STUDY RAIN-3201

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
U.S. IND No.:	[redacted]
EudraCT No.:	2021-001394-23
Investigational Drug Name:	Milademetan (RAIN-32)
Phase:	3
Date of Protocol:	18 March 2022
Version Number:	3.1
Version History/Date:	Original (27 April 2021) Version 1.0 (17 May 2021) Version 2.0 (20 May 2021) Version 2.1 United Kingdom (11 August 2021) Version 2.1 Germany (26 August 2021) Version 2.1 Spain (01 September 2021) Version 3.0 (19 January 2022)

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.

STATEMENT OF THE SPONSOR

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

This study was designed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and is consistent with GCP and applicable regulatory requirements. Foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual study patient and society. Review of the available nonclinical and clinical information support this study and the anticipated benefits justify the risks.

The rights, safety, and well-being of the study patients are the most important consideration. While foreseeable risks have been identified, strategies are included to help mitigate both anticipated and unanticipated risks.

This clinical study is scientifically sound, and the study design is clearly described in this

PROTOCOL REVISION HISTORY

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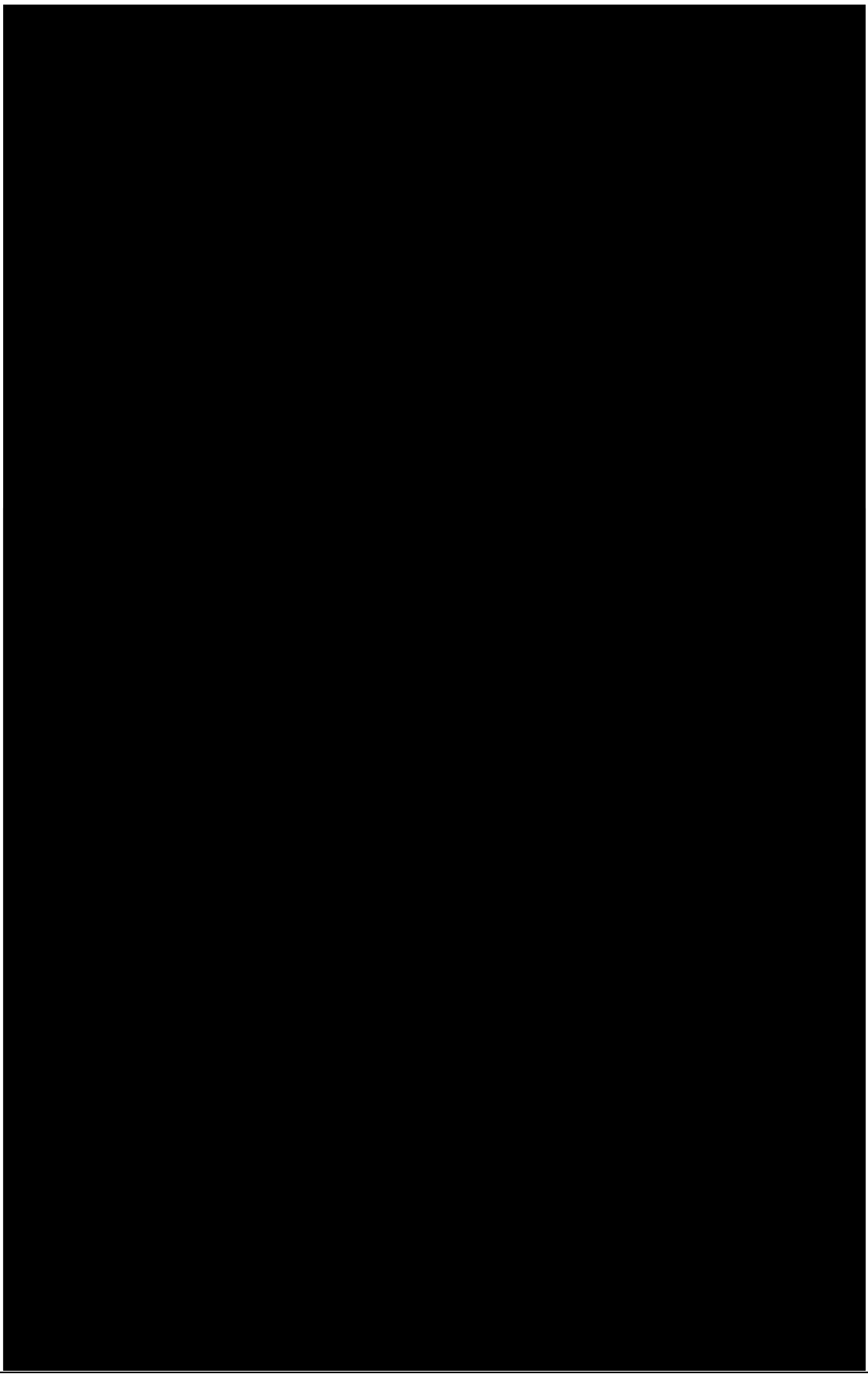

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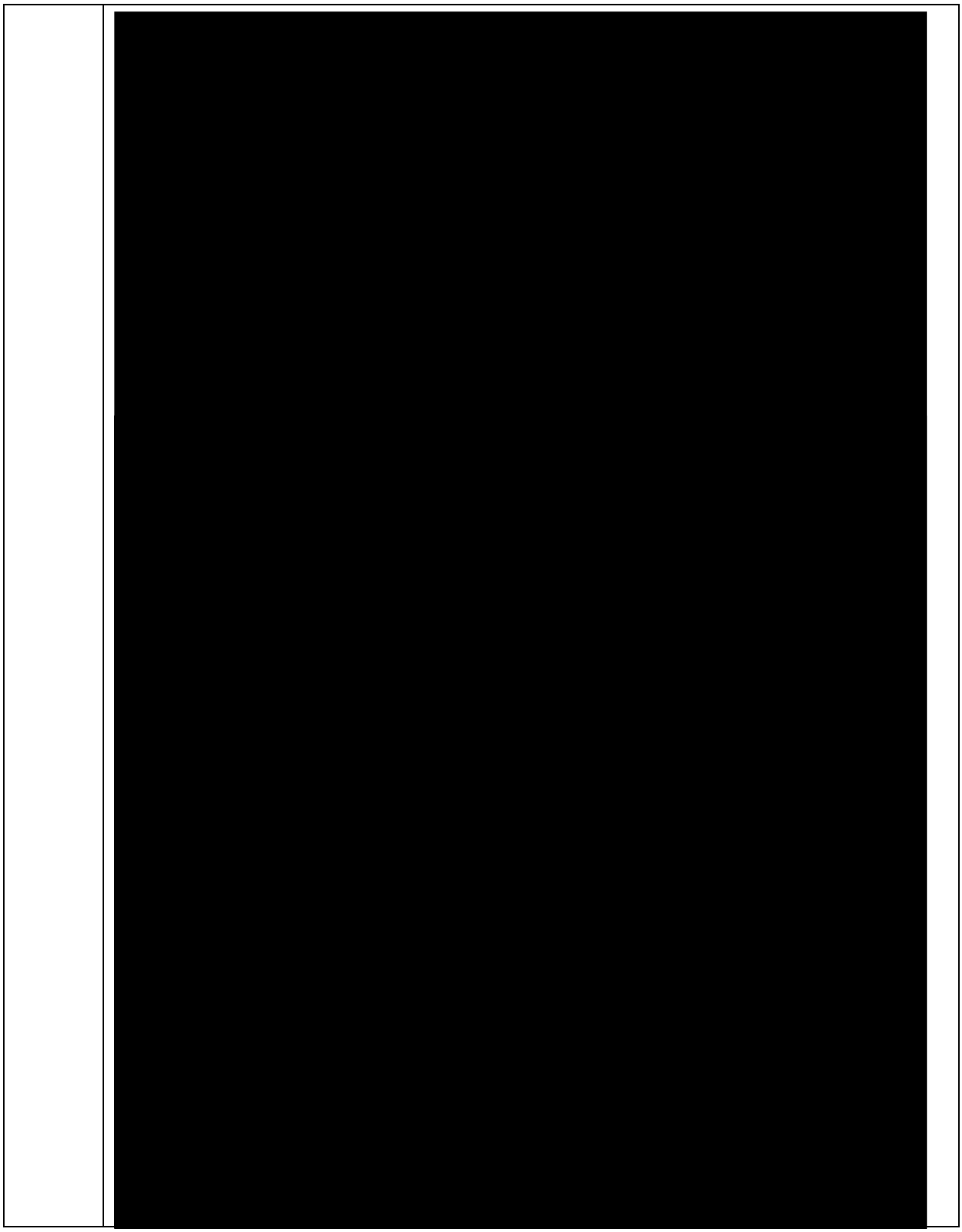


SYNOPSIS

Study Number	RAIN-3201
Sponsor	Rain Therapeutics, Inc.
Phase	3
Study Duration	Estimated to be 4 Years
Objectives	Primary Objective The primary objective is to compare progression-free survival (PFS) between the milademetan treatment arm and trabectedin control arm, 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. Secondary Objectives • To compare the milademetan treatment arm versus the trabectedin control arm for the following efficacy measures: o Overall survival (OS) o Disease control rate (DCR) by BICR and Investigator assessment o Objective response rate (ORR) by BICR and Investigator assessment o Duration of response (DOR) by BICR and Investigator assessment o PFS by Investigator assessment • To assess the safety profile of milademetan • To evaluate patient-reported outcomes of quality of life [redacted]
Study 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. Trabectedin is the chosen active control treatment because it has been approved as a second-line therapy by the United States Food and Drug Administration for patients with liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen. Trabectedin was approved for liposarcoma based on improved PFS. In the current study, the primary endpoint is to compare PFS, as determined by BICR, between patients receiving milademetan versus trabectedin. An independent data monitoring committee (IDMC) will review unblinded safety data during the course of the study and make recommendations to the Sponsor as applicable and outlined in the IDMC charter. Approximately 160 patients will be randomly assigned in a 1:1 ratio to receive milademetan or trabectedin (Figure S1). 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 unequivocal disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST] version 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 first dose of study drug of the last patient enrolled, whichever comes first.

[redacted]

Primary Endpoint: PFS by BICR • For the trabectedin arm (standard of care), median PFS ≤ 3 months • Estimated median PFS = 6 months with milademetan	**Secondary Endpoints:** OS, ORR, DOR, DCR, PFS by Investigator assessment, HRQoL, and safety evaluations

Assumptions:
- Type 1 error = 0.05 assuming a 2-sided test, power = 93.9%
- 1:1 treatment ratio and ~20% dropout rate
- BICR of tumor assessments with RECIST version 1.1
- Final analysis for the primary endpoint will occur after 105 PFS events

BICR = blinded independent central review; DCR = disease control rate; DD = dedifferentiated; DOR = duration of response; HRQoL = health-related quality of life; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; WD = well-differentiated

Intensive ECG and PK Evaluation in a Subgroup of Milademetan-Treated Patients	A subset of approximately 25 patients enrolled across several milademetan (RAIN-32) studies, including the current study, will undergo intensive ECG and PK evaluation at selected study centers. Patients in the ECG/PK subgroup must meet the following criteria to participate in the additional ECG and PK evaluation (if these criteria are not met patients can still participate in the study but will not participate in intensive ECG and PK evaluation): • Has a corrected QT interval (QTc) as calculated according to Fridericia's formula (QTcF) ≤ 450 ms • Does not have atrial fibrillation or atrial flutter • Does not have complete left bundle branch block • Does not have an implanted pacemaker or defibrillator • Does not have a history of Long QT Syndrome, Brugada Syndrome, Wolff Parkinson White Syndrome, or aborted sudden cardiac death In this subset of patients, PK blood samples will be collected on Cycle 1 Day 1 (predose and at 1, 2, 3, 4, 6, 8, and 24 hours after dosing) and Cycle 1 Day 3 (predose and at 1, 2, 3, 4, 6, 8, and 24 hours after dosing). Patients will wear continuous 12-lead Holter recorders from 1 hour before their milademetan dose through 24 hours after their dose on Cycle 1 Day 1 and Cycle 1 Day 3. Each ECG will be extracted from a supine rest period of at least 10 minutes. The PK samples will be collected immediately after the supine rest period.

