Statistical Analysis Plan Cover Page

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Title: A Single-Arm Phase-II Study of Niraparib in Locally Advanced or Metastatic Solid Tumor Patients with PALB2 Mutations

Date: 11DEC2023

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Single-Arm Phase-II Study of Niraparib in Locally Advanced or Metastatic Solid Tumor Patients with PALB2 Mutations
Protocol Number:	TMPS-101
Protocol Version/Date:	Amendment 1 / 06DEC2021
Investigational Product:	Niraparib (GSK3985771)
Sponsor:	Tempus Labs, Inc. 600 West Chicago Ave., Suite 510, Chicago, Illinois 60654
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SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

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VERSION HISTORY

Version	Version Date	Description
1.0	08NOV2022	Original signed version
2.0	11DEC202	On November 9th, 2023, In collaboration with GlaxoSmithKline, Tempus has made the decision to halt enrollment into the study TMPS-101 study: Niraparib in the Treatment of Patients With Advanced PALB2 Mutated Tumors (PAVO). This is due to recruitment challenges alone. The SAP is revised to reflect the study status change. The following changes were made: Removed prior and concomitant medications sections; Efficacy analyses are limited to the endpoints assessed by investigator and changed the definition of CBR to CR, PR and had *SD for 8 weeks or more;* Removed analyses for intracranial ORR and PFS; Removed exploratory assessments; AE summary table limited to all AEs, SAE and AEs of special interest. Removed summaries clinical laboratory tests, vital signs, electrocardiograms, physical examinations, and ECOG performance status. Removed interim analysis section.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
BOP2	Bayesian Optimal Phase 2
BOR	Best overall response
C_{max}	Maximum concentration
CBR	Clinical Benefit Rate
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CR	Complete response
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module
EQ-5D-3L	European Quality of Life 5-Dimensions 3-Level Scale
HRQoL	Health-related quality of life
ICE	Intercurrent event
ICF	Informed Consent Form
ICR	Independent Central Review
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	Not Evaluable
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
tPALB2	Tumor partner and localizer of BRCA2
WHO	World Health Organization

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number TMPS-101 Version Amendment 1 dated December 06, 2021. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2. STUDY OVERVIEW

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to evaluate overall response rate (ORR) as assessed by Independent Central Review (ICR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

2.1.2. Secondary Objectives

The secondary objectives are to:

- Evaluate duration of response (DOR) as assessed by ICR using RECIST v1.1
- Evaluate progression-free survival (PFS) as assessed by ICR using RECIST v1.1
- Evaluate ORR as assessed by Investigator using RECIST v1.1
- Evaluate DOR as assessed by Investigator using RECIST v1.1
- Evaluate PFS as assessed by Investigator using RECIST v1.1
- Evaluate Clinical Benefit Rate (CBR) as assessed by ICR and Investigator
- Evaluate intracranial ORR and PFS in patients with untreated measurable CNS lesions as assessed by ICR and Investigator using RECIST v1.1
- Evaluate safety and tolerability per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0)
- Evaluate overall survival (OS)

2.1.3. Exploratory Objectives

The exploratory objectives are to:

- Evaluate health-related quality of life (HRQoL) and symptoms as assessed by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module (EORTC QLQ-C30) and European Quality of Life 5-Dimensions 3-Level Scale (EQ-5D-3L)
- Evaluate exploratory biomarkers in tumor and/or blood that may be predictive of response including clinical factors
- Evaluate niraparib concentration or pharmacokinetics (PK)

2.2. Study Design

2.2.1. Overview

This is a multicenter study of niraparib in patients with locally advanced or metastatic solid tumors and a confirmed pathogenic or likely pathogenic tumor partner and localizer of BRCA2 (tPALB2) mutation. Patients must have received all standard therapies appropriate for their tumor type and stage of disease or, in the opinion of the Investigator, the patient would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy, or the patient has no satisfactory alternative treatments.

To participate in this study, patients eligibility will be confirmed via scan(s) conducted within 28 days prior to enrollment. While on-study, imaging will be performed every 8 weeks (every 56 [±7] days) from the date of enrollment until disease progression. If at any time radiographic progressive disease (PD) is documented per RECIST v1.1 the patient will come off study.

Each patient will have an End-of-Treatment Visit at the time of discontinuation from study treatment, Safety Follow-up Visits at 30 (±7) days, and Survival Follow-up Assessments which may be conducted via telephone, email, in person visits to the clinic or back-up contacts every 90 (±14) days for 1 year after last dose and then every 180 (±14) days that will continue until death or the end of study data collection.

