Statistical Analysis Plan

A Phase 2 Basket Study of Milademetan in Advanced/Metastatic Solid Tumors

Sponsor:	Rain Oncology, Inc. 8000 Jarvis Avenue Suite 204 Newark, CA 94560 USA
Protocol No.:	RAIN-3202
Investigational Drug Name:	Milademetan (RAIN-32)
Phase:	2
Date of Plan:	V1.0 28 October 2023

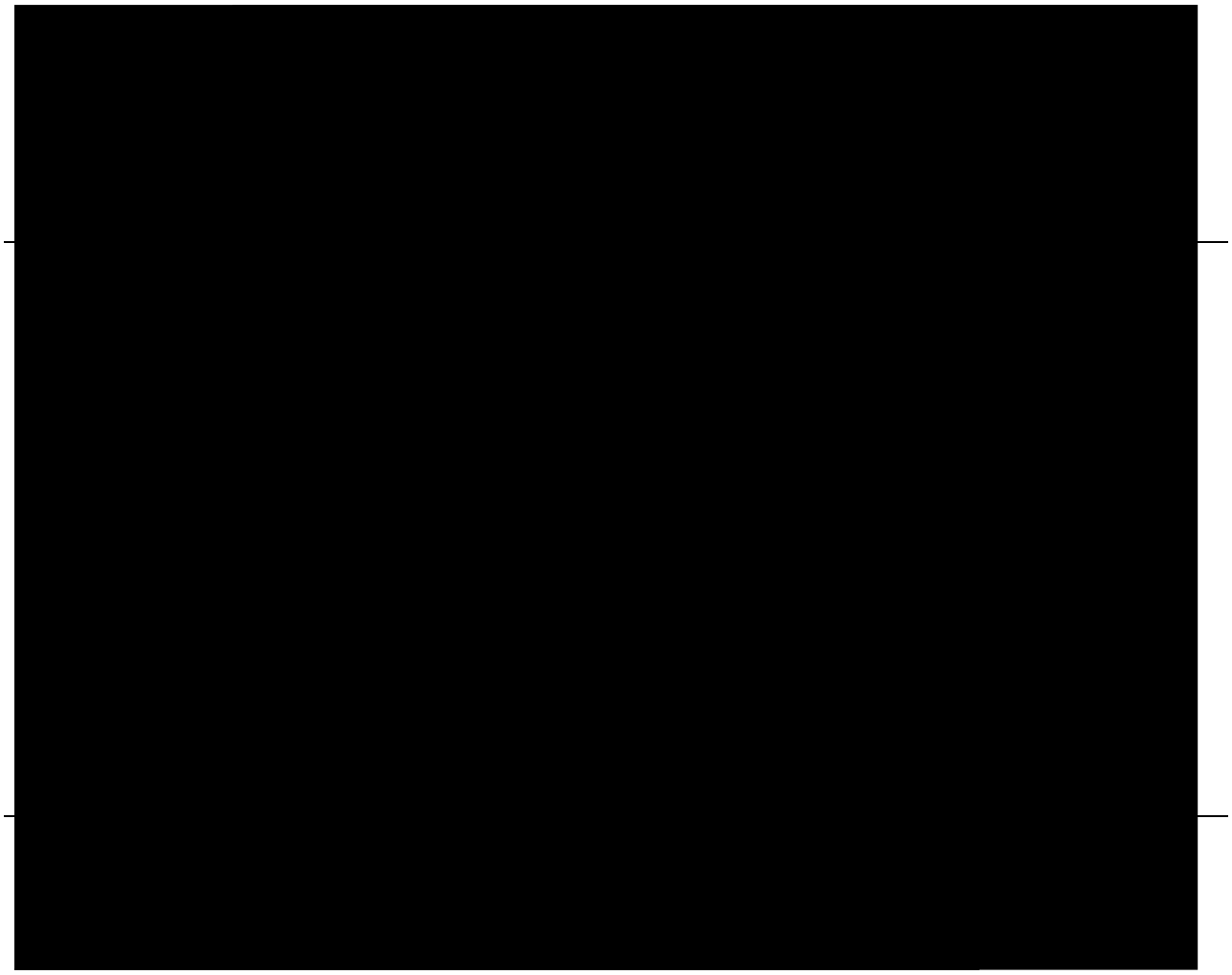
This study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements.