Investigational Treatment (Milademetan)	[redacted] **Dose and Mode of Administration:** 260 mg once daily (QD) on Days 1 to 3 and Days 15 to 17 of each 28-day cycle.
Reference Therapy (Trabectedin)	**Formulation and Packaging:** 1 mg sterile lyophilized powder in single-dose glass vials. Trabectedin will be procured locally and prepared for intravenous (IV) infusion per manufacturer's instructions. **Dose and Mode of Administration:** Trabectedin administered at 1.5 mg/m^2 body surface area as a 24-hour IV infusion, every 3 weeks through a central venous line. **Dose Modification due to Toxicity:** Follow dose modification guidelines for trabectedin as described in the approved label.
Eligibility	**Inclusion Criteria** Each patient must meet all of the following criteria to be enrolled in the study: 1. Is a male or female patient ≥ 18 years old 2. Has a signed and dated informed consent form prior to the start of any study specific qualification procedures 3. Has histologically confirmed DD liposarcoma, with or without a WD component (WD/DD liposarcoma), by local pathologic review; central pathologic review will also be performed but is not required for inclusion [redacted] d 4. Has documented advanced unresectable (i.e., where resection is deemed to cause unacceptable morbidity or mortality) and/or metastatic WD/DD liposarcoma 5. [redacted] 6. Has resolution of any clinically relevant toxic effects of prior chemotherapy, surgery, radiotherapy, or hormonal therapy [redacted] 8. Has an ECOG performance status of 0 or 1 9. Has adequate bone marrow function, defined as: a. Platelet count ≥ 100 × 10^9/L b. Hemoglobin ≥ 9.0 g/dL c. Absolute neutrophil count ≥ 1.5 × 10^9/L 10. Has adequate renal function, defined as creatinine clearance ≥ 30 mL/min, as calculated using the modified Cockcroft-Gault equation (or equivalent glomerular filtration rate calculated using the Chronic Kidney Epidemiology Collaboration formula) 11. Has adequate hepatic function, defined as: a. Alanine aminotransferase and aspartate aminotransferase ≤ 3 × upper limit of normal (ULN) if no liver metastases are present; ≤ 5 × ULN if liver metastases are present

b. Total bilirubin ≤ 1.5 × ULN. Patients with Gilbert's disease who have serum bilirubin level ≤ 3x ULN, may be enrolled

12. Is willing and able to comply with the protocol requirements
13. Patients requiring anticoagulation medication should be on a stable regimen, defined as at least 4 weeks on the same dose
14. Patients requiring antihypertensive medication should be on a stable regimen, defined as at least 4 weeks on the same dose
15. If a woman of childbearing potential, must have a negative serum pregnancy test at screening and a negative urine pregnancy test on Cycle 1 Day 1 before receiving her first dose of study drug or within 72 hours of the first dose of study drug

[redacted]

16. If a male patient, is surgically sterile, willing to use a condom, or remain abstinent upon randomization through the Treatment Period and for 5 months after the final dose of study drug.

[redacted]

Exclusion Criteria

A patient who meets any of the following criteria will not be eligible to participate in the study:

1. Has received prior treatment with any mouse double minute 2 (MDM2) inhibitor or trabectedin
2. Has other primary malignancies that have required systemic antineoplastic treatment within the previous 2 years, except for localized cancers that have apparently been cured (e.g., nonmelanoma skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast) and will not interfere with the study outcomes
3. Has gastrointestinal conditions that could affect the absorption of milademetan, in the opinion of the Investigator
4. Has an uncontrolled infection within the last 7 days from randomization requiring IV antibiotics, antivirals, or antifungals
5. Has known HIV infection or active hepatitis B or C infection
6. Has untreated brain metastases

[redacted]

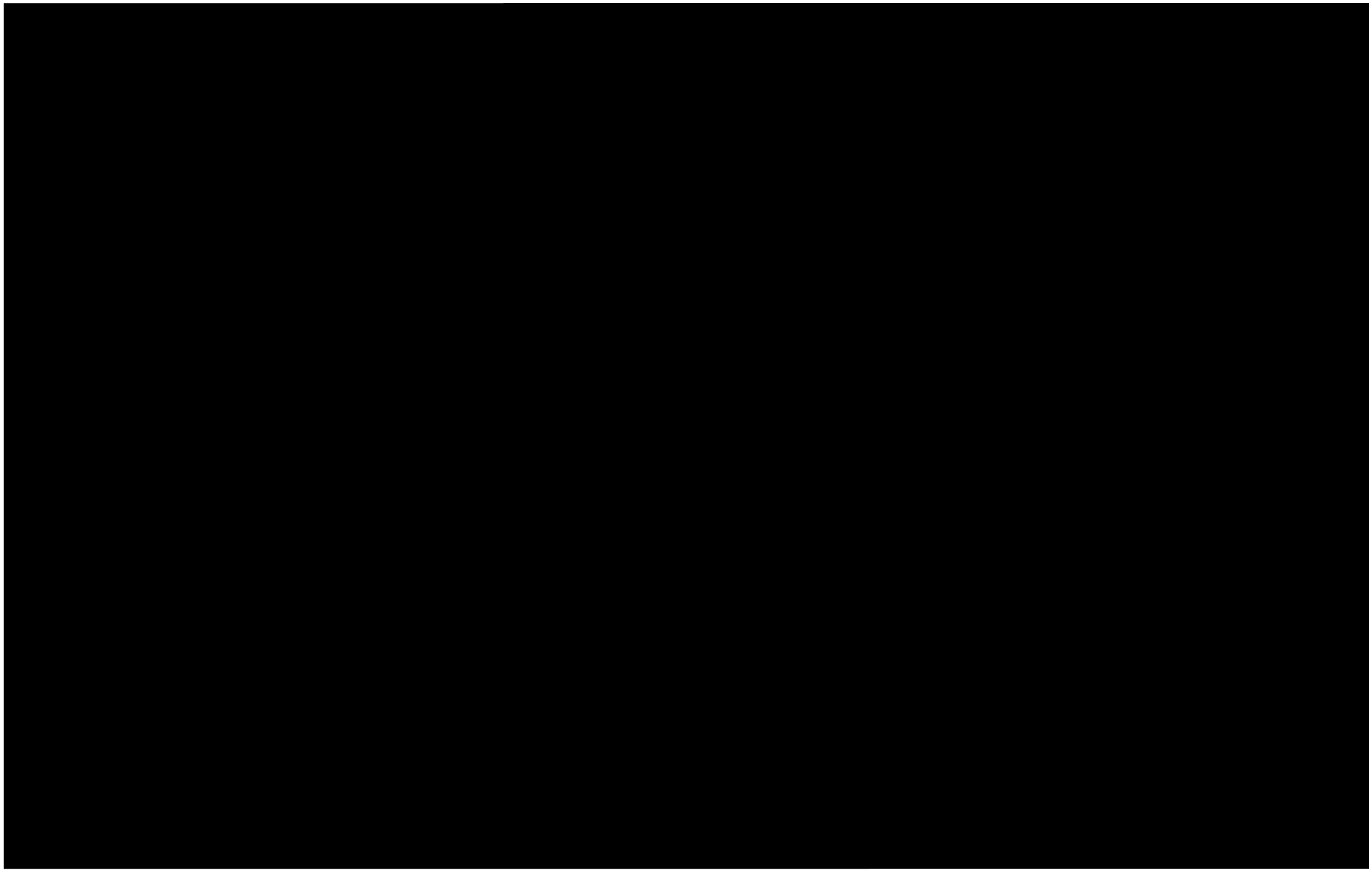
	7. Has not met the minimum washout period before randomization, defined as: a. Cytochrome P450 (CYP) 3A4 isozyme strong inhibitor: 5 elimination half-lives of the inhibitor b. CYP3A strong or moderate inducers (e.g., St. John's wort and modafinil): 4 weeks c. Systemic anticancer therapy (chemotherapy; small molecules, including antibody drug therapy; retinoid therapy; or hormonal therapy) or investigational therapy: 3 weeks or 5 half-lives, whichever is shorter d. Immunotherapy with checkpoint inhibitor: 4 weeks 8. Has had major surgery ≤ 3 weeks from randomization 9. Has had curative-intent radiation therapy ≤ 4 weeks or palliative radiation therapy, defined as ≤ 30 Gy in ≤ 10 fractions (e.g., 20 Gy in 5 fractions or 8 Gy in 1 fraction) ≤ 2 weeks from randomization 10. Has uncontrolled or significant cardiovascular disease, including: a. QTcF at rest, where the mean QTcF interval is > 480 milliseconds (average of triplicate electrocardiograms [ECGs]) b. Myocardial infarction within 6 months prior to screening c. Uncontrolled angina pectoris within 6 months prior to screening d. New York Heart Association Class 3 or 4 congestive heart failure e. Uncontrolled hypertension (resting systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg) 11. Is a female who is pregnant or breastfeeding or intends to become pregnant during the study 12. Has a concomitant medical condition that would interfere with the assessment of efficacy or increase the risk of toxicity, in the opinion of the Investigator or Sponsor
Criteria for Efficacy Evaluation	The primary efficacy endpoint is PFS defined as the time from randomization to the earliest date of the first objective documentation of radiographic disease progression as determined by BICR or death due to any cause. The results of the BICR will provide data for statistical analysis of the primary endpoint of PFS and the secondary endpoints of DCR, ORR, and DOR. Investigator's assessment will also be applied for the secondary efficacy endpoints of PFS, DCR, ORR, and DOR. Additional secondary efficacy endpoints include OS and health-related quality of life (HRQoL). Tumor assessments via imaging (computed tomography scans or magnetic resonance imaging) will be performed by both the Investigator and a blinded central review committee; the evaluation of tumor response will be based on RECIST version 1.1. The primary efficacy endpoint is to compare PFS, as determined by BICR, between patients receiving milademetan versus trabectedin. However, the decision to discontinue study drug for disease progression will be determined locally by the Investigator. Tumor response evaluations will be performed at screening; at the end of Week 8, Week 16, Week 24, and Week 32; and then every 12 weeks (± 1 week [7 days]) while the patient remains on study drug and any other time during the study as clinically indicated. In accordance with RECIST version 1.1, response (partial response [PR] and complete response [CR]) must be confirmed by a subsequent tumor assessment at least 4 weeks after the initial observed response. The secondary endpoints OS, DCR (BICR and Investigator), ORR (BICR and Investigator), and DOR (BICR and Investigator) and PFS by Investigator assessment are defined as: • OS: as measured from the date of randomization to the date of death by any cause

	• DCR: the percentage of patients who achieve CR, PR, or stable disease (SD) for ≥ 16 weeks • ORR: the percentage of patients who achieve a confirmed CR or PR • DOR: the time from date of first response to date of disease progression or death • PFS: the time from randomization to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause HRQoL will be evaluated using: • European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30 (QLQ-C30)
Criteria for PK Evaluation	[redacted]
Exploratory Evaluations	
Criteria for Safety Evaluation	Safety assessments include treatment-emergent AEs (TEAEs) (including serious AEs, TEAEs leading to discontinuation of study drug, and TEAEs leading to study withdrawal); changes in clinical laboratory parameters (hematology, serum chemistry, coagulation, and serum and urine pregnancy tests), deaths, vital signs, and ECG parameters; physical examination results (including ECOG performance status); and use of concomitant medications. All AEs will be graded according to NCI CTCAE version 5.0.
Statistical Methods	[redacted]

	[redacted]

	[redacted]

