NOVARTIS

Clinical Development

Pazopanib

Protocol PZP034X2203 / NCT01956669

A phase II study of pazopanib (GW786034, NSC#737754) in children, adolescents and young adults with refractory solid tumors

Statistical Analysis Plan

End of study analysis

Author: [redacted] ([redacted] study statistician); [redacted] (Novartis Trial Statistcian)

Document type: SAP Documentation

Document status: Amendment 1

Release date: 24-Dec-2019

Number of pages: 44

Changes compared to previous final version of SAP

Reporting and Analysis Plan History

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
10 Sep 2019	Prior to final DB lock	Creation of SAP for end of study analysis	N/A	N/A
24 Dec 2019	Prior to final DB lock	Creation of Amendment 1	Minor updates to - Cover page corrected. Prior version incorecctly titled “Tables, Figures and Listings (TFL) Shells-CSR deliverables”. Updated to “Statistical Analysis Plan” - Reference link for NCI-CTCAE v4.0 provided in the previous version was not working - link updated.	Cover page document title Section 9.4.1- page 25 reference link is updated

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List of abbreviations

AE	Adverse Event
AFP	Alpha Fetoprotein
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC(0-t)	Area under the concentration-time curve from time zero to the last observed concentration
AUC(0-24)	Area under the concentration-time curve from time zero to 24 h after drug administration
BOR	Best overall response
BSA	Body surface area
CI	Confidence Interval
Cmax	Maximum observed drug concentration
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Observed drug concentration before the next dose
DLT	Dose limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GSK	GlaxoSmithKline
I-MIBG	I-metaiodobenzylguanidine
LLOQ	Lower limit of quantitation
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Medical Affairs
mITT	Modified Intent to Treat
MTD	Maximum tolerated dose
MUGA	Multiple-Gated acquisition
NCI	National Cancer Institutes
ORR	Objective Response Rate
OS	Overall survival
P	P value
PD	Progressive Disease
PDCO	Pediatric Committee
PFS	Progression-free Survival

PK	Pharmacokinetics
PKES	Pharmacokinetic extended sampling
PR	Partial Response
PT	Preferred Term
RADIO	Radiotherapy Dataset
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
STD	Study treatment discontinuation
TBL	Total bilirubin
tmax	Time of maximum observed drug concentration
TTP	Time to progression
ULN	Upper Limit of Normal

1. Introduction

This reporting and analysis plan (RAP) details all planned analyses required for the end of study final Clinical Study Report for the study VEG116731. This is a phase II (open label) study of pazopanib in children, adolescents and young adults with refractory solid tumors. Tumors of primary interest are rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma (including synovial sarcoma, alveolar soft part sarcoma and desmoplastic small round cell tumor) and Ewing sarcoma. Tumors of secondary interest include hepatoblastoma, neuroblastoma (measurable and evaluable), and osteosarcoma. This study will examine the efficacy of pazopanib in subjects with a variety of relapsed/refractory solid tumors. The study will also seek to further define the toxicities of pazopanib in subjects with relapsed/refractory solid tumors, characterize the pharmacokinetics (PK) of pazopanib after administration of the powder suspension formulation, as well as examine biologic markers that may help to further define the response characteristics of pazopanib. The details of pharmacodynamics and biomarker related analyses will be described in a separate analysis plan.

For further information on the study design, see the protocol (Amendment 5, 23-May-2017) for Study VEG116731.

The RAP was written by staff [redacted]. The execution of the RAP will be undertaken by staff [redacted] as well.

All decisions regarding the analysis, as defined in this RAP document, will be made prior to Database Freeze (DBF) of the study data. Interim analyses are detailed within Section 4.1, where applicable.

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2. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the investigator-assessed objective response rate of pazopanib in children, adolescents and young adults (subjects) with relapsed or refractory solid tumors of the following types (each defining a cohort): 1. rhabdomyosarcoma 2. non-rhabdomyosarcomatous soft tissue sarcoma, or	• Objective Response Rate (ORR) for the three tumor types of primary interest, confirmation will be based on the disease assessment after the initial response

3. Ewing sarcoma/peripheral Primitive Neuro Ectodermal Tumor (PNET).	
Secondary	
• To determine the investigator assessed objective response rate of pazopanib in children, adolescents, and young adults (subjects) with relapsed or refractory solid tumors of the following types (each defining a cohort): 1. osteosarcoma, 2. neuroblastoma (measurable), 3. neuroblastoma (evaluable), or 4. hepatoblastoma.	• Objective Response Rate (ORR) for the four tumor types of secondary interest. The analysis method will be the same as in the primary endpoint.
• To further define and describe the toxicities of oral pazopanib in subjects with recurrent/refractory solid tumors.	• Adverse Events, Clinical Laboratory Evaluations, Vital signs and ECG and ECHO/MUGA.
• To further characterize the pharmacokinetics (PK) of pazopanib after administration of the powder suspension formulation in children, adolescents and young adults with cancer.	• Pazopanib PK parameters (e.g., Cmax, Tmax, and AUC).
• To determine progression free survival in subjects with relapsed or refractory solid tumors, per cohort.	• Progression-free survival (PFS): defined as the interval between the date of first dose of protocol therapy and the earliest date of disease progression or death due to any cause.
• To determine the time to progression in subjects with relapsed or refractory solid tumors, per cohort.	• Time to progression (TTP): defined as the interval between the date of first dose of protocol therapy and the earliest date of disease

	progression or death due to disease under study.
• To determine the therapeutic activity (a confirmed complete or partial response based on the disease assessment at least one cycle after initial response or stable disease for at least two protocol scheduled disease assessments as per RECIST criteria) per cohort	• Clinical Benefit: defined as the percentage of subjects achieving either a confirmed complete or partial tumor response (at least one cycle after initial response, see section 10.1 for confirmation of CR/PR) or stable disease for at least two protocol scheduled disease assessments as per RECIST criteria.
• To further examine the biologic relationship between tumor response and angiogenic cytokines.	• To be described in a separate biomarker analysis plan.
• To assess the genotype/phenotype relationships of VEGF or other members of the VEGF signaling pathway in children with soft tissue sarcoma.	• To be described in a separate biomarker analysis plan.
• To further explore pazopanib pharmacokinetic/pharmacodynamic relationships with biomarkers and clinical outcomes, including hypertension.	• Pazopanib PK by clinical outcomes, including hypertension. • Pazopanib PK vs biomarkers will be described in a separate biomarker analysis plan.
• To assess overall survival in subjects with relapsed or refractory solid tumors, per cohort	• Overall survival (OS): defined as the time from the first dose of protocol therapy until death due to any cause.
• To assess duration of response in subjects with relapsed or refractory solid tumors, per cohort	• Duration of response (DoR): defined as the time from the initial response (CR/PR) to first documented disease progression or death due to any cause, and will be determined only for those subjects with a confirmed response (CR or PR).

3. Study Design

Pazopanib will be administered orally once daily as a tablet at a dose of 450 mg/m^2/dose or as a powder in suspension at a dose of 225 mg/m^2/dose. 450 mg/m^2/dose was the MTD for tablet as determined by Study ADVL0815, the COG Phase I study, while the dose for oral suspension of 225 mg/m^2/dose exceeds the protocol-specified MTD of 160 mg/m^2/dose established in the same study. This decision was driven by the considerations that the 160 mg/m^2/dose may result in suboptimal exposure for efficacy and that only two isolated and reversible laboratory-defined DLTs were observed at 225 mg/m^2/dose in Study ADVL0815. The maximum dose to be administered daily for tablets is 800 mg and for suspension 400 mg. Each cycle will be defined as 28 days.