APPROVAL & SIGNATURE PAGE

Protocol No.: RAIN-3202

Version: v1.0

The Statistical Analysis Plan has been reviewed and approved by:



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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
BMI	Body Mass Index
CCP	Centrally Confirmed Population
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EOS	End of Study
FAP	Full Analysis Population
GMI	Growth Modulation Index
MedDRA	Medical Dictionary for Regulatory Activities
MDM2	Mouse Double Minute 2
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event

TP53	Tumor Protein 53
TTP	Time to Progression
WHODrug	World Health Organization Drug Reference List

1. INTRODUCTION

This statistical analysis plan (SAP) outlines the statistical methods to be implemented within the scope of Protocol RAIN-3202 entitled “A Phase 2 Basket Study of Milademetan in Advanced/Metastatic Solid Tumors”. 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 data base lock. Results of the proposed 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 determine the objective response rate (ORR) of treatment with milademetan in patients with advanced/metastatic solid tumors with murine double minute 2 (*MDM2*) gene amplification.

2.2 Secondary Objectives

The secondary objectives are:

- To assess treatment with milademetan for the following efficacy parameters:
    - Duration of response (DOR)
    - Progression-free survival (PFS)
    - Growth modulation index (GMI)
    - Disease control rate (DCR)
    - Overall survival (OS)
- To assess the safety profile of milademetan
- To evaluate patient-reported health-related quality of life with the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire, Core 30 (QLQ-C30)

2.3 Exploratory Objectives

[redacted]

[redacted]

3. STUDY DESIGN OVERVIEW

3.1 Overall Design

This is a Phase 2, multicenter, single-arm, open-label basket study designed to evaluate the safety and efficacy of milademetan in patients with advanced or metastatic solid tumors refractory or intolerant to standard-of-care therapy that exhibit wild-type (WT) tumor protein 53 (*TP53*) gene and *MDM2* copy number (CN) ≥ 8 using prespecified biomarker criteria.

Approximately 65 patients will be enrolled to receive milademetan.

Patients will receive the study drug until reaching disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST] version [v]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). Long-term follow-up will continue every 8 weeks (± 7 days) until the endpoint of death, the patient is lost to follow-up, or for 24 months following the final dose of the 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 ORR. The ORR is defined as the percentage of patients who have achieved a confirmed CR or PR. Tumor response will be assessed in accordance with RECIST v1.1.

4.2 Secondary Endpoints

Secondary efficacy endpoints include:

- The DOR, defined as the time from the date of first response to the date of disease progression or death for patients with an objective response
- The PFS, defined as the time from the date of first dose to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause
- The GMI will be determined using the ratio of time to progression (TTP) with n^{th} line of therapy (TTP_n; here defined as milademetan) to the most recent prior line of therapy (TTP_{n-1})
- The DCR, defined as the percentage of patients who have achieved confirmed CR, PR, or stable disease (SD) for ≥ 16 weeks
- Overall survival, as measured from the date of the first dose of the study drug to the date of death due to any cause

Health-related quality-of-life endpoints include the QLQ-C30.

Safety endpoints include the incidence of TEAEs (including SAEs, TEAEs leading to dose reductions and TEAEs leading to discontinuation of study drug); changes in clinical laboratory parameters (hematology, serum or plasma chemistry), deaths, vital signs, and ECG parameters (especially QT intervals); physical examination results; and use of concomitant medications.

4.3 Exploratory Endpoints

[redacted]

5. ANALYSIS POPULATIONS

5.1 Full Analysis Population

[redacted]

5.2 Centrally Confirmed Population

[redacted]

5.3 Pharmacokinetics (PK) Population

The pharmacokinetics population consists of all patients who have evaluable PK data. Exploratory pharmacokinetics analyses will be performed using the PK population.