SCHEDULES OF EVENTS



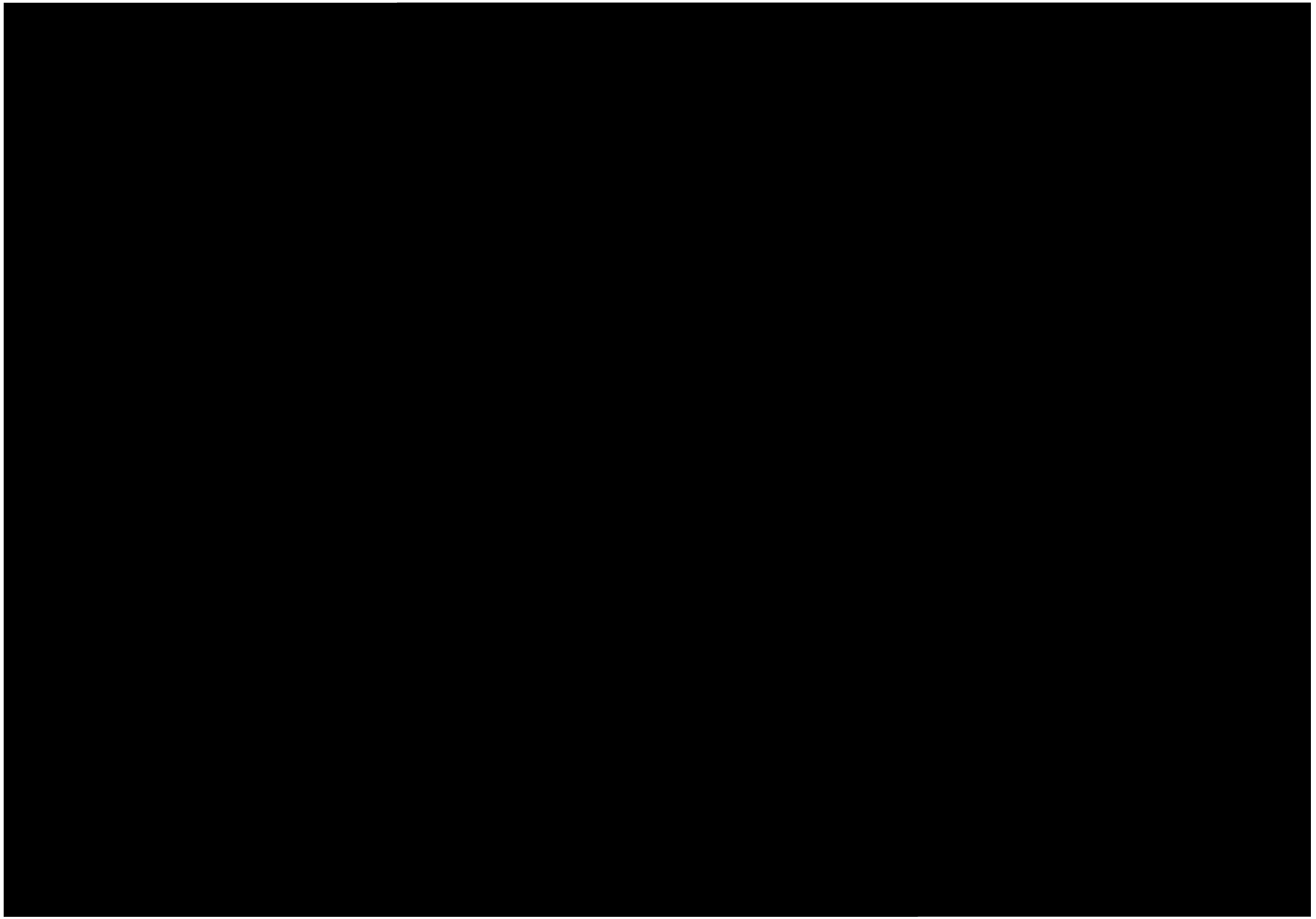
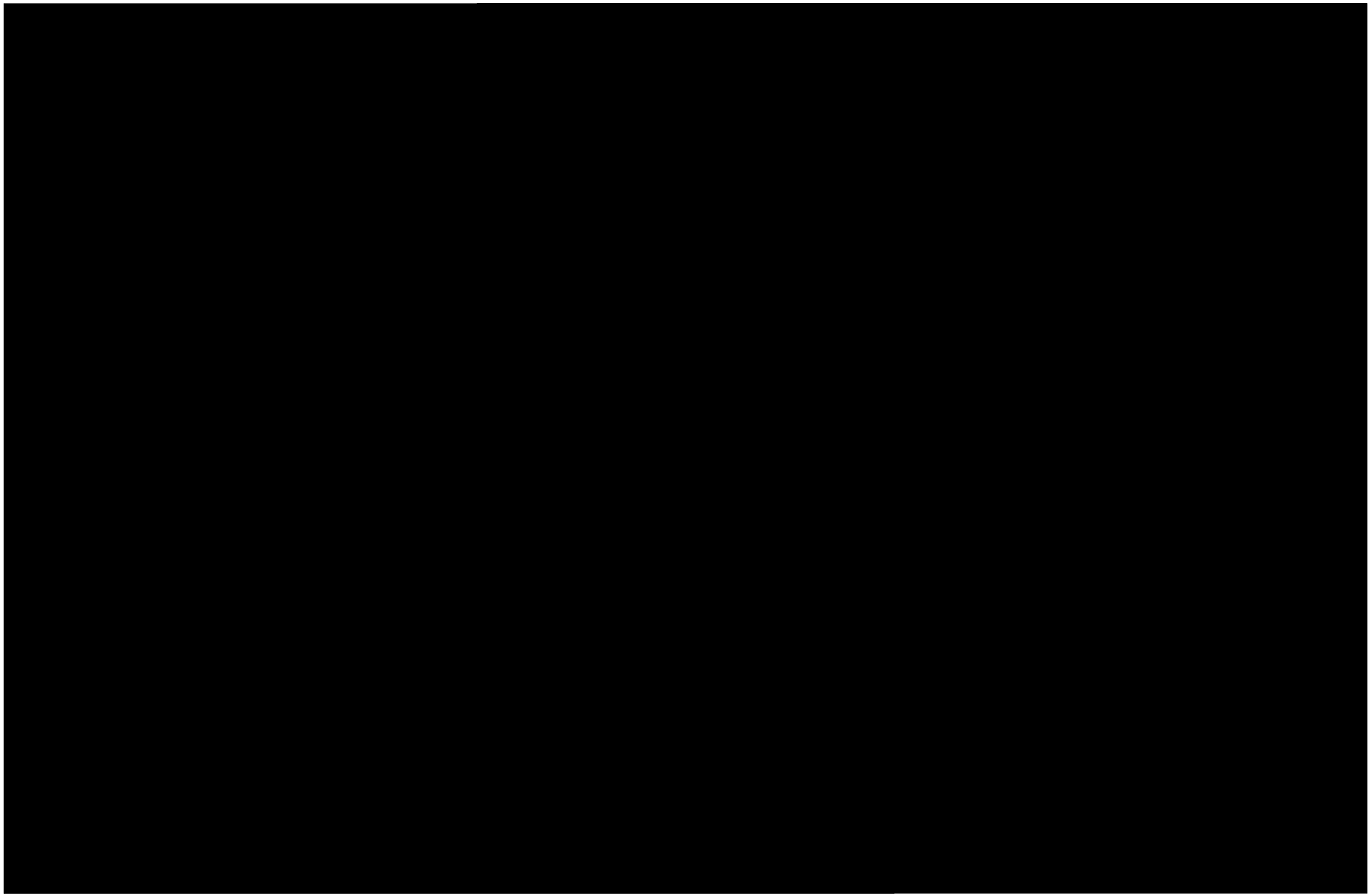
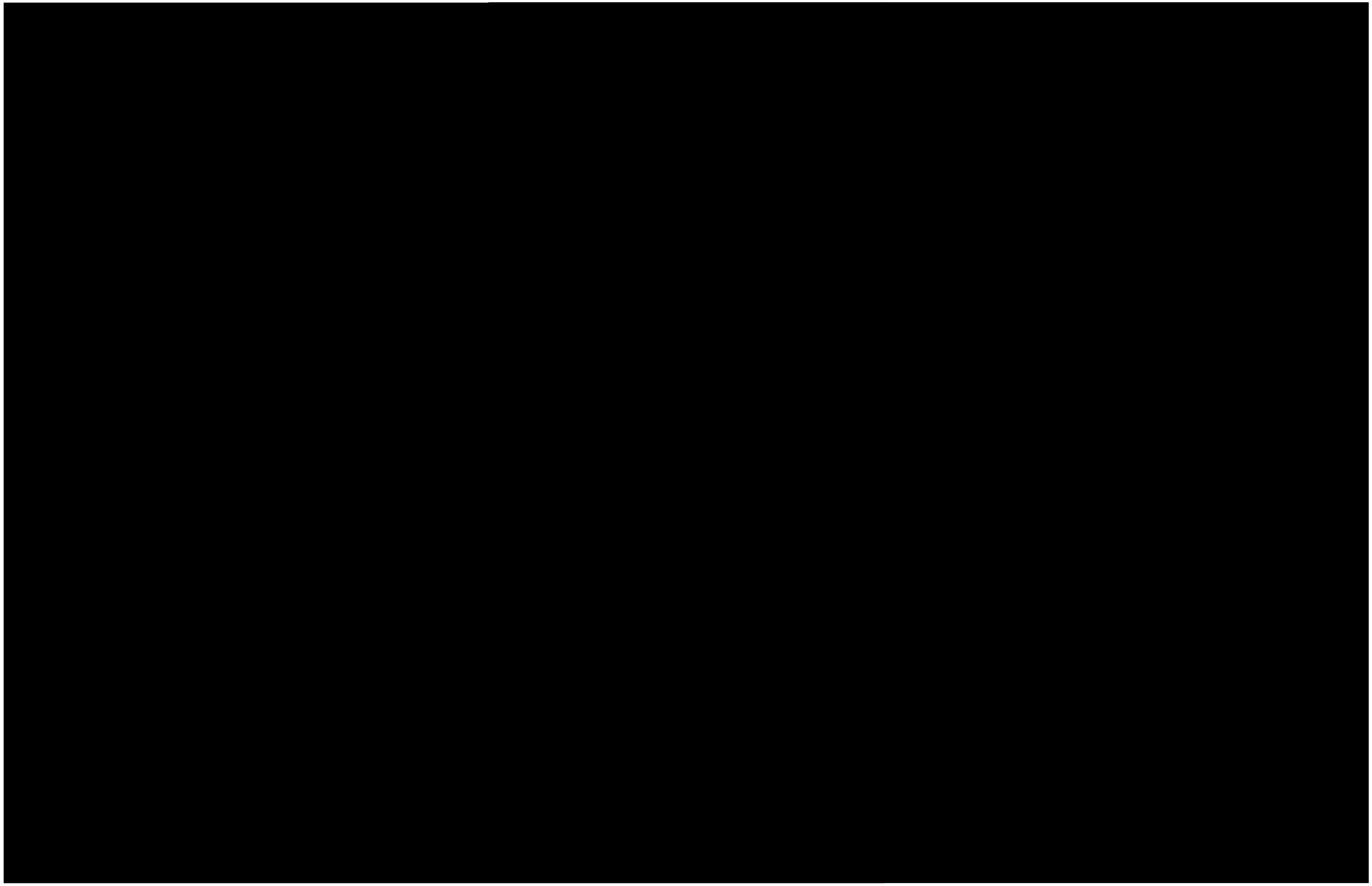


Table 2: Blood Sample Collection Schedule for Laboratory Assessments — Milademetan Arm





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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Definition
5-AZA	5-azacitidine
AE	Adverse event
AML	Acute myeloid leukemia
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-}24h}$	Area under the curve from time 0 to 24 hours after dosing
BCRP	Breast cancer resistance protein
BICR	Blinded independent central review
BSA	Body surface area
CFU-GM	Colony-forming unit granulocyte/macrophage
CFR	Code of Federal Regulations
C_{max}	Maximum peak plasma concentration
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
DCR	Disease control rate
DD	Dedifferentiated
DDI	Drug-drug interaction
DOR	Duration of response
EC_{50}	Half-maximal response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure in utero
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End-of-treatment
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
FSH	Follicle stimulating hormone
GLP	Good Laboratory Practice
HNSTD	Highest non-severely toxic dose

Abbreviation or Specialist Term	Definition
HRQoL	Health-related quality of life
IC_{50}	50% inhibitory concentration
IC_{75}	75% inhibitory concentration
IC_{90}	90% inhibitory concentration
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IRB	Institutional review board
IRR	Infusion-related reactions
IV	Intravenous
Ki	Inhibition constant
MIC-1	Macrophage inhibitory cytokine 1
MDM2	Mouse double minute 2
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect level
NOD SCID	Nonobese diabetic/severe combined immunodeficiency
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PR	Partial response
QD	Once daily
QLQ-C30	Quality of Life Questionnaire, Core 30
QTc	Corrected QT interval
QTcF	Corrected QT interval as calculated according to Fridericia's formula
QWBA	Quantitative whole-body autoradiography
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease

Abbreviation or Specialist Term	Definition
TEAE	Treatment-emergent adverse event
TP53	Tumor protein 53
ULN	Upper limit of normal
WD	Well-differentiated
WOCBP	Women of childbearing potential
WT	Wild-type

1. INTRODUCTION

Milademetan (RAIN-32) is an orally bioavailable small-molecule inhibitor of mouse double minute 2 (MDM2) that disrupts the interactions between MDM2 and the tumor suppressor protein p53. Milademetan is currently being developed by Rain Therapeutics, Inc. (hereafter referred to as Rain) for the treatment of patients with liposarcoma and advanced/metastatic solid tumors with *MDM2* gene amplification. Milademetan was initially developed by Daiichi Sankyo as an oral oncology therapeutic agent for use alone or in combination with other agents.