2.2.2. Sample Size Determination

The primary efficacy endpoint ORR will be assessed using the Bayesian Optimal Phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017). Specifically, let n denote the interim sample size and N denote the maximum sample size. Let p_{eff} denote the ORR and define the null hypothesis $H_0: p_{eff} \leq 0.15$, under which the treatment is deemed as not promising and unacceptable. The trial will stop enrolling patients and claim that the treatment is unacceptable if

$$Pr(p_{eff} > 0.15|data) < \lambda(\frac{n}{N})^{\alpha}$$

where λ=0.96 and α =1 are design parameters optimized to maximize power under the alternative hypothesis H_1: $p_{eff} = 0.3$, (i.e., the probability of correctly claiming that the treatment is acceptable under H_1), while controlling the type I error rate (i.e., the probability of incorrectly claiming that the treatment is acceptable under H_0) at 0.024. This optimization is performed assuming a vague prior Beta (0.15,0.85) for p_{eff}. The above decision rule leads to the following stopping boundaries and yields a statistical power of 0.932 under H_1 when 90 patients are included as evaluable patients for ORR described in Table 2.1.

Table 2.1 Optimized stopping boundaries based on BOP2 design

Analysis	Sample size	Stop if # responses ≤
Interim	40	5
Final	90	20

Based on Table 2.1, the interim analysis will be performed when a total of 40 patients have completed their efficacy assessment on ORR. If 5 or less responders are observed in these 40 patients, the study could be stopped for futility. If 6 or more responders are observed among the 40 patients, the study could continue to enroll a total of 90 patients. At the end of the study the null hypothesis would be rejected and concluded that the treatment is promising if at least 21 responders are observed in the total of 90 patients; otherwise, it will be concluded that the treatment is not promising in the overall population based on ICR. The go/no-go criteria in Table 2.1 are non-binding. In order to achieve 90 evaluable patients a total of approximately 110 patients will be treated.

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoints

The primary endpoint is ORR defined as the proportion of patients who have a partial or complete response to therapy and assessed by ICR using the RECIST v.1.1 criteria.

2.3.2. Secondary Efficacy Endpoints

- DOR is defined as the time between initial response to therapy and subsequent disease progression or relapse and will be assessed by ICR using the RECIST v.1.1 criteria.

- PFS is defined as the time from first dose to the date of first radiographic progression or death from any cause in the absence of progression, whichever occurs first. Progression will be assessed by ICR using the RECIST v.1.1 criteria.
- ORR is defined as the proportion of patients who have a partial or complete response to therapy and will be assessed by Investigator.
- DOR is defined as the time between initial response to therapy and subsequent disease progression or relapse and will be assessed by Investigator using the RECIST v.1.1 criteria.
- PFS is defined as the time from first dose to the date of first radiographic progression or death from any cause in the absence of progression, whichever occurs first. Progression will be assessed by Investigator using the RECIST v.1.1 criteria.
- CBR is defined as the percentage of patients who have achieved complete response, partial response and had stable disease for 8 weeks or more, and will be assessed by ICR and Investigator.
- ORR is defined as the proportion of patients who have a partial or complete intracranial response to therapy as assessed by ICR and Investigator using RECIST v1.1.
- PFS in patients with untreated measurable CNS lesions is defined as the time from first dose to the date of first radiographic progression or death from any cause in the absence of progression, whichever occurs first, and will be assessed by ICR and Investigator using RECIST v1.1.
- Assess the incidence of AEs, serious adverse events (SAEs), and adverse events of special interest (AESIs).
- OS is defined as the time from first dose to the date of death by any cause. Patients who are alive will be censored at the date of last contact. OS includes the following: death attributable to any cause, including primary cancer, secondary cancer, or unknown cause.

2.3.3. Exploratory Efficacy Endpoints

- The EORTC QLQ-C30 and EuroQol EQ-5D-3L will be analyzed descriptively by changes from baseline in overall score, sub scores, and individual items when applicable.
- Blood and tissue samples for the evaluation of exploratory biomarkers will be obtained at screening. The incidence of biomarkers will be summarized using descriptive statistics. Comparisons of efficacy endpoints between biomarker subpopulations may be performed.
- Plasma concentrations or PK parameters of niraparib, as data permit.

