient had withdrawn from study treatment before first evaluation.

Complete responses or PRs were not observed in the patients with Wilms tumour. Stable disease was the best overall response for 5/13 patients (38.5%) and the frequency of PD was 53.8% (7/13 patients). One of 13 patients (7.7%) was not evaluable for response as this patient had a first response of SD and no subsequent evaluation.

Table 19 Objective Response Rate – Non-osteosarcoma Strata (Evaluable Population for Response)

	Ewing sarcoma N=13	RMS N=13	NRSTS N=13	Wilms tumor N=13	Overall N=52
Best overall response					
SD (n (%))	2 (15.4)	1 (7.7)	6 (46.2)	5 (38.5)	14 (26.9)
95% CI	1.9; 45.4	0.2; 36.0	19.2; 74.9	13.9; 68.4	15.6; 41.0
PD (n (%))	8 (61.5)	10 (76.9)	5 (38.5)	7 (53.8)	30 (57.7)
95% CI	31.6; 86.1	46.2; 95.0	13.9; 68.4	25.1; 80.8	43.2; 71.3
Unable to evaluate (n (%)) [a]	3 (23.1)	2 (15.4)	2 (15.4)	1 (7.7)	8 (15.4)
95% CI	5.0; 53.8	1.9; 45.4	1.9; 45.4	0.2; 36.0	6.9; 28.1
Objective response rate (ORR) (CR + PR) (n (%)) [b]	0	0	0	0	0
95% CI	0.0; 24.7	0.0; 24.7	0.0; 24.7	0.0; 24.7	0.0; 6.8
Long term stable disease (n (%))	2 (15.4)	0	5 (38.5)	2 (15.4)	9 (17.3)
95% CI	1.9; 45.4	0.0; 24.7	13.9; 68.4	1.9; 45.4	8.2; 30.3

CI=confidence interval, CR=complete response, N=total number of subjects, n=number of subjects with data, NRSTS=non-rhabdomyosarcoma soft tissues sarcomas, ORR=objective response rate, PD=progressive disease, PR=partial response, RMS=rhabdomyosarcoma, SD=stable disease
Source: Table 14.2.1.1.2. Data cutoff date was 30 June 2021.
[a] Unable to evaluate corresponds to subjects who stopped study treatment before the first evaluation (N=6) and subjects with a first response SD and no other evaluation (N=2).
[b] ORR was assessed within 6 months of the first dose of cabozantinib (first intake date + 365.25/2).

Secondary Efficacy Endpoints

The median TTP was 3.7 months (95% CI: 1.7, 7.8) for patients with Ewing sarcoma, 2.0 months (95% CI: 1.4, 3.5) for patients with RMS, 7.4 months (95% CI: 1.8, 9.0) for patients with NRSTS and 2.5 months (95% CI: 1.7, 7.4) for patients with Wilms tumour (Table **20**).

Table 20 Time to Progression (Kaplan-Meier Method) – Non-osteosarcoma Strata (Evaluable Population for Response)

	Ewing sarcoma N=13	RMS N=13	NRSTS N=13	Wilms tumor N=13	Overall N=52
Number of events (n (%))	10 (76.92)	11 (84.62)	11 (84.62)	12 (92.31)	44 (84.62)
PD within 1-year of follow-up	10	11	11	10	42
PD after 1-year of follow-up	0	0	0	2	2
Number of censored subjects (n (%))	3 (23.08)	2 (15.38)	2 (15.38)	1 (7.69)	8 (15.38)
Subjects without documented PD	3	2	2	1	8
Median TTP [95% CI] (months)	3.7 [1.7; 7.8]	2.0 [1.4; 3.5]	7.4 [1.8; 9.0]	2.5 [1.7; 7.4]	3.3 [1.9; 4.0]
Minimal duration (months)	1.54	0.07	1.74	0.95	0.07
Maximal duration (months)	13.90	9.49	27.17	18.50	27.17
Subjects without progression (n) and survival estimate (%) [95% CI]					
3 months	6 (50.3) [21.1; 73.9]	3 (25.0) [6.0; 50.5]	10 (76.9) [44.2; 91.9]	6 (46.2) [19.2; 69.6]	25 (50.1) [35.7; 63.0]
6 months	3 (25.2) [6.1; 50.7]	2 (16.7) [2.7; 41.3]	7 (53.8) [24.8; 76.0]	4 (30.8) [9.5; 55.4]	16 (32.1) [19.8; 45.1]
9 months	2 (16.8) [2.7; 41.5]	1 (16.7) [2.7; 41.3]	3 (23.1) [5.6; 47.5]	3 (23.1) [5.6; 47.5]	9 (19.3) [9.6; 31.3]
12 months	2 (16.8) [2.7; 41.5]	0	2 (15.4) [2.5; 38.8]	3 (23.1) [5.6; 47.5]	7 (15.0) [6.7; 26.4]

CI=confidence interval, N=total number of subjects, n=number of subjects with data, NRSTS=non-rhabdomyosarcoma soft tissues sarcomas, PD=progression of disease, RMS=rhabdomyosarcoma, TTP=time to progression

The median duration of PFS was 1.9 months (95% CI: 1.7, 4.0) for patients with Ewing sarcoma, 2.0 months (95% CI: 1.4, 3.5) for patients with RMS, 7.4 months (95% CI: 1.8, 9.0) for patients with NRSTS and 2.5 months (95% CI: 1.7, 7.4) for patients with Wilms tumour (Table 21).

Table 21 Progression Free Survival (Kaplan-Meier Method) – Non-osteosarcoma Strata (Evaluable Population for Response)

	Ewing sarcoma N=13	RMS N=13	NRSTS N=13	Wilms tumor N=13	Overall N=52
Number of events (n (%))	13 (100.00)	12 (92.31)	12 (92.31)	13 (100.00)	50 (96.15)
Death without documented PD	3	1	1	1	6
Documented PD	10	11	11	12	44
Number of censored subjects (n (%))	0	1 (7.69)	1 (7.69)	0	2 (3.85)
Alive without documented PD		0	1		1
Unknown status without documented PD		1	0		1
Median PFS [95% CI] (months)	1.9 [1.7; 4.0]	2.0 [1.4; 3.5]	7.4 [1.8; 9.0]	2.5 [1.7; 7.4]	2.9 [1.8; 4.0]
Minimal duration (months)	1.54	0.03	1.74	0.95	0.03
Maximal duration (months)	13.90	9.49	20.60	18.50	20.60
Subjects without progression and alive (n) and survival estimate (%) [95% CI]					
3 months	6 (46.2) [19.2; 69.6]	3 (25.0) [6.0; 50.5]	10 (76.9) [44.2; 91.9]	6 (46.2) [19.2; 69.6]	25 (49.0) [34.8; 61.8]
6 months	3 (23.1) [5.6; 47.5]	2 (16.7) [2.7; 41.3]	7 (53.8) [24.8; 76.0]	4 (30.8) [9.5; 55.4]	16 (31.4) [19.3; 44.2]
9 months	2 (15.4) [2.5; 38.8]	1 (8.3) [0.5; 31.1]	3 (23.1) [5.6; 47.5]	3 (23.1) [5.6; 47.5]	9 (17.6) [8.7; 29.2]
12 months	2 (15.4) [2.5; 38.8]	0	2 (15.4) [2.5; 38.8]	3 (23.1) [5.6; 47.5]	7 (13.7) [6.0; 24.6]

CI=confidence interval, N=total number of subjects, n=number of subjects with data, NRSTS=non-rhabdomyosarcoma soft tissues sarcomas, PD=progression of disease, PFS=progression free survival, RMS=rhabdomyosarcoma

The median OS was 12.9 months (95% CI: 3.5, 13.9) for patients with Ewing sarcoma, 4.9 months (95% CI: 1.8, 22.3) for patients with RMS, 16.2 months (95% CI: 4.0, NC) for patients with NRSTS and 14.3 months (95% CI: 2.2, 17.5) for patients with Wilms tumour.

There are no duration of response and time to response results, as a best overall response of CR or PR was not observed in any of the patients.

A tumour shrinkage ≥30% (the minimum tumour shrinkage for a PR) was observed in two patients in each of the disease groups with RMS, NRSTS and Wilms tumour.

Efficacy results Rare Tumours Strata

Primary Efficacy Endpoints: Objective Response Rate

Following administration of cabozantinib, CRs were not observed in any disease group (

Table 22).

One patient with MTC had a PR until Cycle 6, another patient had a best overall response SD within the first 6 months of cabozantinib treatment; a PR was observed at Cycle 15 and it was maintained until Cycle 27.

Among the four patients with RCC, one patient PR until Cycle 6, another patient had SD and two patients had PD.

Among the eight patients with HCC, two patients had SD and three patients had PD. The other patients were unevaluable for response as follows: two patients had a first response of SD and no subsequent evaluation and one patient had discontinued cabozantinib before the first evaluation.

Among the two patients with hepatoblastoma, one patient had SD as the best overall response one patient had PD.

Among the two patients with adrenocortical carcinoma, one patient had SD as the best overall response and another patient had PD.

Among the five patients in other solid tumours disease group, responses were observed in one patient with DTC who had a PR until Cycle 12 and of three patients with CNS tumours as follow:

- one patient with a brain lesion in the pons had SD at Cycle 2, PR at Cycle 4 and PD at Cycle 6.
- one patient with brain and overlapping lesions in the right cerebellopontine angle had PD at Cycle 2.
- one patient with two CNS lesions had PD at Cycle 2.

For the remaining two patients with CNS tumours response could not be evaluated, due to early withdrawal (refusal of further protocol therapy at cycle 1 day 14) and the second patient response could not be evaluated due to discontinuation of study treatment at cycle 1 day 22 per physician decision.

Table 22 Objective Response Rate - Rare Tumours Strata (Evaluable Population for Response

	MTC N=2	RCC N=4	HCC N=8	Hepatoblastoma N=2	Adrenocortical carcinoma N=2	Other solid tumors N=5	Overall N=23
Best overall response							
PR (n (%))	1 (50.0)	1 (25.0)	0	0	0	1 (20.0)	3 (13.0)
95% CI	1.3; 98.7	0.6; 80.6	0.0; 36.9	0.0; 84.2	0.0; 84.2	0.5; 71.6	2.8; 33.6
SD (n (%))	1 (50.0) [a]	1 (25.0)	2 (25.0)	1 (50.0)	1 (50.0)	1 (20.0)	7 (30.4)
95% CI	1.3; 98.7	0.6; 80.6	3.2; 65.1	1.3; 98.7	1.3; 98.7	0.5; 71.6	13.2; 52.9
PD (n (%))	0	2 (50.0)	3 (37.5)	1 (50.0)	1 (50.0)	2 (40.0)	9 (39.1)
95% CI	0.0; 84.2	6.8; 93.2	8.5; 75.5	1.3; 98.7	1.3; 98.7	5.3; 85.3	19.7; 61.5
Unable to evaluate (n (%)) [b]	0	0	3 (37.5)	0	0	1 (20.0)	4 (17.4)
95% CI	0.0; 84.2	0.0; 60.2	8.5; 75.5	0.0; 84.2	0.0; 84.2	0.5; 71.6	5.0; 38.8
Objective response rate (ORR) (CR + PR) (n (%)) [c]	1 (50.0)	1 (25.0)	0	0	0	1 (20.0)	3 (13.0)
95% CI	1.3; 98.7	0.6; 80.6	0.0; 36.9	0.0; 84.2	0.0; 84.2	0.5; 71.6	2.8; 33.6
Long term stable disease (n (%))	1 (50.0)	0	0	0	0	0	1 (4.3)
95% CI	1.3; 98.7	0.0; 60.2	0.0; 36.9	0.0; 84.2	0.0; 84.2	0.0; 52.2	0.1; 21.9

CI=confidence interval, CR=complete response, HCC=hepatocellular carcinoma, MTC=medullary thyroid carcinoma, N=total number of subjects, n=number of subjects with data, ORR=objective response rate, PD=progressive disease, PR=partial response, RCC=renal cell carcinoma, SD=stable disease

Secondary Efficacy Endpoints

One patient with MTC had a TTP of 7.39 months and another patient 44.12 months. The median TTP of the four patients with RCC was 4.8 months (95% CI: 1.8, 7.2) with a minimum duration of 1.84 months and a maximum duration of 7.20 months. Among the eight patients with HCC, the median TTP was 4.2 months (95% CI: 0.9, 9.0) with a minimum duration of 0.92 months and a maximum of 9.03 months. The patient with hepatoblastoma had no tumour progression for 0.92 months and another patient for 5.19 months. The TTP was 1.84 months for one patient with adrenocortical carcinoma and 5.45 months for another patient. Among the five patients with other solid tumours, the median TTP was 5.3 months (95% CI: 1.4, NC) with a minimum duration of 1.41 months and a maximum of 12.75 months.

One patient with MTC had a duration of PFS of 5.52 months and another patient had a duration of 43.17 months. Among the four patients the median PFS was 4.8 months (95% CI: 1.8, 7.2) (

Table **23**). The median duration of PFS for the eight patients with HCC was 4.2 months (95% CI: 0.9, 9.0). The one patient with hepatoblastoma had a duration of PFS of 0.92 months and another patient had a duration of 5.19 months. The duration of PFS was 1.84 months for one patient with adrenocortical carcinoma and 5.45 months for another patient. For the five patients with other solid tumours, the median PFS was 3.6 months (95% CI: 1.4, NC).

