Document Type	Statistical Analysis Plan
Official Protocol Title	A Phase 2b Study of ZEN003694 in Combination With Talazoparib in Patients With Triple-Negative Breast Cancer
NCT Number	NCT03901469
Document Date	01 September 2023

Statistical Analysis Plan

Zenith Epigenetics Ltd.

ZEN003694-004

A Phase 2 Study of ZEN003694 in Combination with Talazoparib in Patients with Triple-Negative Breast Cancer

Protocol Version: 26 May 2022 (Amendment 6)

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Version	Date
v1	01 SEP 2023

Approval

Upon review of this document, including table, listing, and figure shells, the undersigned approves the Statistical Analysis Plan. The analysis methods and data presentation are acceptable.

Signature	Date
[redacted]	
[redacted]	
[redacted]	

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADaM	Analysis data model
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BMI	Body mass index
C_{max}	Maximum plasma concentration
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DDR	DNA damage repair
DLT	Dosing-limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ICH	International Council for Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NE	Not evaluable
ORR	Objective response rate
PK	Pharmacokinetic(s)
RECIST	Response Evaluation Criteria in Solid tumors
RTF	Rich text format
RP2D	Recommended Phase 2 dose
SAP	Statistical analysis plan
SD	Stable disease
TNBC	Triple negative breast cancer
TEAE	Treatment-emergent adverse event
TLFs	Tables, listings, and figures

DEFINITIONS

Safety Population	Patients who receive at least 1 dose of ZEN003694.
Treatment-Emergent AE	AEs with an onset time after the initial dose of ZEN003694.

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Zenith Epigenetics Ltd. Protocol ZEN003694-004, "A Phase 2 Study of ZEN003694 in Combination with Talazoparib in Patients with Triple-Negative Breast Cancer." The purpose of this plan is to provide specific guidelines from which the statistical analyses will proceed. Any deviations from this plan will be documented in the clinical study report (CSR). On July 10th, 2023, Zenith decided to discontinue the study based on the results of futility analysis. Only patient disposition, demagraphics, exposure, adverse events will be reported in the abbreviated CSR.

2. STUDY DOCUMENTS

The following study documents are used for the preparation of the SAP:

- Protocol version 6, 26 MAY 2022
- Annotated electronic case report form (eCRF) version 9, 16JUN2023
- Data management plan version 2, 01JUN2022

3. STUDY OBJECTIVES

The study objectives described below are separated by study part – Part 1 is dose escalation of ZEN003694 in combination with talazoparib in patients with triple-negative breast cancer. Part 2 is a Simon 2-Stage design once a recommended Phase 2 dose of ZEN003694 in combination with talazoparib has been determined in part 1. The expansion part is implemented following the determination of the recommended Phase 2 dose (RP2D) of ZEN003694 in Part 1 and after meeting the primary endpoint of clinical benefit rate of 35% in Part 2.

3.1 Primary Objective

3.1.1 Part 1: Primary Objectives

- To determine the safety, tolerability, maximum tolerated dose (MTD) and RP2D of ZEN003694 in combination with talazoparib in patients with locally advanced or metastatic triple-negative breast cancer (TNBC)

3.1.2 Part 2: Primary Objectives

- To evaluate the efficacy of ZEN003694 in combination with talazoparib in patients with locally advanced or metastatic TNBC

3.1.3 Expansion: Primary Objectives

- To evaluate the efficacy of ZEN003694 in combination with talazoparib in patients with locally advanced or metastatic TNBC whose cancer was hormone receptor negative at the time of initial breast cancer diagnosis and who have received TROP2-ADC in the unresectable locally advanced or metastatic disease setting.