The current study is a randomized, multicenter, open-label, Phase 3 registration study designed to evaluate the safety and efficacy of milademetan in patients with unresectable and/or metastatic well-differentiated (WD)/dedifferentiated (DD) liposarcoma. Liposarcoma is a malignant life-threatening mesenchymal tumor accounting for almost 20% of adult mesenchymal tumors. It can be found anywhere in the body, but most commonly in the extremities and retroperitoneum; WD and DD liposarcomas comprise the largest subgroups (60%-66%) of liposarcomas.

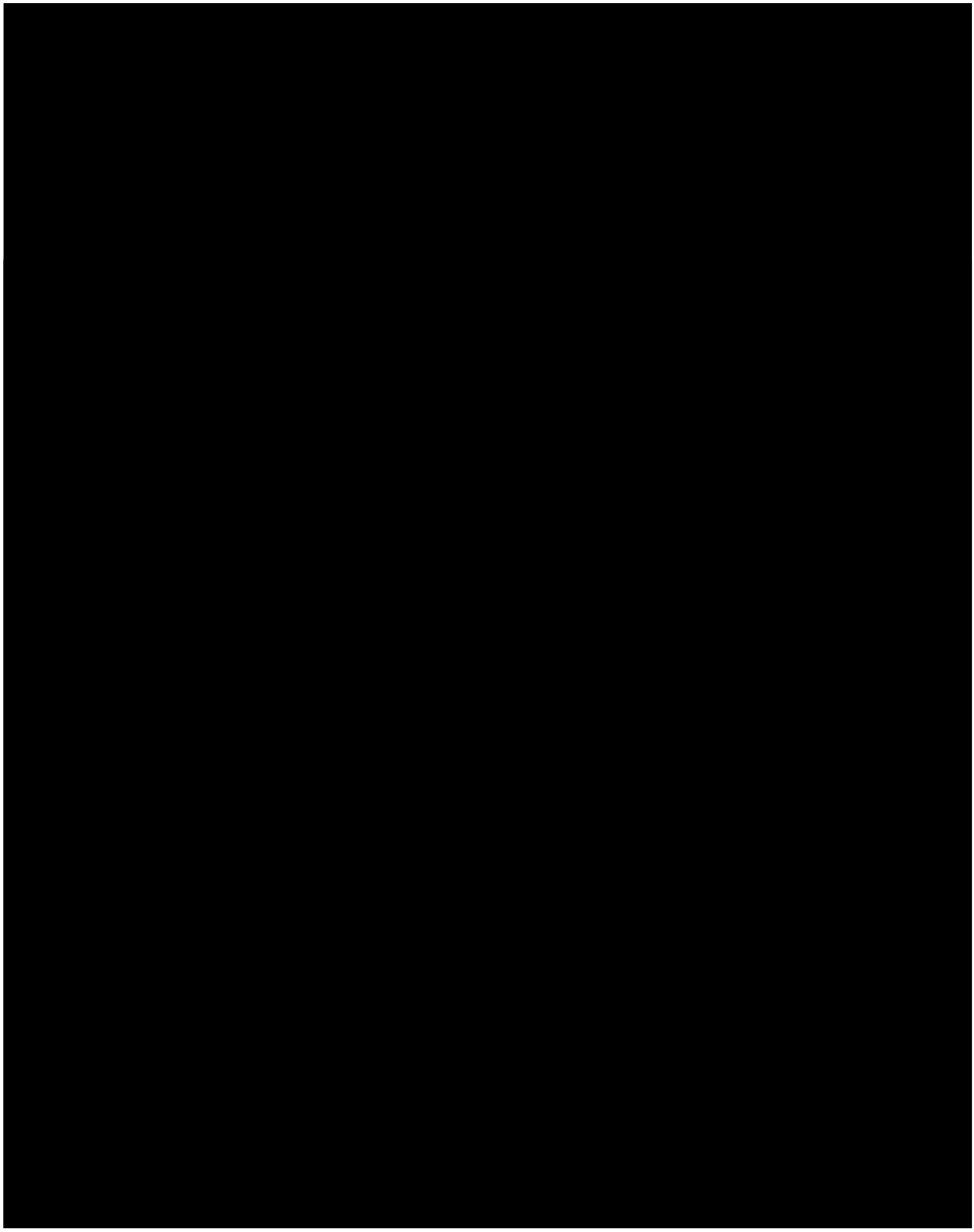
Milademetan disrupts the MDM2-p53 interaction and prevents excessive degradation of p53, a tumor suppressor protein (Noguchi 2019). The mechanism of action is distinct from other chemotherapeutic agents that are currently approved for liposarcoma (trabectedin and eribulin). Trabectedin (an alkylating agent) and eribulin (a microtubule inhibitor), have received full approval from the Food and Drug Administration (FDA) for an indication inclusive of that being sought for milademetan (patients with unresectable or metastatic liposarcoma who progressed on at least 1 prior systemic therapy including at least 1 anthracycline-containing regimens). Notably, no drugs are specifically approved for the WD or DD subtypes of liposarcoma, distinct subtypes of liposarcoma with unique molecular features (*MDM2* amplification) not prevalent in the other subtypes of liposarcoma (myxoid/round cell, and pleomorphic). WD and DD liposarcomas are biologically distinct from other subtypes of liposarcoma in that they are characterized by *MDM2* amplification in up to 100% of cases (Abeshouse 2017).

