Statistical Analysis Plan

A Randomized Multicenter Phase 3 Study of Milademetan Versus Trabectedin in Patients with Dedifferentiated Liposarcoma

Sponsor:	Rain Therapeutics, Inc. 8000 Jarvis Avenue Suite 204 Newark, CA 94560 USA
Sponsor Protocol No.:	RAIN-3201
Investigational Drug Name:	Milademetan (RAIN-32)
Phase:	3
Date of Statistical Analysis Plan:	18 August 2022
Version Number:	1.0 (Original)

This study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements.

APPROVAL & SIGNATURE PAGE

Protocol No.: RAIN-3201

Version: Original v1.0

The Statistical Analysis Plan has been reviewed and approved by:

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BICR	Blinded independent central review
BMI	Body mass index
CCDD	Centrally confirmed dedifferentiated
CDK4	Cyclin dependent kinase 4
CDKN2A	cyclin-dependent kinase inhibitor 2A
CI	Confidence interval
CMH	Cochran-Mantel-Haenzel
CR	Complete response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating rumor DNA
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic case report form
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
FDA	United States Food and Drug Administration
IDMC	Independent data monitoring committee
ITT	Intent to treat
IRT	Interactive response technology
MDM2	Mouse double minute 2
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PRO	Patient reported outcomes

PT	Preferred term
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	Restricted mean survival time
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event
TP53	Tumor protein 53
ULN	Upper limit of normal

1. INTRODUCTION

This statistical analysis plan (SAP) outlines the statistical methods to be implemented for study RAIN-3201 entitled "A Randomized Multicenter Phase 3 Study of Milademetan Versus Trabectedin in Patients with Dedifferentiated Liposarcoma". The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to the primary analysis. Results of the planned analyses in this SAP will become the basis of the clinical study report (CSR) for this protocol.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to assess the effect of milademetan versus trabectedin on progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as determined by blinded independent central review (BICR) in patients with unresectable or metastatic dedifferentiated (DD) liposarcoma, with or without a well-differentiated (WD) component, who progressed on 1 or more prior systemic therapies including at least 1 anthracycline-based therapy.

2.2. Secondary Objectives

The secondary objectives are:

- To compare the milademetan treatment arm versus the trabectedin control arm for the following efficacy measures:
  - Overall survival (OS)
  - Disease control rate (DCR) by BICR and by Investigator
  - Objective response rate (ORR) by BICR and by Investigator
  - Duration of response (DOR) by BICR and by Investigator
  - PFS by Investigator assessment
- To assess the safety profile of milademetan
- To evaluate patient-reported outcomes of milademetan

2.3. Exploratory Objectives

[redacted]

[redacted]

3. STUDY DESIGN OVERVIEW

3.1. Overall Design

This is a randomized, multicenter, open-label, Phase 3 registration study designed to evaluate the safety and efficacy of milademetan compared to trabectedin in patients with unresectable (i.e., where resection is deemed to cause unacceptable morbidity or mortality) or metastatic DD liposarcoma that progressed on 1 or more prior systemic therapies, including at least 1 anthracycline-based therapy.

Approximately 160 patients will be randomly assigned in a 1:1 ratio to receive milademetan or trabectedin. Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1) and number of prior treatments (≤ 2 or > 2) for the patient's liposarcoma.

Patients will receive study drug (i.e., milademetan or trabectedin) until reaching disease progression per RECIST 1.1 as determined by the Investigator, experiencing unmanageable toxicity, or until other treatment discontinuation criteria are met. Patients may be treated beyond tumor progression if they are experiencing clinical benefit based on the assessment of the Investigator in discussion with the Medical Monitor. All patients will be followed for documentation of disease progression and survival information (i.e., date and cause of death) and subsequent treatment information (i.e., date/duration of treatment, response, and subsequent disease progression). Long-term follow-up will continue every 12 weeks (± 7 days) until the endpoint of death, the patient is lost to follow-up, or for 24 months following the final dose of study drug, whichever comes first.