The first subjects enrolled who receive powder suspension will be expected to complete extended pharmacokinetic (PK) sampling in order to obtain PK and safety data in 6 evaluable subjects. If the 225 mg/m^2/dose is not tolerated (≥2 subjects with dose limiting toxicities (DLTs) in the first 6 evaluable subjects), all subsequently enrolled subjects will receive 160 mg/m^2/dose and an additional 6 subjects will be assessed for safety review and PK analysis.

The primary endpoint will be objective response rate by protocol-specified, disease-specific response criteria. The best response of disease to pazopanib will be examined separately in each of the seven disease cohorts.

The following two stage design (Simon, 1989) will be used in each cohort.

	Cumulative Number of Responses	Decision
Stage 1: Enter 10 subjects	0	Terminate the cohort: agent ineffective
	1 or more	Inconclusive result, continue cohort (proceed to Stage 2)
Stage 2: Enter 10 additional subjects	2 or less	Terminate the cohort: agent ineffective
	3 or more	Terminate the cohort: agent effective

We will consider the agent not of sufficient interest for further evaluation in a disease category if the true response rate is 5% and of sufficient activity if the true response rate is 25%. If the agent has a true response rate of 5%, the rule described above will identify the agent to have sufficient activity for further study with probability 0.07 (1-sided type I error), and the trial will have an expected sample size of 14 with 60% probability of early termination. If the agent has a true response rate of 25%, the rule described above will identify the agent to have sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P = 0.25).

4. Planned Analyses

In line with ICH E9 [European Agency for the Evaluation of Medicinal Products, 1998], membership of the analysis populations will be determined using the definitions in Section 6 of this RAP.

4.1. Interim Analyses

No formal interim analysis is planned outside of the study design.

The study team, which includes the Medical Monitor, representatives from Clinical Pharmacology and Safety, and the COG protocol chair will review and discuss safety data periodically over the course of the study. The team will also review the pharmacokinetics, toxicity, safety and tolerability profile of the first 6 initial subjects who receive powder suspension formulation and who are determined to be evaluable for PK and safety analyses. At least 6 evaluable subjects will be included in this assessment.

Expansion of tumor specific cohorts will be done when there is at least one investigator determined confirmed response in that cohort within the first 10 enrolled subjects. A given tumor specific cohort will not be expanded if no response has been reported for the first 10 subjects but all the subjects in the cohort have:

- Progressed
- Discontinued therapy
- Withdrawn consent
- Been determined to be lost-to-follow-up
- Or have been treated for at least 20 weeks, making it unlikely that a response will occur.

4.2. End of Stage 1 Analysis

This is a 2-stage design and therefore implies an analysis for futility based on the number of responders observed in Stage 1. The cut-off date for end of stage 1 analysis will be defined after the last subject enrolled in Stage 1 in the three cohorts of primary interest completes 20 weeks of treatment or discontinues early (as described in the previous section).
Enrollment in the rhabdomyosarcoma cohort was put on temporary halt following end of enrollment in Stage 1 for all cohorts in order to assess the benefit-risk based on the overall data from Stage 1 subjects. Two subjects already pre-identified to participate in the study before assessment of benifit.risk of stage 1 were enrolled in Stage 2 at that time.

Therefore, the data-cut off date for the end of Stage 1 analysis is defined as the date when all subjects (including subjects enrolled in stage 2 for the rhabdomyosarcoma cohort) in the three cohorts of primary interest complete 20 weeks of treatment or discontuine early.

4.3. Primary Analysis

The primary analysis of the study will be performed 20 weeks after the last subject's first visit in the three cohorts with tumors of primary interest, i.e. rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma, or Ewing sarcoma/peripheral PNET. This analysis would be performed after the completion of stage 2 of the primary cohorts.

However, this primary analysis will not be performed if the study is declared futile based on the statistical criteria described in Section 3 and/or clinical assessment of benefit-risk with the end of stage 1 analysis.

Key efficacy and safety data were analysed in the end of stage 1 analysis (with a cut-off date of 31-Jan-2019) and the Request for Modification #06 of the Votrient Paediatric Investigation Plan, was submitted to the PDCO. The study was declared futile based on the clinical assessment of benefit-risk at the end of stage 1 and the decision to terminate the study was approved based on PDCO feedback.

4.4. End of Study Analyses

The study will be completed one year from the date of the last subject's first visit. The end of study analyses will be performed at the time of study completion, when the final study database is frozen and will include cumulative efficacy and safety data.

5. Sample Size Considerations

5.1 Sample Size Assumptions

Review of subject accrual onto recent Phase II solid tumor studies indicates that the following entry rates of subjects with the various tumors under study can be expected:

Disease Group/Cohorts	Subjects/Year
Osteosarcoma	24
Ewing sarcoma	18
Rhabdomyosarcoma	18
Neuroblastoma (measurable disease)	12
Neuroblastoma (evaluable disease)	12
Non-rhabdomyosarcomatous soft tissue sarcomas (including synovial sarcoma, alveolar soft part sarcoma)	10
Hepatoblastoma	7

With these entry rates, the probability of accruing 10 subjects to complete the initial stage of evaluation in the seven named categories within 24 months is 88%. The corresponding probability for enrolling 20 subjects in the seven named disease categories in 48 months is 95%. The study will likely require 2 to 3.5 years for sufficient subject enrolments to evaluate

pazopanib in the stated disease groups. If activity is detected in any category, further trials in subcategories of the category may be conducted at the discretion of the Developmental Therapeutics Steering and study committees. A minimum of 77 subjects and a maximum of 154 subjects are anticipated, after accounting for historical rates of subject inevaluability for the primary endpoint in phase II studies.

5.2 Sample Size Re-estimation

No formal sample size re-estimation is planned.

6. Analysis populations

6.1. Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population is the primary analysis population. The mITT will consist of all subjects who have received at least one dose of protocol therapy.

6.2. Per-Protocol Population

The Per-Protocol (PP) population will consist of a subset of the subjects in the mITT who meet all eligibility criteria and don't have any major protocol deviations leading to exclusion from PP

The protocol deviations leading to exclusion from PP are specified in the protocol deviation specification document which will be stored in CREDI.

For the end of study analysis, the PP and mITT population will be used for the analysis of best overall response (ORR). All other efficacy analyses will be based on mITT only.

6.3. Safety Population

The Safety population will comprise all subjects in the mITT population. The safety population will be used for the analysis of safety data.

In this study, the mITT population and Safety population are identical.

6.4. Pharmacokinetic Population

The Pharmacokinetic (PK) population will comprise all subjects in the mITT population for whom a pharmacokinetic sample is obtained and analyzed.

6.5. Pharmacokinetic Extended Sampling Population

The Pharmacokinetic Extended Sampling (PKES) population will comprise all subjects in the Pharmacokinetic population who received powder suspension and have at least one non pre-dose sample collected using the extended sampling schedule. The PKES population is a subset of the PK population.

7. Treatment comparisons

There will be no treatment comparisons as there is only one treatment arm for each cohort. No comparisons across cohorts will be conducted.

8. general considerations for data analyses

Analysis datasets will be created according to CDISC standards, and data will be listed and summarized according to Novartis reporting standards where applicable. Formatting for dates, times, and decimal places will follow Novartis standards except where specified.

All data in the database will be presented in by-subject data listings.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

Unless otherwise stated, continuous variables will be summarized with n, mean, median, standard deviation, minimum and maximum, and categorical variables will be summarized with frequency counts and percentages

The currently supported version of SAS software (v9.3 or higher) will be used to perform all data analyses, generate tables, figures, and listings.

Deviations from the analyses in the RAP will be identified in the CSR and documented in the RAP Addendum.

8.1. Multicenter Studies

8.2. Other Cohorts and Covariates

In all efficacy analyses, there are no formal plans for any stratification. There are no formal plans for investigating any covariates.

