Statistical Analysis Plan

Protocol EZH-102

A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma

Version Final 2.0
20 October 2021

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SIGNATURE PAGE

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MODIFICATION HISTORY

After approval of version 1.0 of the statistical analysis plan, subsequent versions should be documented below with a brief description of the change from the previous version, as well as, the rationale for the change.

Version, Date	Made by	Brief Description of Change and Rationale
20 October 2021	PPD	Removed the 'initiation of subsequent anti-cancer therapy' from the definition of treatment emergent adverse events in Section 17.1, to be in alignment with the definition specified in the protocol.

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List of Abbreviations and Definitions

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ATC	anatomic therapeutic chemical (classification system)
AUC	area under the concentration-time curve
AUC_{D1}	area under the concentration-time curve on Day 1
AUC_{D15}	area under the concentration-time curve on Day 15
AUC_{0-t}	area under the concentration-time curve from time 0 to the last measurable plasma concentration
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 extrapolated to infinity
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BOR	best overall response
CI	confidence interval
CL/F	oral clearance
C_{max}	maximum plasma concentration
CR	complete response
CSR	Clinical Study Report
CSRC	Clinical Safety Review Committee
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EIAED	enzyme inducing anti-epileptic drug
E_{max}	maximum effect
EPZ-6438	Tazemetostat
ES	epithelioid sarcoma
EZH2	enhancer of zeste homolog-2
GOF	Gain of function
HLGT	high-level group term
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
ITT	Intent-to-Treat
Ka	first-order absorption rate constant
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid

Abbreviation	Term
MRT	malignant rhabdoid tumor
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	objective response rate
PD	progressive disease
PDy	pharmacodynamic(s)
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
QTcF	Fridericia correction of QT interval for heart rate
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RMC	renal medullary carcinoma
RTK	rhabdoid tumors of the kidney
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease or standard deviation
SI	International System of units
SOC	system organ class
$t_{1/2}$	elimination half life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
ULN	upper limit of normal
Vd/F	oral volume of distribution
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analyses, excluding pharmacokinetics (PK), pharmacodynamics (PDy) and exploratory endpoints, to be included in the Clinical Study Report (CSR) for the phase 1 Protocol EZH-102. This SAP is based on Amendment 8.0 of the protocol, dated 20 February 2020. This SAP must be approved, the data base locked, analysis populations defined, and protocol deviations identified prior to performing the analyses described in this document.

Results of the analyses of PK, PDy parameters and exploratory endpoints are presented in separate documents.

2. STUDY OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
• Dose escalation: To determine the maximum tolerated dose (MTD) or the recommended Phase 2 dose (RP2D) of tazemetostat when administered as an oral suspension twice daily (BID) in pediatric subjects with relapsed/refractory rhabdoid tumors, integrase interactor 1 (INI1) negative tumors or synovial sarcoma	• Incidence and severity of treatment-emergent AEs (TEAEs) qualifying as protocol-defined dose-limiting toxicity (DLTs) in Cycle 1. • Establishment of the protocol-defined RP2D and/or MTD.
• Dose Expansion: To evaluate the antitumor activity of tazemetostat as assessed by overall response rate (ORR) in pediatric subjects with relapsed/refractory atypical teratoid rhabdoid tumor (ATRT) (Cohort 1), non-ATRT rhabdoid tumors (Cohort 2), INI1-negative tumors (Cohort 3), and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4) using disease-appropriate standardized response criteria	• ORR: complete response (CR) + partial response (PR) for each cohort

Secondary	
• Dose Escalation: to evaluate the preliminary antitumor activity of tazemetostat as assessed by ORR using disease-appropriate standardized response criteria	• ORR: confirmed CR+PR

• Dose Expansion: to determine the progression-free survival (PFS) and overall survival (OS) at 24 and 56 weeks and overall in pediatric subjects with relapsed/refractory ATRT (Cohort 1), non-ATRT rhabdoid tumors (Cohort 2), INI1-negative tumors (Cohort 3), and tumor types eligible for Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement (Cohort 4) using disease-appropriate standardized response criteria	PFS at 24 and 56 weeks and overall for each cohort OS at 24 and 56 weeks and overall for each cohort
• All Subjects: To assess the safety and tolerability of tazemetostat administered as an oral suspension BID and tablet three times daily (TID)	•Adverse Events (AEs), clinical laboratory tests, and other safety measures
• All Subjects: To assess the pharmacokinetic (PK) parameters of tazemetostat after administration as suspension or tablets in pediatric subjects.	• PK parameters: maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration-time curve from time 0 to last measurable concentration [AUC_{0-t}], area under the concentration-time curve from time 0 to 12 hours post-dose [AUC_{0-12}], elimination half-life ($t_{1/2}$), oral clearance (CL/F), oral volume of distribution (Vd/F), first-order absorption rate constant (Ka); if data permit
• All Subjects: To evaluate the duration of response (DOR) in subjects achieving a complete response (CR) or partial response (PR) according to disease-appropriate standardized response criteria	• DOR

Exploratory
CCI [redacted]

CCI

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a phase 1, multicenter, open-label dose escalation and dose expansion study of tazemetostat in pediatric subjects with select relapsed or refractory INI1- or SMARCA4-negative tumors. Subjects will be screened for eligibility within 14 days of the planned first dose of tazemetostat. A treatment cycle will be 28 days. Treatment with tazemetostat will continue until disease progression, unacceptable toxicity, or withdrawal of consent. Response assessment will be evaluated after 8 weeks of treatment and every 8 weeks thereafter. Subjects may receive tazemetostat for a cumulative maximum of 2 years.

Dose escalation phase

Using a rolling 6 dose-escalation design (**Table 2**) [Skolnik, 2008], approximately 48 subjects will be enrolled into dose cohorts starting at 240 mg/m^2/dose administered orally BID for a total of 480 mg/m^2/day. Up to six subjects may be concurrently enrolled into the study. Dose escalation will proceed in increments of 25-33% and dose de-escalation will proceed in decrements of 50%. The dose levels and corresponding doses of tazemetostat are given in **Table 1**.