3.2. Sample Size Considerations

[redacted]

4. STUDY ENDPOINTS AND COVARIATES

4.1. Primary Endpoint

The primary efficacy endpoint is PFS defined as the time from the date of randomization to the date of documented disease progression as determined per RECIST 1.1 by BICR or death due to any cause, whichever comes first.

4.2. Secondary Endpoints

Secondary efficacy endpoints include:

- OS defined as the time measured from the date of randomization to the date of death by any cause
- DCR defined as the percentage of patients who have achieved complete response (CR), partial response (PR), or stable disease (SD) for ≥ 16 weeks as determined by BICR/Investigator using RECIST 1.1.
- ORR defined as the percentage of patients who achieve a confirmed CR or PR as determined by BICR/Investigator using RECIST 1.1.
- DOR defined as the time from date of first objective response (CR or PR) to date of disease progression as determined by BICR/Investigator using RECIST 1.1. or death, whichever comes first
- PFS defined as the time from the date of randomization to the documented disease progression based on Investigator assessments as determined per RECIST 1.1 or death due to any cause

Health-related quality of life (HRQoL) endpoints include:

- European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire, Core 30 (QLQ-C30)

Safety endpoints include:

- Incidence of treatment-emergent adverse events (TEAEs) including serious adverse events (SAEs)
- Incidence of TEAEs leading to discontinuation of study drug
- Incidence of TEAEs leading to study withdrawal
- Incidence of deaths
- Changes in clinical laboratory parameters (hematology, serum chemistry, coagulation, urinalysis, and serum and urine pregnancy test), vital signs, and electrocardiogram (ECG) parameters (especially QT intervals); physical examination results (including ECOG performance status); and use of concomitant medications.

4.3. Exploratory Endpoints

[redacted]

4.4. Baseline Covariates

The following covariates will be used to examine efficacy in subgroups or in multivariate analyses:

- ECOG performance status: 0 vs. 1
- Number of prior anti-cancer treatments: ≤ 2 vs. >2
- Prior therapy for advanced/metastatic disease: Yes vs. No
- Region: North America, Europe, and Rest of World
- Age: < 65 vs. ≥ 65 years
- Sex: male vs. female
- Race: white and other categories depending on frequency observed
- Well differentiated liposarcoma component: yes vs. no

Covariate values may be discordant if collected via electronic case report form (eCRF) and interactive response technology (IRT) (ECOG performance status, number of prior treatments). For subgroup and multivariate model analyses, the source verified eCRF value will be used to reflect the true clinical relevance of the covariate. For stratified treatment comparisons, however, the IRT value will be used to be consistent with the randomization scheme.

5. ANALYSIS POPULATIONS

5.1. Intent-to-treat (ITT) Population

The intent-to-treat (ITT) population is defined as all subjects who are randomized into the study. Patients will be analyzed according to treatment arm to which they were randomized regardless of treatment received.

[redacted]

5.2. Safety Population

The Safety Population is defined as all randomized patients who received at least one dose of investigational product. Patients will be analyzed based on the treatment actually received regardless of the treatment to which they were randomized.

All safety analyses will be performed using the Safety Population.

5.3. Pharmacokinetics (PK) Population

The pharmacokinetics population consists of all randomized patients who received at least one dose of milademetan for whom data on concentrations of study treatment is available.

[redacted]

5.4. Quality of Life (QoL) Population

The QoL population consists of all patients in the ITT population for who have a baseline and at least one post baseline QoL assessment.

[redacted]

5.5. Centrally Confirmed Dedifferentiated Liposarcoma (CCDD) Population

The Centrally Confirmed Dedifferentiated Liposarcoma Population is defined as all patients with centrally confirmed dedifferentiated liposarcoma disease.

[redacted]

[redacted]

5.7. Per Protocol Population

The Per Protocol Population consists of all randomized patients who have no important protocol deviations thought to impact the efficacy analysis.