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3.2 Secondary Objective

3.2.1 Part 1: Secondary Objectives

- To determine the pharmacokinetics (PK) of ZEN003694, its metabolite, ZEN003791 and talazoparib
- To evaluate the effects of ZEN003694 and talazoparib on mRNA expression of pharmacodynamic markers
- To evaluate the clinical activity of ZEN003694 in combination with talazoparib by radiographic response rate and progression-free survival
- To determine the effect of ZEN003694 and talazoparib on patient reported health status and quality of life

3.2.2 Part 2: Secondary Objectives

- To further evaluate the safety and tolerability of ZEN003694 in combination with talazoparib
- To determine the pharmacokinetics (PK) of ZEN003694, its metabolite, ZEN003791, and talazoparib
- To determine the effect of ZEN003694 and talazoparib on patient reported health status and quality of life

3.2.3 Expansion: Secondary Objectives

- To evaluate the efficacy of ZEN003694 in combination with talazoparib in patients with locally advanced or metastatic TNBC whose cancer was hormone receptor negative (<5%) at the time of initial breast cancer diagnosis and who have not received TROP2-ADC in the locally advanced or metastatic disease setting
- To evaluate the ZEN003694 monotherapy in patients with locally advanced or metastatic TNBC whose cancer was hormone receptor negative at the time of initial breast cancer diagnosis and who may or may not have received prior TROP2-ADC.
- To further evaluate the safety and tolerability of ZEN003694 in combination with talazoparib
- To determine the pharmacokinetics (PK) of ZEN003694, its metabolite, ZEN003791, and talazoparib
- To determine the effect of ZEN003694 and talazoparib on patient reported health status and quality of life

3.3 Exploratory Objectives

[redacted]

- [redacted]

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4. STUDY DESIGN AND PLAN

4.1 Part 1: Dose escalation

Part 1 is an open label, non-randomized, dose escalation of ZEN003694 in combination with talazoparib in patients with TNBC. A standard 3+3 cohort design will be utilized. Cohorts of 3 patients and up to 6 patients will be enrolled at each dose level, and each patient will participate in only one cohort. Each cycle will be 28 days in duration. Patients at each dose level will be treated and observed through the end of the first 28-day cycle before treatment of patients at the next higher dose level can begin.

Dose escalation will continue after all patients enrolled within a cohort have completed the 28-day Cycle 1 DLT observation period with either 0 of 3 patients, or no more than 1 out of 6 patients in a cohort experiencing a DLT. Dose escalation decisions will be made based on clinical safety and (when available) PK data (maximum or peak concentration [Cmax] and area under the curve [AUC]) after review by the Investigators and the Zenith Medical Monitor. If a DLT is observed in 1 of 3 patients in a cohort, 3 additional patients will be enrolled into that cohort. If 1 of 6 patients in a cohort experiences a DLT, then dose escalation may continue in the next cohort or the MTD of the combination can be declared. If $\geq$ 2 of 3 – 6 patients experience DLTs within a cohort, then the MTD will be considered to have been exceeded and further dose escalation will cease. In this case, if fewer than 6 patients have been enrolled at the previous dose level, that cohort will be expanded to 6 patients to confirm the MTD. Should the MTD of the combination be exceeded at Dose Level 1, a cohort may be explored with a reduced dose of ZEN003694 or talazoparib. Cohort management is summarized below.

Number of Patients with Dose-limiting Toxicity	Action
0 of 3 or 1 of 6	Dose escalate to next cohort
1 of 3	Add 3 more patients
1 of 6	Proceed to next dose level
$\geq$ 2 of 3 or $\geq$ 2 of 6	Add 3 more patients in the next lower dose level if only 3 patients were treated in the next lower dose. If 6 patients were treated at the next lower dose level and no more than one patient had DLT, then the next lower dose is the MTD.

Enrollment in the dose escalation part of the study will commence with a 48 mg oral once daily dose as the starting dose for ZEN003694 in combination with a 1 mg oral once daily dose of talazoparib. The dose of ZEN003694 will be held constant throughout Cycle 1, however doses may be held for the management of toxicity. The dose of talazoparib may be held and reduced from the initial 1.0 mg dose in 0.25 mg increments in accordance with the talazoparib label and by agreement with Zenith. Dose escalation/de-escalation of ZEN003694 will proceed per the schema in below table unless intervening toxicity is observed. Alternative dosing schedules may be evaluated based on the evaluation of clinical safety and upon agreement of the Investigators

and Zenith. Alternative dosing schedules may include intermittent dosing that could necessitate a change in the cycle duration from 28 days to 21 days.