3. STATISTICAL METHODOLOGY

3.1. General Considerations

3.1.1. Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2. Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study drug.

3.1.3. Summary Statistics

All statistical analysis will be performed using SAS® version 9.4 or later, unless otherwise stated.

Descriptive statistics (i.e., n, mean, standard deviation, median, minimum, maximum) will be provided for all continuous variables; frequencies and percentages will be tabulated for incidence and categorical variables and 95% CIs based on the Clopper-Pearson exact method provided as appropriate. For parameters

measured over time, observed values and changes from baseline will be described for each time point. For time to event endpoints Kaplan-Meier estimates will be provided.

3.1.4. Hypothesis Testing

No formal statistical testing will be carried out.

3.1.5. Handling of Dropouts and Missing Data

Missing data will be queried during study conduct. Best efforts should be made from Study Monitors to follow up with sites on all missing data queries. Unless otherwise stated, missing data will be simply noted as missing on appropriate tables and listings, missing test results or assessments will not be imputed.

- Overall Response Data
  Overall response (CR or PR) will be derived based on investigator reported tumor assessments. At each time point, missing response data will be considered as non-evaluable; the time point response will be used to derive the best overall response in accordance with RECIST v1.1. In the overall response rate calculation, if a patient has missing tumor outcome across all visits or if he/she had non-evaluable best overall response following RECIST v1.1, the patient will be considered as non-responder, and will be included in the denominator but will not be included in the numerator.
- Time to Event Data
  For the time-to-event endpoints (DOR, PFS, or survival), the missing data handling method will be censoring. Censoring mechanisms for these endpoints are described in Section 3.4.2.

3.2. Analysis Populations

3.2.1. All Screened Population

All Screened Population will include all patients who signed the main study Informed Consent Form (ICF) to participate in the clinical study. Patients in this population will be used for screen failure summary.

3.2.2. Enrolled Population

Enrolled Population will include all the patients that are enrolled per eCRF.

3.2.3. Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will include all patients who were enrolled in the study and who received at least one dose of study drug. This population will be the secondary population for the analysis of efficacy data. Any patient who receives a treatment number will be considered to have been enrolled.

3.2.4. Response Evaluable Population

The Response Evaluable Population will include all patients with measurable disease who received at least one dose of study treatment, who have an adequate baseline tumor assessment and at least one follow-up tumor assessment will be considered evaluable for anti-tumor efficacy using RECIST version 1.1 criteria. Patients who are treated and removed from study prior to first on-study tumor assessment because of disease progression will be considered evaluable for efficacy and counted as failures. This population will be considered the primary population for the analysis of efficacy data.

3.2.5. Safety Population

The Safety Population will consist of all patients who took at least 1 dose of study drug. This population will be used for safety analyses.

3.3. Subject Data and Study Conduct

3.3.1. Subject Disposition

Frequency and percentages of patients who were screened (signed informed consent), discontinued early during screening (screen failures), and enrolled will be summarized based on all screened patients. Reasons for screen failures will also be summarized based on all screened patients.

Frequency and percentages of patients in each analysis population (except All Screened Population) will be summarized based on all enrolled patients.

Frequency and percentages of patients who withdrew from the study drug, discontinued early from the study and completed the study will be summarized based on all enrolled patients. Reasons for early discontinuation of study drug and study will also be summarized, discontinuation due to Coronavirus Disease 2019 (COVID-19) will be summarized separately.

Subject disposition data will be listed.

3.3.2. Protocol Deviations

Frequency and percentages of patients with CSR reportable deviations by deviation category will be summarized based on all enrolled patients.

Protocol deviations data will be listed.

3.3.3. Demographic and Baseline Characteristics

The following demographic characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 years)
- Sex
- Childbearing potential
- Race
- Ethnicity
- Baseline height (cm)
- Baseline weight (kg)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status

The following baseline disease characteristics will be summarized;

- Cancer type
- Time from initial histologic/cytologic diagnosis until the informed consent date (months)
- Tumor stage at time of diagnosis
- Histological grade at initial diagnosis
- TNM staging-tumor at initial diagnosis
- TNM staging-node at initial diagnosis
- TNM staging-metastasis at initial diagnosis
- PALB2 mutation type (Germline, Somatic, Unknown)

In the baseline disease characteristics summary table, additional mutation maybe displayed in the ad hoc analysis. Demographic and baseline disease characteristics will be summarized with descriptive statistics or frequency and percentages of patients as appropriate based on all enrolled patients.