[redacted]

6. INTERIM ANALYSIS AND DATA MONITORING

No interim PFS analysis is planned. One OS interim analysis is planned at the time of the primary PFS analysis. The final OS analysis will be performed at the end of the study when all patients complete the 24-month long-term follow-up.

An independent data monitoring committee (IDMC) will review accumulating data periodically throughout the study and to make recommendations to the Sponsor regarding the conduct of the study in order to safeguard the interests of trial participants while preserving the integrity and credibility of the study. The Sponsor will implement guidelines to provide internal access of unblinded data on a strictly as required basis for the purpose of data capture, cleaning and analysis of this study. An independent biostatistician external to the Sponsor will prepare analyses for the IDMC.

7. STATISTICAL METHODS OF ANALYSIS

7.1. General Principles and Reporting Conventions

The primary goal of the statistical analysis of the study is to demonstrate whether there is an increase in PFS in subjects treated with milademetan versus trabectedin in ITT population. The timing of the primary analyses of PFS will be event-driven based on corresponding pre-specified goals for the target number of 105 PFS events in the ITT population. The primary analysis of PFS and other RECIST endpoints will be according to BICR. Sensitivity analyses using investigator assessed tumor response or disease progression will be performed, using similar analysis sets of local review.

7.2. Subject Accountability

7.2.1. Disposition of Patients

The number and percentage of patients who were screened, randomized and treated with study drug, randomized but not treated with study drug will be tabulated by treatment arm. The number and percentage of patients in each analysis population will be tabulated by treatment arm.

Screen failures will be summarized with reasons. The number and percentage of patients entering and completing each phase of the study will be presented by treatment. End of treatment and end of study will be summarized by reasons.

7.2.2. Protocol Deviations

Protocol deviations will be classified and monitored regularly during the duration of the study. Among other reasons, failure to meet any of the protocol inclusion or exclusion criteria will be considered a protocol deviation. All protocol deviations will be listed and summarized by type and treatment group. Important protocol deviations, thought to potentially impact the study conclusions, will be listed and tabulated using incidence and percentage by deviation type and treatment arm.

7.3. Demographic and Baseline Characteristics

Descriptive statistics will be provided for all demographic and baseline disease characteristics based on the ITT population. Demographic data, medical history, concomitant disease, and concomitant medication will be summarized by means of descriptive statistics or frequency tables, overall and stratified by treatment.

7.3.1. Demographic Characteristics

The following demographic variables will be summarized by treatment group:

- age (years)
- age group (<65, ≥ 65 years; <65, 65 – 85, ≥ 85 years)
- sex
- race & ethnicity
- region (North America, Europe, and Rest of World)

- height (cm)
- weight (kg)
- body mass index (BMI) calculated as: BMI (kg/m^2) = Weight (kg)/ (Height(cm) × $0.01)^2$

7.3.2. Randomization Stratification Factors

[redacted]

7.3.3. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by treatment group:

- Stage at initial diagnosis
- Stage at study entry
- Tumor differentiation
- Mitotic count
- Tumor necrosis
- FNCLCC grade
- TNM stage at study entry
- Time from initial diagnosis to randomization
- Time from metastatic diagnosis to randomization
- Tumor status
- Metastatic sites