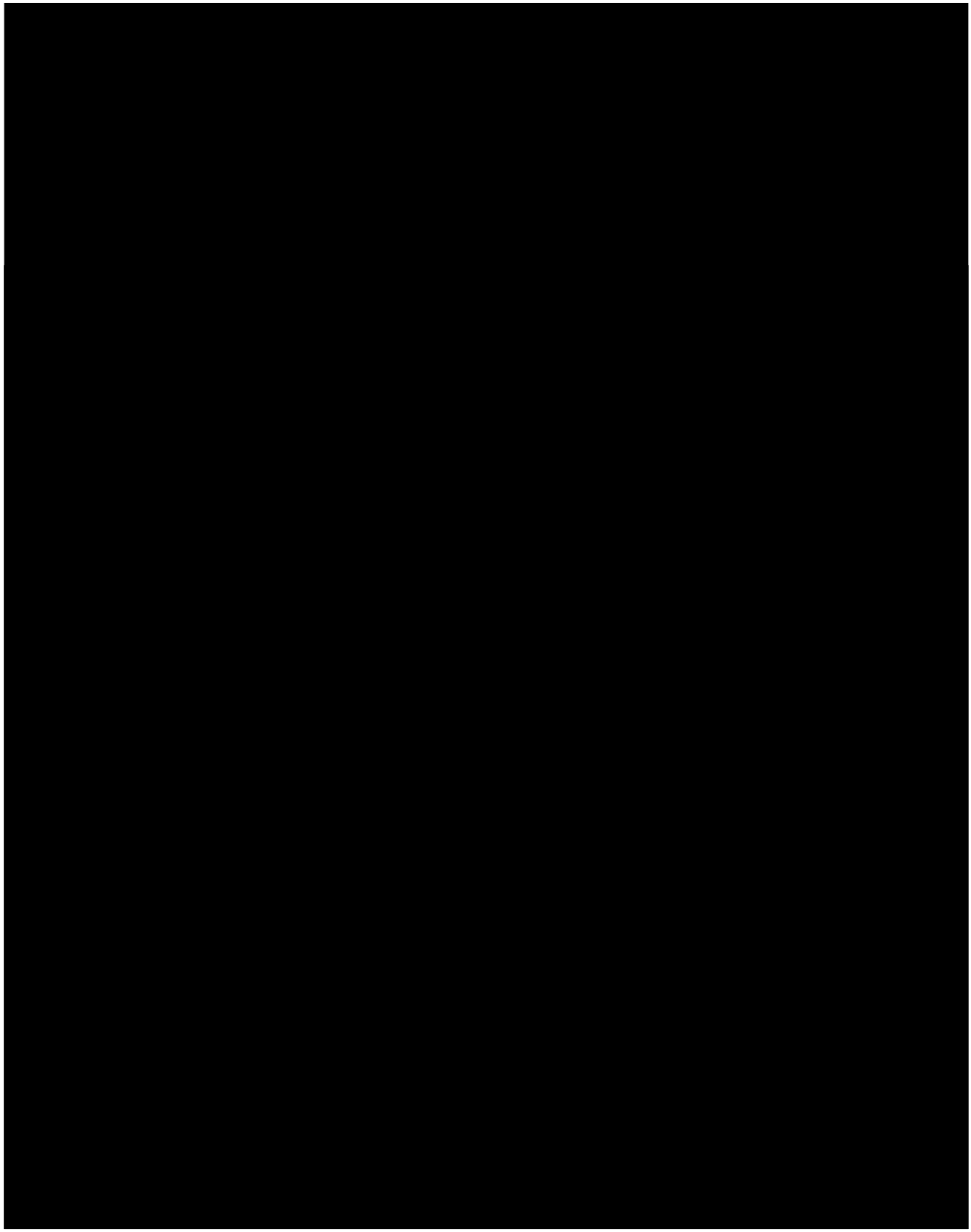
2. BACKGROUND INFORMATION

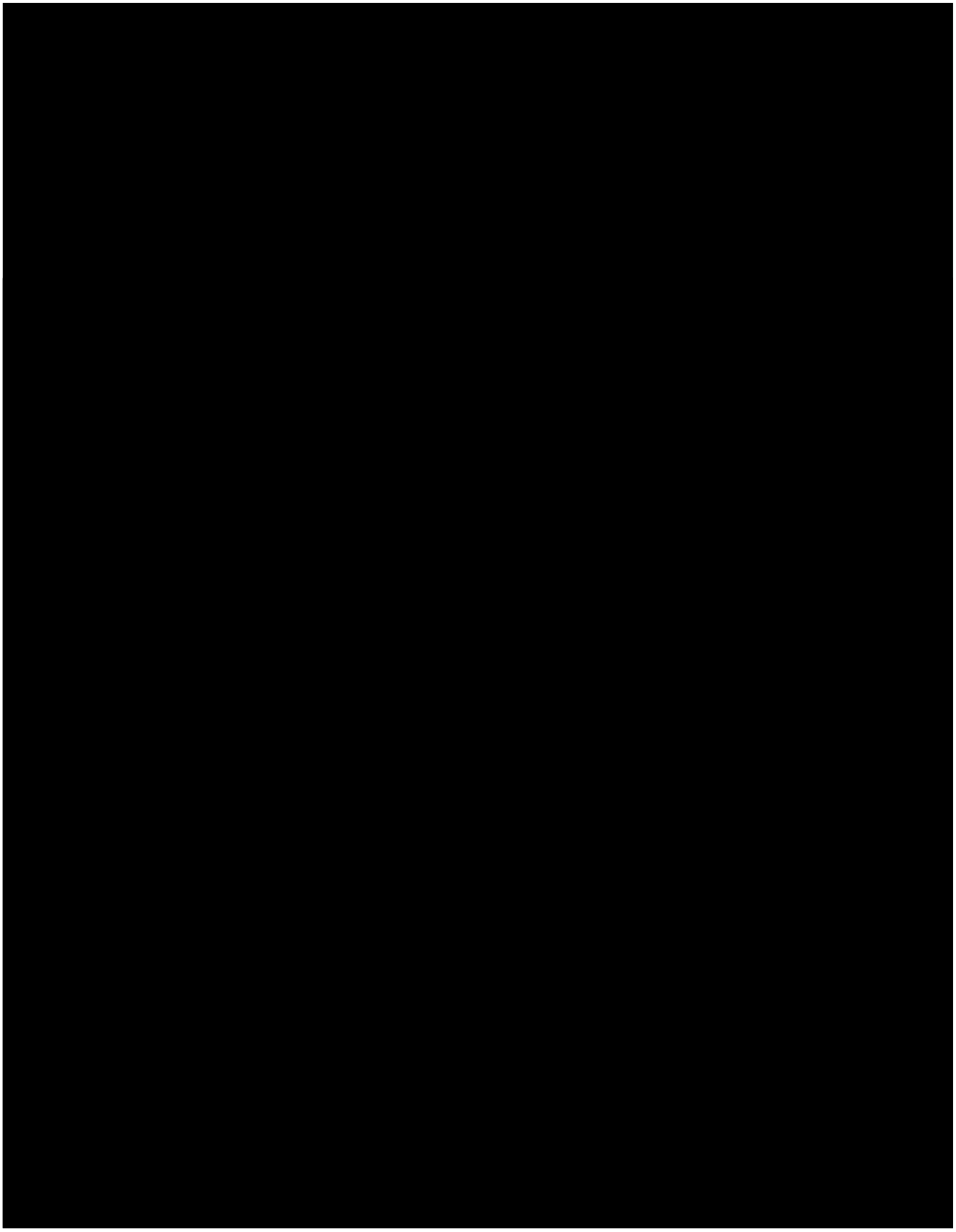
2.1 Investigational Product: Milademetan

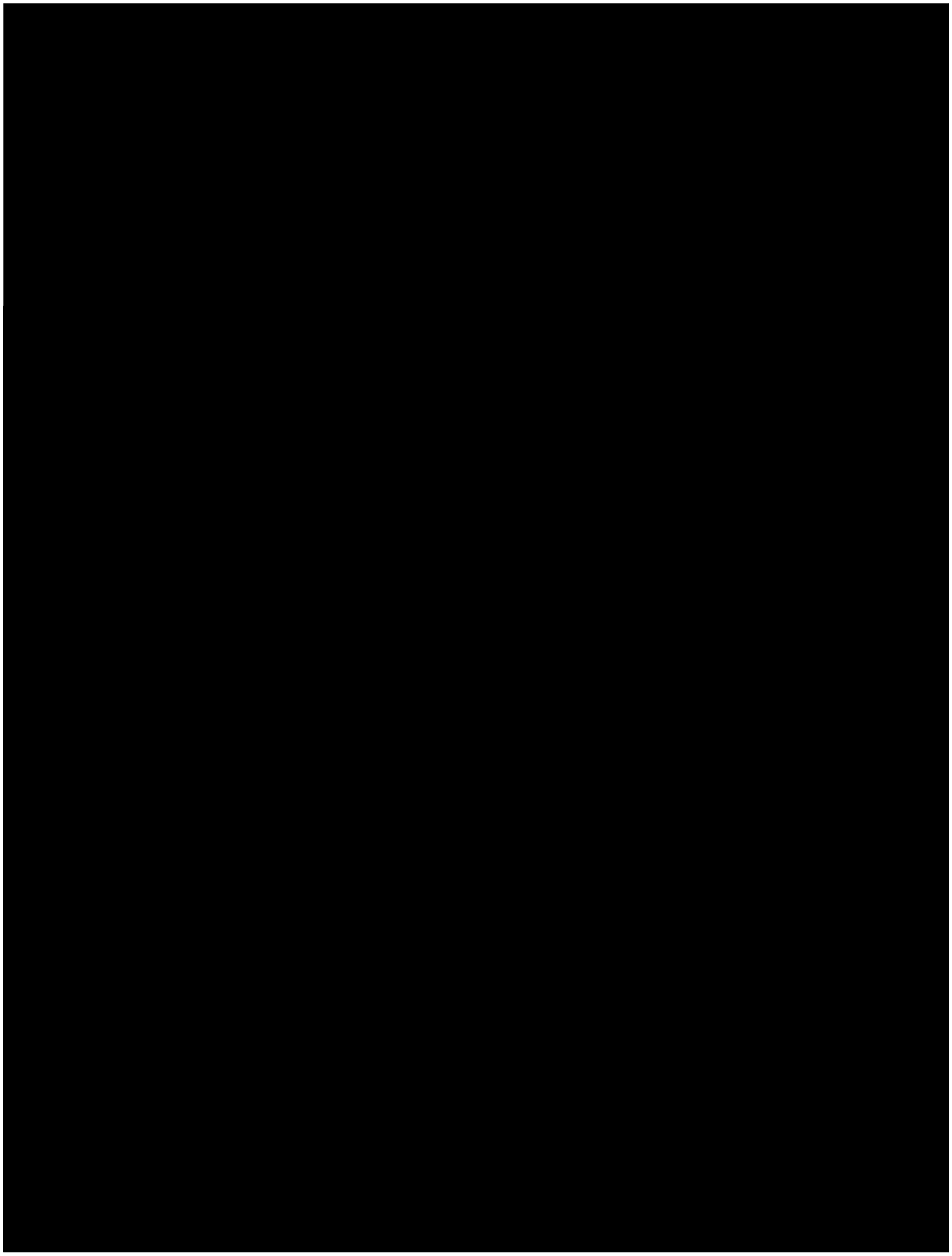
Milademetan is provided as 30-mg and 100-mg, immediate-release capsules for oral administration. A dosing regimen of 2 capsules of each strength is orally administered to obtain total daily dosage of 260 mg QD administered on Days 1 to 3 and Days 15 to 17 of each 28-day cycle.

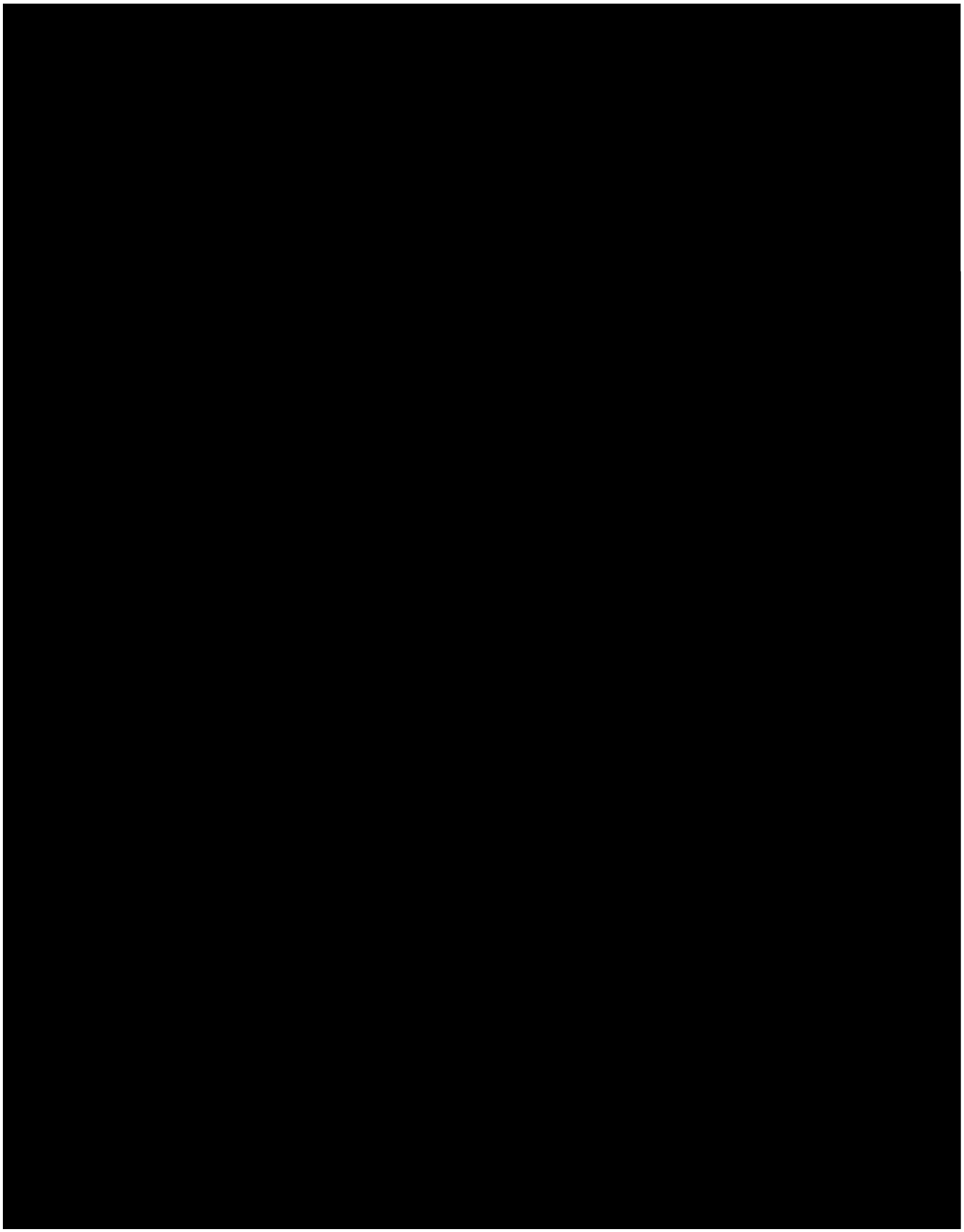
Information on the milademetan packaging, labeling, accountability, and storage instructions will be provided in the Pharmacy Manual.