Dose Escalation Scheme

Dose Level	ZEN003694 (mg) *	Fold Increase from Prior Dose Level
-1	36	0.75
1	48	--
2	72	1.50
* Dose de-escalation from 48 mg is allowed and additional dose levels may be explored based on safety and at the discretion of the Sponsor with agreement from the Investigators		

No intra-patient dose escalation is allowed during the first two cycles of therapy. If a patient has not experienced any Grade 2 or higher drug-related AEs after three cycles, dose escalation up to the highest ZEN003694 dose currently declared tolerable will be allowed and further intra-patient dose escalation(s) will be determined on a cycle-by-cycle basis at the discretion of the Investigators and with approval by the Sponsor.

DLT

Determination of DLT will be made during the first 28 days of treatment (i.e., Cycle 1) in the dose escalation phase. Toxicity will be graded and recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0. A DLT is defined as a clinically significant AE or laboratory abnormality that is considered possibly, probably or definitely related to study drug and which meets any of the following criteria:

- Grade 3 or greater non-hematologic clinical toxicity with the exception of a) Grade 3 nausea or Grade 3/4 vomiting and diarrhea unless persisting more than 72 hours despite maximal medical therapy and b) Grade 3 or 4 amylase or lipase elevation that is not associated with symptoms or clinical manifestations of pancreatitis
- Grade 3 or greater fatigue for at least 1 week
- Grade 4 anemia
- Grade 4 neutropenia lasting more than 5 days
- Grade 3 or greater febrile neutropenia (temperature $\geq 38.5^{o}C$)
- Grade 4 thrombocytopenia; or Grade 3 thrombocytopenia with clinically significant bleeding; or any requirement for platelet transfusion
- Grade 3 or 4 electrolyte abnormality lasting more than 72 hours, unless the patient has clinical symptoms, in which case all Grade 3 or 4 electrolyte abnormalities regardless of duration will be considered a DLT
- Any other Grade 3 or 4 laboratory abnormality that requires hospitalization

- An ALT or AST ≥3x ULN with concomitant total bilirubin > 2x ULN, and serum alkaline phosphatase ≤ 2x ULN (Hy's Law) For patients with hepatic metastases, AST or ALT >8x ULN or AST or ALT >5x ULN for ≥14 days
- Any Grade 3 or 4 visual symptoms
- Any toxicity that results in more than 25% of missed doses during Cycle 1 of the 28 days of treatment, with the exception of a dose hold for Grade 3 thrombocytopenia, in which case a dose hold of both talazoparib and ZEN003694 for 10 consecutive days in Cycle 1 will be allowed and not considered a DLT. For an intermittent schedule of 2-weeks on/1-week off, if any toxicity results in more than 2 missed doses during the 2-week treatment period the toxicity would be considered a DLT.
- In the situation where toxicity requires withholding study drug following the receipt of at least 75% of scheduled dosing during Cycle 1: Failure to begin Cycle 2 within 1 week of the scheduled start date due to ongoing toxicity

All patients experiencing a DLT must discontinue dosing with ZEN003694 and talazoparib, except in the event that the DLT is thrombocytopenia, in which case patients may be re-challenged with ZEN003694 and talazoparib at doses agreed upon with the Sponsor if platelets recover to at least 75,000/µL within a 10 day dose hold. All patients who discontinue treatment must complete the Safety Follow-up visit prior to discontinuation from the study.

Determination of evaluability will be made during the first 28 days of study treatment (i.e., Cycle 1) in the dose escalation phase. Patients who miss more than 25% of ZEN003694 or talazoparib doses (except in the case of a dose hold for thrombocytopenia where 10 consecutive days of missed doses are allowed); or fail to begin Cycle 2 within 1 week of the scheduled start date for reasons other than drug-related toxicity will be considered unevaluable and will be replaced.

4.2 Part 2: Simon 2-Stage

Stage 1:

Once an RP2D of ZEN003694 in combination with talazoparib has been determined in the dose escalation part of the study, 17 patients will be enrolled in Stage 1 of a Simon 2-Stage design (Simon, 1989) for evaluation of objective response (complete response (CR), partial response (PR), or stable disease (SD) for ≥ 4 cycles) by RECIST 1.1 (Eisenhauer, 2009). If there are ≥4 objective responses the study will proceed to Stage 2. If there are <4 responses, the study will be stopped.