Table 23 Progression Free Survival (Kaplan-Meier Method) - Rare Tumours Strata (Evaluable Population for Response)

	MTC N=2	RCC N=4	HCC N=8	Hepatoblastoma N=2	Adrenocortical carcinoma N=2	Other solid tumors N=5	Overall N=23
Number of events (n (%))	0	4 (100.00)	8 (100.00)	2 (100.00)	2 (100.00)	4 (80.00)	20 (86.96)
Death without documented PD		0	2	1	0	1	4
Documented PD		4	6	1	2	3	16
Number of censored subjects (n (%))	2 (100.00)	0	0	0	0	1 (20.00)	3 (13.04)
Alive without documented PD	1					0	1
Unknown status without documented PD	1					1	2
Median PFS [95% CI] (months)	NC [NC; NC]	4.8 [1.8; 7.2]	4.2 [0.9; 9.0]	3.1 [0.9; 5.2]	3.6 [1.8; 5.5]	3.6 [1.4; NC]	4.2 [1.8; 5.5]
Minimal duration (months)	5.52	1.84	0.92	0.92	1.84	1.41	0.92
Maximal duration (months)	43.17	7.20	9.03	5.19	5.45	11.66	43.17
Subjects without progression and alive (n) and survival estimate (%) [95% CI]							
3 months	2 (100) [100; 100]	3 (75.0) [12.8; 96.1]	6 (75.0) [31.5; 93.1]	1 (50.0) [0.6; 91.0]	1 (50.0) [0.6; 1.0]	3 (60.0) [12.6; 88.2]	16 (69.6) [46.6; 84.2]
6 months	1 (100) [100; 100]	1 (25.0) [0.9; 66.5]	2 (25.0) [3.7; 55.8]	0	0	1 (20.0) [0.8; 58.2]	5 (25.4) [9.9; 44.3]
9 months	1 (100) [100-100]	0	1 (12.5) [0.7; 2.3]	0	0	1 (20.0) [0.8; 58.2]	3 (15.2) [4.0; 33.3]
12 months	1 (100) [100-100]	0	0	0	0	12 months NC	1 (10.1) [1.8; 27.2]

CI=confidence interval, HCC=hepatocellular carcinoma, MTC=medullary thyroid carcinoma, N=total number of subjects, n=number of subjects with data, NC=not calculable, PD=progression of disease, PFS=progression free survival, RCC=renal cell carcinoma

One patient with MTC had an OS of 7.39 months and another patient of 44.12 months. Among four patient with RCC the minimum duration of OS was 5.52 months and the maximum was 28.75 months. The median OS was 10.9 months (95% CI: 5.5, NC). Among eight patients with HCC the minimum duration of OS was 2.07 months and the maximum was 12.94 months. The median OS was 9.8 months (95% CI: 2.1, 2.0). One patient with hepatoblastoma had an OS of 2.76 months and another patient had an OS of 5.19 months. One patient with adrenocortical carcinoma had an OS of 8.11 months and another patient had an OS of 17.35 months. Among the five patients with other solid tumours the minimum duration of OS was 2.20 months and the maximum 14.72 months. The median OS was 5.8 months (95% CI: 2.2, 14.7).

Few data on the duration of response is available, as for the total rare solid tumour stratum only 3 patients had a PR. One of two patients with MTC had PR within the first 6 months of cabozantinib treatment; the response was maintained for 1.87 months at the data cut-off. One of four patients with RCC had PR of 5.36 months. One of five patients in the other solid tumours had a PR for 9.46 months.

Time to response was 3.68 months for the patient with MTC, 1.87 months for the patient with RCC and 2.23 months for the patient with DTC.

A tumour shrinkage of ≥30% (the minimum tumour shrinkage for a PR) was observed as follows:

- in both patients with MTC
- in 1/4 patients with RCC
- in 1/8 patients with HCC
- in 1/2 patients with adrenocortical carcinoma
- in one patient with DTC (other solid tumours disease group)

Safety results

Exposure

The mean number of treatment cycles per patient was 4.1 (±4.4) cycles. Dosing was based on BSA using a dosing nomogram and rounded to nearest tablet strength to achieve the most accurate weekly doses, though doses on some days of the week could be different. Study drug was administered in 28-days cycles and dosing was continuous (i.e. no off-treatment weeks, although within a week patients could not take tablets on some days).

The cabozantinib dose for this trial was 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram). This was the recommended phase 2 dose determined from the phase 1 study ADVL1211.

Overall, the median starting dose was 50 mg (min: 40 mg and max: 80 mg) in patients <12 years of age, 60 mg (min: 40 mg and max: 100 mg) in patients aged ≥12 to <18 years and 80 mg (min: 60 mg and max: 100 mg) in patients ≥18 years of age.

Study treatment exposure is summarized in Table 24. Across strata, the median duration of exposure was 9 weeks. The longest exposure was observed in one patient with osteosarcoma and one patient with MTC (rare tumours strata) (115 and 120 weeks, respectively). Ten patients had a exposure of <4 weeks.

Table 24 Duration of Exposure (Weeks) - All Tumour Types (Safety Population)

	Statistics	Osteosarcoma N=29	Non-osteosarcoma N=54	All rare tumors N=25	Overall N=108
Duration of exposure (in weeks)	Mean (StD)	18.6 (21.6)	14.6 (13.3)	18.3 (24.3)	16.5 (18.6)
	Median	13	8	8	9
	Min, Max	4, 115	0, 54	2, 120	0, 120

Max=maximum, Min=minimum, N=total number of subjects, StD=standard deviation

Summary of AEs

All 108 patients who received at least one dose of cabozantinib were included in the safety population. A summary of the AEs by stratum is presented in

Table **25**.
Overall, 102/108 patients (94.4%) had at least one AE, and 70/108 patients (64.8%) had at least one TEAE. The majority of patients (61/108 patients, (56.5%)) had TEAEs that were evaluated as treatment related TEAEs. Seven patients (6.5%) experienced Grade 5 TEAEs (within 30 days following last dose of cabozantinib). Treatment emergent SAEs were reported for 37/108 patients (34.3%), including 18 patients (16.7%) who had treatment related SAEs (as per the investigator's assessment).

Table 25 Overview of Adverse Events - All Tumour Types (Safety Population)

AE Category n (%)	Osteosarcoma N=29	Non-osteosarcoma N=54	All rare tumors N=25	Overall N=108
At least one				
- AE	28 (96.6)	50 (92.6)	24 (96.0)	102 (94.4)
- Serious AE (SAE) [a]	8 (27.6)	20 (37.0)	11 (44.0)	39 (36.1)
- TEAE	21 (72.4)	32 (59.3)	17 (68.0)	70 (64.8)
- Grade 1 TEAE	0	2 (3.7)	4 (16.0)	6 (5.6)
- Grade 2 TEAE	5 (17.2)	7 (13.0)	6 (24.0)	18 (16.7)
- Grade 3 TEAE	18 (62.1)	31 (57.4)	16 (64.0)	65 (60.2)
- Grade 4 TEAE	1 (3.4)	4 (7.4)	3 (12.0)	8 (7.4)
- Grade 5 TEAE	1 (3.4)	4 (7.4)	2 (8.0)	7 (6.5)
- Treatment-related TEAE	20 (69.0)	26 (48.1)	15 (60.0)	61 (56.5)
- TEAE leading to dose-limiting toxicity	17 (58.6)	24 (44.4)	12 (48.0)	53 (49.1)
- TEAE reported for growth plate toxicity	0	0	0	0 (0.0)
- TEAE require hospitalization or prolonged hospitalization	7 (24.1)	15 (27.8)	9 (36.0)	31 (28.7)
- Treatment emergent SAE	8 (27.6)	18 (33.3)	11 (44.0)	37 (34.3)
- Treatment emergent-related SAE	5 (17.2)	9 (16.7)	4 (16.0)	18 (16.7)
- Treatment emergent SAE leading to dose-limiting toxicity [b]	5 (17.2)	9 (16.7)	4 (16.0)	18 (16.7)
- Treatment emergent SAE require hospitalization or prolonged hospitalization	6 (20.7)	14 (25.9)	9 (36.0)	29 (26.9)

AE=adverse event, N=total number of subjects, n=number of subjects with data, SAE=serious adverse event, TEAE=treatment emergent adverse event
Source: Table 14.3.2.2.1.4. Data cutoff date was 30 June 2021.
The denominator is the number of subjects in the given column (N).
[a] Definition of SAE per Section 11.2 of the protocol (Appendix 16.1.1).
[b] Events of dose-limiting toxicities are listed in Section 5.1 of the protocol (Appendix 16.1.1).

Forty-five of 70 children (64.3%) and 25/38 adults (65.8%) had a TEAE. SAEs were reported for 34.3% and 39.5% of patients in the two groups, respectively. Four children (5.7%) and three adults (7.9%) had a Grade 5 TEAE that occurred within 30 days following the last dose of cabozantinib.

Most Frequently Reported Adverse Events

Frequent TEAEs (i.e. those reported for ≥2% of patients) in the safety population are summarized in Table 26.
Overall, 70/108 patients (64.8%) treated with cabozantinib had at least one TEAE reported during the

study. The TEAEs with the highest incidence (reported for ≥5% of patients) by decreasing frequency were AST increased (10.2%), ALT increased, lipase increased and neutrophil count decreased (9.3% each), vomiting and hypertension (7.4% each), weight decreased and anaemia (6.5% each). There were four patients (3.7%) who experienced TEAEs of pneumothorax. The incidence of Palmar-plantar erythrodysesthesia syndrome (PPES) also known as hand-foot syndrome was low (2.8%).

Table 26 Most Common (≥2% of Patients) TEAEs by System Organ Class and Preferred Term - All Tumour Types (Safety Population)

	Osteosarcoma (N=29)		Non-osteosarcoma (N=54)		All rare tumors (N=25)		Overall (N=108)	
Primary SOC PT	**n (%)**	**nAE**	**n (%)**	**nAE**	**n (%)**	**nAE**	**n (%)**	**nAE**
At least one TEAE	21 (72.4)	49	32 (59.3)	122	17 (68.0)	79	70 (64.8)	250
Investigations	**11 (37.9)**	**17**	**19 (35.2)**	**38**	**13 (52.0)**	**30**	**43 (39.8)**	**85**
Aspartate aminotransferase increased	3 (10.3)	3	2 (3.7)	2	6 (24.0)	7	11 (10.2)	12
Alanine aminotransferase increased	1 (3.4)	1	3 (5.6)	3	6 (24.0)	6	10 (9.3)	10
Lipase increased	2 (6.9)	2	8 (14.8)	10	0	0	10 (9.3)	12
Neutrophil count decreased	2 (6.9)	2	4 (7.4)	5	4 (16.0)	7	10 (9.3)	14
Weight decreased	2 (6.9)	2	4 (7.4)	4	1 (4.0)	2	7 (6.5)	8
Blood bilirubin increased	0	0	1 (1.9)	2	3 (12.0)	3	4 (3.7)	5
Platelet count decreased	0	0	3 (5.6)	3	1 (4.0)	1	4 (3.7)	4
White blood cell count decreased	1 (3.4)	1	2 (3.7)	2	1 (4.0)	1	4 (3.7)	4
Lymphocyte count decreased	0	0	3 (5.6)	4	0	0	3 (2.8)	4
Metabolism and nutrition disorders	**5 (17.2)**	**6**	**8 (14.8)**	**9**	**5 (20.0)**	**6**	**18 (16.7)**	**21**
Dehydration	0	0	3 (5.6)	3	2 (8.0)	2	5 (4.6)	5
Hyponatraemia	0	0	2 (3.7)	2	2 (8.0)	2	4 (3.7)	4
Decreased appetite	1 (3.4)	1	1 (1.9)	1	1 (4.0)	1	3 (2.8)	3
Hypophosphataemia	1 (3.4)	2	2 (3.7)	2	0	0	3 (2.8)	4
Gastrointestinal disorders	**2 (6.9)**	**5**	**10 (18.5)**	**19**	**5 (20.0)**	**10**	**17 (15.7)**	**34**
Vomiting	1 (3.4)	2	4 (7.4)	6	3 (12.0)	4	8 (7.4)	12
Nausea	1 (3.4)	1	3 (5.6)	4	1 (4.0)	1	5 (4.6)	6
Diarrhoea	1 (3.4)	2	3 (5.6)	3	0	0	4 (3.7)	5
Abdominal pain	0	0	1 (1.9)	1	2 (8.0)	2	3 (2.8)	3
General disorders and administration site conditions	**3 (10.3)**	**3**	**9 (16.7)**	**10**	**5 (20.0)**	**6**	**17 (15.7)**	**19**
Disease progression	0	0	2 (3.7)	2	2 (8.0)	2	4 (3.7)	4
Fatigue	1 (3.4)	1	2 (3.7)	2	1 (4.0)	1	4 (3.7)	4
Non-cardiac chest pain	1 (3.4)	1	2 (3.7)	2	0	0	3 (2.8)	3
Pyrexia	0	0	1 (1.9)	1	2 (8.0)	2	3 (2.8)	3
Respiratory, thoracic and mediastinal disorders	**2 (6.9)**	**4**	**7 (13.0)**	**14**	**2 (8.0)**	**4**	**11 (10.2)**	**22**
Pneumothorax	2 (6.9)	4	2 (3.7)	2	0	0	4 (3.7)	6
Dyspnoea	0	0	3 (5.6)	3	0	0	3 (2.8)	3
Hypoxia	0	0	3 (5.6)	3	0	0	3 (2.8)	3
Pleural effusion	0	0	2 (3.7)	2	1 (4.0)	1	3 (2.8)	3
Vascular disorders	**2 (6.9)**	**2**	**5 (9.3)**	**6**	**4 (16.0)**	**4**	**11 (10.2)**	**12**
Hypertension	2 (6.9)	2	3 (5.6)	3	3 (12.0)	3	8 (7.4)	8
Infections and infestations	**1 (3.4)**	**1**	**5 (9.3)**	**7**	**3 (12.0)**	**3**	**9 (8.3)**	**11**
Pneumonia	0	0	1 (1.9)	2	2 (8.0)	2	3 (2.8)	4
Blood and lymphatic system disorders	**0**	**0**	**3 (5.6)**	**3**	**4 (16.0)**	**4**	**7 (6.5)**	**7**
Anaemia	0	0	3 (5.6)	3	4 (16.0)	4	7 (6.5)	7
Musculoskeletal and connective tissue disorders	**2 (6.9)**	**2**	**2 (3.7)**	**3**	**3 (12.0)**	**4**	**7 (6.5)**	**9**
Pain in extremity	2 (6.9)	2	1 (1.9)	1	1 (4.0)	1	4 (3.7)	4