Table 1: Dose Escalation

Dose level	Dose of Tazemetostat
Level 0	120 mg/m^2 BID = 240 mg/m^2/day
Level 1 (starting dose)	240 mg/m^2 BID (starting dose) = 480 mg/m^2/day
Level 2	300 mg/m^2 BID = 600 mg/m^2/day
Level 3	400 mg/m^2 BID = 800 mg/m^2/day
Level 4	520 mg/m^2 BID = 1040 mg/m^2/day
Level 5	700 mg/m^2 BID = 1400 mg/m^2/day
Level 6	900 mg/m^2 BID = 1800 mg/m^2/day
Level 7	1200 mg/m^2 BID = 2400 mg/m^2/day
Level 8	1600 mg/m^2 BID = 3200 mg/m^2/day

BID = twice daily

For dose escalation decisions, a minimum of 22 days of toxicity data (80% of one cycle) must be available for each subject.

Decisions as to whether to enroll a new subject onto the current, next highest, or next lowest dose level will be made based on available data at the time of new subject enrollment and will be made by the Clinical Safety Review Committee (CSRC) (see protocol Section 11). The dose level assigned will be based on the number of subjects currently enrolled in the cohort, the number of DLTs observed, and the number of subjects at risk for developing a DLT (i.e., subjects enrolled, but who were not yet evaluable for toxicity).

Table 2: Rolling 6 Escalation/De-escalation Parameters

Subjects Enrolled	# Subjects with DLT	# Subjects without DLT	# Subjects with Toxicity Data Pending	Decision When Next Subject Enrolled
2	0, 1	Any	Any	Stay
2	2	0	0	De-escalate
3	0	0, 1, 2	3, 2, 1	Stay
3	0	3	0	Escalate
3	1	0, 1, 2	2, 1, 0	Stay
3	≥2	Any	Any	De-escalate
4	0	0, 1, 2, 3	4, 3, 2, 1	Stay
4	0	4	0	Escalate
4	1	0, 1, 2, 3	3, 2, 1, 0	Stay
4	≥2	Any	Any	De-escalate
5	0	0 1, 2, 3, 4	5, 4, 3, 2, 1	Stay
5	0	5	0	Escalate
5	1	0, 1, 2, 3, 4	4, 3, 2, 1, 0	Stay
5	≥2	Any	Any	De-escalate
6	0	0, 1, 2, 3, 4	6, 5, 4, 3, 2	Suspend
6	0	5, 6	1, 0	Escalate
6	1	0, 1, 2, 3, 4	5, 4, 3, 2, 1	Suspend
6	1	5	0	Escalate
6	≥2	Any	Any	De-escalate

DLT = dose limiting toxicity

The MTD will be determined based on the incidence of DLTs in Cycle 1, although toxicities occurring in subsequent cycles will also be reviewed. If serious toxicities are observed at the MTD in later cycles, a reduction of the MTD may be considered.

The Clinical Safety Review Committee (CSRC) convened on 06-Jul. 2017 to review safety and PK from subjects at the 1200 mg/m^2 dose level. No DLTs were observed at 1200 mg/m^2 dose level. Although the Rolling 6 statistical design supported the escalation to the next dose level of 1600 mg/m^2, elevated chloride levels were observed in 3 of 6 evaluable subjects in the 1200 mg/m^2 dose level, and at previous dose levels as well. As tazemetostat is formulated as a hydrobromide salt, it was considered that the hyperchloremia could be an artifact of elevations in serum bromide. Thus, bromide levels were evaluated in 2 of 5 subjects on active treatment and were found to be elevated, though without any associated clinical signs or symptoms of

neurologic toxicity associated with bromism. CCI [redacted]
Given the occurrence of the elevated bromide levels, as well as PD data, a decision was made by the CSRC to proceed to the dose expansion phase of the protocol with the putative RP2D determined to be 1200 mg/m^2 BID dose level with the understanding that bromide levels as well as clinical signs and symptoms of bromide toxicity would be closely monitored in all newly and currently enrolled subjects receiving tazemetostat with guidelines for immediate dose reduction as indicated.

Dose expansion at MTD or RP2D:

Approximately 72 subjects will be enrolled into the dose expansion in the following cohorts:

- Cohort 1 – approximately 20 subjects with ATRT
- Cohort 2 – approximately 20 subjects with malignant rhabdoid tumors (MRT)/rhabdoid tumors of the kidney (RTK)/selected tumors with rhabdoid features
- Cohort 3 – approximately 20 subjects with INI-negative tumors as follows:
  - Epithelioid sarcoma
  - Epithelioid malignant peripheral nerve sheath tumor
  - Extraskeletal myxoid chondrosarcoma
  - Myoepithelial carcinoma
  - Renal medullary carcinoma
  - Chordoma (poorly differentiated or de-differentiated)
  - Other INI1-negative malignant tumors with Sponsor approval
- Cohort 4 – approximately 12 subjects with one of the tumor types defined in Cohorts 1 through 3 or synovial sarcoma with SS18-SSX rearrangement

Subjects enrolled in cohorts 1-3 will receive the RP2D of 1200 mg/m^2 BID of tazemetostat in oral suspension. Subjects enrolled in cohort 4 will initially receive 800 mg/m^2 TID (2400 mg/m^2/day) of tazemetostat administered as tablets, with the possibility to switch to BID tablet dosing or suspension dosing in subsequent cycles if unable to comply with the TID schedule. Cohort 4 was added to evaluate the administration of the tazemetostat tablet formulation in pediatric subjects who can swallow tablets, which may be more palatable.

Escalation and Expansion

Subjects will discontinue study treatment at the time of disease progression, development of an unacceptable toxicity, withdrawal of consent by subject and/or parent, or after 2 years of cumulative dosing or termination of the study.