Stage 2:

If at least 4 patients in Stage 1 have an objective response (CR, PR or SD for ≥ 4 cycles) by RECIST 1.1, 20 patients will be enrolled in Stage 2 of the Simon 2-Stage design. Patients will receive daily RP2D doses of ZEN003694 in combination with 1 mg talazoparib. Patients may continue receiving ZEN003694 in combination with talazoparib until radiographic or clinical progression, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from study.

4.3 Expansion

The expansion of the study will be implemented under amendment following the determination of the RP2D of ZEN003694 in Part 1 and after meeting the primary endpoint of clinical benefit rate of 35% in Part 2. The study will be expanded to enroll an additional 120 patients with locally advanced or metastatic TNBC that is without germline BRCA1/BRCA2 mutations and was hormone receptor negative (<5%) at the time of initial breast cancer diagnosis.

Expansion Cohort A: Combination Treatment in post-TROP2-ADC patients:
Eighty (80) patients who have received prior TROP2-ADC treatment will receive daily RP2D doses of ZEN003694 (48mg QD) in combination with talazoparib (0.75mg QD). Patients may continue receiving ZEN003694 in combination with talazoparib until radiographic or clinical progression, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from the study.

Expansion Cohort B: ZEN003694 Monotherapy:
As mandated by the FDA to assess any potential single agent ZEN003694 activity, ten (10) patients will initially receive daily doses of 48mg ZEN003694 as monotherapy with the option to cross-over to combination treatment of 48mg ZEN003694 plus 0.75mg talazoparib at the time of disease progression (but no sooner than after 6 weeks of monotherapy). Patients in the cross-over group may continue receiving ZEN003694 in combination with talazoparib until radiographic or clinical progression, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from study.

Expansion Cohort C: Combination Treatment in TROP2-ADC-naïve patients:
Thirty (30) patients who have not received prior TROP2-ADC will receive daily RP2D doses of ZEN003694 (48mg QD) in combination with talazoparib (0.75mg QD). Patients may continue receiving ZEN003694 in combination with talazoparib until radiographic or clinical progression, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from the study.

5. DETERMINATION OF SAMPLE SIZE

The sample size for Part 1 of was not based on any formal statistical considerations.

The sample size for Part 2 was based on statistics of clinical benefit rate (CBR). The null hypothesis that the true CBR is 20 % will be tested against a one-sided alternative. (CBR of 20% is not of clinical interest whereas CBR 40% warrants further investigation)

In the first stage, 17 patients will be accrued. The study will be stopped if there are less than 4 patients with clinical benefit. Otherwise, 20 additional patients will be accrued for a total of 37. The null hypothesis will be rejected if 11 or more patients show clinical benefit out of 37 patients.

This design yields a type I error rate of 0.1 when the true CBR is 20% and power of 90% when the true CBR is 40%. The probability of early termination is 0.55.

In the expansion cohort A, approximately 80 evaluable patients are planned to establish the ORR and further define the safety profile of the combination ZEN003694 + talazoparib. An observed ORR (by blinded independent central review) of at least 30% represents a significant improvement over current available therapies in this patient population. With 80 patients, 24 or more responders will provide an observed ORR of at least 30% and a lower limit of the 95% confidence interval above 20%.

In the expansion cohort B, approximately 10 evaluable patients are planned to assess the anti-tumor activity of ZEN003694 monotherapy. According to FDA discussions, if no more than 1 patient has a confirmed objective response (complete response or partial response), it can be concluded that ZEN003694 monotherapy does not have anti-tumor activity (clinical benefit) when given as a single drug treatment.

In the expansion cohort C, approximately 30 evaluable patients are planned to establish the ORR and further define the safety profile of the combination ZEN003694 and talazoparib.

6. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Council for Harmonisation (ICH) numbering convention will be used for all TLFs. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums and valid cases.

Categorical variables will be summarized by counts and by percentage of patients in corresponding categories. Percentages for missing values are omitted and do not account for the percent calculation of other categories. Percentages are routinely based on the total category count excluding the missing category if not otherwise mentioned. Percentages showing a rate relative to the total number of patients in this group are given in special tables (e.g. adverse event [AE] tables). Footnotes will specify the percent basis. All summary tables will be presented by treatment group, total and overall. The total column includes Part 1 and Part 2 cohorts. The overall column includes Part 1, Part 2 and expansion cohorts. No imputations will be made for missing values except as described for missing start and stop dates for AEs. Summaries will be based on observed data only.