Skin and subcutaneous tissue disorders	**2 (6.9)**	**3**	**1 (1.9)**	**1**	**1 (4.0)**	**1**	**4 (3.7)**	**5**
Palmar-plantar erythrodysaesthesia syndrome	1 (3.4)	2	1 (1.9)	1	1 (4.0)	1	3 (2.8)	4
Injury, poisoning and procedural complications	**2 (6.9)**	**2**	**0**	**0**	**1 (4.0)**	**1**	**3 (2.8)**	**3**
Wound dehiscence	2 (6.9)	2	0	0	1 (4.0)	1	3 (2.8)	3

MedDRA=Medical dictionary for regulatory activities, N=total number of subjects, n=number of subjects with data, nAE=number of events, NCI-CTCAE=National Cancer Institute Common Terminology for Adverse Events, PT=preferred term, SOC=system organ class, TEAE=treatment emergent adverse event
Source: Table 14.3.2.2.1.12. Data cutoff date was 30 June 2021.
The denominator is the number of subjects in the given column (N).
TEAEs are defined as events which started or worsened on or after the first dose of study drug administration up to 30 days (gap period) after the last dose of study drug administration. If there is more than one TEAE reported under the same SOC and PT, the subject is counted only once under that SOC and PT. If there is more than one TEAE reported under the same SOC, the subject is counted only once under that SOC. The SOCs with all PTs less than 10% incidence are not included in this table.
Adverse events were coded using MedDRA Version 24.1. Adverse events were graded using NCI-CTCAE version 5.0.

In children, the TEAEs reported for ≥5% of patients, by decreasing frequency, were AST increased (12.9%), ALT increased (11.4%), hypertension (10.0%), neutrophil count decreased and anaemia (8.6% each), lipase increased (7.1%), blood bilirubin increased and vomiting (5.7% each).
The TEAEs reported for ≥5% of adults, by decreasing frequency, were lipase increased and weight decreased (13.2% each), neutrophil count decreased, nausea and vomiting (10.5% each), diarrhoea, hypophosphatemia, dyspnoea and pneumothorax (7.9% each), ALT increased, AST increased, lymphocyte count decreased, white blood cell count decreased, dehydration, hypoxia, fatigue, seizure and pericardial effusion (5.3% each).

Grade 3 or Higher TEAEs

A summary of most frequent Grade 3 to 4 TEAEs (i.e. those reported for ≥2% of patients) regardless of causality is provided in

Table 27.

Overall, 64/108 patients (59.3%) had at least one maximum Grade 3 TEAE and 8/108 patients (7.4%) had at least one maximum Grade 4 TEAE during the study. The most frequent Grade 3 TEAEs (≥5% incidence) reported for all patients in descending order of incidence were AST increased, ALT increased, lipase increased and neutrophil count decreased (8.3% each), hypertension (7.4%), vomiting and anaemia (6.5% each) and weight decreased (5.6%). Grade 4 TEAEs of AST increased, lipase increased, neutrophil count decreased, blood bilirubin increased, platelet count decreased, lymphocyte count decreased, hypocalcaemia, respiratory failure, hypotension, sepsis and leukaemia were reported for one patient each (0.9%).

Table 27 Summary of Grade 3 and Grade 4 TEAEs by System Organ Class and Preferred Term (≥ 2% Incidence) - All Tumour Types (Safety Population)

	Osteosarcoma (N=29) n (%)		Non-osteosarcoma (N=54) n (%)		All rare tumors (N=25) n (%)		Overall (N=108) n (%)	
Primary SOC PT	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
At least one maximum grade TEAE	18 (62.1)	1 (3.4)	31 (57.4)	4 (7.4)	15 (60.0)	3 (12.0)	64 (59.3)	8 (7.4)
Investigations	**10 (34.5)**	**1 (3.4)**	**18 (33.3)**	**2 (3.7)**	**10 (40.0)**	**3 (12.0)**	**38 (35.2)**	**6 (5.6)**
Aspartate aminotransferase increased	3 (10.3)	0	2 (3.7)	0	4 (16.0)	1 (4.0)	9 (8.3)	1 (0.9)
Lipase increased	1 (3.4)	1 (3.4)	8 (14.8)	0	0	0	9 (8.3)	1 (0.9)
Neutrophil count decreased	2 (6.9)	0	4 (7.4)	0	3 (12.0)	1 (4.0)	9 (8.3)	1 (0.9)
Alanine aminotransferase increased	1 (3.4)	0	3 (5.6)	0	5 (20.0)	0	9 (8.3)	0
Weight decreased	2 (6.9)	0	3 (5.6)	0	1 (4.0)	0	6 (5.6)	0
Platelet count decreased	0	0	2 (3.7)	1 (1.9)	1 (4.0)	0	3 (2.8)	1 (0.9)
White blood cell count decreased	1 (3.4)	0	2 (3.7)	0	1 (4.0)	0	4 (3.7)	0
Blood bilirubin increased	0	0	1 (1.9)	0	1 (4.0)	1 (4.0)	2 (1.9)	1 (0.9)
Lymphocyte count decreased	0	0	2 (3.7)	1 (1.9)	0	0	2 (1.9)	1 (0.9)
Amylase increased	0	0	2 (3.7)	0	0	0	2 (1.9)	0
Blood alkaline phosphatase increased	1 (3.4)	0	0	0	0	0	1 (0.9)	0
Ejection fraction decreased	1 (3.4)	0	0	0	0	0	1 (0.9)	0
Gamma-glutamyltransferase increased	0	0	0	0	1 (4.0)	0	1 (0.9)	0
Investigation abnormal	0	0	0	0	1 (4.0)	0	1 (0.9)	0
Urine output decreased	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Metabolism and nutrition disorders	**5 (17.2)**	**0**	**8 (14.8)**	**1 (1.9)**	**4 (16.0)**	**0**	**17 (15.7)**	**1 (0.9)**
Dehydration	0	0	3 (5.6)	0	1 (4.0)	0	4 (3.7)	0
Hyponatraemia	0	0	2 (3.7)	0	2 (8.0)	0	4 (3.7)	0

	Osteosarcoma (N=29) n (%)		Non-osteosarcoma (N=54) n (%)		All rare tumors (N=25) n (%)		Overall (N=108) n (%)	
Primary SOC PT	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Decreased appetite	1 (3.4)	0	1 (1.9)	0	1 (4.0)	0	3 (2.8)	0
Hypophosphataemia	1 (3.4)	0	2 (3.7)	0	0	0	3 (2.8)	0
Hypokalaemia	2 (6.9)	0	0	0	0	0	2 (1.9)	0
Hyperammonaemia	0	0	0	0	1 (4.0)	0	1 (0.9)	0
Hypernatraemia	1 (3.4)	0	0	0	0	0	1 (0.9)	0
Hypocalcaemia	0	0	0	1 (1.9)	0	0	0	1 (0.9)
Gastrointestinal disorders	**1 (3.4)**	**0**	**9 (16.7)**	**0**	**4 (16.0)**	**0**	**14 (13.0)**	**0**
Vomiting	1 (3.4)	0	4 (7.4)	0	2 (8.0)	0	7 (6.5)	0
Abdominal pain	0	0	1 (1.9)	0	2 (8.0)	0	3 (2.8)	0
Diarrhoea	1 (3.4)	0	2 (3.7)	0	0	0	3 (2.8)	0
Nausea	0	0	2 (3.7)	0	1 (4.0)	0	3 (2.8)	0
Constipation	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Oesophageal stenosis	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Oral pain	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Pancreatitis	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Stomatitis	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Respiratory, thoracic and mediastinal disorders	**2 (6.9)**	**0**	**7 (13.0)**	**1 (1.9)**	**2 (8.0)**	**0**	**11 (10.2)**	**1 (0.9)**
Pneumothorax	2 (6.9)	0	2 (3.7)	0	0	0	4 (3.7)	0
Hypoxia	0	0	3 (5.6)	0	0	0	3 (2.8)	0
Pleural effusion	0	0	2 (3.7)	0	1 (4.0)	0	3 (2.8)	0
Dyspnoea	0	0	2 (3.7)	0	0	0	2 (1.9)	0
Atelectasis	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Pleuritic pain	0	0	1 (1.9)	0	0	0	1 (0.9)	0

	Osteosarcoma (N=29) n (%)		Non-osteosarcoma (N=54) n (%)		All rare tumors (N=25) n (%)		Overall (N=108) n (%)	
Primary SOC PT	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Productive cough	0	0	0	0	1 (4.0)	0	1 (0.9)	0
Respiratory failure	0	0	0	1 (1.9)	0	0	0	1 (0.9)
Vascular disorders	**2 (6.9)**	**0**	**4 (7.4)**	**1 (1.9)**	**4 (16.0)**	**0**	**10 (9.3)**	**1 (0.9)**
Hypertension	2 (6.9)	0	3 (5.6)	0	3 (12.0)	0	8 (7.4)	0
Embolism	0	0	2 (3.7)	0	0	0	2 (1.9)	0
Hypotension	0	0	0	1 (1.9)	1 (4.0)	0	1 (0.9)	1 (0.9)
Infections and infestations	**1 (3.4)**	**0**	**5 (9.3)**	**0**	**1 (4.0)**	**1 (4.0)**	**7 (6.5)**	**1 (0.9)**
Pneumonia	0	0	1 (1.9)	0	1 (4.0)	0	2 (1.9)	0
Varicella	0	0	2 (3.7)	0	0	0	2 (1.9)	0
Eye infection	1 (3.4)	0	0	0	0	0	1 (0.9)	0
Influenza	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Sepsis	0	0	0	0	0	1 (4.0)	0	1 (0.9)
Skin infection	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Upper respiratory tract infection	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Blood and lymphatic system disorders	**0**	**0**	**3 (5.6)**	**0**	**4 (16.0)**	**0**	**7 (6.5)**	**0**
Anaemia	0	0	3 (5.6)	0	4 (16.0)	0	7 (6.5)	0
Musculoskeletal and connective tissue disorders	**2 (6.9)**	**0**	**2 (3.7)**	**0**	**3 (12.0)**	**0**	**7 (6.5)**	**0**
Pain in extremity	2 (6.9)	0	1 (1.9)	0	1 (4.0)	0	4 (3.7)	0
Flank pain	0	0	0	0	2 (8.0)	0	2 (1.9)	0
Back pain	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Muscular weakness	0	0	0	0	1 (4.0)	0	1 (0.9)	0
Musculoskeletal chest pain	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Nervous system disorders	**1 (3.4)**	**0**	**4 (7.4)**	**0**	**2 (8.0)**	**0**	**7 (6.5)**	**0**

	Osteosarcoma (N=29) n (%)		Non-osteosarcoma (N=54) n (%)		All rare tumors (N=25) n (%)		Overall (N=108) n (%)	
Primary SOC PT	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Dysaesthesia	0	0	0	0	1 (4.0)	0	1 (0.9)	0
Dysarthria	0	0	0	0	1 (4.0)	0	1 (0.9)	0
Haemorrhage intracranial	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Headache	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Hemiparesis	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Paraesthesia	0	0	0	0	1 (4.0)	0	1 (0.9)	0
Seizure	1 (3.4)	0	0	0	0	0	1 (0.9)	0
Spinal cord compression	0	0	0	0	1 (4.0)	0	1 (0.9)	0
Syncope	0	0	1 (1.9)	0	0	0	1 (0.9)	0
General disorders and administration site conditions	**2 (6.9)**	**0**	**3 (5.6)**	**0**	**1 (4.0)**	**0**	**6 (5.6)**	**0**
Fatigue	1 (3.4)	0	1 (1.9)	0	0	0	2 (1.9)	0
Face oedema	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Gait disturbance	0	0	0	0	1 (4.0)	0	1 (0.9)	0
Non-cardiac chest pain	1 (3.4)	0	0	0	0	0	1 (0.9)	0
Pain	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (3.4)**	**0**	**0**	**1 (1.9)**	**1 (4.0)**	**0**	**2 (1.9)**	**1 (0.9)**
Tumor pain	1 (3.4)	0	0	0	1 (4.0)	0	2 (1.9)	0
Leukaemia	0	0	0	1 (1.9)	0	0	0	1 (0.9)
Skin and subcutaneous tissue disorders	**2 (6.9)**	**0**	**0**	**0**	**1 (4.0)**	**0**	**3 (2.8)**	**0**
Palmar-plantar erythrodysaesthesia syndrome	1 (3.4)	0	0	0	1 (4.0)	0	2 (1.9)	0
Skin exfoliation	1 (3.4)	0	0	0	0	0	1 (0.9)	0
Cardiac disorders	**1 (3.4)**	**0**	**1 (1.9)**	**0**	**0**	**0**	**2 (1.9)**	**0**
Angina pectoris	0	0	1 (1.9)	0	0	0	1 (0.9)	0