Subjects also will undergo medical history assessment, physical examinations (PEs); vital sign measurements; echocardiogram (ECHO); performance status (Lansky/Karnofsky) assessments, blood sample collection for hematology, chemistry, PK, and PD markers; electrocardiograms (ECGs); adverse event (AE) assessments; concomitant medication assessments; and pregnancy testing for females of childbearing potential.

The study duration is approximately 24 months for each subject. The duration of screening for each subject will be approximately 14 days. The subject accrual period is planned for approximately 15 months. The duration of treatment will vary for each subject. Subjects may receive tazemetostat for a cumulative maximum of 2 years. Subjects will be followed for safety for approximately 30 days after the last dose of tazemetostat. For subjects that discontinue dosing, participation will continue for survival follow-up and response for 2 years from first dose of tazemetostat.

The completion of the primary endpoint of the study is expected to occur approximately 6 months after the date the last subject is enrolled to treatment and evaluated for response. The end of study will occur when the last subject discontinues the study treatment and has had the opportunity to complete the safety follow-up visit (30 days after last dose of tazemetostat) or the long-term survival follow-up period (2 years from first dose of tazemetostat), whichever is later. The study may end prior to this if 80% of enrolled subjects are deceased prior to the collection of the last survival follow-up.

Survival follow-up will continue for 2 years for each subject or until 80% of treated subjects have died.

All patients are to discontinue participation on the study after 2 years of cumulative treatment, regardless of whether they came off study due to clinical response or if they reduced dose.

3.2. CHANGES TO ANALYSES FROM PROTOCOL

- Section 14.5.4 of the protocol indicates that laboratory analytes will be summarized descriptively as value and change from baseline, as well as shifts from baseline (based on low, normal, high categorization) at each visit. To allow for more focused presentation of values most likely to represent a safety concern, laboratory analytes will be summarized as shift from the baseline to the worst post-baseline category (based on National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v 4.03 severity grades).

- In the protocol, PFS is to be summarized using 90% and 95% CIs. However, to be consistent and following standard analyses, PFS will be summarized using % CIs.

- In the protocol, ORR is to be summarized using 80%, 90% and 95% CIs. However, to be consistent and following standard analyses, ORR will be summarized using 95% CIs. In addition, it was indicated that the 95% CI would be done only for expansion phase cohorts with at least 20 patients, however the 95% CI would be provided for all expansion phase cohorts.

- No subgroup analyses were planned in the protocol, however, to assess the possible effect of tazemetostat on previously irradiated lesions, a subgroup analysis of ORR by prior radiotherapy

(Yes vs No) will be performed for the expansion phase by cohort and overall, and for the entire study by dose level and overall.

4. PLANNED ANALYSES AND SAMPLE SIZE

4.1. INTERIM ANALYSIS

Dose Escalation: The CSRC will review available safety data, PK and tazemetostat exposure data from each dose level cohort to make recommendations regarding dose escalation in subsequent cohorts.

Dose Expansion: No interim analysis will be performed.

4.2. PRIMARY ANALYSIS

The primary analysis for each cohort of the study may occur separately when each cohort has at least met its primary objective (further described in Section 15.1). Details regarding the timing of the PK, PD, genetics, and cellular pharmacologic analyses will be described in detail under separate SAPs.

4.3. FINAL ANALYSIS OF PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL

Depending on the maturity of PFS and OS data at the time of the primary analysis, analyses of PFS and OS may be repeated when data are mature.

4.4. SAMPLE SIZE

Dose Escalation: The sample size is not based on a statistical consideration. The number of subjects will be determined based in part on the number of dose escalations required to determine the protocol defined MTD and/or RP2D. It is expected that up to approximately 48 subjects will be enrolled with the "Rolling 6" dose-escalation design (subjects who discontinue in absence of a DLT prior to the completing of the DLT evaluation period may be replaced).

The MTD and RP2D are defined as the dose level below which >1 subject of 3 or ≥2 subjects of 6 experience a DLT on the dose-escalation portion of the study during Cycle 1. In the event that MTD is not reached, the RP2D will be that dose that results in a mean $AUC_{(0\text{-}24)}$ of at least 5900 ng•h/mL (~80% of the mean value observed after administration of 800 mg BID in adults) or provides biologic and/or clinical activity in subjects in this study.

Dose Expansion: The sample size for dose expansion (Cohorts 1 to 3) is based on the hypothesized improvement in ORR over historical rates. An ORR no higher than 5% would

have no clinical benefit over existing therapies; an ORR of 20% is considered of clinical interest. For each dose expansion cohort separately, using a one-sided test and targeting a Type I error rate of 10% and a Type II error rate of 20% requires 20 pediatric subjects to be enrolled per cohort, in Cohorts 1 to 3. To establish that the data support tazemetostat, at least 3 of 20 subjects will be required to have an objective response (i.e., an observed 15% ORR) within a cohort. Due to the discrete nature of the primary endpoint, this statistical test achieves a Type I error rate of 8% (i.e., probability of deciding for tazemetostat when the true ORR is 5%), and a Type II error rate of 21% (i.e., probability of deciding against tazemetostat when the true ORR is 20%). Twelve subjects were to be enrolled in dose expansion Cohort 4 to evaluate the PK of tazemetostat when administered as a tablet formulation to pediatric subjects. Sufficient information to describe the PK of tazemetostat was obtained after administration of tazemetostat tablets to 4 pediatric subjects. Therefore, Cohort 4 was closed to further enrolment. Approximately 72 subjects will be enrolled across the 4 Dose Expansion cohorts.

5. ANALYSIS POPULATIONS

The **Intent-to-Treat (ITT) population** consist of all subjects who receive at least one dose of tazemetostat. The ITT population will be used for summaries and analysis of demographics, baseline disease characteristics, prior treatment, surgical and medical history and efficacy endpoints.

The **Safety population** consist of all subjects in the ITT population who have at least one post-dose safety observation recorded. The Safety population will be used for summaries and analysis of safety and tolerability.