3.3.4. Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. Frequency and percentages of patients with medical history by system organ class and preferred term will be summarized based on all enrolled patients. A by-patient listing will also be provided.

3.3.5. Study Drug Exposure

The following summaries will be presented using Safety Population and also based on Response Evaluable Population.:

- Total number of treatment cycles started will be summarized with frequency and percentage.
- The number of patients with dose modification will be summarized with frequency and percentage by visit.
- Duration of drug treatment will be calculated as follows:

  Duration of drug treatment (days)=Date of last dose – Date of first dose + 1

  and will be summarized with descriptive statistics
- Actual cumulative dose is defined as the sum of all doses of study drug administered during the treatment period (i.e. duration of drug treatment) and will be summarized with descriptive statistics.

Study drug exposure data collected will be listed.

3.4. Efficacy Assessment

3.4.1 ORR Assessed by Investigator

ORR is defined as the proportion of patients with a best overall response (BOR) characterized as confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1 definitions, as assessed by Investigator.

BOR is defined as the best response as recorded from the start of the treatment until documented objective disease progression using RECIST version 1.1. Each patient's BOR will be categorized in the order of CR, PR, stable disease (SD), progressive disease (PD), or not evaluable (NE). CR/PR must be confirmed at the immediate next evaluable assessment at least 4 weeks after the response is first documented to be included. A CR or PR that is not confirmed will be considered as a best overall response of SD as long as the minimum duration of stable disease is met. The minimum duration of stable disease in order to be considered as best overall response will be at least 6 weeks after baseline. Patients without baseline or post-baseline tumor assessments will be treated as NE for BOR. The determination of the BOR by RECIST v1.1 is summarized in the table below:

Table 3.1: BOR RECIST Assessment Considering Requirement for Confirmation

Response Category at First Time Point	Response Category at Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	PD unless minimum criteria for SD duration met [a], in which case SD (possible PR [b])
CR	SD	SD if minimum criteria for SD duration met [a], otherwise PD if no further assessment
CR	PD	SD if minimum criteria for SD duration met [a], otherwise PD if no further assessment

CR	NE	SD if minimum criteria for SD duration met [a], otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD if minimum criteria for SD duration met [a], otherwise PD
PR	NE	SD if minimum criteria for SD duration met [a], otherwise NE
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	PD	SD if minimum criteria for SD duration met [a], otherwise PD if no further assessment
SD	NE	SD if minimum criteria for SD duration met, [a] otherwise NE
NE	CR	SD
NE	PR	SD
NE	SD	SD
NE	PD	PD
NE	NE	NE

a. Assignment of SD requires that ≥ 1 post-baseline scan was obtained at least 6 weeks after baseline from start of study therapy and met criteria for SD or better response.

b. If a true CR occurs at the first time point, then any disease seen at a subsequent time point (even disease meeting PR criteria relative to baseline) results in a best overall response of PD (because the disease must have reappeared after the CR). The best overall response assessment would depend on whether the minimum duration for SD was met. For a patient who retrospectively had only an apparent CR (with small lesions still present, i.e., the patient had PR, not CR, at the first time point, the original CR should be converted to a PR and the best overall response should be assessed as PR.

ORR assessed by investigator will be summarized with frequency and percentage along with Clopper–Pearson 95% CI based on the Response Evaluable Population. Waterfall plots will be used to depict graphically for individual patients of their best change (%) or largest reduction (%) from baseline in the sum of the diameters in target lesions using Response Evaluable Population. Swimmer plot will also be provided based on Response Evaluable Population.

3.4.2 Duration of Response

DOR is defined as the time from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. DOR will be censored following the censoring rule of PFS in Table 3.2. DOR will be calculated as follows:

DOR (month) = 12*(Date of progression/death/censoring – Date of first response date + 1)/365.25

Kaplan-Meier estimates will be provided along with 95% CI for the median DOR. These analyses will be presented for the investigator assessments.

3.4.3 Progression-Free Survival

PFS is defined as the time from first dose to the date of first radiographic progression or death from any cause in the absence of progression, whichever occurs first. Progression will be assessed using the RECIST v.1.1 criteria. Patients who are treated and removed from study prior to first on-study tumor assessment because of disease progression will be considered as PD. General censoring rules for the analysis of PFS are described in Table 3.3.