	Osteosarcoma (N=29) n (%)		Non-osteosarcoma (N=54) n (%)		All rare tumors (N=25) n (%)		Overall (N=108) n (%)	
Primary SOC PT	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Cardiac failure	1 (3.4)	0	0	0	0	0	1 (0.9)	0
Left ventricular dysfunction	1 (3.4)	0	0	0	0	0	1 (0.9)	0
Pericardial effusion	0	0	1 (1.9)	0	0	0	1 (0.9)	0
Injury, poisoning and procedural complications	**0**	**0**	**0**	**0**	**1 (4.0)**	**0**	**1 (0.9)**	**0**
Wound dehiscence	0	0	0	0	1 (4.0)	0	1 (0.9)	0
Renal and urinary disorders	**0**	**0**	**0**	**0**	**1 (4.0)**	**0**	**1 (0.9)**	**0**
Proteinuria	0	0	0	0	1 (4.0)	0	1 (0.9)	0

MedDRA=Medical dictionary for regulatory activities, N=total number of subjects; n=number of subjects with data, nAE=number of events, NCI-CTCAE=National Cancer Institute Common Terminology for Adverse Events, PT=preferred term, SOC=system organ class, TEAE=treatment emergent adverse event

Source: Table 14.3.2.2.1.24. Data cutoff date was 30 June 2021.

The denominator is the number of subjects in the given column (N).

TEAEs are defined as events which started or worsened on or after the first dose of study drug administration up to 30 days (gap period) after the last dose of study drug administration. If there is more than one TEAE reported under the same SOC and PT, the subject is counted only once under that SOC and PT. If there is more than one TEAE reported under the same SOC, the subject is counted only once under that SOC. The SOCs with all PTs less than 10% incidence are not included in this table.

Adverse events were coded using MedDRA Version 24.1. Adverse events were graded using NCI-CTCAE version 5.0.

Forty of 70 children (57.1%) had at least one maximum Grade 3 TEAE and 6/70 patients (8.6%) had at least one maximum Grade 4 TEAE during the study. The most frequent Grade 3 TEAEs (≥5% incidence) reported for all children in descending order of incidence were AST increased, ALT increased and hypertension (10.0% each), anaemia (8.6%), neutrophil count decreased (7.1%) and lipase increased (5.7%). Grade 4 TEAEs of AST increased, neutrophil count decreased, lipase increased, blood bilirubin increased, platelet count decreased, hypotension, sepsis and respiratory failure were reported by one patient each (1.4%).

In adults, 24/38 patients (63.2%) experienced at least one maximum Grade 3 TEAE and 2/38 patients (5.3%) experienced at least one maximum Grade 4 TEAE. The most frequent Grade 3 TEAEs (≥5% incidence) reported for all adults in descending order of incidence were lipase increased (13.2%), neutrophil count decreased, weight decreased and vomiting (10.5% each), hypophosphatasaemia and pneumothorax (7.9% each), ALT increased, AST increased, white blood cell count decreased, dehydration, diarrhoea, nausea, dyspnoea and hypoxia (5.3% each). Grade 4 TEAEs of lymphocyte count decreased, hypocalcaemia and leukaemia were reported by one patient each (2.6%)

SAEs

Deaths

Grade 5 TEAEs were reported for 7/108 patients (6.5%) as follows:

- 1/29 patients (3.4%) in the osteosarcoma stratum
- 4/54 patients (7.4%) in non-osteosarcoma strata
- 2/25 patients (8.0%) in rare tumours strata

Investigator assessed the primary cause of death for all these patients disease progression.

Patients with a Grade 5 TEAEs are discussed below:

- One patient with metastatic, refractory osteosarcoma experienced multiple AEs during the study: anaemia, anorexia, dyspnoea, pleural effusion, proteinuria and alkaline phosphatase increased. All but one AE of anorexia, assessed as possibly related, were unrelated to study treatment. Patient received study treatment for six cycles. On study Day 152 (Cycle 6), patient experienced constipation, persistent pain and severe vomiting. On the same day administration of cabozantinib was interrupted as the patient was unable to tolerate per os medication. Patient died on study Day 156; the investigator assessed the Grade 5 event of death not otherwise specified (NOS) as not related to study treatment. Per investigator assessment the primary

cause of death was disease progression.

- One patient with RMS received cabozantinib for two cycles. On study Day 51 (Cycle 2), the patient experienced multiple episodes of bilious emesis, mild altered mental status, somnolence and confusion. A CT of the head demonstrated significant left frontal hemorrhagic stroke, likely stemming from underlying metastatic tumor. On study Day 54, a cerebrovascular accident (Grade 5) was reported; the patient developed seizure and died. The investigator assessed the Grade 5 TEAE as unlikely related to cabozantinib. The primary cause of death per investigator assessment was disease progression.
- One patient with Wilms tumor received two cycles of cabozantinib. On study Day 61 (Cycle 2), the patient experienced vomiting (Grade 3), constipation (Grade 3) and dyspnoea (Grade 3). The following day the patient developed hypoxia (Grade 3) and pneumothorax (Grade 3). Patient died on study Day 66, due to disease progression (Grade 5).
- One patient with Ewing sarcoma received cabozantinib for two treatment cycles. On study Day 43 (Cycle 2), patient had an echocardiogram that demonstrated pericardial effusion with concern of possible developing tamponade physiology. On Day 51 the patient developed a pericardial tamponade (Grade 5) and died. The investigator assessed the event as unrelated to study treatment. The primary cause of death per investigator assessment was disease progression.
- One patient with Wilms tumor received three cycles of cabozantinib. On study Day 90 (Cycle 3) treatment with cabozantinib was withheld due to weight loss (Grade 3). On study Day 106 (Cycle 3) treatment with cabozantinib was discontinued due to tumor progression. Patient died on study Day 108 due to disease progression (Grade 5).
- One patient with CNS tumor received cabozantinib for six cycles. On study Day 161 (Cycle 6), patient was removed from protocol therapy due to progressive disease. Last dose of cabozantinib was taken on Day 160. Patient died on Day 175 due to disease progression (Grade 5) during the 30-day follow-up period.
- One patient with CNS tumour received treatment with cabozantinib for two cycles. On study Day 44 (Cycle 2), the patient discontinued treatment with cabozantinib due to disease progression. The last dose of study drug was administered on Day 42. Patient died on Day 67 due to progressive disease (Grade 5).

In addition to these seven patients who died during or in the 30 day follow up period after last dose of cabozantinib, 73 other patients died during the follow up period. All deaths and associated Grade 5 TEAEs of death NOS, cardiovascular accident and cardiac tamponade occurred during the study were attributed per investigator assessment to disease progression.

Other SAEs

There were 37/108 patients (34.3%) who experienced treatment emergent SAEs during the study. By PT, SAEs reported for ≥2% of patients were the followings: disease progression and pneumothorax (3.7% each), non-cardiac chest pain, pyrexia, dyspnoea, hypoxia, pleural effusion, pneumonia, vomiting, AST increased, blood bilirubin increased and dehydration (2.8% each).

There were 18 of the 108 patients (16.7%) with SAEs that were evaluated by the investigator as treatment related. The most frequent treatment related SAEs (≥1% incidence) by decreasing frequency were AST increased (2.8%), pneumothorax, pneumonia, vomiting, blood bilirubin increased, weight decreased, hyponatraemia and embolism (1.9% each).

There were 23/70 children (32.9%) and 14/38 adults (36.8%) who experienced treatment emergent SAEs during the study.

By PT, SAEs reported for ≥2% of children were the followings: disease progression, pyrexia, AST increased, blood bilirubin increased and dehydration (4.3% each), ALT increased, non-cardiac chest pain, pneumonia, varicella, hyponatraemia, abdominal pain, vomiting, pleural effusion, hypotension, flank pain and tumour pain (2.9% each).

There were 11 of the 70 children (15.7%) with SAEs that were evaluated by the investigator as treatment related. The most frequent treatment related SAEs (≥2% incidence) by decreasing frequency were AST increased (4.3%), blood bilirubin increased, hyponatraemia and vomiting (2.9% each).

Four children (5.7%) had fatal outcome due to SAEs during the study treatment period: three children experienced SAEs of disease progression and one child experienced one SAE of cardiac tamponade; all SAEs with a fatal outcome were assessed as not related to study treatment.

In adults, the SAEs reported for ≥5% of patients were the followings: dyspnoea and pneumothorax (7.9% each), hypoxia, seizure and pericardial effusion (5.3% each); other events were each experienced by one patient (2.6%).

There were 7/38 adults (18.4%) with SAEs that were evaluated by the investigator as treatment related. Treatment related SAEs were pneumothorax, hypoxia, headache, oral pain, pneumonia, skin infection, hypophosphatemia, weight decreased and embolism (2.6% each).

Three adults (7.9%) had fatal outcome due to SAEs during the study treatment period: events of disease progression, death NOS and cerebrovascular accident were experienced by one patient each; all SAEs with a fatal outcome were assessed as not related to study treatment.

Adverse Events Leading to Withdrawal

The TEAEs that led to discontinuation of study drug were not recorded.

Dose Limiting Toxicities

TEAEs leading to DLTs were reported by 53/108 patients (49.1%). The most frequent TEAEs leading to DLT (reported for ≥5% patients) by PT were AST increased (8.3%), ALT increased (7.4%), lipase increased and weight decreased (6.5% each).

Among children, the most frequent TEAEs leading to DLTs (reported for ≥5% patients) by PT were AST increased (11.4%), ALT increased (8.6%) and lipase increased (5.7%).

In adults, the most frequent TEAEs leading to DLTs (reported for ≥5% patients) by PT were weight decreased (13.2%), lipase increase and nausea (7.9% each), ALT increased, vomiting and fatigue (5.3% each).

Treatment Emergent Adverse Events of Special Interest

Pneumothorax

Two of the 29 patients (6.9%), one adult and one child, in the osteosarcoma stratum had experienced two events of pneumothorax each, during the treatment period (including the 30-day follow-up period after last dose of cabozantinib). Further, 2 of the 54 patients (3.7%) in non-osteosarcoma strata, both adults, and one child in the rare tumours strata (1/25 patients (4.0%)) experienced one event of pneumothorax.

Tibial Growth Plate Assessment

There were no tibial growth plate related effects (evidence of growth plate thickening) noted during the study in patients with open tibial growth plate at baseline.

Clinical Laboratory Evaluations

The CRF did not record the laboratory parameters at the specific timepoints throughout the study.

2.3.4. Summary and discussion on clinical aspects

This report concerns a paediatric work sharing for which the clinical study report of study ADVL1622 is submitted. No changes in the indication or any other section of the SmPC are proposed by the applicant.

Study design

ADVL1622 is a multicentre, open label two stage phase 2 trial to assess the activity of cabozantinib in selected paediatric solid tumours. The study includes the following solid tumour strata; Ewing sarcoma, rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), osteosarcoma, Wilms tumour and other rare solid tumours. The study is part of the approved PIP (study 7) EMEA-001143-PIP01-11, other studies included in the PIP are;

- A quality study to develop an age appropriate formulation (study 1)
- A juvenile toxicity and toxicokinetic study (study 2)
- An in vitro and in vivo non-clinical efficacy testing study for paediatric malignancies (study 3)
- An open-label trial to evaluate toxicity, tolerability, PK and PD of cabozantinib in children age 2 years and above to less than 18 years of age with refractory or relapsed malignant solid tumours (study 4)
- A trial to evaluate relative bioavailability (in adults) (study 5)
- A randomised, double-blind, controlled, parallel-group safety and efficacy clinical of cabozantinib in patients aged from birth to less than 18 years with a malignant solid tumour(s) determined based on results of studies 3 and 4 (study 6)

PIP studies 2, 3, 4 and 5are already completed before.

In ADVL1622 cabozantinib was administered orally once daily in tablet strength of 20 mg and 60 mg, on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m^2/day (cumulative weekly dose of 280 mg/m^2 using a dosing nomogram). The dose was based on results of study ADVL1211 (study 4 of the PIP), that was already assessed during the paediatric worksharing procedure EMEA/C/002640/II/0036. During that procedure it was concluded that the selection of 40 mg/m^2 may not be the optimum dose for paediatric patients. PK of cabozantinib in the paediatric patients (at single dose and at steady state) could not be characterised sufficiently. However as more PK data would become available no further questions were raised.