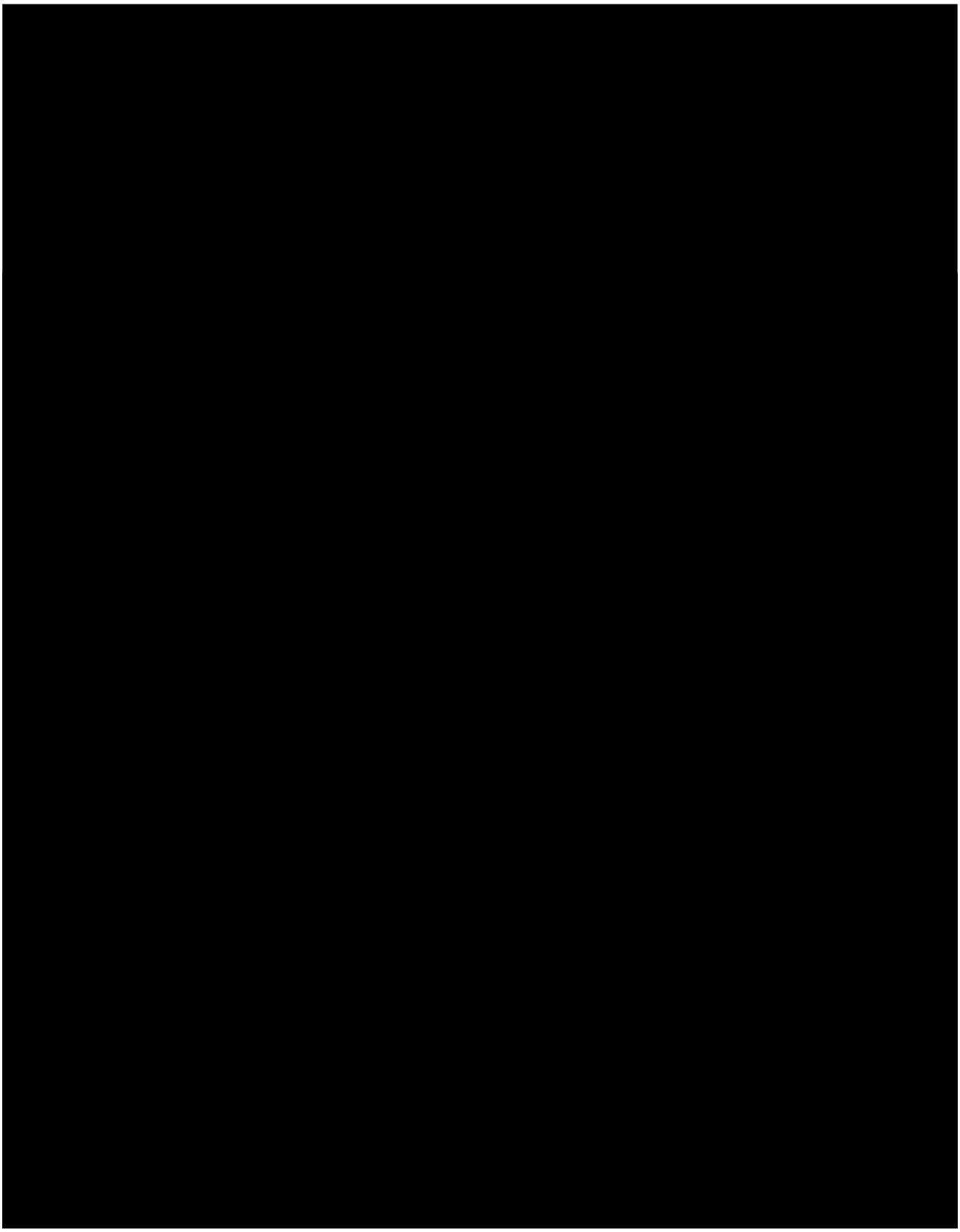
7.3.4. Prior Cancer Therapy

Prior radiation, cancer related surgery, cancer therapy will be summarized with indication and by treatment arm. Number of prior lines of therapy for metastatic disease, best response and reason for treatment discontinuation of each therapy will be summarized by treatment arm.

7.3.5. Medical History

Medical history data including chronic conditions, relevant surgical procedures, symptoms, any medical conditions that require medication and cancer history will be collected at screening, within 14 days before Cycle 1 Day 1. Medical history data will be summarized and listed by treatment arm.