For AEs, no imputation of partial or missing dates will be performed except for the determination for treatment emergence. The most conservative approach will be systematically considered for determining treatment emergence. If the AE onset date is missing or incomplete, it is assumed to have occurred during the study treatment phase (ie, considered a treatment-emergent adverse event [TEAE]) unless the partial onset date or other data, such as the stop date, indicates differently.

Unless otherwise noted, baseline is defined as the last non-missing value recorded prior to the first dose of ZEN003694. If the date is the same as first dose of ZEN003694, it will be baseline unless a time is collected then we compare it with dosing time.

Individual patient data obtained from the case report forms (CRFs) will be presented by patient in data listings.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock.

All analyses and tabulations will be performed using SAS® Version 9.4 or higher. Tables, listings, and figures will be presented in RTF format.

7. NOTATION OF TREATMENT GROUPS AND VISITS

The following notation of **treatment groups** will be used throughout the report:

Notation as used throughout all listings
ZEN003694 48mg + Talazoparib 1mg, Part 1 Dose Escalation
ZEN003694 48mg + Talazoparib 0.75mg, Part 1 Dose Escalation
ZEN003694 36mg + Talazoparib 1mg, Part 1 Dose Escalation
ZEN003694 48mg + Talazoparib 0.75mg, Part 2
ZEN003694 48mg + Talazoparib 0.75mg, Expansion Cohort A
ZEN003694 48mg, Expansion Cohort B
ZEN003694 48mg + Talazoparib 1mg, Expansion Cohort B
ZEN003694 48mg + Talazoparib 0.75mg, Expansion Cohort C

Notation as used throughout all tables and figures
Part 1 Dose Escalation, ZEN 48mg + TAL 1mg
Part 1 Dose Escalation, ZEN 48mg + TAL 0.75mg
Part 1 Dose Escalation, ZEN 36mg + TAL 1mg
Part 2, ZEN 48mg + TAL 0.75mg
Expansion Cohort A, ZEN 48mg + TAL 0.75mg
Expansion Cohort B, ZEN 48mg
Expansion Cohort B, ZEN 48mg + TAL 1mg
Expansion Cohort C, ZEN 48mg + TAL 0.75mg

Note: The table shells are created based on all treatment groups used in the protocol. However, actual table programming may/may not necessarily include all of these doses if they were not included in the study.

The following **visit terminology** will be used in some reports:

Visit	***Notation as used throughout all tables, listings and figures***
Screening	Screening
Cycle X Day X	CXDX, Baseline

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8. ANALYSIS POPULATIONS

The following patient population will be used for demographic, baseline characteristics and primary endpoints:

- Safety population

Note, for all analyses, treatment group will be based on the treatment the patient was assigned to when enrolled in the study.

9. STUDY POPULATION

9.1 Patient Disposition

Patient disposition information will be summarized for all patients by dose regimen. Summaries will include: the number of enrolled patients, the number of patients in each analysis population, the number of cycles a patient completed, and the primary reason for study completion/discontinuation.

Information for screen failures will be described separately in the CSR.

9.2 Demographic and Baseline Characteristics

Demographic variables include: age, sex, ethnicity and race. Age will be calculated in years relative to the informed consent date. Baseline characteristics include height (cm), weight (kg), body mass index (BMI) (kg/m^2), and Eastern Cooperative Oncology Group (ECOG) performance status.

Descriptive statistics will be presented for age, height, weight and BMI. Frequency counts and percentages will be presented for sex, ethnicity, race, medical history, and ECOG performance status. Demographic and baseline characteristics will be summarized for the Safety Population.

10. EFFICACY ANALYSES

No efficacy analysis will be performed for the abbreviated CSR.

11. SAFETY ANALYSES

All safety analyses will be based on the safety population.

11.1 Extent of Exposure

Study drug exposure will be summarized for each ZEN003694 dose level using the actual number of doses taken, number of cycles, duration of treatment (days) and compliance.