Patients were ≥2 and ≤30 years of age at the time of study entry for all strata, except for the MTC, RCC and HCC strata the upper age limit was ≤18 years.

The primary objective of the study is to determine the ORR (CR+PR) of cabozantinib in children and young adults several selected tumour types (Ewing sarcoma, RMS, NRSTS, Wilms tumour rare tumour including MTC, RCC, HCC, Hepatoblastoma, adrenocortical carcinoma and paediatric solid tumours with known molecular alterations in the targets of cabozantinib). Furthermore the primary objective for the osteosarcoma stratum was to estimate whether cabozantinib therapy either improves the disease control rate at 4 months in patients with recurrent measurable osteosarcoma as compared to a historical COG experience or produces an ORR. Secondary objectives include safety PK, and to estimate 1-year TPP, PFS and OS for each stratum and if feasible to compare to historical control.

ORR is accepted as endpoint for phase 2 studies, especially when results are mainly used to determine anti-tumour activity and select the tumour types against which cabozantinib is most effective. The secondary time dependent endpoints are difficult to interpret without a control arm.

Based on the mode of action of cabozantinib, tumour types in which the key targets are known to be involved in development and maintenance of the cancer were selected. This applies for the sarcoma strata. In addition, other tumour types were included as cabozantinib is likely to be active because cabozantinib efficacy has previously been reported in paediatric or adult patients with these tumour types, i.e. MTC, RCC, nephroblastoma, hepatocellular carcinoma and hepatoblastoma. For most strata patients were not specifically selected based on the presences of biomarkers. Therefore it is not clear whether or not the study population includes indeed the patients that are most likely to benefit from cabozantinib treatment. According to the key binding elements of the PIP, also PD markers should be assessed i.e. VEGF and HGF/MET pathway inhibition in blood and archival tumour tissues, circulating plasma levels of HGF, sMET, VEGF-A, sVEGFR2 and PIGF, furthermore, immunohistochemistry for MET, PD1 and PCR for MET in available samples, was requested in the PIP.

Currently a PIP modification is ongoing in which the applicant is requesting to delete this requirement because based on results from study the collected PD data was not considered to show clinically relevant results. However this conclusion is considered still premature as the PD analysis from study 4 was based on a limited sample size.

The study had a two stage study design; a predefined number of patients (n=13 for the non-osteosarcoma strata, N= 19 for the osteosarcoma stratum) was included in stage 1, and based on the number of responders (at least one patient with PR or CR for the non-osteosarcoma strata and at least 5 patients with disease control or 2 patients with PR or CR in the osteosarcoma stratum), additional patients were included at stage 2 (n=7 for the non-osteosarcoma strata, N=10 for the osteosarcoma stratum).

A total of 109 patients were enrolled of whom 108 received at least one dose of cabozantinib. In total 29 patients were included in the osteosarcoma stratum, and 13 patients each in the Ewing sarcoma, RMS, NRSTS, Wilms tumour strata (all belonging to the non-osteosarcoma strata). The rare tumour strata included 2 patients with MTC, 4 with RCC, 8 with HCC, 2 hepatoblastoma patients, 2 with adrenocortical carcinoma and 5 with another solid tumour.

In the osteosarcoma stratum 17 patients were below the age of 18, for the non-osteosarcoma strata 31 and for the rare tumour strata 22 patients were younger than 18 years of age.

Efficacy analyses were performed using the evaluable population for response and included all patients in the osteosarcoma stratum (n=29), 53 out of 55 of the patients included in the non-osteosarcoma strata and 23 out of 25 of the patients in the rare tumours strata. At baseline, most patients (39/108 patients (36.4%)) had one measurable target lesion to be followed for response. Overall, the majority of patients (104/108 (96.3%)) had received at least one anti-cancer therapy prior to baseline. The most frequent prior therapies were chemotherapy with multiple agents (93/104 patients (89.4%)), surgery (76/104 (73.1%)) and radiation therapy (57/104 patients (54.8%)).

Results

The primary endpoints for the osteosarcoma stratum were ORR and DCR. ORR was 6.9% (95% CI: 0.8, 22.8; n=2 PR) and DCR was 34.5% (95% CI: 17.9, 54.3). SD (n=9) was the best overall response; 31.0% (95% CI: 15.3, 50.8). Results for adults seemed to be slightly better than for children (DCR 50% vs 20-25% in adults and children respectively), however, the number of patients per age group are low and no definitive conclusions can be drawn. The median duration of disease control was 6.4 months

(95% CI: 2.7, NC). Two patients had a relative long DoR; one child with a median DoR of 23.72 months and one adult with a median DoR of 6.9 months. The median TTP for patients with osteosarcoma was 4.6 months (95% CI: 2.1, 6.6), median duration of PFS was 4.6 months (95% CI: 2.1, 6.0), and median OS was 9.3 months (95% CI; 6.3, 12.2).

The non-osteosarcoma disease groups were not expanded beyond the initial 13 patients as none of the patients in any of the strata had a CR or PR. In total 14 of 52 patients included in the non-osteosarcoma strata had a SD (2 with Ewing sarcoma, 1 with RMS, 6 with NRSTS and 5 with Wilms tumour). A tumour shrinkage ≥30% was observed in two patients in each of the disease groups with RMS, NRSTS and Wilms tumour. Also in the osteosarcoma cohort four patients had a tumour shrinkage ≥30%. The decision limit for PR is at least a tumour shrinkage of 30%. Acknowledging that tumour shrinkage (or increase) was not an official secondary endpoint, the number of patients who had more than 30% tumour shrinkage, in all tumour cohorts, is higher than the number of patients with PR. This discrepancy should be clarified by the applicant.

In the rare tumours strata, one (of the 2) patient with MTC, one (of the 4) patient with RCC, and one patient (out of five patients with other solid tumours) with DTC, had a PR. Tumour shrinkage of ≥30% was reported for 2 out of 2 MTC patients, 1 out of 4 RCC, 1 out of 8 HCC, 1 out of 2 adrenocortical carcinoma and 1 out of 5 other solid tumours.

Safety

All 108 patients who received at least one dose of cabozantinib were included in the safety population.

Overall, 102/108 patients (94.4%) had at least one AE, and 70/108 patients (64.8%) had at least one TEAE. Seven patients (6.5%) experienced Grade 5 TEAEs (within 30 days following last dose of cabozantinib). Treatment emergent SAEs were reported for 37/108 patients (34.3%), including 18 patients (16.7%) who had treatment related SAEs (as per the investigator's assessment). Forty-five of 70 children (64.3%) and 25/38 adults (65.8%) had a TEAE. SAEs were reported for 34.3% and 39.5% of patients in the two groups, respectively. Four children (5.7%) and three adults (7.9%) had a Grade 5 TEAE that occurred within 30 days following the last dose of cabozantinib.

The TEAEs with the highest incidence (reported for ≥5% of patients) by decreasing frequency were AST increased (10.2%), ALT increased, lipase increased and neutrophil count decreased (9.3% each), vomiting and hypertension (7.4% each), weight decreased and anaemia (6.5% each). There were four patients (3.7%) who experienced TEAEs of pneumothorax. Across strata, the frequency of TEAEs was slightly higher in the osteosarcoma stratum compared to non-osteosarcoma and rare tumours strata (72.4%, 59.3% and 68.0%, respectively).

The most frequent Grade 3 TEAEs (≥5% incidence) reported for all patients in descending order of incidence were AST increased, ALT increased, lipase increased and neutrophil count decreased (8.3% each), hypertension (7.4%), vomiting and anaemia (6.5% each) and weight decreased (5.6%). Grade 4 TEAEs of AST increased, lipase increased, neutrophil count decreased, blood bilirubin increased, platelet count decreased, lymphocyte count decreased, hypocalcaemia, respiratory failure, hypotension, sepsis and leukaemia were reported for one patient each (0.9%). The frequency of Grade 4 and Grade 5 TEAEs was higher in non-osteosarcoma and rare tumours strata compared to osteosarcoma stratum (7.4%, 12.0% vs 3.4%, respectively, for Grade 4 TEAEs and 7.4%, 8.0% vs 3.4%, respectively, for Grade 5 TEAEs).

There were 37/108 patients (34.3%) who experienced treatment emergent SAEs during the study. By PT, SAEs reported for ≥2% of patients were the followings: disease progression and pneumothorax

(3.7% each), non-cardiac chest pain, pyrexia, dyspnoea, hypoxia, pleural effusion, pneumonia, vomiting, AST increased, blood bilirubin increased and dehydration (2.8% each).

Seven patients died during treatment or in the 30 days follow up period. The primary cause of death for all of these patients was disease progression.

A review of pneumothorax and cabozantinib was conducted during the study as part of the request for continuing monitoring by the Pharmacovigilance Risk Assessment Committee. There were six treatment emergent events of pneumothorax in this study among four subjects, however all subjects had metastases to the lung prior to receiving cabozantinib.

A specific commitment to review events related to hepatobiliary disorders, decreased lymphocyte count, decreased neutrophil count, hair colour changes and skin hypopigmentation was requested from review of ADVL1211. In the overall safety population, there were no events noted under the System Organ Class (SOC) Hepatobiliary disorders; however, there were 12 events of AST increased, 10 of ALT increased and five events of blood bilirubin increased under the SOC Investigations. Of these, the majority, 11/12, 8/10 and 4/5 events, respectively, were considered related. Four events of AST increased, two of ALT increased and three of blood bilirubin increased were considered serious events. There were 14 events of neutrophil decreased and four each of white blood cell count decreased and lymphocyte decreased of which 12/14, 3/4 and 3/4, respectively, were considered related. None of these events were considered serious. There were no events of hair colour change or skin hypopigmentation.

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.

Conclusion

Based on the efficacy results provided there seems to be limited anti-tumour activity of cabozantinib against all tumour types included in this study. For the paediatric clinical studies tumour types were selected, based on the mode of action of cabozantinib, tumour types in which the key targets are known to be involved in development and maintenance of the cancer were included in the study. For most strata, patients were not specifically selected based on the presences of biomarkers. Therefore it is not clear whether or not the study population includes indeed the patients that are most likely to benefit from cabozantinib treatment. The low response rates seen, might partly be due to inclusion of patients who do not have a tumour harbouring alterations in one of the cabozantinib targets.

According to the predefined definition of success, for the non-osteosarcoma strata the agent was already considered ineffective after 13 patients were included in each of the strata, as none of these patients had a PR or CR. Limited efficacy was seen for osteosarcoma. For the osteosarcoma stratum both stages of the study were performed, after inclusion of the first 19 patients in stage 1 the results were considered inconclusive therefore an additional 10 patients were recruited. In the end 9 patients had disease control success (which was the minimum number for a positive study), 2 of these patients had a PR, the DoR for at least one paediatric patients was quite long.

Overall, the safety profile observed in subjects <18 years of age across all tumour strata was in line with the known safety profile of cabozantinib established in adults. No new safety findings were identified.

The applicant is requested to present their further plans for the development of cabozantinib in paediatric tumours and whether additional data/information might be expected. The applicant is

requested for a text proposal for section 4.2, 4.8 and 5.1, as results of all paediatric studies should be included in the SmPC, also in case results of the studies are not sufficient for a paediatric indication.

3. Rapporteur's overall conclusion and recommendation

☐ **Fulfilled:**
☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide additional clarification on the exposure in children, and on the long term stability of some of the samples used, furthermore the further plans of the applicant with regard to the development of the product for paediatric use is requested, and finally a proposal to include study results and paediatric information in the SmPC of Cabometyx, should be provided as part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information

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

1. It is unclear how the adult dose (Cometriq dose is administered as 140 mg once daily and Cabometyx is administered as 60 mg once daily) compares to the BSA-based dosing schedule in the paediatric population. BSA was implemented in the model using power functions on clearance and volume of distribution terms and, if BSA-adequately scales exposure, these terms were expected to be close to 1 (instead of 0.6 and 1.9). The applicant is requested to discuss and also to clarify whether the plasma exposure in adolescent and paediatric patients included in studies ADVL1211 and ADVL1622 can be considered similar to adult patients (and a justification for clinically relevant exposure metric should be provided). The paediatric exposure in different age ranges and a comparison with adults should be described in section 5.2 of the SmPC or it should be justified that the current statement is still appropriate.
2. Some samples were analysed after the confirmed long-term stability period. The applicant is requested to justify how many samples were analysed after the long-term stability period, confirm this stability period and discuss clinical implications.
3. While no PR or CR is seen in the non-osteosarcoma cohort, a tumour shrinkage ≥30% was observed in two patients in each of the disease groups with RMS, NRSTS and Wilms tumour. Also in the osteosarcoma cohort four patients had a tumour shrinkage ≥30%. The response limit for PR is at least a tumour shrinkage of 30%. Acknowledging that tumour shrinkage (or increase) was no official secondary endpoint, the number of patients who had more than 30% tumour shrinkage, in all tumour cohorts, is higher than the number of patients with a PR. This discrepancy should be clarified by the applicant.
4. The applicant is requested on their further plans for the development of cabozantinib in paediatric tumours and whether additional data/information might be expected.
5. A text proposal to include information obtained form Study ADVL1211 and ADVL1622 in section 4.2, 4.8 and 5.1 of the SmPC, should be submitted.