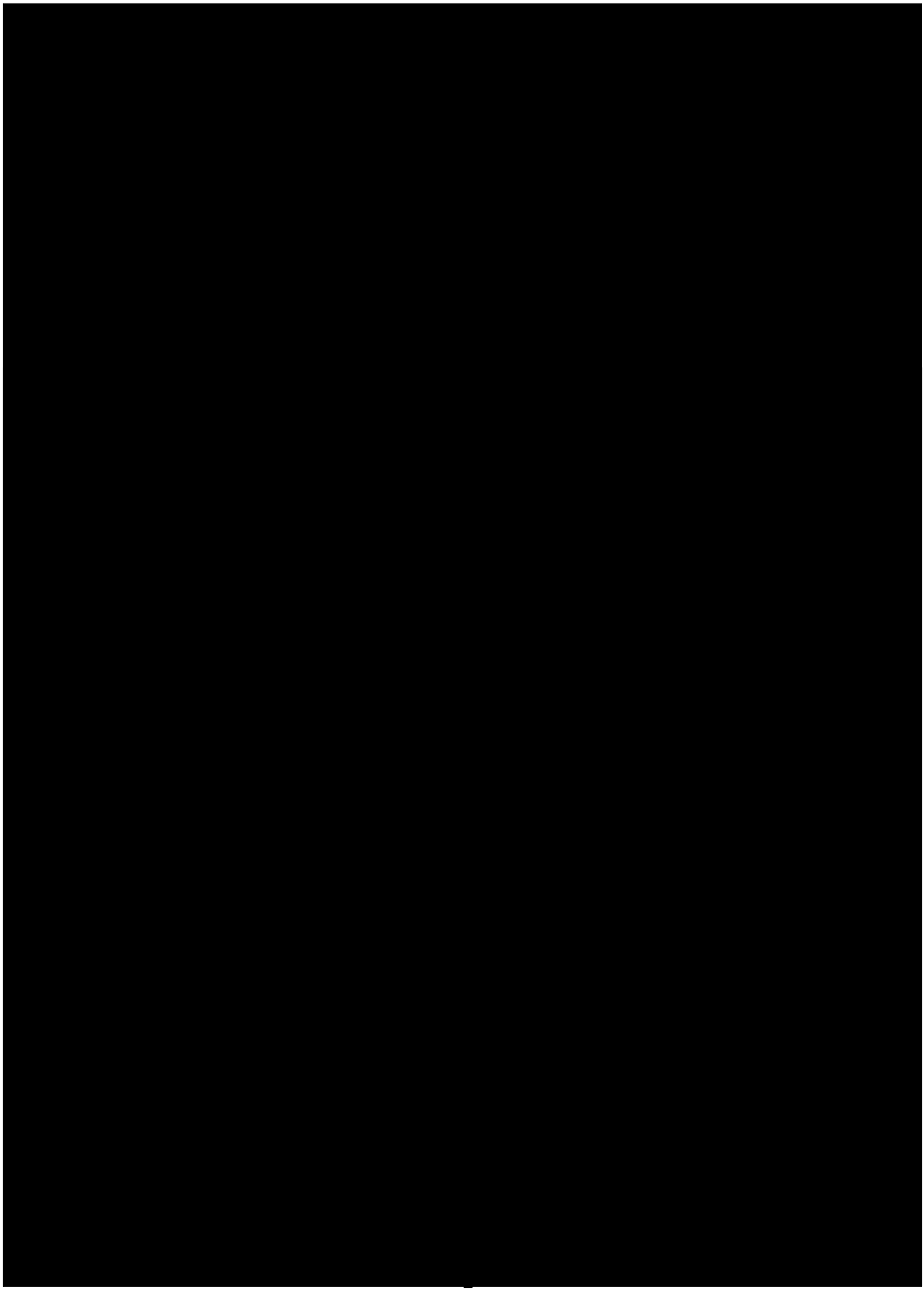


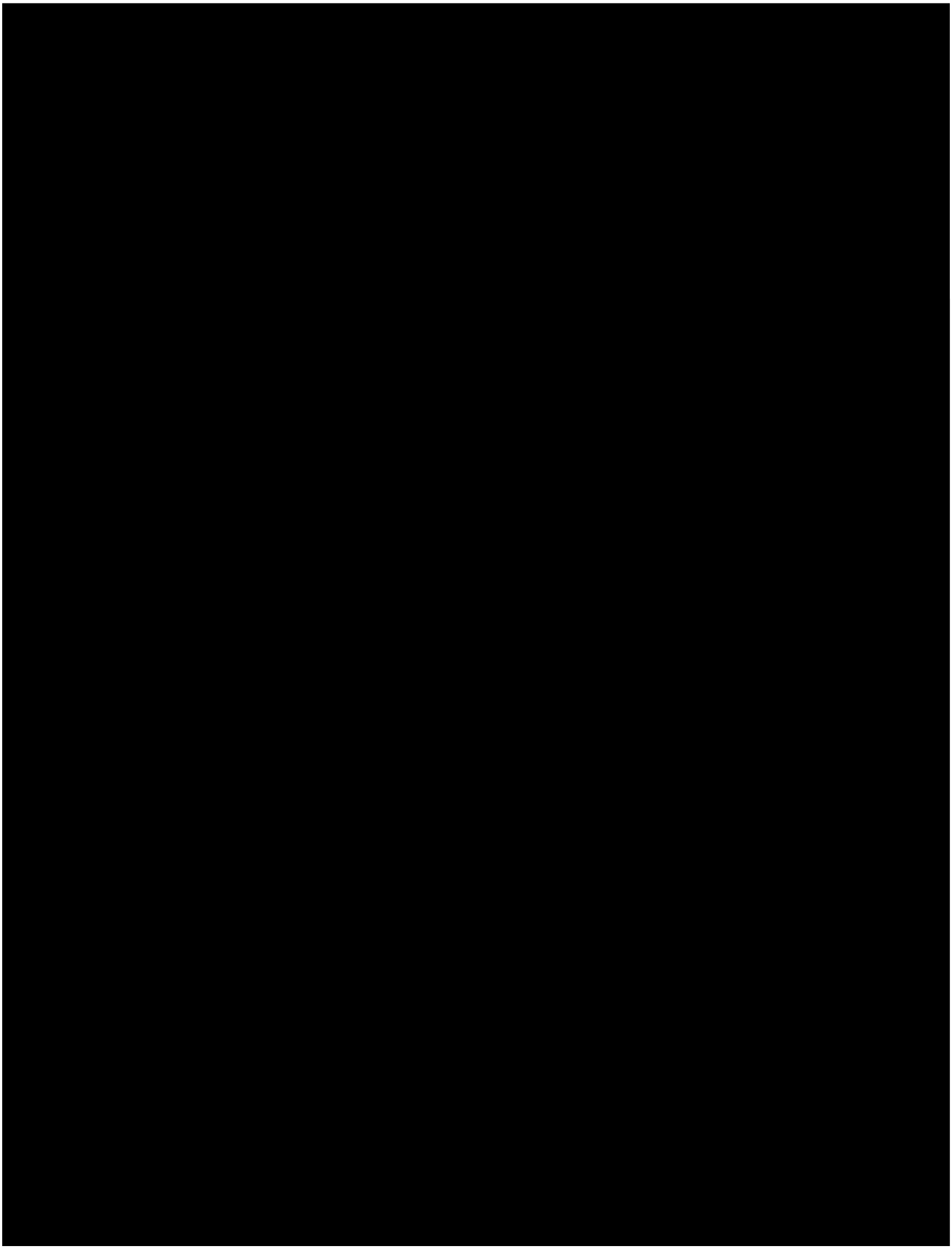


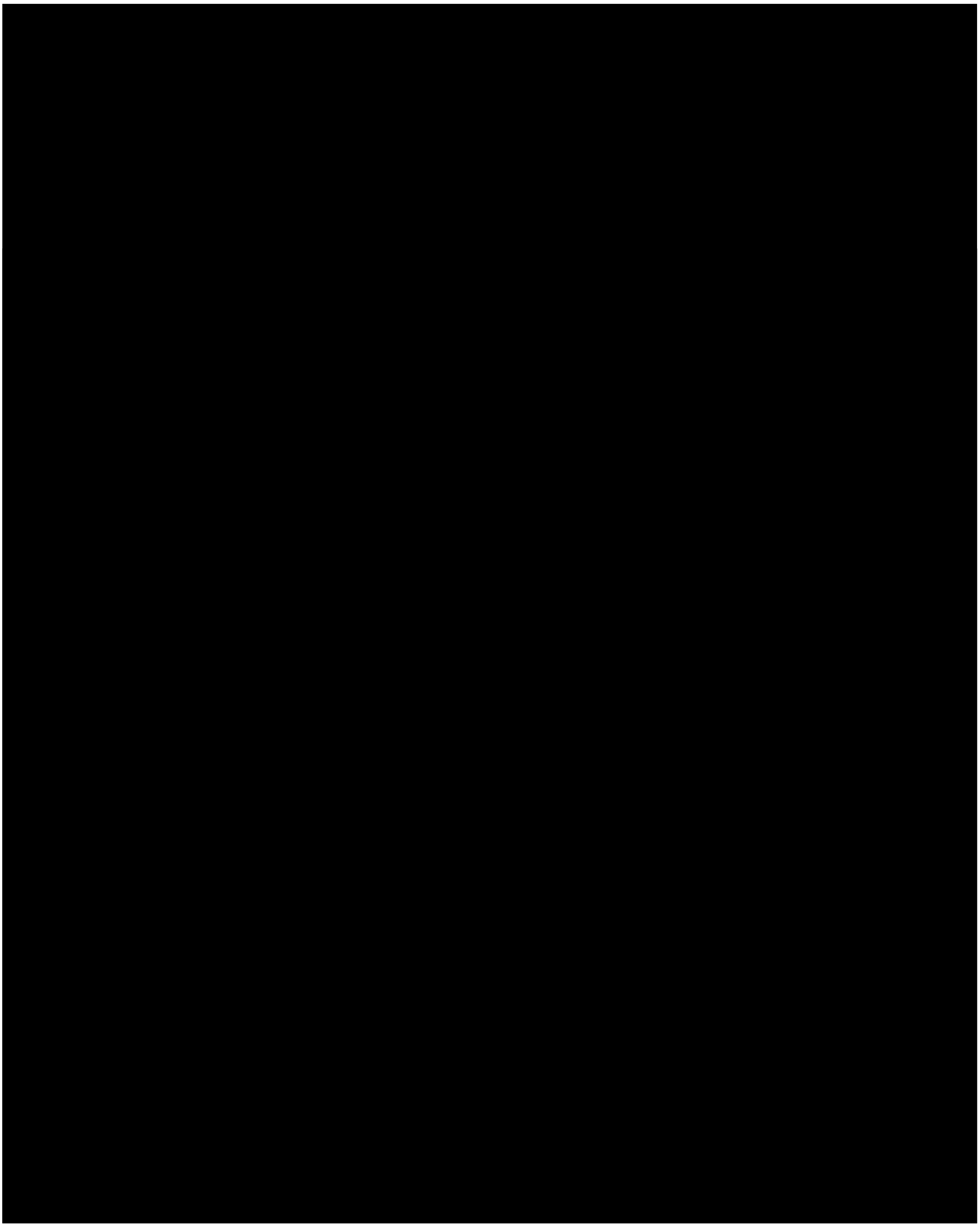


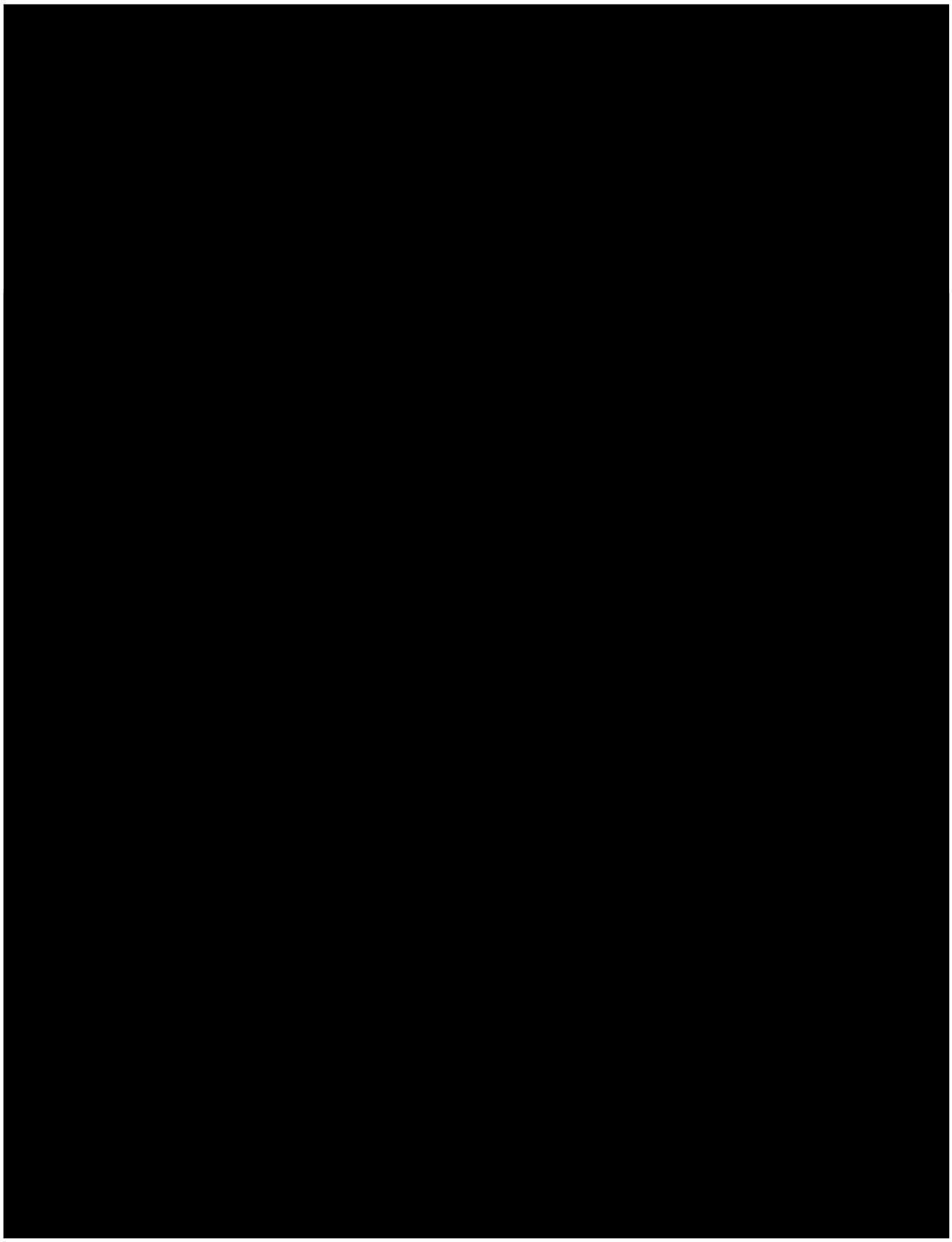


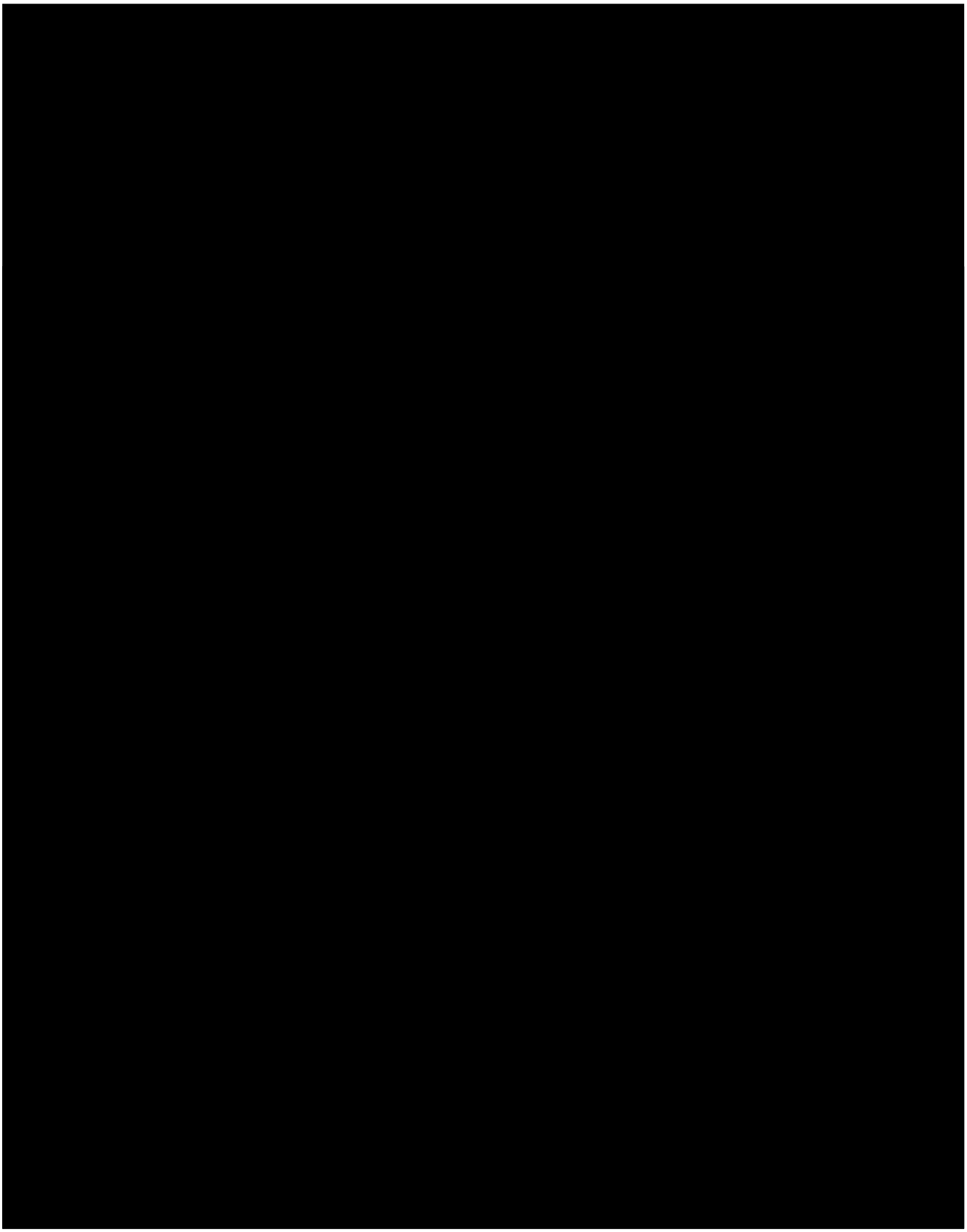












3. STUDY OBJECTIVES AND PURPOSE

The purpose of this study is to evaluate the safety and efficacy of milademetan compared to trabectedin in patients with unresectable or metastatic DD liposarcoma. To be eligible, patients must have progressed on 1 or more prior systemic therapies, including at least 1 anthracycline-based therapy.

3.1 Primary Objective

The primary objective is to compare PFS between the milademetan treatment arm and trabectedin control arm, as determined by blinded independent central review (BICR), in patients with unresectable or metastatic DD liposarcoma, with or without a WD component, who progressed on 1 or more prior systemic therapies including at least 1 anthracycline-based therapy.

3.2 Secondary Objectives

Secondary objectives are:

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

[redacted]

4. STUDY DESIGN

4.1 Study Design Overview

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. Trabectedin is the chosen active control treatment because it has been approved as a second-line therapy by the US FDA for patients with liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen. Trabectedin was approved for liposarcoma based on improved PFS. In the current study, the primary objective is to compare PFS, as determined by BICR, between patients receiving milademetan versus trabectedin.

An independent data monitoring committee (IDMC) will review unblinded safety data during the course of the study and make recommendations to the Sponsor as applicable and outlined in the IDMC charter.

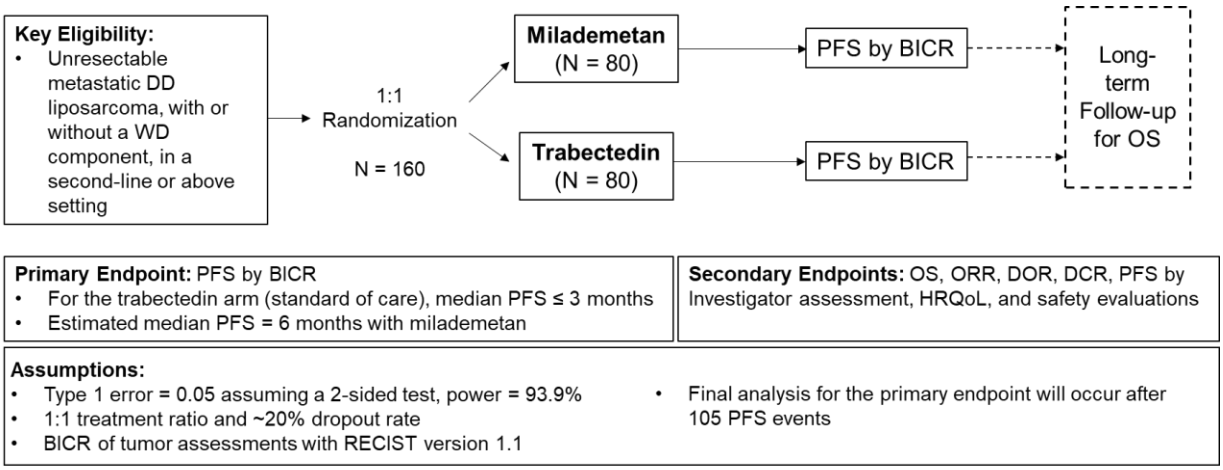
Approximately 160 patients will be randomly assigned in a 1:1 ratio to receive milademetan or trabectedin. Randomization will be stratified based on Eastern Cooperative Oncology Group

(ECOG) performance status (0 or 1) and number of prior therapies (≤ 2 or > 2) for the patient's liposarcoma.

Patients will receive study drug (i.e., milademetan or trabectedin) until reaching unequivocal disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST] version 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 first dose of study drug of the last patient enrolled, whichever comes first.