6. STATISTICAL METHODS OF ANALYSIS

6.1 General Principles and Reporting Conventions

In general, efficacy and safety analysis in this study will be summarized across all tumor types. Analysis may be performed for specific tumor types when appropriate.

[redacted]

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

6.2 Subject Accountability

6.2.1 Disposition of Patients

The number and percentage of patients who were enrolled and treated with study drug will be tabulated. End of treatment and end of study will be summarized by reasons.

6.3 Demographic and Baseline Characteristics

Demographic data, medical history, concomitant disease, and concomitant medication will be summarized by means of descriptive statistics or frequency tables for the FAP.

6.3.1 Demographic Characteristics

The following demographic variables will be summarized:

- age (years)
- age group (<65, ≥ 65 years)
- sex
- race (Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- height (cm)
- weight (kg)
- body mass index (BMI) calculated as: BMI (kg/m^2) = Weight (kg)/ (Height(cm) * $0.01)^2$

6.3.2 Baseline Disease Characteristics

The following baseline disease characteristics will be summarized:

- ECOG
- Number of prior lines of therapy
- Tumor type
- Stage at initial diagnosis
- Stage at study entry
- TNM stage
- MDM2 copy number (central and local)
- Time from initial diagnosis
- Time from metastatic diagnosis

- Tumor status
- Brain metastases (Present/Absent)

6.3.3 Prior Cancer Therapy

Prior radiation, cancer related surgy, cancer therapy will be summarized with indication. Number of prior lines of therapy for metastatic disease, best response of each line of therapy will be summarized.

6.3.4 Medical History

Medical history data will be summarized in frequency table. 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/ Day1 in accordance with the Schedule of Procedures included in the protocol.

6.3.5 Prior and 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 (WHODrug) dictionary B3 Global March 2021 and summarized in a frequency table.

6.4 Efficacy Analyses

The efficacy analysis of the study will be performed in the CCP. The analysis of ORR and other RECIST endpoints will be according to the investigator's tumor assessments.

6.4.1 Objective Response Rate (ORR)

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

[redacted]

6.4.2 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 progressive disease (PD) or death is objectively documented. Patient is censored at the last valid tumor assessment if PD or death has not been documented.

[redacted]

6.4.3 Progression Free Survival (PFS)

The PFS is defined as the time from the date of the first dose of the study drug to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause according to Investigator assessment. Patients without documented 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 first dose date.

[redacted]

6.4.5 Disease Control Rate (DCR)

The DCR is defined as the percentage of patients with confirmed CR, PR, or SD for at least 16 weeks (+/- 1 week window) according to RECIST v1.1 recorded in the period between the date of first study drug dose and disease progression or death due to any cause.

[redacted]

6.5 Safety Analysis

6.5.1 Overview of Safety Analysis Methods

All safety analysis will be performed for all patients in the Full Analysis Population. The following assessments will be used to evaluate the safety of milademetan:

- Adverse events (AEs)
- Medical history
- Vital sign measurements
- Physical examination findings
- Electrocardiogram (ECG)
- Liver Function Tests results (Hy's law)
- Eastern Cooperative Oncology Group (ECOG) performance status
- Laboratory assessments

6.5.2 Extent of Exposure

Extent of exposure to milademetan will be summarized by total dose, number of cycles, number of dose interruptions and number of dose reductions.

Dose intensity and relative dose intensity for milademetan will also be summarized.

Dose intensity will be calculated as the cumulative dose of the drug divided by total number of scheduled dosing days during the treatment. [redacted]

[redacted]

6.5.1 Concomitant Medications

Concomitant medications will be defined as medications documented on the Concomitant Medications CRF and started on or after the C1D1. Concomitant medications will be coded using the World Health Organization (WHODrug) dictionary B3 Global March 2021 version and summarized in a table.

6.5.2 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 MedDRA v24.0 or later and graded by the Investigator according to the NCI CTCAE v5.0 or later.