The **Dose-Limiting Toxicity (DLT) Population** will consist of all dose escalation subjects in the Safety Population who:

- Experience a DLT during Cycle 1 as defined in Protocol Section 6.3
  OR
- Are not removed from Cycle 1 for reasons other than toxicity and did not have an interruption in study treatment for more than 14 days during Cycle 1

6. GENERAL CONSIDERATIONS

6.1. GROUPING OF SUBJECTS AND TABLE PRESENTATION

Subjects will be grouped and summarized by dose level for the escalation phase, by cohort for the expansion phase and by overall for each study phase. In addition, ORR will be summarized by dose level and overall across the dose escalation and expansion phases. Also, a subgroup analysis of ORR by prior radiotherapy (Yes vs No) will be performed.

6.2. TIME POINT CONVENTIONS

6.2.1. STUDY DAY CONVENTIONS

Start of study treatment will use the date of first dose of tazemetostat.

Depending on the context, listings may present assessments in terms of 'Study Day' label where the first day of treatment is identified as 'Day 1' and the day prior to the first day of treatment is identified as 'Day -1' (with no intervening 0). Study Day will be calculated as follows:

- Assessment date ≥ first dose date: Study Day = (assessment date – first dose date) + 1
- Assessment date < first dose date: Study Day = (assessment date – first dose date)
- Assessment date > last dose date: Study Day = (assessment date – last dose date); Displayed as "## days post tx".

Study Day will appear as missing in the listings if the event date is partial.

6.2.2. BASELINE ASSESSMENTS

Baseline is defined as the last non-missing (including unscheduled) assessment prior to starting study drug. Unless the collection time or label indicates otherwise, assessments performed on the same day as the first dose of tazemetostat will be considered as performed prior to treatment. AEs and medications with a start date on the date of first dose of tazemetostat will be considered to have occurred after the start of treatment. Baseline will be determined separately for each laboratory analyte.

6.2.3. VISIT ASSESSMENTS

For by-visit summaries, nominal visits will be presented (i.e. visit windowing will not be applied). Unscheduled measurements will not be included in by-visit table summaries but will contribute to worst-case values table summaries. Listings will include both scheduled and unscheduled data.

7. STATISTICAL CONSIDERATIONS

Unless noted otherwise, the statistical considerations below will be applied. Data from all centers will be pooled for analyses.

- The issue of statistical multiplicity will not apply to this study.
- CIs will be presented as 2-sided 80% and 90% CIs, where noted in subsequent sections.

- Safety data will not be imputed except for incomplete dates associated with AEs and medications (rules in Appendix 1) and missing severity or relationship (rules in Section 17.1).

- Missing response data will be handled as described in Section 15.

- Summary statistics will include the number and percentage of patients in each category for discrete variables and the sample size, mean, median, standard deviation (SD), minimum, and maximum for continuous variables.

- When the denominator includes subjects with missing values, a "missing" category may be added for completeness and displayed last in the category summary.

- Time-to-event statistics will include the minimum, 25th percentile, median, 75th percentile, and maximum, provided they are estimable.

- All mean, median, and quartile values will be formatted to one more decimal place than the measured value. SD values will be formatted to two more decimal places than the measured value.

- The number and percentage of responses will be presented in the form xx (xx.x%) with percentage rounded to one decimal place.

- Change from baseline = post baseline value – baseline value

- Duration in days = end date – start date + 1 (divide by 7 to convert to weeks, divide by 30.44 to convert to months, and divide by 365.25 to convert to years; round result to 1 decimal place

- Listings typically will be sorted by study part, dose level / cohort, subject identification number (concatenated site and subject number), date, and time, if collected.

All analyses will be conducted using SAS version 9.4 or higher.

8. ANALYSIS POPULATIONS AND ENROLLMENT

The number of subjects in each analysis population (ITT, Safety, and DLT populations) will be summarized on the ITT population. Subjects in the ITT population but not in the S population will be counted in a 'Not Treated' column for table summaries on the Enrolled population. A subject listing indicating analysis population will be presented for the ITT population.

9. DISPOSITION

Subject disposition, including reasons for study withdrawal, will be summarized and listed based on the ITT population.

10. PROTOCOL DEVIATIONS

Protocol deviations will be summarized by major and minor category and by study part for the ITT population. All protocol deviations will be listed for the ITT population. Predefined categories of major protocol deviations include:

- Violation of inclusion/exclusion criteria
- Prohibited medications
- Study drug compliance

Additional categories may be added during the course of the study but will be determined prior to database lock.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and baseline characteristics will be summarized and listed for the ITT population. Demographics will include age (in years; descriptive statistics and by category: age <12, age ≥12), sex, race, ethnicity, and baseline Karnofsky/Lansky performance status. Baseline disease characteristics will include tumor type, location of primary tumor at diagnosis, and tumor stage (0, I, II, III, IV, or unknown). Time (in months) from date of last disease progression until the informed consent date, inclusive, and time from initial disease diagnosis until the informed consent date will be summarized as continuous measures. Partial dates will be interpreted as July 1 when only a year is recorded and as the 15th of the month when only a month and year are recorded. If this interpretation yields a date of last progression or initial disease diagnosis after the informed consent date, then the partial date of last progression or initial disease diagnosis will be interpreted as January 1 when only a year is provided and the 1st of the month when only a month and year are provided. Other combinations of missing date elements will be handled as missing values.

Baseline tumor burden for subjects assessed under the RECIST 1.1 criteria will include descriptive statistics on the sum of target lesion diameters, number of target and non-target lesion, as well as presence of target lesions (yes/no), presence of lymph node target lesions (yes/no), and presence of non-target lesions (yes/no).

Baseline tumor burden for subjects assessed under the RANO criteria will include descriptive statistics for the sum of the product of target lesion diameters, the number of target lesions, the

number of non-target T1/Gd+ lesion and the number of T2/FLAIR lesions, as well as, presence of target lesions (yes/no), presence of non-target T1/Gd+ lesions (yes/no), presence of non-target T2/FLAIR lesions (yes/no).

12. PRIOR SURGICAL AND MEDICAL HISTORY

Surgical and medical history occurring prior to study treatment will be summarized and listed for the ITT population.

Verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time of the analysis. The number and percentage of subjects with any surgical and medical history will be summarized. Medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT).

Surgical history will be summarized by the MedDRA high-level group term (HLGT) and PT. Prior surgeries will be defined as surgeries performed on or prior to the date of first dose of study drug. Partial dates that cannot conclusively be identified as occurring after the start of treatment will be assumed to have occurred prior to start of treatment. Listings will include start date and stop date or notation of ongoing for conditions continuing into treatment.

13. MEDICATIONS AND PROCEDURES

Medications will be coded using World Health Organization (WHO) Drug Dictionary version in effect at the time of the analysis. For incidence summaries of medications by coded WHO Anatomical Therapeutic Chemical (ATC) category, a subject will be counted once per specific ATC category (likewise for preferred drug name).

13.1. PRIOR ANTI-CANCER THERAPY AND RADIOTHERAPY

Prior anti-cancer therapy and radiotherapy will be summarized and listed for the ITT population. The summary for prior anti-cancer therapies will include:

- Number of regimens (descriptive statistics and by category: 0, 1, 2, or more than 2 prior regimens)
- Number of regimens in the advanced/metastatic setting (0, 1, 2, or more than 2 prior regimens)
- Number of prior lines (descriptive statistics and by category: 0, 1, 2, 3, 4, or more than 4 prior lines)
- Therapy setting (Neoadjuvant, Adjuvant, Therapeutic for Advanced/Metastatic Disease, Consolidation, Maintenance, or Unknown); A subject may be counted in multiple

categories

- Incidence of prior anti-cancer therapies by WHO Drug ATC level 4 and preferred drug name
- Time from last PD to study entry
- Time for last anti-cancer treatment to study entry
- Best response

The summary for the prior radiotherapy will include:

- Number of prior courses (descriptive statistics and by category: 0, 1, or 2 or more courses)
- Sites of prior radiotherapy. A subject may be counted in multiple categories
- Type of radiation (total body irradiation, total marrow irradiation, proton therapy, radio surgery, gamma knife, other) by frequency.

Prior radiotherapy is defined as radiotherapy performed on or prior to the date of first dose of study drug. Partial dates that cannot conclusively be identified as occurring after the start of treatment will be assumed to have occurred prior to start of treatment.

13.2. PRIOR, CONCOMITANT AND POST-TREATMENT MEDICATIONS

Medications will be summarized and listed for the Safety population. Summary tables will include incidence (number and percentage) of subjects receiving any medication and incidence of specific medications by WHO Drug ATC level 4 and preferred drug name.
Prior, concomitant, and post-treatment medications will be summarized separately.
Categorization will be defined as follows:

- Prior medications will include medications which stopped prior to the first dose of study drug.
- Concomitant medications will include medications taken any time from the start of the first dose of study drug through 30 days following end of study drug administration or until the start of a subsequent anti-cancer therapy, whichever is earlier. Medications that started prior to the first dose of study drug but continued into treatment are considered as prior and concomitant.
- Post-treatment medications include medications which started more than 30 days after the end of study drug administration or after the start of a subsequent anti-cancer therapy,

whichever is earlier.

Appendix 1 provides additional detail for the interpretation of partial dates for medications.

13.3. CONCURRENT SURGERY AND PALLIATIVE RADIOTHERAPY

Concurrent anti-cancer surgery and palliative radiotherapy will be summarized for coded terms in the same manner as prior surgeries and prior radiotherapy. Concurrent anti-cancer surgery and palliative radiotherapy are those procedures that conclusively can be identified as occurring after the date of first dose of study drug up to, and including, the date of last dose of study drug.

13.4. POST-TREATMENT ANTI-CANCER THERAPY AND RADIOTHERAPY

Post-treatment anti-cancer therapies will include anti-cancer therapies which started after discontinuation of study drug. The number and percentage of subjects with post-treatment anti-cancer therapy noted during survival follow up, as well as the incidence (number and percentage) of anti-cancer therapies by WHO Drug ATC level 4 and preferred drug name will be summarized. Post-treatment anti-cancer therapy will be listed for ITT population. Post-treatment radiotherapy will be listed together with prior and concomitant radiotherapies for ITT population.

14. STUDY DRUG EXPOSURE AND COMPLIANCE

Study drug exposure and compliance will be summarized and listed by study part and overall, by dose level and cohort within the study parts for the Safety population. Listings will include details on dose interruption and/or dose modification.

14.1. STUDY DRUG EXPOSURE

The following summaries of study drug exposure will be presented:

- Duration of exposure (weeks) = [(last dose date of tazemetostat – first dose date of tazemetostat) + 1]/7. Except for the first and last dose dates, this calculation is not adjusted for periods where dosing is interrupted or dose is recorded as 0.

- Total number of cycles of study drug categorized as follows:
  - Cycle 1 (Days 1-28; weeks 1-4)
  - Cycle 2 (Days 29-56; weeks 5-8)
  - Cycle 3 (Days 57-84; weeks 9-12)
  - Cycle 4 (Days 85-112; weeks 13-16)
  - Cycle 5 (Days 113-140; weeks 17-20)
  - Cycle 6 (Days 141-168; weeks 21-24)
  - Cycle 7 (Days 169-196; weeks 25-28)

  - Cycles 8 through 12 (Day 197-336; weeks 29-48); Note, cycles may be summarized individually if sufficient subjects are dosed at those cycles.
  - Cycle 13 or more (Day 337 and beyond; week 49 and beyond); Likewise for Cycle 13 and beyond.

- Total amount of study drug taken (mg)

- For Cohorts 1 through 3: Average dose intensity (mg BID/day) = total amount of study drug taken (mg) / [2 * duration of exposure (days)]

- For Cohort 4: Average dose intensity (mg TID/day) = total amount of study drug taken (mg) / [3*duration of exposure (days)]

- Numbers of subjects requiring dose reductions, treatment interruption or treatment discontinuation in response to AEs (based on action taken for reported AEs)

14.2. STUDY DRUG COMPLIANCE

The following summaries of study drug compliance will be presented:

- Cohorts 1 through 3: Percentage study drug taken (summarized as a continuous variable) = 100% * Average dose intensity (mg BID/day) / assigned dose (mg BID/day).