5. MAH responses to Request for supplementary information

As part of cabozantinib procedures EMEA/H/C/004163/P46/006 (Cabometyx) and EMEA/H/C/002640/P46/021 (Cometriq) the responses provided to questions 2 and 3 are similar. However, responses to questions 1, 4 and 5 are specific to each product and are therefore separately assessed below.

Question 1 (Cabometyx)

It is unclear how the adult dose (Cometriq dose is administered as 140 mg once daily and Cabometyx is administered as 60 mg once daily) compares to the BSA-based dosing schedule in the paediatric population. BSA was implemented in the model using power functions on clearance and volume of distribution terms and, if BSA-adequately scales exposure, these terms were expected to be close to 1 (instead of 0.6 and 1.9). The applicant is requested to discuss and also to clarify whether the plasma exposure in adolescent and paediatric patients included in studies ADVL1211 and ADVL1622 can be considered similar to adult patients (and a justification for clinically relevant exposure metric should be provided). The paediatric exposure in different age ranges and a comparison with adults should be described in section 5.2 of the SmPC or it should be justified that the current statement is still appropriate.

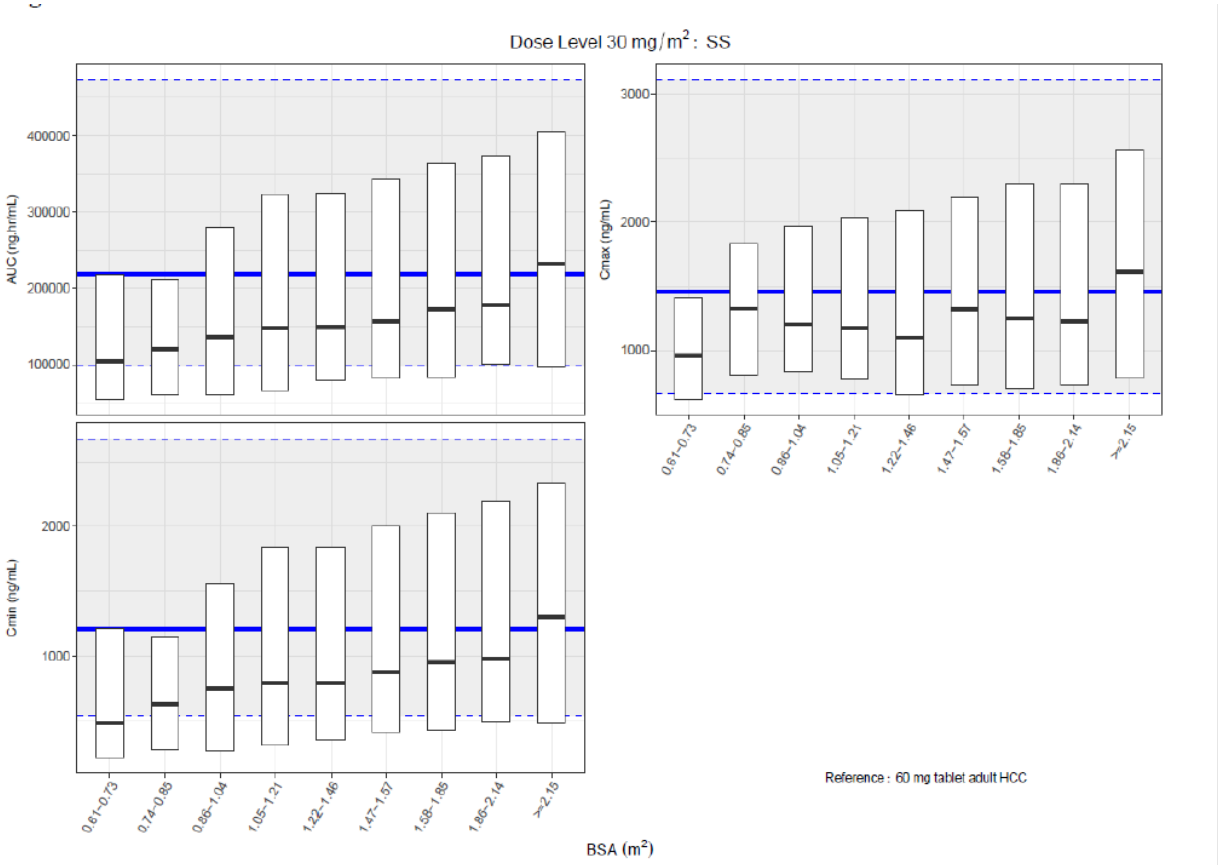
Summary of the Applicant's Response

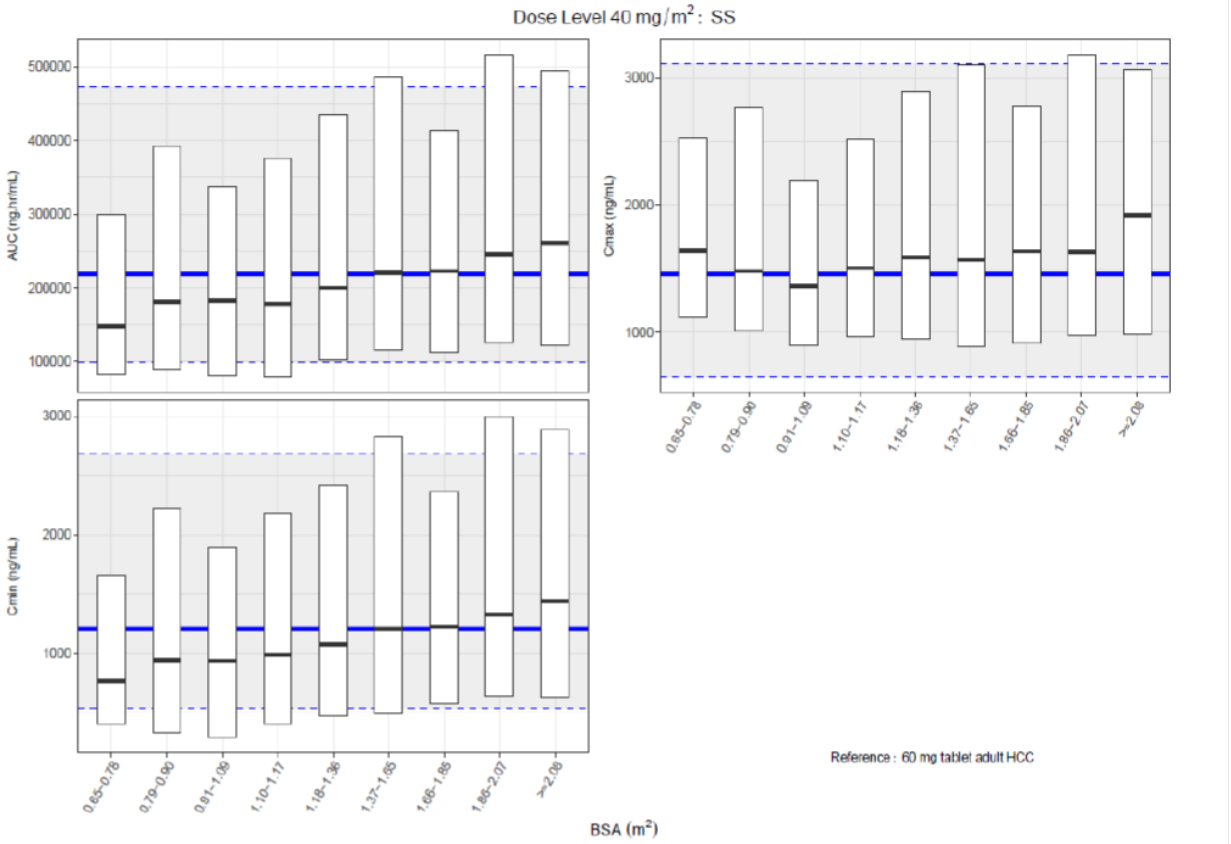
Simulated cabozantinib exposures in children and adolescents following administration of body surface area (BSA)-adjusted doses of 30, 40 and 55 mg/m² cabozantinib tablet were compared to simulated exposures in adults (e.g. patients with hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC), and healthy volunteers) who received 60 mg of cabozantinib tablet once daily (QD). The tablet formulation was similar for both populations (children and adolescents, and adults). The adult dose of 60 mg cabozantinib QD was chosen as it corresponds to the starting dose of cabozantinib monotherapy in adult patients (e.g. RCC and HCC patients). The adult Population pharmacokinetic (PK) model was used to simulate AUC, C_{max} and C_{min} over a week at steady-state following administration of cabozantinib 60 mg tablet QD in 1,000 adult patients sampled from the adult Population PK analysis (XL184-309.PopPK.001 report). From previous analyses in adults, it is known that several safety and efficacy endpoints are driven by PK exposure parameters such as AUC, C_{max} and C_{min}.

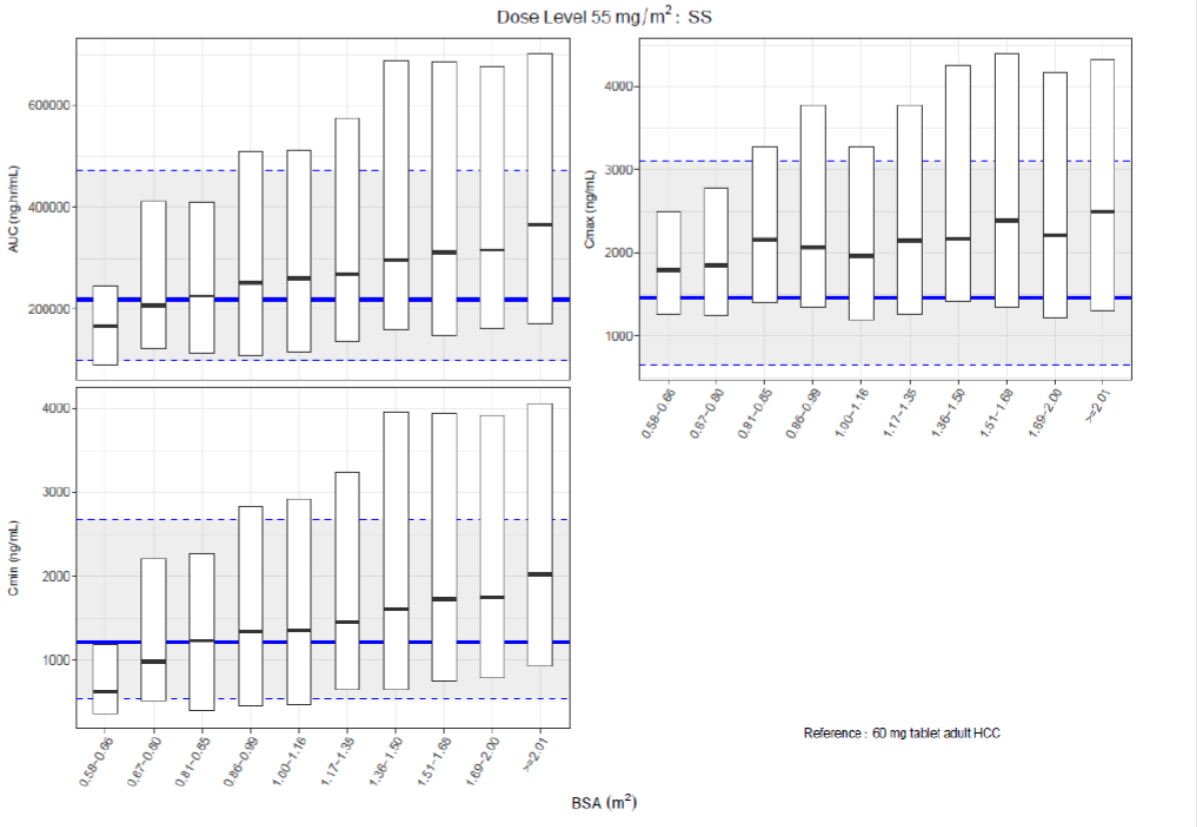
The children and adolescents Population PK model was used to perform simulations in a virtual population of 1,000 children and adolescent subjects (age range: 4 to 18 years) based on the BSA-based dosing nomogram for cabozantinib that was used in the ADVL1211 and ADVL1622 clinical studies. In the Population PK model in children and adolescents, the BSA coefficients on distribution PK parameters were estimated, and this model was found to better fit the data in comparison to the fixed allometric parameters. Moreover, there was no evidence that age, sex, race, ethnicity and tumor type affected cabozantinib PK in children and adolescents. Simulated medians and 90% prediction intervals of the predicted exposures in children and adolescent subjects were displayed by BSA category and compared to simulated medians and 90% prediction intervals of the predicted exposures in adult patients with HCC (Figure 1, Figure 2 and Figure 3). The HCC population was chosen to be presented below as the Population PK model for HCC includes the largest number of patients and is considered the most informative.

Figure 1. Box Plots of Predicted Cabozantinib Exposures at Steady-state following 30, 40 and 55 mg/m^2 Dose Level in Children and Adolescents Compared to Predicted Exposure in Adult Patients with HCC Administered 60 mg. Center line represents median, top and base of the box represent 5th and 95th

percentiles of the predicted exposure in children and adolescents. Solid blue line represents median of adult exposure. Shaded area represents 90% prediction interval for adult exposure.