8.3. Examination of Subgroups

There is no subgroup analyses required for safety but there will be subgroups analysis in PK analysis.

8.4. Multiple Comparisons and Multiplicity

There are no comparisons of interest and no formal statistical hypothesis will be tested.

9. Data Handling Conventions

9.1. Premature Withdrawal and Missing Data

Subjects will be treated until disease progression, until the subject is no longer obtaining clinical benefit from continued treatment, unacceptable toxicity, the study is terminated, or the subject withdraws consent. All subjects who withdraw from the study will be included in analyses up to the time of withdrawal, regardless of the duration of treatment.

As the period of treatment for any subject will be dependent on treatment efficacy and toxicity, the duration of protocol therapy will vary across subjects. Similarly the duration of follow-up will also vary across subjects. Subjects with shorter treatment and follow-up due to the natural history of their disease or medical necessities of the treatment of their disease will not be considered to have missing data. Consequently, there will be no imputation for missing data. Where appropriate, available data will be summarized over specified intervals (e.g. from study entry until withdrawal from the study) using suitable summary statistics.

For endpoints which determine the percentage of responders, subjects with unknown or missing overall response will be assumed to be non-responders, and will be included in the denominator when calculating the percentages.

For the secondary PFS endpoint, the date associated with the last adequate disease assessment will be used for those subjects who are alive and have not progressed at the time of analysis; such subjects will be considered censored in the analysis.

For the secondary OS endpoint, the date associated with the last contact will be used for those subjects who are alive at the time of analysis; such subjects will be considered censored in the analysis.

In the event that the study is terminated, all available data will be listed and a review will be carried out by the study team to assess which statistical analyses are still considered appropriate.

“Missing data” occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a “blank” in subject listing displays. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

For adverse events (AEs) and serious adverse events (SAEs), if relationship to study treatment is missing it will be assumed to be “Yes”. There will be no other imputation for missing data other than what’s described in Section 9.2.5 for partial dates and for missing exposure end dates.

9.2. Derived and Transformed Data

The following sections provide a general description of the derived and transformed variables used to describe and analyze the data. Separate analysis dataset specifications provide full details on all data derivations and transformations including descriptions of core standard algorithms and standard Oncology algorithms. The analysis dataset specifications will clearly communicate the content and source of the datasets supporting the statistical analyses.

9.2.1. Reference dates

There are two reference dates:

- Because age is an eligibility requirement, the reference date for age is the date of screening.

- The study reference date is the treatment start date, and will be used to calculate study day for all safety and efficacy measures.

9.2.2. Study Day

If the date of interest occurs on or after the study reference date then the study day will be calculated as (date of interest - study reference date) + 1. If the date of interest occurs before the study reference date then the study day will be calculated as (date of interest – study reference date). There is no study day 0.

9.2.3. Study Day for Efficacy

Since study is not randomized, we will use same study day in Section 9.2.2.

9.2.4. Duration and Elapsed Time

Durations (e.g., the duration of an adverse event, duration of exposure, etc.) are calculated as the stop date minus the start date plus one.

For elapsed time (e.g., the time since initial diagnosis):

- if the reference date is on or after the event date, then the elapsed time is the reference date minus the event date + 1.

- if the reference date is before the event date then the elapsed time is the reference date minus the event date.

When calculating time to event durations in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25. These algorithms for time to event return decimal numbers, and ignore the actual numbers of days in the months or years between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

9.2.5. Imputation of Partial Dates

Only the year of birth is being collected within the EDC system, subject birth date and month will be defaulted to ‘30/JUN’. For example, if birth year is 1989 then birthdate will be 30/Jun/1989.

With the exception of new anti-cancer start date on the time to event (PFS, TTP, OS) analysis dataset and exposure end date on the Exposure analysis dataset, imputed dates will not be stored on datasets.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In

addition partial dates may be imputed for 'slotting' data to study time periods (see Section 9.3) or for specific analysis purposes as outlined below.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D='Day': indicates that the day portion of the date is imputed

M='Month': indicates that the month and day portions of the date are imputed

Y='Year': indicates that the entire date (year, month, and day) is imputed

Example of Date Variables:

XYZD_ - character date variable

XYZDT - numeric date variable

XYZDTFL - flag variable

Details on imputing partial dates for specific datasets are outlined below.

9.2.5.1. Adverse events

There will be no attempt to impute the following

- Missing AE start dates
- AE start dates missing the year
- Partial/missing AE end dates

Table 1 explains the abbreviations used.

Table 1 AE/Treatment Date Abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

Table 2 describes the possible combinations and their associated imputations. The upper text indicates the imputation (NC, A, B, C etc) and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 2 Imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The legend to the above table is shown in Table 3.

Table 3 Imputation algorithm legends

Relationship		
	Before TRTSTD	Indicates AE start date prior to Treatment Start Date
	After TRTSTD	Indicates AE start date after Treatment Start Date
	Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation calculation		
	NC / Blank	No convention/imputation
	(A)	01MONYYYY
	(B)	TRTSTD+1
	(C)	15MONYYYY
	(D)	01JULYYYY
	(E)	01JANYYYY

Few examples are shown in Table 4.

Table 3 Example scenarios

Partial AE start date	Treatment start date	Relationship with TRTSTD	Imputation Calculation	Imputed Date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
ddNOV2001	20OCT2001	After	(A)	01NOV2001

If imputed start date is greater than the end date of the adverse event, when end date is available, the imputed start date will be set equal to the end date

9.2.5.2. Concomitant medication date imputation

The imputation of the start date of concomitant medication will follow the same conventions as for AE date. Partial/missing concomitant medication end dates will not be imputed.

9.2.5.3. Diagnosis and extent of cancer

The following variables require imputation when incomplete:

a. Date of initial diagnosis of primary site of cancer
b. Date of first recurrence/relapse
c. Date of most recent recurrence/relapse

Missing day is defaulted to 15 and missing month and day is defaulted to January 01, unless any of the following applies:

First recurrence/progression date:

- **If day is missing AND** occurred in the same month of the most recent relapse/progression, then day of first recurrence/progression will be imputed as the minimum between 15 and day of the most recent relapse/progression.

Most recent relapse/progression date:

- **If day is missing AND** occurred in the same month of the first recurrence/progression, then day of most recent relapse/progression will be imputed as the maximum between 15 and day of first recurrence/progression.
- **If month and day are missing AND** occurred in the same year of the first recurrence/progression, then month and day of most recent relapse/progression will be imputed as the maximum between January 01 and month and day of first recurrence/progression

9.2.5.4. Anti-cancer therapy

Prior therapies

- **Start date:** The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that: for scenario (B) will be replaced to be treatment start date -1.
- **End date:**
  - Imputed date = min (reference end date, DEC 31) , if month and day are missing.
  - Imputed date = min (reference end date, last day of the Month) , if day is missing.
  - Reference end date will be treatment start date.
- If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.
- If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date

Post therapies

- **Start date:**
  - If Day is missing, then impute to the max (reference start date, first day of the month).
  - Day and month are missing then impute to the max(reference start date, Jan 1)
  - Reference start date will be last date of study treatment administration + 1.
- **End date:** No imputation

9.2.5.5. Last contact or death date(s)

All dates must be completed with day, month and year. If the day is missing, the 1st of the month will be used for incomplete death dates or dates of last contact.

9.2.5.6. Incomplete dates for last treatment administration

Scenario 1: If the last treatment administration date is completely missing and there is no study treatment discontinuation (STD) page and no death date:

- The subject should be treated as on-going and use the cutoff date as the last dosing date up to date.