Table 3.2 Date of Event or Censoring for PFS

Situation	Date of event or censoring	Outcome

PD on or prior cutoff date	Date of first radiographic progression	Event
Death in the absence of progression	Date of death	Event
Death or PD after more than one consecutive missed tumor assessments	Date of last evaluable tumor assessment with documented non-PD	Censored
Alive and no objective tumor progression while on study	Date of the last evaluable tumor assessment	Censored
No baseline or postbaseline tumor assessment response available	Date of first dose of treatment	Censored
Treated and withdraw due to disease progression prior to on-study tumor assessment	End of treatment date	Event
New anti-cancer therapy started prior to documented PD or death	Date of the last evaluable tumor assessment prior to the start of the new therapy, or date of first dose of treatment if no post-baseline tumor assessment available	Censored

PFS will be calculated as follows:

PFS (month) = 12*(Date of progression/death/censoring − Date of first dose +1)/365.25.

Kaplan-Meier estimates for PFS per investigator assessment will be provided including median PFS, 6- and 12 months PFS together with 95% CIs based on the Response Evaluable Population.

3.4.4 Clinical Benefit Rate

CBR is defined as the percentage of patients who have achieved complete response, partial response and had stable disease for 8 weeks or more. CBR assessed by investigator will be summarized with frequency and percentage along with Clopper–Pearson 95% CI based on the Response Evaluable Population.

3.4.5 Overall Survival

OS is defined as the time from the date of first dose of study drug to the date of death due to any cause and will be calculated as:

OS (in months) = 12* (date of death − date of first dose +1)/365.25.

For patients still alive at the time of the analysis, for those who are lost to follow-up, and those who withdraw consent for additional follow-up, the OS will be censored on the last date that patients were known to be alive. Patients lacking data beyond the first dose will have their OS censored at the date of first dose. Kaplan-Meier estimates for OS will be provided including median OS, 6- and 12 months OS with corresponding 95% CIs based on the Response Evaluable Population.

3.5. Pharmacokinetic Assessment

PK data will not be analyzed.

3.6. Safety Assessment

Safety data will be summarized based on the Safety Population.

3.6.1. Adverse Events (AEs)

AEs will be reported from the start of treatment until 30 days after the last dose of study treatment, until the patient withdraws consent for study participation, or until the patient starts subsequent anticancer treatment, whichever occurs first. SAEs assessed as related to study participation or related to study treatment will be collected and reported until study closeout. SAEs assessed by the Investigator as related

to study treatment and all AESIs, regardless of causality, are to be collected until study closeout. All AEs will be coded to system organ class and preferred term using MedDRA version 24.1 and graded according to the NCI-CTCAE v5.0. Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug. If it is not possible to determine whether an AE is or is not treatment emergent, or whether an AE starts in the on-treatment period, due to completely or partially missing dates, the dates will be imputed in a conservative way so that the AE will be considered as treatment emergent, i.e., starting in the on-treatment period.

Adverse events of special interest (AESI) include MDS or AML, along with other secondary cancers (new malignancies other than MDS or AML).

An overview of AEs will be provided including frequency and percentages of patients with the following:

- Any AEs (overall and by maximum severity)
- Any TEAEs
- Any study drug related TEAEs
- Any AEs of special interest
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESEAEs)
- Any TEAEs leading to study drug interrupted/delayed
- Any TEAEs leading to dose reduce of study drug
- Any TEAEs leading to discontinuation of study drug
- Any TEAEs leading to discontinuation of study
- Any AEs leading to death

Frequency and percentages of patients will also be presented by system organ class and preferred term for all AEs, SAEs and AE of special interest.

Listings will be presented for all AEs, SAEs and TEAEs leading to discontinuation of study drug, AEs leading to death and AEs of special interest.

4. CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

Table 6.1: Changes from protocol-specified analysis

Protocol section	Description of change	Rational of change
Section 3: Study Objectives and Endpoints	Change the definition of CBR from “the percentage of participants who have achieved complete response, partial response and stable disease’ to “the percentage of participants who have achieved complete response, partial response and had stable disease for 8 weeks or more”	

Section 9.4: Statistical Analyses	Removed the analyses for efficacy endpoints assessed by ICR Removed analyses of exploratory endpoints Limited safety analyses to summary of AEs Removed interim analysis	Study early termination

5. PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. Detailed Programming Specifications will be provided in a separate document.