Dose Level 40 mg/m²: SS
AUC (ng·hr/mL)
Cmax (ng/mL)
Cmin (ng/mL)
0.65–0.78
0.79–0.90
0.91–1.09
1.10–1.17
1.18–1.36
1.37–1.65
1.66–1.85
1.86–2.07
>=2.08
BSA (m²)
Reference : 60 mg tablet adult HCC


Dose Level 55 mg/m²: SS
AUC (ng·hr/mL)
Cmax (ng/mL)
Cmin (ng/mL)
0.58–0.66
0.67–0.80
0.81–0.85
0.86–0.99
1.00–1.16
1.17–1.35
1.36–1.50
1.51–1.68
1.69–2.00
>=2.01
BSA (m²)
Reference : 60 mg tablet adult HCC

When given as tablet formulation, the cabozantinib exposures in children and adolescents after a dose of 40 mg/m² are similar to adult exposures after a dose of 60 mg QD. The conclusion is the same when using patients with HCC, RCC or healthy volunteer adults as a reference population. The 30 mg/m² and 55 mg/m² BSA-based doses led to lower and higher exposures, respectively, in comparison with adult exposures of 60 mg QD. A text proposal summarizing the paediatric cabozantinib exposure including a comparison with exposure in adults has been added to Section 5.2 of the Cabometyx SmPC, which is part of the submission package.

Assessment of the Applicant's Response

The Applicant did not discuss which exposure metrics can be considered the most relevant for efficacy and safety nor provided any results of exposure-response analyses. However, as no indication is currently requested, information in the SmPC will be limited to exposure metrics that demonstrate equivalent exposure to the adult dose.

In the population pharmacokinetic model, body size scaling of the cabozantinib pharmacokinetics in paediatrics was performed using BSA (in the form of a power equation). The physiological basis for this is not understood and also the BSA-based exponents (0.6 and 1.9) indicate that a BSA-based dosing regimen might not be optimal for dosing of paediatric patients as these deviates from 1 (which would indicate that the pharmacokinetics scale linearly with body surface area). Nonetheless, BSA is able to explain some variability in the pharmacokinetics and the simulations can therefore be considered reliable.

Based on the population pharmacokinetic model, it can be agreed that the exposure metrics for paediatric patients, using a dose of 40 mg/m^2, are most similar to the 60 mg adult dose (compared to 30 mg/m^2 and 55 mg/m^2). However, as indicated before, a more optimal posology can presumably be obtained using an alternative posology.

The Applicant proposes the following wording in the SmPC section 5.2:

"Data obtained from simulation performed with the population pharmacokinetic model developed in healthy subjects as well as adult patients with different type of malignancies show that in adolescent patients aged 12 years and older, a dose of 40 mg of cabozantinib once daily for patients < 40 kg, or a dose of 60 mg once daily in patients ≥ 40 kg results in a similar plasma exposure attained in adults treated with 60 mg of cabozantinib once daily (see section 4.2).

In the two clinical studies conducted by the COG in paediatric patients with solid tumours (ADVL1211 and ADVL1622), cabozantinib was dosed based on body surface area (BSA) according to a dosing nomogram, using available 20 mg and 60 mg tablets intended for adults. Among the 55 patients, median age was 13 years (range: 4 to 18 years). A population PK analysis was built using PK data collected in both studies. The PK of cabozantinib was adequately described by a two-compartment model with first-order elimination and first-order absorption processes. There was no evidence that age, sex, race ethnicity and tumour type affected cabozantinib PK in children and adolescent patients. Only BSA was found to be a significant predictor of cabozantinib PK. No dose dependency was seen in the developed model across the three tested dose levels (30, 40 and 55 mg/m²). The exposures in children and adolescent subjects following an administration of a BSA-based dose of 40mg/m² are similar to exposures in adults with a fixed dose of 60mg QD."

This wording is acceptable.

Conclusion

Issue resolved.

Question 1 (Cometriq)

It is unclear how the adult dose (Cometriq dose is administered as 140 mg once daily and Cabometyx is administered as 60 mg once daily) compares to the BSA-based dosing schedule in the paediatric population. BSA was implemented in the model using power functions on clearance and volume of distribution terms and, if BSA-adequately scales exposure, these terms were expected to be close to 1 (instead of 0.6 and 1.9). The applicant is requested to discuss and also to clarify whether the plasma exposure in adolescent and paediatric patients included in studies ADVL1211 and ADVL1622 can be considered similar to adult patients (and a justification for clinically relevant exposure metric should be provided). The paediatric exposure in different age ranges and a comparison with adults should be described in section 5.2 of the SmPC or it should be justified that the current statement is still appropriate.

Summary of the Applicant's Response

The Population pharmacokinetic (PK) model in children and adolescents was developed with data from ADVL1211 and AVL1622 paediatric studies run by Children's Oncology Group (COG). Both studies tested cabozantinib tablet formulation. Thus, a comparison of cabozantinib exposures in paediatric and adult populations was only performed for tablet formulation. The capsule and tablet formulations are not interchangeable; therefore, no simulations with cabozantinib capsule formulation could be performed in children and adolescents. Results of simulated cabozantinib exposures (tablet formulation) in paediatric and adult populations are provided below and are intended for information purposes only.

Section 5.2 of Cometriq SmPC remains unchanged as the Population PK model was developed for the 60 mg cabozantinib tablet (Cabometyx formulation) and there is no interchangeability between the two cabozantinib formulations (tablet and capsule).

Assessment of the Applicant's Response

There is currently no paediatric information in the SmPC of Cometriq. Cometriq, the capsule formulation of cabozantinib, is not bioequivalent with Cabometyx, the tablet formulation of cabozantinib, and is administered for different indications. The current SmPC of Cometriq, both section 4.2 and 5.2, do not mention that there is paediatric data available for the tablet formulation, which is acceptable given the fact that the formulations are used for different indications.

Conclusion

Issue resolved.

Question 2

Some samples were analysed after the confirmed long-term stability period. The applicant is requested to justify how many samples were analysed after the long-term stability period, confirm this stability period and discuss clinical implications.

Summary of the Applicant's Response

The quantitation of cabozantinib (XL184) in human K_2EDTA plasma samples collected in the ADVL1622 study was performed by Alturas Analytics (ADVL1622 bioanalytical report AD20-1089) using Alturas Analytics' procedure described in the validation report (AV11-XL184-01, dated 6 July 2011). In addendum 2 of this validation report (AV11-XL184-01 addendum 2, dated 27 June 2014), Alturas Analytics demonstrated 209 days stability for XL184 in K_2EDTA plasma samples stored at -70°C.

Consequently, for the analysis of ADVL1622 samples, Alturas Analytics referred to the long-term stability previously demonstrated during the validation of the BA-M-003 method performed by Exelixis, Inc. This method was described in the "Validation Report of a Method for the Determination of XL184 in Human Plasma by LC/MS/MS," addendum 2 (Doc. No. BA-VR-003.02, dated 28 February 2011) and demonstrated up to 840 days stability for XL184 in human K_2EDTA plasma stored at -70 °C (XL184-BA-VR-003-02 report).

After reception, the ADVL1622 study samples were stored at nominal -70±10 °C and analyzed within 993 days from collection. Consequently, Alturas Analytics mentioned that 14 out of 120 samples collected in the ADVL1622 study were analyzed outside the demonstrated long term stability window. These samples are flagged in Table 10-3 of Alturas Analytics' bioanalytical report AD20-1089. However, in April 2020, XL184 stability in K2EDTA human plasma was demonstrated for at least 2,219 days in samples stored at -70°C in the ATM-1950 LC-MS/MS bioanalytical method whose validation is described in the Worldwide DCN report No 3007304 and 3007304-am1, 3007304_am2 and 3007304-am3 for long term stability (WWCT3007304, XL184-401.PK.001 and WCT-DCN 4004482 reports). This method was used to determine XL184 levels in the XL184-401 clinical study (see XL184-401.PK.001 and WCT-DCN 4004482 reports).

Consequently, as recently demonstrated, XL184 is stable for at least 2,219 days in human K_2EDTA plasma stored at -70°C and samples collected in the ADVL1622 study were not analyzed out of the demonstrated stability window. No clinical implication can be anticipated.

Assessment of the Applicant's Response

The Applicant clarified that long-term stability was demonstrated for 2219 days in human K_2EDTA plasma stored at -70°C, instead of the mentioned 840 days stability period. Therefore, it is agreed with the Applicant that no clinical consequences are to be expected. No addendums to the long-term stability results have been provided in this procedure, but this issue is not further pursued.

Conclusion

Issue not further pursued.

Question 3

While no PR or CR is seen in the non-osteosarcoma cohort, a tumour shrinkage ≥30% was observed in two patients in each of the disease groups with RMS, NRSTS and Wilms tumour. Also in the osteosarcoma cohort four patients had a tumour shrinkage ≥30%. The response limit for PR is at least a tumour shrinkage of 30%. Acknowledging that tumour shrinkage (or increase) was no official secondary endpoint, the number of patients who had more than 30% tumour shrinkage, in all tumour cohorts, is higher than the number of patients with a PR. This discrepancy should be clarified by the applicant.

Summary of the Applicant's Response

The best overall response (BOR) presented in the Table 20 and 28 of the ADVL1622 clinical study report (CRS, represents a mixture of disease assessment per Children's Oncology Group (COG) central review and per Investigator. The waterfall plots in the CRS (Figures 4 and 5) are based on the Applicant's (Ipsen's) derivation per tumour measurement. Ipsen recognized the discrepancy between the assignment of BOR and the maximum tumour shrinkage shown in the water fall plots. The discrepancy is due to non-equivalent requirement for the BOR assignment and the maximum (target lesion) tumour shrinkage, and programming errors in producing the waterfall plots. Updated waterfall plots (Figure 4 and Figure 5) and discrepancy details for patients with at least 30% maximum tumour shrinkage but not being assigned a BOR of partial response (PR) are provided in the second part of the response. The

entire set of updated waterfall plots is provided in the ADVL1622 CSR addendum 1 which is part of the submission package. The maximum tumour shrinkage is solely based on the target lesion assessment compared with baseline over the course of the study. However, the BOR determination in this study depends not only on the quantification of tumor shrinkage at a specific time point, but also on other determinant factors, such as pre-specified response criteria for the tumour type of interest, confirmation of central review, timepoint response (target lesion response, non-target response etc.) sequence, and limited response evaluation period.

For patients with non-central nervous system (CNS) solid tumour, end-of-cycle response depends on the tumour shrinkage (sum of the longest diameters in the target lesions), appearance of any new lesions or not, and progression status of non-target lesions. A patient with non-CNS solid tumour would be assigned an end-of-cycle response of PR if having at least 30% tumour shrinkage without the appearance of any new lesions and no progression of non-target lesions. Therefore, a patient could be assigned an end-of-cycle response of progressive disease (PD) based on the appearance of a new lesion despite a tumor shrinkage of at least 30%.
For patients with CNS tumor, the overall response assessment at each timepoint considers assessments of target, non-target, marker and new lesions. For target lesion response, a PR requires at least 50% decrease from baseline in the sum of the product of the two perpendicular diameters of all target lesions. Similarly, a patient could be assigned an overall response of PD due to the appearance of a new lesion or progression of the existing non-target lesions despite having more than 30% tumour shrinkage in terms of sum of longest diameter.
The BOR determination in this study depends on two consecutive disease assessments performed at least 3 weeks apart. A BOR of PR requires at least two consecutive PRs or a PR followed by a complete response (CR). A patient who reached an end-of-cycle response of PR would not be assigned a BOR of PR without a consecutive PR or CR.
As stated in Section 9.4 of the protocol, the evaluation period for BOR determination is 6 treatment cycles. A patient would not be assigned a BOR of PR if the first assessment of a PR and the associated consecutive disease assessment of CR/PR do not occur within the response evaluation period.
Discrepancies between maximum (target lesion) reduction and BOR assignment are listed below.

Osteosarcoma stratum
Two patients in the osteosarcoma stratum were identified as having a maximum tumor shrinkage ≥30% but not attaining a BOR of PR. Detailed tumor measurements and response information are provided in Table 1.
In one subject the BOR of PD was determined by Investigator assessment. Although a maximum tumor reduction of 37% was observed at Cycle 4, a timepoint response of PD was assigned due to appearance of a new lesion. The new lesion was retrospectively identified at the Cycle 2 scan with the following comment from the Investigator:
Lesion #3 was present on patient's 7/24 scan. It was only seen in retrospect when the case was re-reviewed on 9/24. Measurements on 7/24 were 1.2x1.4x1.2 cm. This has been documented by the physician.

In the other subject the BOR of SD was determined per central review assessment with two consecutive disease assessments of SD, being separated by at least a 3-week period at Cycle 2 (Day 29) and Cycle 4 (Day 85). The maximum tumor reduction of 30.4% is based on Investigator assessment at Cycle 4, along with assignment of a PR as timepoint response. At the subsequent tumor assessment (Cycle 5, Day 113) a PD was assigned per Investigator review due to new lesions identified at pelvic bone, sacrum, coccyx and associated joints; therefore, the previous PR was not confirmed.