The study design is illustrated in Figure 5.

Figure 5: RAIN-3201 Study Design Diagram



BICR = blinded independent central review; DCR = disease control rate; DD = dedifferentiated; DOR = duration of response; EU = European Union; HRQoL = health-related quality of life; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; TP53 = tumor protein p53; WD = well-differentiated

4.2 Imaging Assessments by Blinded Independent Central Review

[redacted]

4.2.1 Intensive Electrocardiogram and Pharmacokinetics Evaluation in a Subgroup of Miladametan-Treated Patients

[redacted]

4.3 Endpoints and Criteria for Evaluation

4.3.1 Primary Endpoint

The primary efficacy endpoint is PFS defined as the time from randomization to the earliest date of the first objective documentation of radiographic disease progression as determined by BICR or death due to any cause. Tumor response will be assessed in accordance with RECIST version 1.1.

4.3.2 Secondary Endpoints

Secondary efficacy endpoints include:

- OS as measured from the date of randomization to the date of death by any cause
- DCR defined as the percentage of patients who have achieved CR, PR, or SD for ≥ 16 weeks by BICR and Investigator assessment
- ORR defined as the percentage of patients who achieve a confirmed CR or PR by BICR and Investigator assessment
- DOR defined as the time from date of first response to date of disease progression or death by BICR and Investigator assessment
- PFS defined as the time from randomization to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause, based on Investigator assessments

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

4.3.3 Exploratory Endpoints

[redacted]

4.4 Measures Taken to Minimize/Avoid Bias

If a patient withdraws from the study, the data (including tested and untested samples) collected to the point of withdrawal will remain part of the study database and will not be removed.

Response criteria are based on objective measurements as defined in RECIST version 1.1 by site radiologists. All responses will be source verified; copies of tumor assessment scans will be collected and provided for evaluation by BICR (Section 4.2).

Biometrics representatives from the Sponsor team and BICR will remain blinded throughout the conduct of the study and described in a separate trial integrity document.