Scenario 2: If the last treatment administration date is completely or partially missing and there is either STD page or death date available:

If only Year is available and Year < Year of min (DISC date, death date);

Imputed date= Dec31yyyy

If both Year and Month are available, Year = Year of min(DISC date, death date) and Month < the month of min(DISC date, death date)

Imputed date= last day of the Month

All other cases imputed date= min (DISC date, death date)

The imputed date will be compared with start date of treatment. If the imputed date is < start date of treatment, set the last treatment administration date to be the treatment start date; otherwise use the imputed date.

9.2.5.7. Assessment date of tumor assessments

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise – if overall lesion response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

9.2.6. Handling of concentrations below LLOQ or missing

Missing values of concentrations will not be imputed. When summarizing concentrations, zero values will be excluded from the calculation of geometric means and CV% geometric mean. However, they will be included for all other summary statistics and the number of non-zero concentrations will be reported. All concentration values below the lower limit of quantitation (LLOQ) of 0.1 µg/mL are set to zero, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK parameters will not be imputed.

9.2.7. Baseline Definition

Baseline will be defined as the most recent, non-missing value prior to or on the first study treatment dose date. For laboratory data, baseline will be defined as the most recent, non-missing value from a central laboratory prior to or on the first study treatment dose date. If there are no central labs collected prior to or on the first dose date of study treatment, the most recent, non-missing value from a local laboratory prior to or on the first date of study treatment will be defined as the baseline value.

For subjects who did not receive study treatment during the study, baseline will be defined as the latest, non-missing collected value.

9.2.8. Change from baseline

Change from baseline will be presented for safety data as described in Section 11.

Change from baseline is calculated as:

- For records occurring after baseline: (visit value) – baseline value.

Percent change from baseline is calculated as:

- For records occurring after baseline: ((change from baseline) / baseline value) * 100

If either the baseline or visit value is missing, the change from baseline and/or percent change from baseline is set to missing as well.

9.2.9. Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). Unscheduled data will only be included in “post-baseline” summaries for capturing a worst case across all scheduled and unscheduled visits after the first dose of protocol therapy.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

9.2.10. Cardiac Scan Modalities (ECHO/MUGA)

The same modality (ECHO or MUGA) for determining cardiac scan data (e.g., left ventricular ejection fraction (LVEF)) should be used to follow a subject throughout the study. The absolute change from baseline values will not be calculated for any subjects where the post-baseline value was determined by a cardiac scan modality that is different than the one used to determine baseline value.

9.2.11. Derived and Transformed Variables

See Section 10 in this RAP for details on analyses for objective response rate, clinical benefit, progression-free survival, overall survival and time to progression.

For pharmacokinetic parameters, between-subject coefficient of variation (CVb%) will be calculated by the following methods, where SD is the standard deviation of the PK parameter data, calculated using either the raw data (untransformed) or the natural logarithm of the raw data (transformed).

Untransformed Data: 100 * (SD/Mean)

Transformed Data: 100 * (square root[exp(SD^2)-1])

See Section 12 in this RAP for derivation of PK parameters.

ECG Corrected QT Intervals

The QTc values based on Bazett's formula is derived by QT interval / ((RR interval/1000)^1/2), where RR interval is in msec.

9.3. Study Time Periods

9.3.1. Time in Relation to Treatment

Adverse events, serious adverse events, death, laboratory data, vitals, ECG, and ECHO/MUGA will be assigned to the study time periods defined below. Partial dates will be imputed into full dates, if applicable, for slotting data to the appropriate categories below (see Section 9.2.5). Flag variables (time in relation to study treatment) indicating the study time periods will be added to these datasets.

The overall observation period will be divided into three mutually exclusive segments:

Pre-therapy is defined as the time prior to the subject's first dose of study treatment.

On-therapy is defined as the time from first dose of study treatment to the date of the last dose of study treatment + 28 days.

Post-therapy is defined as any time beyond the on-therapy period.

Some datasets include the first dose day as On-therapy and some exclude the first dose date as On-Therapy. The first dose day (Day 1) is considered pre-therapy for ECOG, ECG, vital signs, liver events, lab tests, and cardiac scan. The first dose day (Day 1) is considered to be on-therapy for adverse events and concomitant medications.

All safety data (including those from the post-therapy period) will be listed and those occurring during the pre-therapy and post-therapy periods are to be flagged.

9.3.2. Study Time Periods for Concomitant Medications

Concomitant Medication start and end dates will be assigned to study time periods in relation to first dose of study treatment as defined below. The start date references time flag variables and end date reference time flag variables will be added to the concomitant medication dataset.

- Start **relative to therapy:** Assign to 'BEFORE' if start date is prior to study treatment start date or if subject has not taken any study treatment or (start date is missing and end date is before study treatment start date). Else assign to 'DURING' if the start date falls into the on-therapy period as defined above or if subject is ongoing (not all study treatment discontinuation records completed) or start date is missing. Else assign to 'AFTER' if start date is after the on-therapy period.
- End **relative to therapy**: Assign to 'BEFORE' if end date is prior to study treatment start date or if subject has not taken any study treatment. Else assign to 'DURING' if end date falls into the on-therapy period or if subject is ongoing (not all study treatment discontinuation records completed) or (end date is missing and start relative to treatment not 'AFTER'). Else assign to 'AFTER' if end date is after the on-therapy period or (end date is missing and start relative to treatment='AFTER').

Concomitant medication start relative to treatment and end relative to treatment flags are used to select data to include in the Concomitant Medication summaries as follows:

- Summary of Concomitant Medications: This summary will contain medications including those with start date prior to study treatment start date and continue (missing end date or end date after study treatment start date) on therapy. Note that any medications with start date and end date prior to study treatment start date will be excluded. In addition, any medication that was started during post-therapy will be excluded. Include concomitant medication records where start relative to treatment in ('BEFORE','DURING') and end relative to treatment in ('DURING','AFTER').
- Summary of Concomitant Medications with On-Therapy Onset: This summary will contain medications with start date after study treatment start date. In addition, any medication that was started during post-therapy (see above for definition of post-therapy) will be excluded. Include concomitant medication records where start relative to treatment in ('DURING').

9.4. Values of Potential Clinical Importance

9.4.1. Laboratory Parameters

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) will be used to assign grades to the relevant laboratory parameters. NCI-CTCAE v4.0 can be found at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

When reporting grade shifts for Biochemistry and haematology data, the records in the LAB dataset will be used.

For laboratory data which are not listed in the NCI CTCAE v4.0, a summary of values outside the normal range will be provided.

9.4.2. ECG Parameters

The following criteria will be used to flag electrocardiogram (ECG) values that are values of potential clinical importance:

To identify QTc (Bazett's) values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign grades (see adverse event 'Electrocardiogram QT corrected interval prolonged'). Note that there is a slight inconsistency between CTCAE v4.0 and ICH E14 (Absolute QTc interval prolongation). It was decided to align with CTCAE for the oncology standard categories.

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute QTcB interval	<450 ≥450 to <480 (Grade 1) ≥480 to <500 (Grade 2) ≥500 (Grade 3)	Msec
Absolute QTcF interval	<450 ≥450 to <480 (Grade 1) ≥480 to <500 (Grade 2) ≥500 (Grade 3)	Msec
Increase from baseline QTcB	Increase of ≥30 to <60 Increase of ≥60	Msec

The following criteria will be used to flag other ECG values that are values of potential clinical importance:

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
PR interval	<110 (L) and >220 (H)	Msec
QRS interval	<75 (L) and >110 (H)	Msec

Normal values per age group for QTcB and QTcF, derived from the 2nd and 98th percentile values in healthy children will be used to identify the values out of normal ranges within each age group.