Non-osteosarcoma strata

Five patients in the non-osteosarcoma strata were identified as having a maximum tumor shrinkage ≥30% but not attaining a BOR of PR. Detailed tumor measurements and response information are provided in Table 2

In one patient with non-rhabdomyosarcoma soft tissue sarcoma, the BOR of SD was determined per Investigator assessment with two consecutive disease assessments of SD at least 3 weeks apart at Cycle 2 (Day 29) and Cycle 3 (Day 57). The maximum tumor reduction (in terms of sum of diameters) of 33.3% occurred at Cycle 3. To be noted that the patient was enrolled with brain/CNS tumor and the target lesion response of PR for having at least 50% reduction in sum of product of perpendicular diameters (PPD) reduction was not met.

In another patient with Non-rhabdomyosarcoma soft tissue sarcoma, the maximum tumor reduction of 40.9% was observed at Cycle 2 per Investigator assessment and the timepoint response of PR was assigned. However, the disease was considered progressive as a new lesion was identified at Cycle 3. Therefore, the BOR of PD per Investigator assessment was recorded.

In one patient with Wilms tumor the BOR of SD was determined per central review with two consecutive disease assessments of SD, being separated by at least a 3-week period at Cycle 3 (Day 84) and Cycle 4 (Day 112). Although a timepoint response of PR at Cycle 6 was assigned per central review, BOR of SD was determined based on 6-cycle best response assessment period. The maximum tumor reduction of 42.4% is based on Investigator assessment at Cycle 4 and a timepoint response of PR was assigned accordingly. Of note, tumor measurements at Cycles 6 and 8 were unable to be determined due to pleural effusion obstructing the view, and a PD was assigned at Cycle 8.

In another patient with Wilms tumor, the BOR of SD was determined per central review with two consecutive disease assessments of SD, being separated by at least a 3-week period at Cycle 2 (Day 53) and Cycle 3 (Day 88). The maximum tumor reduction of 73% was observed at Cycle 9. Of note, the local radiologist indicated that the target lesions 1 and 2 are not clearly visible on scan and reported 0 mm as the longest diameter.

One patient with Rhabdomyosarcoma had a maximum tumor reduction of 72% which occurred at Cycle 2 with disappearance of target lesion 2, and a timepoint response of PR was assigned per Investigator assessment. At Cycle 4, the target lesion 2 reappeared. As such, a timepoint response of PD was assigned at Cycle 4, and a BOR of PD was recorded.

Figure 4 Waterfall Plot of the Maximum Tumor Shrinkage - Osteosarcoma Stratum – Evaluable Population for Response

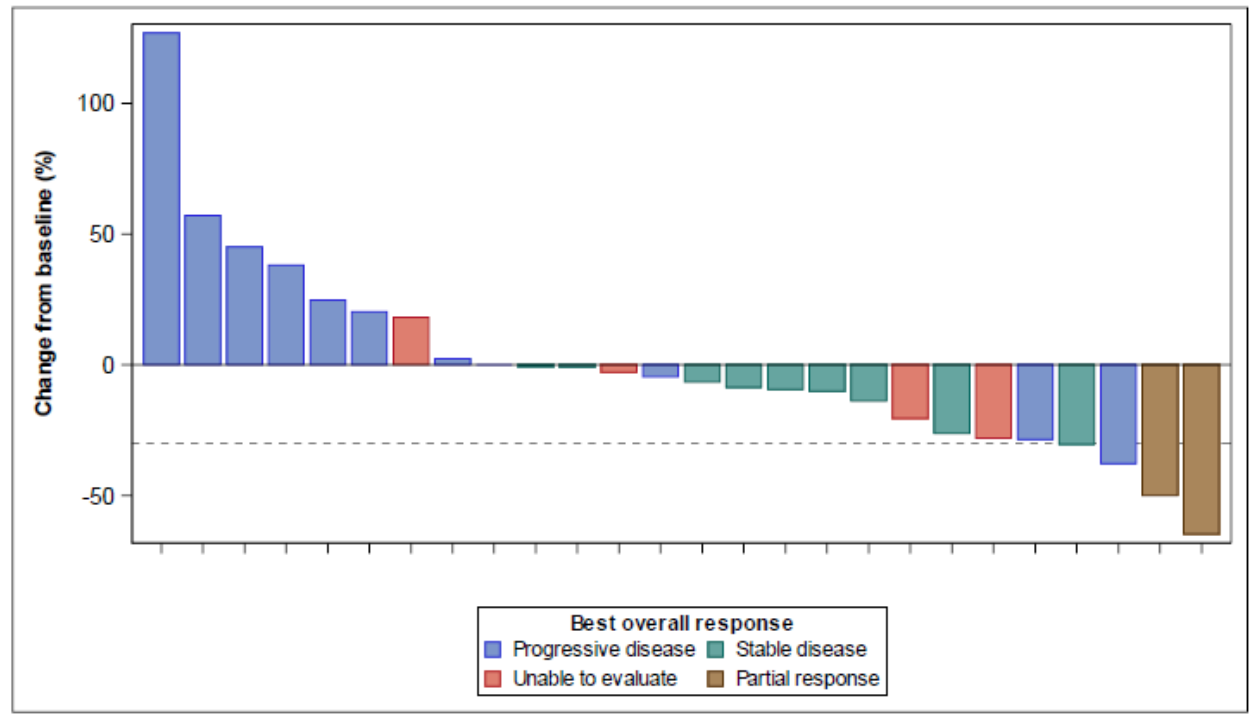


Figure 5 Waterfall Plot of the Maximum Tumor Shrinkage - Non-osteosarcoma Strata – Evaluable Population for Response

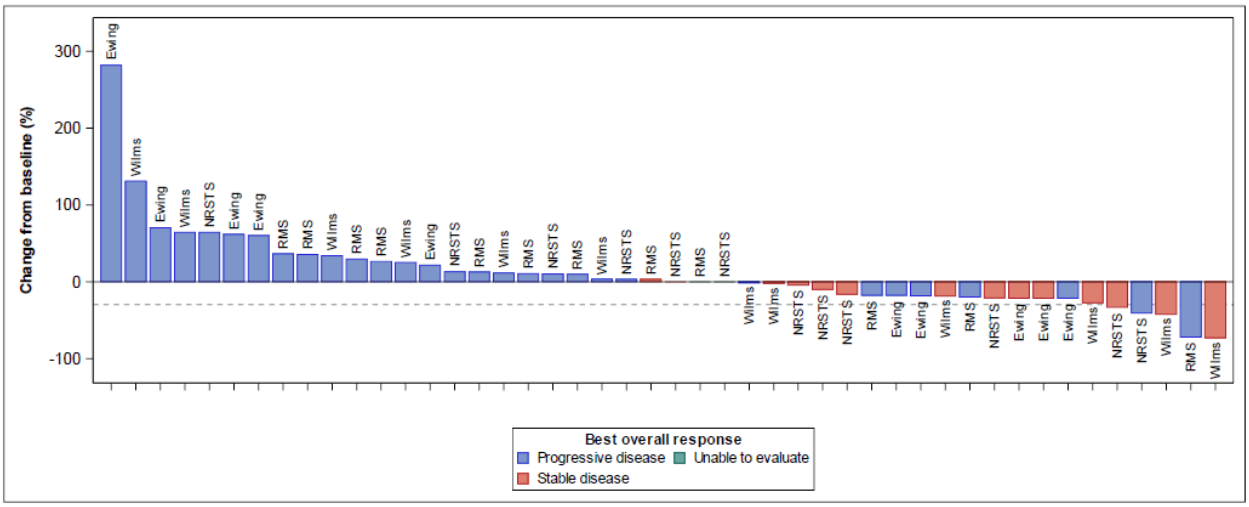


Table 1 List of Patients with at least 30% Tumor Reduction and not Attaining BOR of PR in Osteosarcoma Stratum

BOR (Evaluator)	Evaluator	Baseline		Post-baseline					
		Sum of Diameters (mm)	Non-target Lesion Identified [a]	Visit	Timepoint Response	Sum of Diameter (mm)	% Change	Non-target Lesion Disappear	New Lesion
PD (Investigator)	Investigator	37	N	Cycle 2	PD	26	-29.7	NA	N
				Cycle 4	PD	23	-37.8	NA	Y
SD (Central Review)	Central Review	46.3	NA	Cycle 2	SD	39.6	-14.5	NA	N
				Cycle 4	SD	38.8	-16.2	NA	N
				Cycle 5	SD	41.7	-9.9	NA	N
	Investigator	46	N	Cycle 2	SD	34	-26.1	NA	N
				Cycle 4	PR	32	-30.4	NA	N
				Cycle 5	PD	35	-23.9	NA	Y

BOR=best overall response, N=no, NA=not applicable, PD=progressive disease, PR=partial response, SD=stable disease, Y=yes
[a] The non-target lesion was not assessed or followed-up per central review.

Table 2 List of Patients with at least 30% Tumor Reduction and not Attaining BOR of PR in Non-osteosarcoma Strata

Subject Number	BOR (Evaluator)	Evaluator	Baseline		Post-baseline					
			Sum of Diameters (mm)	Non-target Lesion Identified [a]	Visit	Timepoint Response	Sum of Diameter (mm)	% Change	Non-target Lesion Disappear	New Lesion
757531	SD (Investigator)	Investigator	21	Y	Cycle 2	SD	20	-4.8	N	N
					Cycle 3	SD	14	-33.3	N	N
					Cycle 4	SD	21	0	N	N
					Cycle 6	SD	21	0	N	N
873873	PD (Investigator)	Investigator	44	Y	Cycle 2	PR	26	-40.9	N	N
					Cycle 3	PD	26	-40.9	N	Y
872271	SD (Central Review)	Central Review	91.5	NA	Cycle 1	SD	78.2	-14.5	NA	N
					Cycle 3	SD	76.4	-16.5	NA	N
					Cycle 4	SD	76.7	-16.2	NA	N
					Cycle 6	PR	64.4	-29.6	NA	N
		Investigator	141	Y	Cycle 1	SD	114	-19.1	N	N
					Cycle 3	PR	95.4	-32.3	N	N
					Cycle 4	PR	81.2	-42.4	N	N
					Cycle 6	PR	NA	NA	N	N
					Cycle 8	PD	NA	NA	N	Y

BOR (Evaluator)	Evaluator	Baseline		Visit	Post-baseline				
		Sum of Diameters (mm)	Non-target Lesion Identified [a]		Timepoint Response	Sum of Diameter (mm)	% Change	Non-target Lesion Disappear	New Lesion
SD (Central Review)	Central Review	110.8	NA	Cycle 2	SD	99.4	-10.3	NA	N
				Cycle 3	SD	88.9	-19.8	NA	N
				Cycle 4	SD	88.7	-19.9	NA	N
				Cycle 6	SD	89.4	-19.3	NA	N
	Investigator	152	Y	Cycle 2	PR	101	-33.6	N	N
				Cycle 3	PR	77	-49.3	N	N
				Cycle 4	PR	68	-55.3	N	N
				Cycle 6	PR	49	-67.8	N	N
				Cycle 9	PR	41	-73.0	N	N
PD (Investigator)	Investigator	43	Y	Cycle 2	PR	12	-72.1	N	N
				Cycle 4	PD	45	4.7	N	N

BOR=best overall response, N=no, NA=not applicable, PD=progressive disease, PR=partial response, SD=stable disease, Y=yes
[a] The non-target lesion was not assessed or followed up per central review.

Assessment of the Applicant's Response

The applicant explained the discrepancy between the number of patients with a tumour shrinkage of 30% and the number of patients with a PR. There are non-equivalent requirements for the BOR assignment and for the measurement of maximum (target lesion) tumour shrinkage. The maximum tumour shrinkage is solely based on the target lesion assessment compared with baseline over the course of the study, whereas the BOR determination in this study depends not only on the quantification of tumour shrinkage at a specific time point, but also on other determinant factors, such as pre-specified response criteria for the tumour type of interest, confirmation of central review, timepoint response (target lesion response, non-target response etc.) sequence, and limited response evaluation period. The applicant showed that for some of the patients a certain time point tumour shrinkage of more than 30% in the target lesions was reported, whereas also a new lesion appeared by which in the end the patients were assigned to have PD. For other patients the reported percentage of tumour shrinkage was not confirmed at the time of the next tumour assessment or by central review.

Conclusion

Clarification has been provided by the applicant, issue resolved.

Question 4

The applicant is requested on their further plans for the development of cabozantinib in paediatric tumours and whether additional data/information might be expected.

Summary of the Applicant's Response

Ipsen is currently engaged in the development of study 6 as part of its Paediatric Investigation Plan with cabozantinib tablet formulation. A pre-submission meeting occurred on 15 November 2022 to discuss the study design and key elements of study 6. If additional data are generated for the study population, the information will be added to the Cabometyx SmPC, as appropriate.

Assessment of the Applicant's Response

The applicant provided the requested information, currently the development of study 6 is planned and a pre-submission meeting to discuss the study design occurred on 15 November 2022.

Conclusion

Issue resolved.

Question 5

A text proposal to include information obtained form Study ADVL1211 and ADVL1622 in section 4.2, 4.8 and 5.1 of the SmPC, should be submitted.

Summary of the Applicant's Response

A text proposal has been added to the concerned sections of the Cabometyx SmPC, which is part of the submission package.

Assessment of the Applicant's Response

See assessment in the SmPC.

6. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

In view of the available data regarding Study ADVL1211 and ADVL1622 the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.