- Cohort 4: Percentage study drug taken (summarized as a continuous variable) = 100%*Average dose intensity (mg TID/day) / 800 (mg TID/day)

- Category of percentage of study drug taken (using categories ≥ 90%, 80% to < 90%, 70% to < 80%, and < 70%).

15. EFFICACY ANALYSES

Investigator assessments of best overall response (BOR), ORR, PFS and OS will be summarized and listed for the ITT population. PFS and OS at weeks 24 and 56 will also be summarized.

15.1. OBJECTIVE RESPONSE RATE AND DURATION OF RESPONSE

Best Overall Response (BOR)

The summaries of BOR will include number and percentage of subjects in each of these categories:

- Complete response (CR)

- Partial response (PR)
- Stable disease (SD)
- Progressive disease (PD)
- Not Evaluable (NE)
- Unknown/Missing

Confirmation of CR/PR is required at least 28 days after the initial CR/PR was first met. Subjects will be evaluated for response based on the following disease appropriate criteria:

- For CNS tumors, response will be assessed based on RANO (Wen PY, 2010).
- Solid tumors will be assessed based on RECIST version 1.1 (Eisenhauer EA, 2009).

Objective Response Rate

ORR is defined as the percentage of subjects achieving a confirmed CR or PR from the start of tazemetostat until PD or the start of subsequent anti-cancer therapy, whichever is earlier, according to the appropriate disease evaluation criteria.

Subjects with not evaluable, unknown or missing best response will be handled as non-responders, i.e. they will be included in the denominator when calculating the ORR.

For dose escalation, ORR (secondary endpoint) will be summarized by dose level and overall.

For dose expansion, ORR (primary endpoint) will be summarized by cohort and overall. An exact 95% binomial CI for ORR in each cohort and overall will be provided as well.

In addition, ORR will be summarized by dose level across the dose escalation and dose expansion phases and overall. For each dose level and overall, an exact 95% CI for ORR will be calculated.

Also, a subgroup analysis of ORR by prior radiotherapy (Yes vs No) will be performed for the expansion phase by cohort and overall, and for the entire study by dose level and overall.

A plot of the maximum percent tumor reduction from baseline in target lesions for each subject will be provided.

Duration of Response

DOR will be calculated only for subjects with a confirmed CR or PR. DOR is defined as the interval of time from the first documented evidence of confirmed CR or PR until the first

documented PD or death due to any cause, whichever occurs first.

DOR censoring rules will follow those of the PFS analysis defined in **Table 3** below.

DOR will be analysed using Kaplan-Meier methods for each dose level within and across study parts, cohorts (if more than one) and overall. The median DOR, first quartile, and third quartile will be presented. The associated 2-sided 95% CIs will be estimated using the Brookmeyer-Crowley method (Brookmeyer 1982).

Table 3: Date of Event or Censoring for DOR

Situation	Date of event or censoring	Outcome
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Event
Subsequent anticancer treatment started before disease progression or death (without disease progression beforehand)	Date of last adequate assessment[1] prior to start of subsequent anticancer treatment	Censored
Death or disease progression after missing two or more consecutively scheduled disease assessments	Date of last adequate assessment visit without documentation of disease progression before the first missed visit	Censored
Alive and without documented disease progression	Date of last adequate assessment	Censored

[1]An adequate assessment is defined as a radiological assessment where CR, PR, or SD was determined

15.2. PROGRESSION-FREE SURVIVAL

- PFS per appropriate criteria will be analyzed and listed for the ITT population only for the dose expansion phase of the study. PFS is be defined as the interval of time (in weeks) from the date of first dose of study drug and the earliest date of disease progression or death, from any cause. For subjects who progressed or died after an extended period without adequate assessment, PFS will be censored at their date of last adequate assessment prior to progression or death even if subsequent information is available regarding progression or death. An adequate assessment is defined as an assessment where the Investigator determined response is CR, PR, or SD. The date of response at that assessment will be used for censoring.

- For subjects who receive subsequent anticancer therapy prior to the date of documented progression or death, PFS will be censored at the last adequate assessment (i.e., last assessment of CR, PR or SD) prior to the initiation of that anticancer therapy.

- For subjects who do not progress or die, PFS will be censored at the date of the last adequate tumor assessment.

PFS censoring rules are defined in Table 4 below.

In dose expansion, PFS will be summarized by cohort and overall. PFS will be analysed using the Kaplan-Meier method. Median PFS, first and third quartiles and associated 95% 2-sided CIs, will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982]. PFS at 24 weeks and 56 weeks along with the associated 2-sided 95% CIs, will be provided. Kaplan-Meier PFS curves also will be provided.

Table 4: Date of Event of Censoring for PFS

Situation	**Date of Event (PD/Death) or Censoring**	**Outcome: Event (PD/Death) or Censored**
No *(or inadequate)* baseline tumor assessments and the subject has not died	Date of Study Day 1	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)	Date of Study Day 1	Censored
Progression documented between scheduled visits	Date of assessment of progression[1]	Event
No progression *(or death)* and no new anti-cancer treatment documented	Date of last 'adequate' assessment of response[2]	Censored
No progression *(or death)* and new anti-cancer treatment documented	Date of last 'adequate' assessment of response[2] on or prior to starting anti-cancer therapy	Censored
New anti-cancer treatment started *(prior to documented disease progression or death).*[3]	Date of last 'adequate' assessment of response[2] on or prior to starting anti-cancer therapy	Censored
Death before first PD assessment (or Death at baseline or prior to any adequate assessments)	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death or progression after one missed visit (with 2 week window)	Date of last 'adequate' assessment of response[2] prior to missed assessments	Censored

[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 measured lesions (if progression is based on increase in sum of measured lesions)

[2] An adequate assessment is defined as a radiological assessment where CR, PR, or SD was determined.