Study drug compliance over the study will be calculated as follows:

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$$\text{Compliance [\%]} = \frac{\text{Actual Number of Doses}}{\text{Duration of Study Treatment (days)}} \times 100\%$$

All in-clinic study drug administration is reported on the ZEN003694 Administration – Single Dose CRF and all out-clinic study drug administration is reported on the ZEN003694 Administration Log CRF.

In order to calculate the actual number of doses used, the number of administration days will be determined by adding each administration day from the ZEN003694 Single Dose CRF and the number of days of administration reported in the ZEN003694 Administration Log CRF. The minimum number of doses were not taken reported on the ZEN003694 Administration Log CRF will not be included in the calculation of actual number of doses used. Since the dose is taken once daily, it is assumed that 1 day is equal to 1 dose.

Duration of study treatment is defined as the last dose date minus the first dose date plus 1.

Individual ZEN003694 exposure data will be presented in patient listings.

11.2 Adverse Events

All AE summaries will be restricted to TEAEs, which are defined as those AEs that occurred after dosing and those existing AEs that worsened during the study. In this study, only events that started after administration of study drug until 30 days after the last dose of study drug are considered AEs and recorded. Those that started before study drug administration were to be recorded on the Medical History CRF. If it cannot be determined whether the AE is treatment emergent due to a partial onset date then it will be counted as treatment emergent. Verbatim terms on CRFs will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) (version 26.0).

Each AE summary will be displayed by treatment group. Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of patient incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

Overall summary of TEAEs which contain an overview of each item below.

- Patient incidence of TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Patient incidence of TEAEs by MedDRA system organ class, preferred term, and highest severity. At each level of patient summarization a patient is classified according to the highest severity if the patient reported 1 or more events. AEs with missing severity will be considered life threatening for this summary.
- Patient incidence of TEAEs by MedDRA system organ class, preferred term, and relationship (Related/Not Related) to ZEN003694, Talazoparib, and either study drug. Related AEs are those reported as “Related” and unrelated AEs are those reported as “Not Related.” At each level of patient summarization, a patient is classified according to

the relationship if the patient reported 1 or more events. Adverse events with a missing relationship will be considered related for this summary.

- Patient incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA system organ class and preferred term.
- Patient incidence of serious TEAEs by MedDRA system organ class, preferred term, and highest severity. At each level of patient summarization a patient is classified according to the highest severity if the patient reported 1 or more events. AEs with missing severity will be considered life threatening for this summary.
- Patient incidence of serious TEAEs by MedDRA system organ class, preferred term, and relationship (Related/Not Related) to ZEN003694, Talazoparib, and either study drug. Related AEs are those reported as "Related" and unrelated AEs are those reported as "Not Related." At each level of patient summarization a patient is classified according to the relationship if the patient reported 1 or more events. Adverse events with a missing relationship will be considered related for this summary.
- Patient incidence of TEAEs leading to death as an outcome by MedDRA system organ class and preferred term
- Patient incidence of TEAEs leading to study discontinuation by MedDRA system organ class and preferred term.

12. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

[redacted] Zenith decided to discontinue the study [redacted] Only patient disposition, demagraphics, exposure, adverse events will be reported in the abbreviated CSR.

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13. REFERENCES

Simon, R. (1989) Optimal Two-Stage Designs for Phase II Clinical Trials. *Controlled Clinical Trials* 10:1-10

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., . . . Verweij, J. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer, 45*(2), 228-247. doi: 10.1016/j.ejca.2008.10.026

Guidance for Industry *E14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs,* U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), October 2005.

US Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry. E14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs. October 2005.

14. APPENDICES

Appendix A: Presentation of Data and Programming Specifications

General

- Specialized text styles, such as bold, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters are to be used in tables and data listings.
- Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used on a table, figure, or data listing.
- Hexadecimal character representations are allowed (e.g., μ, a, ß).
- All footnotes will be left justified and at the bottom of a page. Footnotes should be used sparingly and must add value to the table, figure, or data listing.