7.4. Efficacy Analyses



[redacted]

7.4.1. Progression Free Survival (PFS)

Progression free survival (PFS) is defined as the time interval from the date of randomization until the first date on which progression (per RECIST v1.1) or death due to any cause, is documented, whichever comes first. Assessment of PFS will be performed for all patients at baseline, at the end of W8, W16, W24, W32, and then every 12 weeks (± 1 week), regardless of treatment schedule modification (e.g., dose delay), until documented disease progression, initiation of new anticancer therapy, or discontinuation from the study (death, withdrawal of consent, or loss to follow-up). Subjects without documented progressive disease (PD) or death, including those who dropped out, will be censored at their last tumor assessment. Patients who did not have any tumor assessments after the screening visit will be censored on the randomization date.

[redacted]

7.4.2. Overall Survival (OS)

Overall survival is defined as the time from the date of randomization to the date of death due to any cause, censored at the last date known alive on or prior to the data cutoff date. Patients who had PD and started new anticancer therapy will continue to be followed for the OS assessment.

[redacted]

7.4.3. Disease Control Rate (DCR)

Disease control rate is the proportion of patients who achieve overall tumor response (confirmed CR or PR) or SD as assessed by RECIST 1.1 at least 16 (-1 week tumor assessment window) weeks from randomization. [redacted]

7.4.4. Objective Response Rate (ORR)

Objective response rate is defined as the proportion of patients demonstrating an objective response during the study. Objective response includes CR and PR as defined in the RECIST 1.1 criteria and must be subsequently confirmed at least 4 weeks later. [redacted]

7.4.5. Duration of Response (DOR)

Duration of response is measured from the time at which measurement criteria are first met for CR or PR (whichever status is recorded first) until the first date of PD is objectively documented or death. It is censored at the last valid tumor assessment if PD or death has not been documented. [redacted]

7.5. Efficacy Analysis Methods

7.5.1. Primary Analysis of PFS

[redacted]