[3] If PD and subsequent 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 adequate assessments, censoring date should be the date of Study Day 1.

15.3. OVERALL SURVIVAL

OS will be analyzed and listed for the ITT population. OS is defined as the interval of time (in weeks) between the date of first dose of study drug and the date of death from any cause. Subjects who have not died will be censored at the date of last contact which may be identified from a visit date, study assessment (physical examination, vital signs, performance status, ECG, study drug record, radiological evaluation), AE, medication, or disposition information.

In dose expansion, OS will be summarized by cohort and overall.

OS will be analysed using the Kaplan-Meier method. Median OS, first and third quartiles and associated 95% 2-sided CIs, will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982]. OS at 24 weeks and 56 weeks along with the associated 2-sided 95% CIs, will be provided. Kaplan-Meier OS curves also will be provided.

Listings of efficacy response data and overall survival will be provided.

16. PERFORMANCE STATUS ANALYSIS

Karnofsky/Lansky performance status score will be analyzed and listed for the ITT population. Performance status will be summarized at baseline and by best and worst post-baseline value, by dose level and cohort and overall. A summary of shift from baseline to the best post-baseline value and to the worst post-baseline value during the study, by study part and overall will be provided. Best and worst post-baseline values will be flagged in the listing.

17. SAFETY OUTCOMES

Safety summaries will be based on the Safety population (except for summaries on DLTs which will be based on the DLT population).

17.1. ADVERSE EVENTS

Verbatim AEs terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time of the analysis. Summary tables will be based on treatment emergent adverse events (TEAEs) which are defined as AEs that started or worsened

in severity on or after the day of the first dose of study drug through 30 days after the end of study drug. Missing or partially missing start and end dates for AEs and SAEs will be handled according to the conventions described in Appendix A. For cases in which it is not possible to ascertain treatment-emergence, the event will be classified as treatment-emergent. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Each summary table will include the incidence (number and percentage) of subjects reporting any TEAE, as well as, by SOC and PT. A subject will be counted once within an SOC, even if the subject experienced more than one TEAE within a specific SOC (likewise for PT).

Investigator assessed severity grade will be based on the National Cancer Institute CTCAE, version 4.03. For summary purposes, TEAEs with a missing severity will be classified as missing. A subject will be counted once at the worst severity grade within a SOC and/or PT.

Investigator assessed causality to study drug will be categorized as "not related," "unlikely related," "possibly related," or "related" to study drug. For summary purposes, treatment-related TEAEs will include events with relationship to study drug classified as "possibly related" or "related". A TEAE with a missing causality will be classified as "possibly related" to study drug. A subject will be counted once at the strongest causality within a SOC and/or PT.

TEAEs of special interest are defined in Section 10.4 of the protocol. In consultation with study clinicians, this subset of TEAEs will be identified using MedDRA terms.

An overview summary table of subjects with TEAEs will be provided by study part and overall and will include the number of subjects with any TEAE, any TEAE Grade 3 or 4, any TEAE DLT (as defined in the protocol Section 6.3), any treatment-related TEAE, any treatment-related TEAE Grade 3 or 4, any TEAE leading to dose reduction, any TEAE leading to study drug interruption, any TEAE leading to discontinuation of study drug, any TEAE leading to study discontinuation, any serious TEAE (TESAE), any treatment-related TESAE, any protocol defined TEAE of special interest. In accordance with the TEAE table presentation described above, AEs will be summarized by study part and overall as follows:

- TEAEs
- TEAEs with ≥ 10% incidence overall based on PT
- TEAEs of grade 3 or 4
- Treatment-related TEAEs
- Treatment-related TEAEs of grade 3 or 4
- TEAEs leading to dose interruption
- TEAEs leading to dose reduction

- TEAEs leading to discontinuation of study drug
- TEAEs leading to discontinuation from study
- Treatment-emergent serious adverse events (SAEs)
- Treatment-related treatment emergent SAEs
- TEAEs of special interest
- DLTs

Additionally, separate listings of DLTs, SAEs, , TEAEs leading to discontinuation of study drug and TEAEs leading to dose modifications (interruption and dose reduction). A listing of TEAEs of special interest will be also provided.

Adverse events with CTCAE Grade 5 or outcome of death are excluded from AE summary tables and summarized under death related tables.

Deaths

Deaths will be summarized and listed as follows:

- Summary and listing of subjects who died during and till 30 days after last dose of study drug
- Summary and listing of subjects who died during and till 30 days after last dose of study drug with treatment-related TEAEs
- Summary and listing of subjects who died after 30 days after the last dose of study drug with treatment-related AEs

The summary and listing will include the reason for death:

- Any AE (by MedDRA preferred Term)
- Any treatment related TEAE
- Progression
- Tumor progression
- Disease under Study

- Unknown/Other causes

17.2. LABORATORY EVALUATIONS

Section 8.5.10 of the protocol identifies the hematology, chemistry, and urinalysis analytes collected for the study. Laboratory evaluations will be performed by local laboratories. Summaries and listings of laboratory data will be presented in international system (SI) of units, where applicable. Separate listings and summary tables (by study part and overall) will be produced for each laboratory test group (hematology, serum chemistries (liver, renal [with creatinine clearance, if creatinine is abnormal] and metabolism). Listings for coagulation profile and urinalysis will be provided.

Laboratory values that are reported as 'below the detectable limit' of an assay will be analyzed as half the detectable limit when required for analysis purposes but listed as originally reported. The following summaries will be provided for laboratory data:

- Post-baseline CTCAE grade 3 or 4 laboratory values in subjects who had normal limits at baseline

- Shift from baseline grade to worst post-baseline grade based on NCI CTCAE v4.03 (for analytes where CTCAE grading applies). A missing baseline grade will be assumed to be grade 0.

- Shift from baseline to worst post-baseline value that is < 0.25 x lower limit of normal (LLN) or > 2.5 x upper limit of normal (ULN) for analytes not gradable by NCI CTCAE v4.03.