Tables

- Formal organization of tabulations may be changed during programming if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than 1 variable may be split into several tables.
- Descriptive statistics include mean, median, standard deviation, minimum and maximum.
- Means and medians will be presented to one decimal place. Standard deviations will be presented to two decimal places. Minimums and maximums will be presented to one decimal place.
- Percentages will be presented to the tenths place.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.
- Lower and upper confidence interval values should be presented to one decimal place.
- Percentiles (e.g., 25%, 75%) should be presented to one decimal place.
- For all inferential analyses, p-values will be rounded to four decimal places (or at the highest level of precision) with a leading zero (0.0001). P-values less than 0.0001 will be presented as "<0.0001".
- The last footnotes will be
  - "Source: xxx", where xxx indicates the source table number(s) if applicable (in case aggregated results like mean or median are plotted) or the source listing(s) (in case individual responses are plotted) and/or source datatset(s) (eg, analysis data model [ADaM]).

Listings

- Formal organization of the listing may be changed during programming if appropriate, e.g., additional variables may be included, change in the column order, or the listing may be split into multiple parts due to space constraints, etc.
- If not otherwise specified, all data listings will be sorted by sequence/treatment, center, patient number, visit, and date/time as appropriate.
- All date values will be presented in a SAS date (e.g., 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.
- The last footnote will be
  - "PROGRAM SOURCE: ...\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".

where extract date is the datestamp of the data snapshot used.

Missing or incomplete dates (i.e., AEs)

The most conservative approach will be systematically considered. If the AE onset date is missing / incomplete, it is assumed to have occurred during the study treatment phase (i.e., considered a TEAE) except if the partial onset date or other data such as the stop date, indicates differently.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of first dose of study drug, provided the start month and year are the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the missing day portion will be estimated as '01'.
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of first dose of study drug, provided the start year is the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g., ??-???-2013 is estimated as 01-JAN-2013).
- If the start date is completely missing and the stop date is either after the dose of study drug or completely missing, the start date will be estimated to be the day of study drug dosing. Otherwise, the start date will be estimated to be the first day of the same year as the stop date. All other non-AE and non-concomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing while January 1 will be employed if both the month and day parts of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day will be assumed to the last of the month (e.g., ??-JAN-2013 will be treated as 31-JAN-2013).

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- If both the day and month of resolution are unknown, the event will be assumed to have ceased on the last day of the year (e.g., ??-???-2013 will be treated as 31-DEC-2013).
- If the stop date is completely missing or the event is continuing, the event will be assumed to be after first dose of study drug and will be imputed using the last known date on the study.

Standard Calculations
Variables requiring calculation will be derived using the following formulas:

- **Days –** A duration expressed in days between one date (*date1*) and another later date (*date2*) is calculated using the formulas noted below:

  duration in days = date2 – date1 + 1, where date1 ≥ first dose date

  duration in days = date2 – date1, where date1 < first dose date
- **Months –** A duration expressed in months is calculated as the number days divided by 365.25/12 (~30.4).
- **Years –** A duration expressed in years between one date (*date1*) and another later date (*date2*) is calculated using the formula noted below:
  duration in years = (date2-date1+1)/365.25
- **Age –**Age is calculated as the number of years from the date of birth (*DOB*) to the date of informed consent (*DOIC*). If the month of DOIC < month of DOB or the month of DOIC=DOB and the day of DOIC < day of DOB, then the following formula is used:

  age (years) = year of DOIC – year of DOB – 1.

  Otherwise, the following formula is used:

  age (years) = year of DOIC – year of DOB.
- **Body Mass Index (BMI) –** BMI is calculated using height (cm) and weight (kg) using the following formula:
  BMI (kg/m^2) = weight (kg) / [[height (cm)/100]^2]
- **Change from baseline –** Change from baseline will be calculated as:
  Change = post baseline value – baseline value
- **Percent change from baseline –** Change from baseline will be calculated as:
  Percent change from baseline = post baseline value – baseline value / baseline value x 100

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Appendix B: SAS programming QC requirements

Derived datasets are independently reprogrammed by a second programmer. The separate datasets produced by the 2 programmers must match 100%. Detailed specifications for the derived datasets are documented in the study Analysis Dataset (ADaM) Specifications provided to the client at study conclusion.

Tables are independently reprogrammed by a second programmer for numeric results.

Listings are checked for consistency against corresponding tables, figures, and derived datasets.

Figures are checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.

The entire set of TLFs is checked for completeness and consistency prior to its delivery to the client by the lead biostatistician and a senior level, or above, reviewer.