Age group	0-1 month	1-3 month	3-6 month	6-12 month	1-3 years	3-5 years	5-8 years	8-12 years	12-16 years
QTcB (ms) Boys	413 (378, 448)	419 (396, 458)	422 (391, 453)	411(379, 449)	412 (383, 455)	412 (377, 448)	411(371, 443)	411(373, 440)	407 (362, 449)
QTcB (ms) Girls	420(379, 462)	424(381, 454)	418 (386, 448)	414(381, 446)	417(381, 447)	415(388, 442)	409 (375, 449)	410 (365, 447)	414(370, 457)

Data shown above as median (2nd percentile, 98th percentile)

9.4.3. Vital Signs

Heart rate:

To identify heart rate values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Sinus bradycardia', 'Sinus tachycardia', 'Supraventricular tachycardia', and 'Ventricular tachycardia'.

Normal values per age group for heart rate, derived from the values in healthy children will be used to identify the values out of normal ranges within each age group. The following criteria will be used to flag vital sign values that are values of potential clinical importance:

Age group	0-1 month	1-3 month	3-6 month	6-12 month	1-3 years	3-5 years	5-8 years	8-12 years	12-16 years
HR (bpm) Boys	160(125, 190)	152(125, 185)	134(110, 165)	128(105, 165)	119(95, 155)	98(75, 125)	88(60, 115)	78(55, 100)	73(50, 100)
HR (bpm) Girls	155(135, 215)	154(125, 200)	139(120, 190)	134(105, 185)	128(95, 180)	101(80, 125)	89(70, 115)	80(60, 110)	76(50, 100)

Data shown above as median (lower limit of normal, upper limit of normal)

Blood pressure:

To identify blood pressure values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypertension'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline Systolic Blood Pressure	≥120 to <140 (Grade 1) ≥140 to <160 (Grade 2) ≥160 (Grade 3)	mmHg
Increase from baseline Diastolic Blood Pressure	≥80 to <90 (Grade 1) ≥90 to <100 (Grade 2) ≥100 (Grade 3)	mmHg

To identify blood Pressure >95th percentile for specific age, gender and percentile of height, refer to Protocol appendix 5 Blood pressure Levels for children.

Weight (kg):

The weight values of potential clinical importance will be increase >=10% or decrease >=10% from baseline weight.

Temperature:

To identify temperature values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypothermia' and 'Fever'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline temperature	Increase to ≥38	Degrees C
Decrease from baseline Diastolic Blood Pressure	Decrease to ≤35	Degrees C

9.4.4. Left Ventricular Ejection Fraction

The following criteria will be used to flag left ventricular ejection fraction (LVEF) values that are values of potential clinical importance:

To identify LVEF values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Ejection fraction decreased'.

LVEF Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute change from baseline LVEF	• No change or any increase • Any decrease o >0-<10 decrease o 10-19 decrease o ≥20 decrease o ≥10 decrease and ≥ LLN o ≥10 decrease and below LLN o ≥20 decrease and ≥ LLN o ≥20 decrease and below LLN	%
Relative change from baseline LVEF	• ≥20 decrease and ≥ LLN • ≥20 decrease and below LLN	%

9.5. Disposition of Subjects

A summary of the number of subjects in each of the analysis populations described in Section 6 will be provided. A listing of subjects included or excluded from each of analysis populations will also be provided.

The following summaries will be provided:

- Number (%) of subjects who are still on-therapy (based on the 'Study Treatment Discontinuation' page not completed)
- Number (%) of subjects who discontinued the study treatment (based on the 'Study Treatment Discontinuation' page)
- Primary reason for study treatment discontinuation (based on the 'Study Treatment Discontinuation' page)
- Number (%) of subjects who have entered the survival follow up (based on the 'Study Treatment Discontinuation' page)
- Number (%) of subjects not being followed for study evaluation

A summary of the number and percentage of subjects who completed the study treatment as well as prematurely discontinued/withdrew from the study treatment will be displayed. Reasons for discontinuation/study treatment withdrawal will be presented by cycle, overall, and by cohort.
A listing of study completion and discontinuation/withdrawal will be generated which will include last dose date, and reasons for study treatment discontinuation/withdrawal.

9.6. Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. Major protocol deviations

and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in protocol deviation plan.

The number and percentage of subjects in the mITT population with any protocol deviation will be tabulated by deviation category. All protocol deviations will be summarized and listed including inclusion/exclusion deviations as well as other deviations. The major protocol deviations will be flagged.

9.7. Demographic and Baseline Characteristics

The demographic characteristics (i.e., age, race, ethnicity, sex, baseline height, and baseline body weight, childbearing potential, Karnofsky/Lansky performance status, and body surface area (BSA)) will be summarized and listed. Age, height, weight and BSA will be summarized using the mean, standard deviation, minimum, median, and maximum. Categorical data (i.e., sex, age groups: 1 year to <2 years, 2-<12 years, 12-<18 years, race, ethnicity, Karnofsky/Lansky performance status, woman of childbearing potential) will be summarized by frequency counts and percentages; the number and percentage of subjects with missing data will be provided.

Disease history and characteristics at initial diagnosis and screening will be summarized and listed. This summary will include the following: for solid tumor, summarize primary tumor type, location of primary tumor type, histological grade, stage at screening, time since initial diagnosis, and time since most recent relapse/progression to start of study drug, TNM staging at screening for primary tumor, regional lymph nodes and distant metastasis, metastatic disease location and time since initial diagnosis; for neuroblastoma, summarize bone marrow lesions , staging at initial diagnosis and staging at screening. The summay will also include subject tibial growth plate status and its evidence of thickening.

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be listed by cohort using reported term. Separate listing will be presented for liver disease medical conditions

Prior anti-cancer therapy will be coded using the World Health Organization Drug Dictionary (WHO-DD), then listed and summarized by ATC class, preferred term, overall and cohort by means of frequency counts and percentages. A summary of the number of prior anti-cancer therapy regimens will also be produced.

Prior anti-cancer radiotherapy and prior cancer related surgeries will be summarized and listed.

9.8. Concomitant Medications

Concomitant medications include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD), and summarized by lowest ATC class and preferred term using frequency counts and percentages.

These summaries will include:

1. Medications starting on or after the start of study drug but no later than 28 days after last dose of study drug and
2. Medications starting prior to start of study drug and continuing after the start of study drug.

All concomitant medications will be listed. Any concomitant medications starting and ending prior to the start of study treatment or starting more than 28 days after the last date of study treatment will be flagged in the listing.
The safety population will be used for all concomitant medications tables and listings.

10. Efficacy

All efficacy analyses will be based on mITT population unless otherwise specified. All analyses will be presented by cohort.
Subjects from different disease cohorts are assigned to one of the following categories for assessment of response: a) the revised RECIST guideline (version 1.1) for solid tumor and measurable disease, b) Response Criteria for neuroblastoma with ^{123}I-MIBG positive lesions, (neuroblastoma subjects who do not have MIBG positive lesions should be assessed for response as solid tumor subjects with measurable disease), c) RECIST-based and/or Alpha Fetoprotein (AFP)-based response for hepatoblastoma. Investigator assessments will be considered as primary assessments. For more detailed information, see protocol Section 10.

10.1. Primary Efficacy Analysis

Objective Response Rate (ORR)
The primary aim of the study is to determine the investigator-assessed objective response rate of pazopanib in children, adolescents and young adults (subjects) with relapsed or refractory rhabdomyosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma, and Ewing sarcoma.

Objective Response Rate (ORR) is defined as the percentage of subjects achieving either a complete or partial tumor response as per response criteria. The response rate will be calculated from the investigator review. Confirmation will be based on the disease assessment performed 1 cycle or the next scheduled visit after the initial response. The objective response rate will be computed for the 3 tumor types of primary interest.