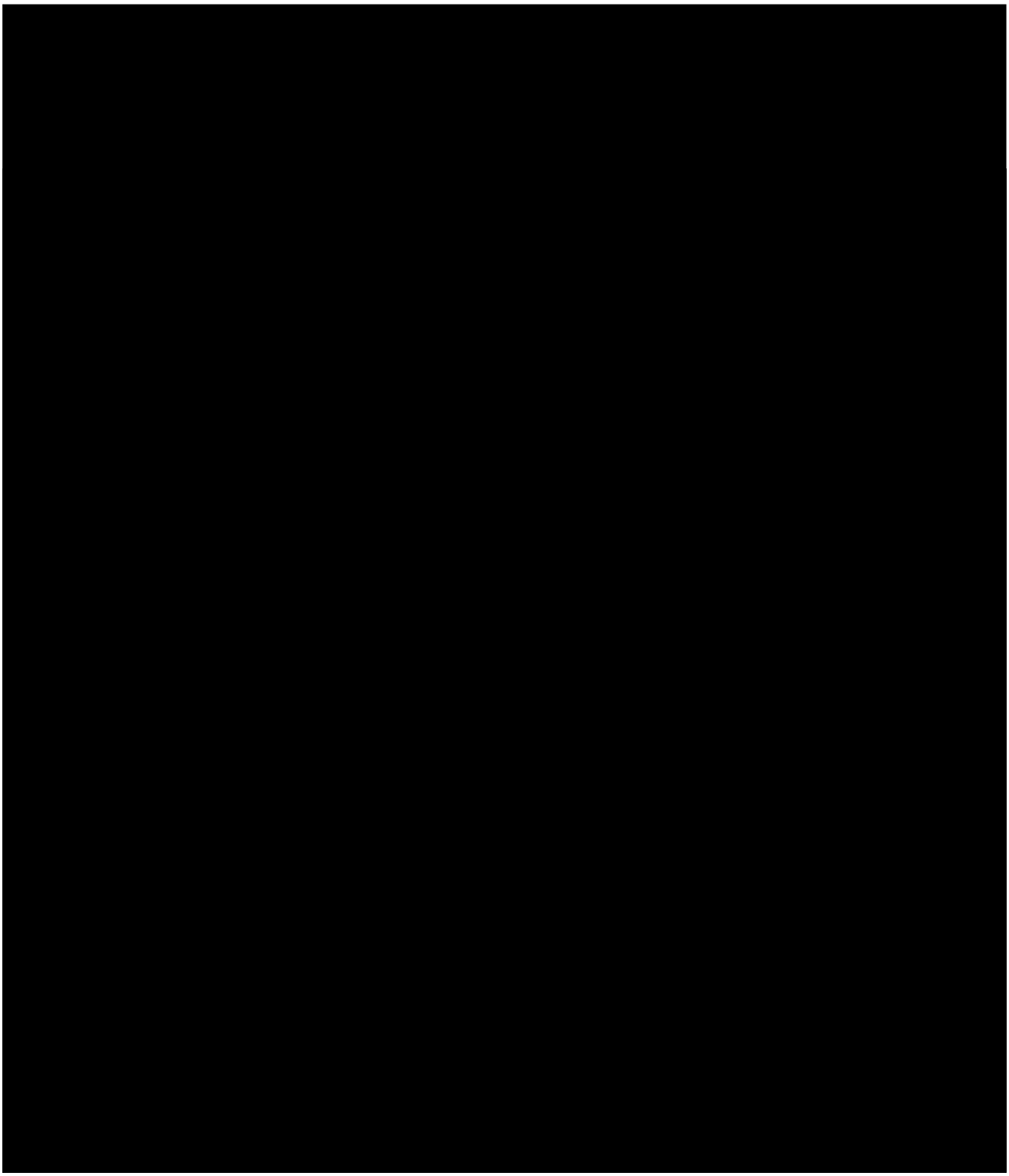
7.5.2. Sensitivity Analyses of PFS

[redacted]

[redacted]

7.5.3. Secondary Efficacy Endpoints Analyses

[redacted]



7.6. Safety Analysis

7.6.1. Overview of Safety Analysis Methods

All safety analysis will be performed for all patients in the Safety population. The following assessments will be used:

- Adverse events (AEs)
- Medical history
- Physical examination findings
- Vital sign measurements
- Laboratory assessments
- ECOG performance status
- ECG
- Liver Function Tests results

All safety endpoints will be summarized by treatment group and visit when appropriate.

7.6.2. Extent of Exposure

Extent of exposure to each investigational product will be summarized by total dose, number of cycles, treatment duration, dose intensity, relative dose intensity, number of missed doses, number of dose delays and number of dose reductions.

[redacted]

7.6.3. Concomitant Medications

Concomitant medications will be defined as medications documented on the Concomitant Medications CRF. Concomitant medications will be coded using the World Health Organization Drug Reference List (WHODrug) dictionary 2021 version and summarized in a table and a data listing.

7.6.4. Adverse Events, Serious Adverse Events, and Deaths

All AEs and SAEs will be reported until 30 days after the last dose of investigational product(s) and will be followed until resolution or until condition stabilizes. AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) 24.1 and graded by the Investigator according to the NCI CTCAE v5.0 or later.

Summaries of adverse event will, in general, focus on TEAEs which is defined as adverse event that occurs or worsens on or after first dose of investigational product and up to 30 days after the last dose. Missing data for safety endpoints will not be imputed. If dates are missing or incomplete for adverse event therefore TEAE status cannot be determined, then this AE will be included as an TEAE in the safety analysis.

Subject incidence of the following events will be tabulated in two formats: 1) system organ class (SOC), preferred term (PT), and grade by treatment group; 2) PT only and by treatment group.