Summaries of adverse event will in general focus on treatment emergent adverse events (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.

Subject incidence of the following events will be tabulated:

- All TEAEs
- SAEs
- SAEs not associated with transfusion
- Treatment-related TEAEs

- Treatment-related SAEs
- Grade 3 or 4 TEAEs
- TEAE leading to treatment discontinuation, dose reduction, dose interruption

Listings of TEAEs leading to IP discontinuation, and SAEs will be provided. Listings will be sorted by patient ID and study day; All AE listings will include patient ID, study day, SOC, PT, reported term, 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 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.

6.5.3 Clinical Laboratory Evaluation

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 value and the change from baseline. Additionally, clinically significant abnormalities in laboratory results will be summarized for the post-baseline cycles/visits using frequencies and percentages. Shifts in CTCAE grade between baseline and subsequent visits will be summarized as well.

6.5.4 Vital Signs and Physical Examinations

Vital signs, including systolic and diastolic blood pressure, heart rate, and body temperature, as well as respiration rate will be collected each visit.

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 value and the change from baseline.

Physical examination results will be summarized, and the frequency of clinically significant changes will be tabulated.

6.5.5 Electrocardiograms

The ECG will include heart rate, RR, PR, QRS, and QT intervals. The ECG will be read and interpreted at the investigational site for patient safety monitoring.

[redacted]

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

6.5.6 Liver Function Test Results

A listing will be generated for patients potentially meeting Hy's Law criteria (total bilirubin >= (2xULN) and AST or ALT > (3xULN) 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.

6.5.7 ECOG Performance Status

ECOG performance status will be assessed at Day 1 and Day 15 in Cycles 1 to 3, Day 1 only in Cycles 4 and beyond, 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.

6.6 Pharmacokinetics Analysis

Standard PK parameters will be estimated for milademetan based on available drug concentration data. PK data will be summarized in tables using descriptive statistics at each time point.

6.7 Exploratory Biomarker Analysis

[redacted]

7. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

[redacted]

8. LIST OF PLANNED TABLES

Category	Title
Disposition	Summary of Subject Disposition
Demography and Baseline Characteristics	Summary of Demographics
	Summary of Baseline Disease Characteristics
Medical History	Summary of Medical History
Prior Cancer Therapy	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
Study Medication	Summary of Treatment Exposure
	Summary of Treatment Dose Reduction
	Summary of Treatment Dose Hold
Efficacy	Summary of Objective Response Rate
	Summary of PFS
	Summary of Disease Control Rate
	Summary of GMI
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 Serious 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 Preferred Term
	Incidence of Grade 3 or 4 TEAE by System Organ Class, and Preferred Term

	Summary of Death
Laboratory	Mean and Mean Change from Baseline in Numeric Laboratory Data: Hematology/ Clinical Chemistry/Coagulation/Urinalysis
	Frequency Table of Clinically Significant Laboratory Data: Hematology/ Clinical Chemistry Coagulation//Urinalysis
	Shift from Baseline in Laboratory Data: Hematology/ Clinical Chemistry/ Coagulation/Urinalysis
PK	Summary of Plasma Concentration of Milademetan by Scheduled Time Point
	Summary of PK parameters of Milademetan
Vital Signs	Mean and Mean Change from Baseline in of Vital Signs Data
	Frequency Table of Clinically Significant Vital Signs Data
Physical Exam	Summary of Physical Examination
ECG	Mean and Mean Change from Baseline in ECG Data
	Frequency Table of Clinically Significant Values in ECG
Liver Function	Summary of Liver Function Parameters for Potential Hy's Law
ECOG	Summary of ECOG by Visit

9. LIST OF PLANNED FIGURES

Category	Title
[redacted]	

10. LIST OF PLANNED DATA LISTINGS

Category	Title
Safety	Listing of Serious Adverse Events
	Listing of Adverse Events Leading to Treatment Discontinuation
	Listing of Deaths
	Listing of Potential Hy's Law Cases

11. REFERENCES

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