In other words, ORR = (number of subjects with a confirmed BOR of CR + number of subjects with a confirmed BOR of PR) divided by the total number of subjects in the cohort. The assessment of activity of treatment within each histology cohort will be based on the decision rule outlined in Section 3 in this RAP.

Analyses of the primary endpoint will also be done on the mITT and Per-Protocol populations based on all cumulative data collected up to the final database lock date.

Refer to Table 1, Table 2 and Table 3 in Protocol section 10.7 for response criteria at each disease assessment and derivation of best overall response (BOR).

90% confidence intervals will be provided to characterize the variability around the response rate.

All data relating to response from the investigator will be listed including lesion measurements, response assessments and best overall response.

A waterfall plot of the best percent change in target lesions from baseline until disease progression will be provided. The plot will be pattern-coded for best overall response.

Indication of the subject number, cohort and best overall response will also be provided in the plot of duration of exposure to study treatment.

10.2. Secondary Efficacy Analyses

Objective Response Rate (ORR)

The objective response rate will be computed for the 4 tumor types of secondary interest osteosarcoma, neuroblastoma (measurable), neuroblastoma (evaluable) and hepatoblastoma. The analysis method will be the same as that described in Section 10.1 (Primary Efficacy Analyses).

If recruitment is stopped in the non-primary histology group(s) and it has less than 10 subjects, the response data will display summary statistics and the rule in the table under Section 3 in this RAP will not apply.

The detailed response criteria for hepatoblastoma subjects are provided in Protocol section 10.6, and displayed in Table 4 in Protocol section 10.7.

Progression-Free Survival (PFS)

Progression-Free survival (PFS) is defined as the interval between the date of first dose of protocol therapy and the earliest date of disease progression or death due to any cause.

Progression will be based on the investigator assessment. Subjects are considered to have progressive disease if they have documented progression based on radiologic assessment as determined by investigator review (defined in protocol section 10). The date of death should be taken from the Death page in eCRF. Death on study due to any cause will be included. For subjects who do not progress or die, progression-free survival will be censored at the date of last adequate assessment prior to starting new anti-cancer therapy.

If there is no adequate baseline assessment, the subjects will be censored at their treatment start date. Subjects without any adequate post-baseline tumor assessments will also be censored at their treatment start date.

For subjects who receive subsequent anti-cancer therapy the following rules will apply:

- If the start date of the anti-cancer therapy is partial (i.e. either missing the day but has the month and year available or missing both day and month), the imputation rules described in Section 9.2.5.4 will be applied. No imputation will be made for completely missing dates.
- If anti-cancer therapy is started without documented disease progression or is started prior to documented disease progression, then PFS will be censored at the date of the last adequate assessment that is no later than the date of initiation of anti-cancer therapy (i.e. if an assessment occurs on the same day as the start of new anti-cancer therapy the assessment will be used - as it will be assumed the assessment occurred prior to the administration of new anti-cancer therapy).
- If a subject has only a baseline visit or does not have an adequate assessment that is no later than the date of initiation of anti-cancer therapy, PFS will be censored at the treatment start date.

If a subject has neither progressed nor died nor started new anti-cancer therapy, then PFS will be censored at the date of the last adequate assessment defined as an assessment where the Investigator determined is CR, or PR, or SD. The date of assessment will be used as the censoring date.

A summary of the assignments for progression and censoring dates for PFS are specified in the following table.

Table 5: Assignments for Progression and Censoring Dates for PFS Analysis

Situation	**Date of Event (Progression/Death) or Censoring**	**Outcome Event (Progression/Death) Or Censored**
No (or inadequate) baseline tumor assessments	Treatment start date	Censored
No post-baseline assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	Treatment study date	Censored

Situation	Date of Event (Progression/Death) or Censoring	Outcome Event (Progression/Death) Or Censored
Progression documented between scheduled visits	Date of assessment of progression[1]	Event
No progression (or death)	Date of last 'adequate' assessment of response[2]	Censored
New anticancer treatment started (prior to documented disease progression).[3]	Date of last 'adequate' assessment of response[2] (on or prior to starting anti-cancer therapy)	Censored
Death without PD	Date of death	Event

1. The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non-target lesions, or (iii) Date of last radiological assessment of target lesions (if progression is based on increase in sum of target lesions)
2. An adequate assessment is defined as an assessment where the Investigator] determined response is CR, PR, or SD.
3. If PD and New anti-cancer therapy occur on the same day assume the progression was documented first e.g., outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any post-baseline adequate assessments, censoring date should be the treatment start date.

PFS will be summarized using a Kaplan-Meier survival curve. The Kaplan-Meier estimate for the median progression-free survival time and the first and third quartiles will be presented, along with a naive approximate 90% confidence interval if there are a sufficient number of progressions or deaths. This analysis will be repeated on the mITT population as a supportive analysis of PFS.

Overall Survival (OS)

Overall Survival (OS) is defined as the time from the first dose of the study medication until death due to any cause. The length of this interval is calculated as the date of death minus the date of treatment start plus one. Subjects who have not died at the time of the analyses will be censored at the date of last contact (as recorded in the eCRF). Last date of contact will be defined as the maximum date of any visit date or the survival follow-up date. Only subject contacts recorded in the eCRF can be used for the calculation of last date of contact.

OS will be summarized using Kaplan-Meier survival curves. The Kaplan-Meier estimate for the median OS time and the first and third quartiles will be presented, along with a naïve approximate 90% confidence interval if there are a sufficient number of deaths.

Clinical Benefit

This is defined as the percentage of subjects achieving either a complete or partial tumor response or stable disease for at least two protocol scheduled disease assessments as per RECIST criteria. 90% confidence intervals will be produced to characterize the variability around the point estimate. Supportive analyses will be done using the mITT and PP populations.

Time to Progression (TTP)

Time to Progression (TTP) is defined as the interval between the date of of first dose of protocol therapy and the earliest date of disease progression or death due to disease under study. Subjects are considered to have progressive disease if they have documented progression based on radiologic assessment as determined by investigator review.

The data structure on how to assign the event and censoring to a subject is same as that defined in the Table 5 under PFS analysis. TTP will be calculated as the date of event/censoring minus the date of first protocol therapy for each subject plus one.

TTP will be summarized using a Kaplan-Meier survival curve. The Kaplan-Meier estimate for the median time to progression and the first and third quartiles will be presented, along with a naive approximate 90% confidence interval if there are a sufficient number of events.

Duration of Response (DOR)

Duration of response (DOR) is defined as the time from the initial response (CR/PR) to first documented disease progression or death due to any cause, and will be determined only for those subjects from mITT population with a confirmed response (CR or PR). This will be based on investigator assessed response. If a subject has not had an event (disease progression or death), DOR is censored at the date of last adequate tumor assessment. The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. The date of response at that assessment will be used for censoring.

DOR will be summarized only if there are 5 or more responders from each cohort. Otherwise it will be presented in a listing for all the responders.

11. Safety Analyses

Unless otherwise specified, all the safety analyses will be based on the Safety population as defined in Section 6 and summaries will include all events or assessments collected during the study.

All safety data will be reported by cohort. Safety analyses will include but not limited to summaries of AEs, laboratory measures, and vitals. AEs will be summarized by maximum toxicity grade for each cohort. The toxicity grade for laboratory data will be calculated using NCI CTCAE v4.0 The lab data will then be summarized according to the subjects' baseline grade and maximum grade for each cycle of therapy.

11.1. Extent of Exposure

The duration of exposure to Pazopanib in days (from first day to last day of treatment) will be summarised by cohort. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated for time on study treatment. Exposure categories (in weeks) will also be summarized.