- All TEAEs
- SAEs
- Treatment-related TEAEs
- Treatment-related SAEs
- Grade 3 or 4 TEAEs
- TEAE leading to treatment discontinuation, dose reduction, dose interruption
- TEAEs with an incidence >10%
- TEAEs with at least a 5% difference in incidence rates between treatment groups

Listings of TEAEs, TEAEs leading to IP discontinuation, TEAEs related to study treatment, and SAEs will be provided. Listings will be sorted by treatment, patient ID and study day; SAEs will be flagged. All AE listings will include treatment arm, patient ID, study day, SOC, PT, reported term, dose, Cycle/day, AE onset date, AE end date, outcome, duration, relationship to drug, action taken, and severity.

The incidence of death will be summarized by cause of death, treatment arm, and on-study status at time of death (within 30 days of last dose vs. more than 30 days after last dose). Patient death listings will include all death data available including date of death, cause of death and any AEs resulting in death.

AE of special interest may be identified and summarized.

7.6.5. Clinical Laboratory Evaluation

Samples for clinical chemistry, hematology, and other lab parameters will be collected during screening, before study drug administration, on day 1 (and day 15 in milademetan arm) of each treatment cycle and at the treatment discontinuation visit.

Laboratory data will be summarized in tables using descriptive statistics for baseline and each cycle/visit. Descriptive statistics will be calculated on both the actual score and the change from baseline score. Additionally, clinically significant abnormalities in laboratory results will be summarized for the post-baseline cycles/visits using frequencies and percentages. Shifts from baseline to minimum post-baseline and baseline to maximum post-baseline value (according to NCI Common Toxicity Criteria version 5.0 grading) will be presented for each treatment group.

7.6.6. Vital Signs and Physical Examinations

Vital signs, including systolic and diastolic blood pressure, pulse, and body temperature, as well as weight will be collected during screening and on day 1 (and day 15 in milademetan arm) of each cycle.

Summary tables will include descriptive statistics (number of patients, mean, std, median, Q1, Q3, min, and max) for baseline and each cycle/visit. Descriptive statistics will be calculated on both the actual score and the change from baseline score.

Physical examinations will be collected during screening, before study drug administration, on day 1 (and day 15 in milademetan arm) of each treatment cycle and at the Treatment Discontinuation Visit. Physical examination results will be summarized, and the frequency of clinically significant changes will be tabulated by treatment.

7.6.7. Electrocardiograms

Single standard 12 lead digital ECG will be performed during screening, at Cycle 1 Day 1 (and Day 15 in milademetan arm), and on the treatment discontinuation visit. For the triplicates at baseline, the average will be included in the summary.

The ECG (measured after resting in a supine position for 10 minutes) will include heart rate, rhythm, and RR, PR, QRS, QT and QTc intervals. The ECG will be read and interpreted at the investigational site for patient safety monitoring, and documentation stored with the source documents.

[redacted]

[redacted]

All ECG parameters, their change from baseline, and the frequency of abnormal ECG events will be summarized across study time points by treatment arm using descriptive statistic. All ECG values will be listed by patient.

[redacted]

7.6.9. Liver Function Test Results

A listing will be generated for patients potentially meeting Hy's Law criteria (total bilirubin ≥ 2× upper limit of normal [ULN] and aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 3×ULN at any time during the study). Plots or tables of on therapy peak total bilirubin vs. peak AST (or ALT) will also be generated to help identify potential Hy's Law cases.

7.6.10. ECOG Performance Status

ECOG performance status will be assessed at screening, Day 1 of every cycle (and Day 15 in milademetan arm), and at treatment discontinuation.

The ECOG status will be included in the baseline and demographic variables. The number and percentages of patients in each ECOG category will be presented by treatment.

[redacted]

8. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

This section is to be filled out if there are any changes to the analyses prior to finalization of the SAP.

LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

List of Planned Tables

Category	Title
Disposition	Summary of Randomization
	Summary of Analysis Population
	Summary of Subject Disposition
	Summary of Protocol Deviations
	Summary of Follow-up Time
Demography and Baseline Characteristics	Summary of Demographics
	Summary of Baseline Characteristics
Medical History	Summary of Medical History
Cancer History	Summary of Prior Cancer History
	Summary of Prior Anticancer Medications
	Summary of Prior Anticancer Radiotherapy
	Summary of Prior Anticancer Surgical Therapy
	Summary of Biomarkers
Concomitant Medications	Summary of Concomitant Medications
	Summary of Concomitant Surgery
Study Medication	Summary of Treatment Exposure
	Summary of Treatment Dose Reduction
	Summary of Treatment Dose Hold
Efficacy	Summary of Progression-Free Survival by Central Review
	Summary of Progression-Free Survival by Investigator
	Summary of PFS in Subgroups
	Summary of Objective Response Rate
	Summary of Duration of Response
	Summary of Disease Control Rate
	Summary of Overall Survival
	Summary of Overall Survival in Subgroups
	Concordance of Central PFS and Local PFS

Category	Title
	Summary of Subsequent Anti-cancer Treatment
Health Outcomes	Summary of EORTC QLQ-C30 Observed Results and Change from Baseline
	Summary of EORTC QLQ-C30 Mixed Model Between Treatment Comparison
	Summary of Time to EORTC QLQ-C30 Deterioration
Safety	Summary of Overall Safety
	Incidence of TEAE by Preferred Term
	Incidence of TEAE by System Organ Class, Preferred Term, and Grade
	Incidence of Serious Adverse Events by Preferred Term
	Incidence of Serious Adverse Events by System Organ Class, Preferred Term, and Grade
	Incidence of TEAE Related to Study Treatment
	Incidence of TEAE Leading to Study Discontinuation
	Incidence of TEAE Leading to Study Drug Reduction
	Incidence of TEAE Leading to Study Drug Hold
	Incidence of Grade 3 or 4 TEAE by System Organ Class, and Preferred Term
	Summary of TEAE with Incidence >= 10% by Preferred Term
	Summary of Death
	Summary of TEAE of Special Interest
Laboratory	Mean and Mean Change from Baseline in Numeric Laboratory Data: Hematology/ Clinical Chemistry
	Shift from Baseline in Laboratory Data: Hematology/ Clinical Chemistry
Vital Signs	Mean and Mean Change from Baseline in of Vital Signs Data
	Frequency Table of Potentially Clinically Significant Vital Signs Data
Physical Exam	Summary of Physical Examination
ECG	Mean and Mean Change from Baseline in ECG Data
	Summary of Abnormality in ECG
Liver Function	Summary of Liver Function Parameters for Potential Hy's Law
ECOG	Summary of ECOG by Visit

List of Planned Figures

Category	Title
Efficacy	Kaplan-Meier Plot of Progression-free Survival by Central Review
	Kaplan-Meier Plot of Progression-free Survival by Investigator
	Forest Plot of Progression-free Survival by Central Review
	Forest Plot of Progression-free Survival by Investigator
	Kaplan-Meier Plot of Overall Survival
	Forest Plot of Overall Survival
	Kaplan-Meier Plot of Duration of Response by Central Review
	Kaplan-Meier Plot of Duration of Response by Investigator
QoL	Mean Plot of Observed EORTC QLQ-C30 by Visit
	Mean Plot of EORTC QLQ-C30 Change from Baseline by Visit
Safety	Hy's Law Plot

List of Planned Data Listings

Category	Title
Disposition	Listing of Protocol Deviations
	Listing of Enrollment by Country
Safety	Listing of Serious Adverse Events
	Listing of Adverse Events Leading to Treatment Discontinuation
	Listing of Adverse Events Leading to Hospitalization
	Listing of Adverse Events Leading to Dose Reduction
	Listing of Adverse Events Leading to Dose Hold
	Listing of Treatment Related Adverse Events
	Listing of Deaths
	Listing of Potential Hy's Law Cases
Study Drug	Listing Study Drug Lot Numbers

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