- Post-baseline creatinine clearance meeting pre-defined criteria

- Post-baseline liver function test findings meeting potentially clinically significant abnormal criteria

The summaries will include the worst-case shift from baseline during the post-baseline period, which will include both planned (scheduled) and unscheduled visits after the first dose of study drug.

All laboratory data will be listed. Subjects with laboratory data outside of normal range will be flagged as "L" (Low) or "H" (High) in the data listing.

Additionally, listings of grade 3 or 4 (per NCI CTCAE) values and values < 0.25 x LLN or > 2.5 x ULN for analytes not gradable by NCI CTCAE will be provided. For subjects with a post-baseline analyte that is grade 3 or 4, all values for that analyte will be listed. Similarly, for subjects with a post-baseline analyte value that is < 0.25 x LLN or > 2.5 x ULN, all values for that analyte will be listed.

17.3. ELECTROCARDIOGRAM EVALUATIONS

Single 12-Lead ECG measures will be collected according to the schedule of assessments in Appendix 3. Triplicates or additional unscheduled time points may be collected, if clinically indicated. When triplicates are collected, the averages (as calculated by the central ECG vendor ERT) will be used in the summaries.

The following pre-dose and post-dose 12-lead ECGs parameters will be collected at select scheduled time points:

- PR Interval (msec)
- RR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc, Fridericia [QTcF] Interval (msec)
- HR (bpm)

The following summaries will be provided for the 12-lead ECG measurements listed above:

- Shift from baseline to worst post-baseline in QTcF status categorized as markedly abnormal or not (defined in the table below)
- Number and percentage of subjects whose worst-case changes from baseline in QTcF measurements meet markedly abnormal criteria (described in the **Table 5** below).

Table 5: QTcF Marked Abnormality Criteria

QTcF Measure	Markedly Abnormal Criteria
Observed Measures	450–480 msec, inclusive [CTCAE grade 1] 481–500 msec, inclusive [CTCAE grade 2] > 500 msec [CTCAE grade 3 or higher]
Observed Change from Baseline	31–60 msec, inclusive, increase from baseline >60 msec increase from baseline

The listings will include the individual ECG values and other information collected from the 12-lead ECG. QTcF measures meeting the markedly abnormal criteria as defined in the table above will be flagged on the listing.

17.4. VITAL SIGNS

Weight (kg) and height at screening (cm), as well as vital signs for systolic blood pressure (mmHg), sitting diastolic blood pressure (mmHg), sitting heart rate (bpm), respiratory rate (breaths/min), and temperature (C^{o}) will be collected and listed. Summaries of heart rate, temperature, systolic blood pressure, and diastolic blood pressure will be based on markedly abnormal criteria defined in Ta**ble 6** below:

Table 6: Vital Signs Marked Abnormality Criteria

Vital Sign	**Markedly Abnormal Criteria**
Heart rate (bpm)	< 60 bpm > 100 bpm
Temperature (^{o}C)	≤ 35 ^{o}C ≥ 38 ^{o}C
Systolic blood pressure (mmHg)	120-139 mmHg, inclusive (CTCAE grade 1) 140–159 mm Hg, inclusive (CTCAE grade 2) ≥ 160 mmHg (CTCAE Grade 3)
Diastolic blood pressure (mmHg)	80–89 mmHg, inclusive (CTCAE grade 1) 90–99 mm Hg, inclusive (CTCAE grade 2) ≥ 100 mmHg (CTCAE grade 3)

Incidence of markedly abnormal worst-case values will be presented. For heart rate and temperature, both high and low values will be presented separately such that subjects can be counted in both categories. Markedly abnormal vital sign values will be flagged as such on the vital signs listing.

17.5. ECHO/MUGA

For ECHO/MUGA left ventricular ejection fraction, results will be listed along with the type of assessment (MUGA or echocardiogram).

18. REFERENCES

Skolnik JM, Barrett JS, Jayaraman B, et al. Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol. 2008;26(2):190-195.

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Eisenhauer EA, et. al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *European Journal of Cancer.* 2009; (45): 228-247.

Wen PY. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group. *J Clin Oncol*. 2010;28(11):1963-1972.

APPENDIX 1. PARTIAL DATES CONVENTIONS

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known/Partial /Missing	If start date < study drug start date, then not TEAE If start date >= study drug start date and < (end of treatment + 30 days) or start date of new anti-cancer therapy, whichever is sooner, then TEAE If start date > (end of treatment + 30 days) start date of new anti-cancer therapy, whichever is sooner, then not TEAE
Partial, but known components show that it cannot be on or after study drug start date	Known/Partial /Missing	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= end of treatment + 30 days, assign as concomitant If stop date >= study drug start date and start date > 30 days after the end of treatment, assign as post-treatment
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= end of treatment + 30 days , assign as concomitant If stop date >= study drug start date and start date > 30 days after the end of treatment, assign as post-treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment + 30 days, assign as concomitant If start date > 30 days after the end of treatment, assign as post-treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= end of treatment + 30 days, assign as concomitant If stop date >= study drug start date and start date > 30 days after the end of treatment, assign as post-treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= end of treatment + 30 days, assign as concomitant If stop date >= study drug start date and start date > 30 days after the end of treatment, assign as post-treatment

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment + 30 days, assign as concomitant If start date > 30 days after the end of treatment, assign as post-treatment
Missing	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant Cannot be assigned as post-treatment
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant Cannot be assigned as post-treatment
	Missing	Assign as concomitant

APPENDIX 2. CENSORING RULES: PROGRESSION-FREE SURVIVAL

Timing Window Allowances for PK Sampling and ECGs

Pharmacokinetic Sampling	
Timepoint	**Tolerance Window**
0 hour	-60 minutes to 0 hour
Electrocardiograms (ECGs)	
Timepoint	**Tolerance Window**
0 hour	-240 minutes to 0 hour
>0 hour – 1 hour	-15 minutes/+ 15 minutes