Average daily dose will be calculated as Cumulative dose (mg) / Duration of exposure to study treatment (day), and summarized by cohort, using the mean, standard deviation, median, minimum, and maximum. Actual duration of exposure will be calculated as the date of last dosing-date of first dosing+1.

Study drug dose received will be summarized by cohort. Cumulative dose, actual dose intensity and relative dose intensity will be presented. Actual dose intensity will be calculated as actual total dose/actual duration of exposure. Relative dose intensity will be calculated as (actual dose intensity/planned dose intensity)*100. Planned dose intensity will be calculated as planned total dose/planned duration of exposure, where planned duration of exposure will be the same as actual duration of exposure.

A by-subject listing of data on subject exposure including dose reduction, dose interruptions and the corresponding reasons will be produced.

The safety population will be used for all summaries and listing of study treatment.

11.2. Adverse Events

AE summaries will include all AEs occurring during on-therapy period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on therapy period will be flagged in the listings.

An overview summary of AEs, including counts and percentages of subjects with any AE, grade ¾ AEs, AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, AE leading to dose reductions, AEs leading to dose interruptions, SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment will be produced

A summary of on-therapy AEs will be provided by primary system organ class (SOC) and preferred term (PT) and by PT only All non-serious adverse events, regardless of study drug relationship, by SOC and PT will be summarized.

Adverse events (AEs) will be graded according to the CTCAE, Version 4.0. Adverse events will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA).

In AE summaries, the frequency and percentage of AEs (all grades) will be summarized and displayed in two ways: 1) in descending order of total incidence by PT only and 2) in descending order of total incidence by System Organ Classes (SOC) and PT. In the SOC row, the number of subjects with multiple events under the same system organ class will be

counted once. The primary system organ class (SOC) will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency.

In addition, a summary of number and percentage of subjects with any on-therapy adverse events by maximum grade will be produced. AEs will be sorted by preferred term (PT) in descending order of total incidence. The summary will use the following algorithms for counting the subject:

- **Preferred term row**: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row**: Each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

A separate summary will be provided for study treatment-related AEs. A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing. The summary table will be displayed in descending order of total incidence by SOC and PT and by PT only. Note all treatment-related AEs will be included in the summary regardless of assessment window.

All AEs will be listed.

A listing of adverse events recorded as dose-limiting toxicities will be provided. Additionally, a summary of the number of subjects experiencing DLT's in each cohort will be provided.

11.3. Identified and Potential Risks

N.A.

11.4. Deaths and Serious Adverse Events

In the event that a subject has withdrawn consent, no data after the withdrawal of consent date from this subject including death is supposed to appear in the database. Ensuring that this rule is followed should be part of the data cleaning process.

All deaths will be summarised based on the number and percentage of subjects. This summary will classify subject status (dead, alive at last contact follow-up ended, alive at last contact follow-up ongoing), subjects by time of death relative to the last dose of medication (>28 days or ≤28 days), and primary cause of death. A supportive listing will be generated to provide subject-specific details on subjects who died.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event by cohort. Separate summaries will also be provided for study treatment-related SAEs, fatal SAEs and study treatment related fatal SAEs. Treatment-related SAE by SOC, PT, and maximum CTC grade will be summarized. The summary tables will be displayed in descending order of total incidence by SOC and PT and by PT only.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' for missing.
SAEs are included in the listing of all adverse events. Separate supportive listings with subject-level details will be generated for

- Fatal SAEs
- Non-Fatal SAEs.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables will be generated.

(1) On-therapy adverse events which are not serious adverse events with an incidence greater than 5%.

If for a same subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE

(2) On-therapy deaths and serious adverse event by system organ class and preferred term including the number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of treatment.

11.5. Adverse Events Leading to Discontinuation of Study Treatment and/or Withdrawal from the Study and Other Significant Adverse Events

The following categories of AEs will be summarized separately in descending order of total incidence by SOC and PT and separate supportive listings will be generated with subject level details for those subjects:

- AEs Leading to Discontinuation/Withdrawal of Study Treatment
- AEs Leading to Dose Interruptions
- AEs Leadings to Dose Reductions

11.6. Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If subjects become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

11.7. Clinical Laboratory Evaluations

Data from all sources (central and local laboratories) will be combined. The summaries will include all laboratory assessments collected no later than 28 days after the last study treatment administration date. All laboratory assessments will be listed and those collected later than 28 days after the last study treatment date will be flagged in the listings.

Laboratory data will be classified into CTC grades according to the NCI CTCAE v4.0. For all reports, CTC grade is always obtained on the converted measurement in SI unit. Grade 5 will not be used. The CTC grade 0 will be assigned as below in different scenarios:

1. For lab parameters defined by criteria based on normal range only, a severity grade of 0 will be assigned when the value is within normal limits.
2. For lab parameters whose grade is defined by criteria based on normal range and absolute values (e.g. platelet count decrease). A severity grade of 0 will be assigned when the value is within normal limits.
3. For lab parameters whose grade is defined by criteria based on normal range and the change from baseline value, with no other associated clinical criteria such as concomitant medication (e.g. creatinine increased) the following will be applied. For the baseline grading and for the grading of post-baseline lab values with missing baseline grading, the grade will be derived using the criteria based only on the normal range as per CTCAE v4.0. A severity grade of 0 will be assigned when the post-baseline value is ≤ ULN (for hyper) or ≥ LLN (for hypo).

Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

The following summaries will be produced by cohort for the hematology and Biochemistry laboratory data:

- Shift tables using CTCAE grades to compare baseline to the worst post-baseline value.

- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst post-baseline value.

The following listings will be produced for laboratory data:

- Listing of subjects with laboratory abnormalities of CTC grade 3 or 4
- Listing of subjects with laboratory values outside the laboratory normal ranges with values flagged to show the corresponding CTCAE grades and the classification relative to the laboratory normal range. Non- normal lab values collected outside the on-threapy period will be also reported in listings and flagged accordingly.

Summaries will include data from scheduled assessments only except for the worst case post baseline which will include all post baseline assessments including unscheduled visits, and all data will be reported according to the nominal visit date for which it was recorded; no visit windows will be applied.

Summary of lab values and change from baseline by scheduled visits using mean, median, standard deviation, minimum and maximum will be provided. Supporting listings of all laboratory data will be provided including scheduled and unscheduled assessments and values identified from SAE reports.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

11.7.1. Analyses of Liver Function Tests

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above. Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP).

Possible Hy's law cases are defined as any elevated AST or ALT>3×ULN, total bilirubin≥2×ULN and ALP<3×ULN/missing. Total bilirubin≥2×ULN can be within 28 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥ 35% of total bilirubin. ALP<3xULN/missing means the criteria is satisfied unless the ALP is ≥3xULN at any time of bilirubin elevation within the 28 days window.

Following supporting listings will be provided:

- Listing of Potential Hy's Law Cases

- Listing of Liver Events in Relation to Time of Treatment

listing of laboratory data (virology) will be provided.

11.8. Other Safety Measures

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

Vital Signs

Values of vital signs (blood pressure, heart rate, and temperature) and weight as well as the change from baseline collected on-therapy will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum. Values measured outside of on-therapy period will be flagged in the listing.

For analysis of vital signs, the clinically notable vital sign criteria are provided in Section 9.4.3. **Error! Reference source not found.** Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced by cohort for systolic blood pressure, diastolic blood pressure, heart rate, and body temperature. Baseline is defined as the last non-missing value prior to or coinciding with first dose. The worst post-baseline value refers to the worst post-baseline value on therapy.

Performance Status

Lansky and Karnofsky performance status will be summarized at baseline and each post-baseline scheduled visit. Summaries will use frequency and percentage of subjects at each planned assessment time. A summary of change from baseline by scheduled visits will be performed, as well as the worst case post-baseline and the best case post-baseline changes during the study.

A supporting listing will also be provided.

ECG

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits as well as for the worst case post-baseline.

All ECG summaries will include assessments performed no later than 28 days after the last date of study drug. All ECG assessments will be listed, and those collected later than 28 days after study drug discontinuation will be flagged in the listing.

The number and percentage of subjects with clinically notable ECG values will be presented by cohort. The clinically notable ECG criteria are provided in Section 9.4.2.

For each of the QTc and QT intervals, shift tables based on notable parameter categories (<450, 450 - <480, 480 - <500, ≥500 ms) and normal range at baseline and the worst post-baseline value observed will be produced.

The changes in QTc values will be categorized into the clinical concern ranges which are specific to changes in QTc: 31-60 and >60 msec. A summary of change in QTc value will display the number and percentage of subjects with a change within each range at each scheduled assessment time and in the worst case post-baseline assessment. Subjects with missing baseline values will be excluded from this summary.

Unscheduled ECG measurements will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters for the worst case post baseline assessment.

Listings of abnormal ECG findings and a listing of ECG values will be provided.

LVEF

Absolute change from baseline in LVEF will be summarized at each scheduled assessment time and in the worst case post-baseline. Only the post-baseline assessments that used the

same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline. The change from baseline will be categorized as follows:

- Any increase
- No change
- Any decrease:
  - 0 - <10% Decrease
  - 10 - <20% Decrease
  - ≥20% Decrease
- ≥10% decrease and ≥ LLN
- ≥10% decrease and < LLN
- ≥20% decrease and ≥ LLN
- ≥20% decrease and < LLN

LVEF results will also be listed with subject level details including absolute change from baseline.

12. Pharmacokinetic Analyses

12.1. Sampling Schedule

All subjects will have pre-dose blood samples on Cycle 1 Day 1 and Cycle 1 Day 15 and a 3-4 hours post-dose sample on Cycle 1 Day 15 collected for analysis of pazopanib plasma concentration. Pre-dose blood sample will be collected on every subsequent odd-numbered cycle (Cycles 3, 5, etc.).

Extended PK sampling will be done during Cycle 1 in the first subjects who receive the powder suspension formulation, until 6 subjects are considered evaluable for the PK analysis. These subjects will have a blood sample for analysis of the plasma pazopanib concentration collected at the following time points on both Cycle 1 Day 1 and Cycle 1 Day 15: pre-dose and at 30 min, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours after the dose.

12.2. Pharmacokinetic Analysis

The PK and PKES population will be used for listings and summaries. The PKES population will be used for the figures.

Pazopanib concentrations will be listed by dose and cohort. Summary tables for PK and PKES populations for pazopanib concentrations will be presented by cycle/day, dose, and cohort. Similar summary tables of pazopanib concentrations will be presented by cycle/day and dose combining data from all cohorts. The following summary statistics for pazopanib plasma concentrations will be calculated: n, median, minimum, maximum, arithmetic mean, CV% mean, standard deviation, geometric mean, CV% geometric mean.

Steady state trough plasma pazopanib concentrations will be determined for all subjects in the PK population. A concentration will be considered to be at steady state if the subject has taken 10 consecutive daily pazopanib doses without a dose reduction or interruption. A pre-dose concentration will be considered a trough sample if collected between 22-26 hours after the previous dose of pazopanib. Concentrations which are not at steady-state will be listed and flagged but excluded from summary tables for steady state concentrations. Similarly, concentrations which are not considered trough (blood sample taken after dosing or outside window 22-26 hours after previous dose) will be listed and flagged but excluded from summary tables.

The change in steady state trough plasma pazopanib concentrations will be characterized at the first cycle and each odd cycle after the first. The effect of cycle on change in steady-state plasma trough concentrations for each cohort will be assessed for each dose graphically by plotting median steady state trough concentrations against Cycle number.

If no substantial effect of the cycle is observed, steady-state trough concentrations will be combined for all sampling occasions and summarized by dose and cohort. Similar summary table will be presented by dose combining data from all cohorts.

A summary table summarizing pazopanib concentrations at each sampling occasion and a figure for pazopanib concentrations versus time by sampling occasion (Cycle 1 Day 1 and Cycle 1 Day 15) will be generated using PKES population combining data from all cohorts.

12.3. Pharmacokinetic parameters

The following pharmacokinetic parameters will be determined from the plasma concentration-time data for pazopanib from subjects who received pazopanib suspension and had extended pharmacokinetic sampling (Table 6).

Table 6 Non-compartmental PK parameters for pazopanib

AUC0-24	The AUC from time zero to 24 hours post dose (ng*hr*mL-1) (Day 15 only)
AUClast	The AUC from time zero to the last measurable plasma concentration sampling time (tlast) (ng*hr*mL-1) (Day 1 and Day 15
Cmax	The maximum (peak) observed plasma concentration following a single dose administration (ng/mL)
Tmax	The time to reach maximum (peak) plasma concentration following a single dose administration (hr)

The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to the Sponsor's current working practices and using WinNonlin version 6.3 or higher. The analysis to assess pazopanib pharmacokinetics after administration of the suspension prior to continuing enrollment on the suspension cohort may be performed using

scheduled time. All calculations of non-compartmental parameters for the final analysis will be based on actual sampling times.

12.3.1. Statistical Analysis of Pharmacokinetic Parameters

All derived pharmacokinetic parameter values will be listed by dose, formulation, cycle/day, and cohort. PK parameters will be summarized by dose, formulation and cohort for both Cycle 1 Day 1 and Cycle 1 Day 15. PK parameters will also be summarized for both Cycle 1 Day 1 and Cycle 1 Day 15 combining data from all cohorts. For each of the PK parameters except Tmax, the following summary statistics will be calculated: n, median, minimum, maximum, arithmetic mean, CV% mean, standard deviation, geometric mean, CV% geometric mean. For Tmax, n, median, maximum and minimum will be calculated.

Steady state trough plasma pazopanib concentration values will be combined for all sampling occasions and summarized by age subgroups (28 days to <2 years, 2 to <12 years old, 12 to 18 years old) for each dose, cohort, and formulation unless a cycle effect on steady-steady trough concentration is identified. A similar analysis will combine data across all disease cohorts unless pharmacokinetic differences between the cohorts are observed.

PK parameters will be summarized by age subgroups (28 days to <2 years, 2 to <12 years old, 12 to 18 years old) for each dose, cohort and formulation. A similar analysis will combine PK parameters across all disease cohorts unless pharmacokinetic differences between the cohorts are observed.

12.4. Assessment of pazopanib exposure from suspension formulation

Pazopanib exposures in subjects on the suspension formulation will be assessed by numerical comparison against exposures associated with efficacy in adult subjects. The proportion of subjects with steady state trough values above 20.5 (ug/mL), which is the efficacy threshold identified in subjects with advanced RCC (Shuttle et al 2014) will be calculated for each formulation, dose level, and cohort. A similar calculation will be presented combining subjects from all cohorts. If there is more than 1 steady state trough value for each subject, the first will be used.

12.5. Exploration of pharmacokinetic and pharmacodynamic relationship

Pazopanib PK/PD relationship will be explored between pazopanib steady state exposure (trough concentration) and biomarkers (angiogenic cytokines), efficacy (clinical benefits) or safety (drug related grade 2 and above hypertension). The analysis of the correlation of PK and biomarker will be described in a separate analysis plan. The proportion of subjects with steady state trough concentration above 20.5 ug/mL will be summarized for those with clinical benefits and those who do not have any clinical benefits. The steady state trough concentration will also be summarized by drug-related grade 2 and above hypertension.

13. REFERENCES

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