4.5 Duration of Study Treatment

Patients will continue to receive study drug (i.e., either milademetan or trabectedin) until documented disease progression or unacceptable toxicity. See Section 6.5 for treatment beyond progression.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in the study:

1. Is a male or female patient ≥ 18 years old
2. Has a signed and dated informed consent form prior to the start of any study-specific qualification procedures

3. Has histologically confirmed WD/DD liposarcoma, by local pathologic review; central pathologic review will also be performed, but is not required for inclusion

[redacted]

4. Has documented advanced unresectable (i.e., where resection is deemed to cause unacceptable morbidity or mortality) and/or metastatic WD/DD liposarcoma
5. [redacted]
6.
7. Has resolution of any clinically relevant toxic effects of prior chemotherapy, surgery, radiotherapy, or hormonal therapy

[redacted]

8. Has an ECOG performance status of 0 or 1
9. Has adequate bone marrow function, defined as:
    a. Platelet count $\geq 100 \times 10^9$/L
    b. Hemoglobin ≥ 9.0 g/dL
    c. Absolute neutrophil count $\geq 1.5 \times 10^9$/L
10. Has adequate renal function, defined as creatinine clearance ≥ 30 mL/min, as calculated using the modified Cockcroft-Gault equation (or equivalent glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration formula)
11. Has adequate hepatic function, defined as:
    a. Alanine aminotransferase and aspartate aminotransferase $\leq 3 \times$ upper limit of normal (ULN) if no liver metastases are present; $\leq 5 \times$ ULN if liver metastases are present
    b. Total bilirubin $\leq 1.5 \times$ ULN. Patients with Gilbert's disease who have serum bilirubin level $\leq 3 \times$ ULN, may be enrolled
12. Is willing and able to comply with the protocol requirements
13. Patients requiring anticoagulation medication should be on a stable regimen, defined as at least 4 weeks on the same dose
14. Patients requiring antihypertensive medication should be on a stable regimen, defined as at least 4 weeks on the same dose

15. If a woman of childbearing potential (WOCBP), must have a negative serum pregnancy test at screening and a negative urine pregnancy test on Cycle 1 Day 1 before receiving her first dose of study drug or within 72 hours of the first dose of study drug

16. If a male patient, is surgically sterile, willing to use a condom, or remain abstinent upon randomization through the Treatment Period and for 5 months after the final dose of study drug

5.2 Exclusion Criteria

A patient who meets any of the following criteria will not be eligible to participate in the study:

1. Has received prior treatment with any MDM2 inhibitor or trabectedin
2. Has other primary malignancies that have required systemic antineoplastic treatment within the previous 2 years, except for localized cancers that have apparently been cured (e.g., nonmelanoma skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast) and will not interfere with the study outcomes
3. Has gastrointestinal conditions that could affect the absorption of milademetan, in the opinion of the Investigator
4. Has an uncontrolled infection within the last 7 days from randomization requiring IV antibiotics, antivirals, or antifungals
5. Has known HIV infection or active hepatitis B or C infection
6. Has untreated brain metastases

7. Has not met the minimum washout period before randomization, defined as:

a. CYP3A4 strong inhibitor: 5 elimination half-lives of the inhibitor
b. CYP3A strong or moderate inducers (e.g., St. John's wort and modafinil): 4 weeks
c. Systemic anticancer therapy (chemotherapy; small molecules, including antibody drug therapy; retinoid therapy; or hormonal therapy) or investigational therapy: 3 weeks or 5 half-lives, whichever is shorter
d. Immunotherapy with checkpoint inhibitor: 4 weeks

8. Has had major surgery ≤ 3 weeks from randomization
9. Has had curative-intent radiation therapy ≤ 4 weeks or palliative radiation therapy, defined as ≤ 30 Gy in ≤ 10 fractions (e.g., 20 Gy in 5 fractions or 8 Gy in 1 fraction) ≤ 2 weeks from randomization
10. Has uncontrolled or significant cardiovascular disease, including:
    a. QTcF at rest, where the mean QTcF interval is > 480 milliseconds (average of triplicate ECGs)
    b. Myocardial infarction within 6 months prior to screening
    c. Uncontrolled angina pectoris within 6 months prior to screening
    d. New York Heart Association Class 3 or 4 congestive heart failure
    e. Uncontrolled hypertension (resting systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg)
11. Is a female who is pregnant or breastfeeding or intends to become pregnant during the study
12. Has a concomitant medical condition that would interfere with the assessment of efficacy or increase the risk of toxicity, in the opinion of the Investigator or Sponsor

5.3 Study Completion

Patient study "completion" refers to completion of study procedures and follow-up assessments or the patient has died, is lost to follow-up, or withdrawn consent before end of study.

5.4 Patient Withdrawal Criteria

All patients are free to discontinue study drug or withdraw from the study at any time. All patients wishing to discontinue from study drug or withdraw from the study will be queried to determine the reason for withdrawal while respecting the privacy of the patient. The reason a patient decided to withdraw from study drug will be recorded.

In the event of consent withdrawal, the Investigator should make every effort to ensure that the patient is followed for AEs for a minimum of 30 days after their last dose of study drug or until the initiation of a new anticancer treatment, whichever comes first, with documented patient agreement.

Patients will be discontinued from study drug if any of the following events occur:

- PD according to RECIST version 1.1 at any time during the study (unless approved by the Medical Monitor [See Section 6.5])

- Clinical progression (e.g., symptomatic deterioration) not meeting the RECIST version 1.1 criterion for PD but considered by the Investigator to require withdrawal from study drug
- Patient is unable to tolerate dosing after 3 dose reductions (for the milademetan arm) or is unable to maintain treatment with trabectedin following the dose modification guidelines provided in the local package insert/label (for the trabectedin arm)
- Patient is unable to restart trabectedin after a dosing delay of > 3 weeks due to a persistent adverse reaction
- Significant deviation from the protocol or eligibility criteria. These patients may continue study drug following a discussion and agreement between the Investigator and the Medical Monitor and subsequent approval by the institutional review board (IRB) or independent ethics committee (IEC).
- Pregnancy
- Patient withdrawal of consent and/or election to discontinue study drug
- Termination of the study by the Sponsor
- Any other reason which, in the opinion of the Investigator, would justify removing the patient from the study drug

A patient may also be withdrawn from study drug by the Sponsor, Regulatory Authorities, or IECs/IRBs.

If a patient discontinues study drug due to the ongoing coronavirus disease 2019 (COVID-19) global pandemic, information should be captured in the electronic case report form (eCRF) so this information can be summarized in the clinical study report at the end of the study, in line with the FDA guidance (FDA 2020). The reason for discontinuation should be recorded in the eCRF as COVID-19, if applicable, and include as many details as possible. For example, specific reasons may include, but are not limited to:

- The patient exhibits symptoms consistent with COVID-19.
- The patient has a positive test result for COVID-19.
- The patient has neither symptoms nor a positive test for COVID-19 but has decided to discontinue treatment due to personal choice related to COVID-19 concerns.

Patients who discontinue study drug for reasons other than PD by RECIST version 1.1 should undergo scans for tumor assessment according to the original tumor assessment schedule (every 8 to 12 weeks [± 1-week window (7 days)] from Cycle 1 Day 1) until any of the following occurs, whichever comes first:

- PD by RECIST version 1.1
- Initiation of new anticancer treatment
- Discontinuation from the study (death, withdrawal of consent, or loss to follow-up)

After discontinuation from study drug, all patients will have an EOT Visit. The EOT Visit should take place 30 days (± 7 days) after the last study drug administration or before starting new anticancer treatment. If the patient begins another form of anticancer therapy before the end of the 30-day period, every effort will be made to complete all EOT assessments before commencing the new therapy. If there is an AE in need of monitoring beyond the EOT Visit, patients will be followed until resolution or confirmed stability of the AE. Long-term follow-up visits, to obtain survival information, after the EOT will be performed every 12 weeks (± 7 days) until the endpoint of death, the patient is lost to follow-up, or for 24 months following the first dose of study drug of the last patient enrolled, whichever comes first.

Withdrawal from the study should be in a step-wise fashion. As mentioned above, patients may withdraw or be withdrawn from study drug. Any patient who withdraws or is withdrawn from study drug should be encouraged to complete all planned safety and follow-up assessments. If the patient wishes to withdraw from all study assessments, permission should be requested to contact the patient, a designated contact person, or the patient's primary care provider for long-term survival follow-up. If the patient does not wish any direct follow-up, permission should be requested to conduct periodic medical record review and/or contact the patient's medical care provider for long-term follow-up. If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. Where allowed by local regulations, public records may still be consulted for the patient's survival status.

6. TREATMENT OF PATIENTS

6.1 Patient Enrollment

Before any study related assessments, all potential patients will provide written informed consent. After written informed consent has been obtained and eligibility has been established, the study site will obtain the patient's identification number and treatment assignment from the Interactive Response Technology System. Once a patient identification number has been assigned, it will be used to identify the patient throughout the study, and it cannot be reassigned to another patient.

Investigational sites will provide the Medical Monitor with a completed Eligibility Checklist and relevant redacted source documents for medical history and concomitant medications for Sponsor review. Patients who meet the eligibility criteria may be enrolled. Patients will be considered enrolled upon randomization.

Patients who cannot complete the procedures within the Screening window or are not initially eligible may be rescreened. In this situation, a new patient identification number will be assigned. For rescreening within the original Screening window, certain Screening procedures may not need to be repeated. Reconsent is required for rescreening outside the original Screening window.

An investigational drug accountability log must be used for drug accountability. For additional details on investigational study drug management, please refer to the Pharmacy Manual. Patients will be provided with a patient diary to record study product administration and compliance.

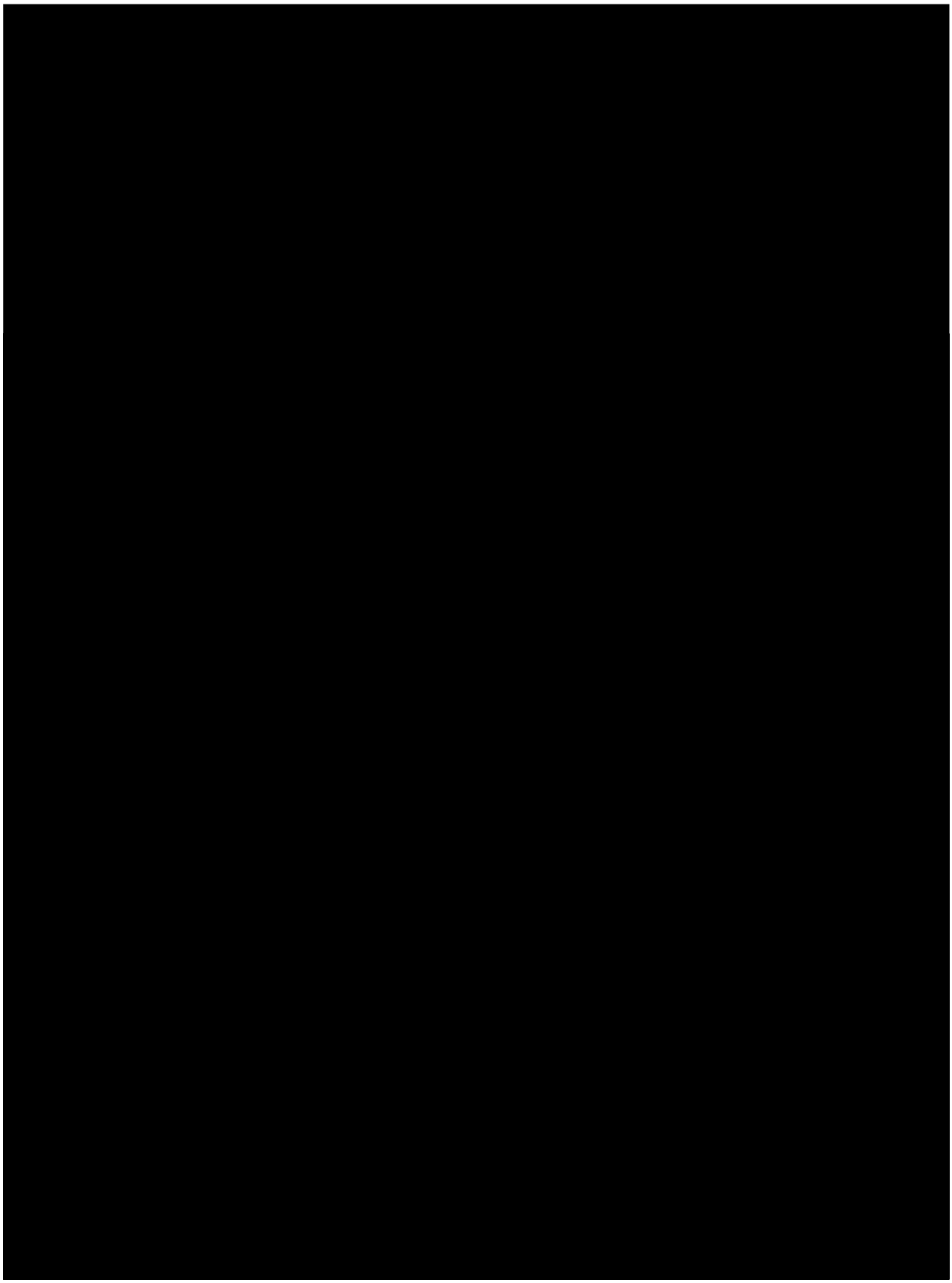
6.2 Mladademetan Administration

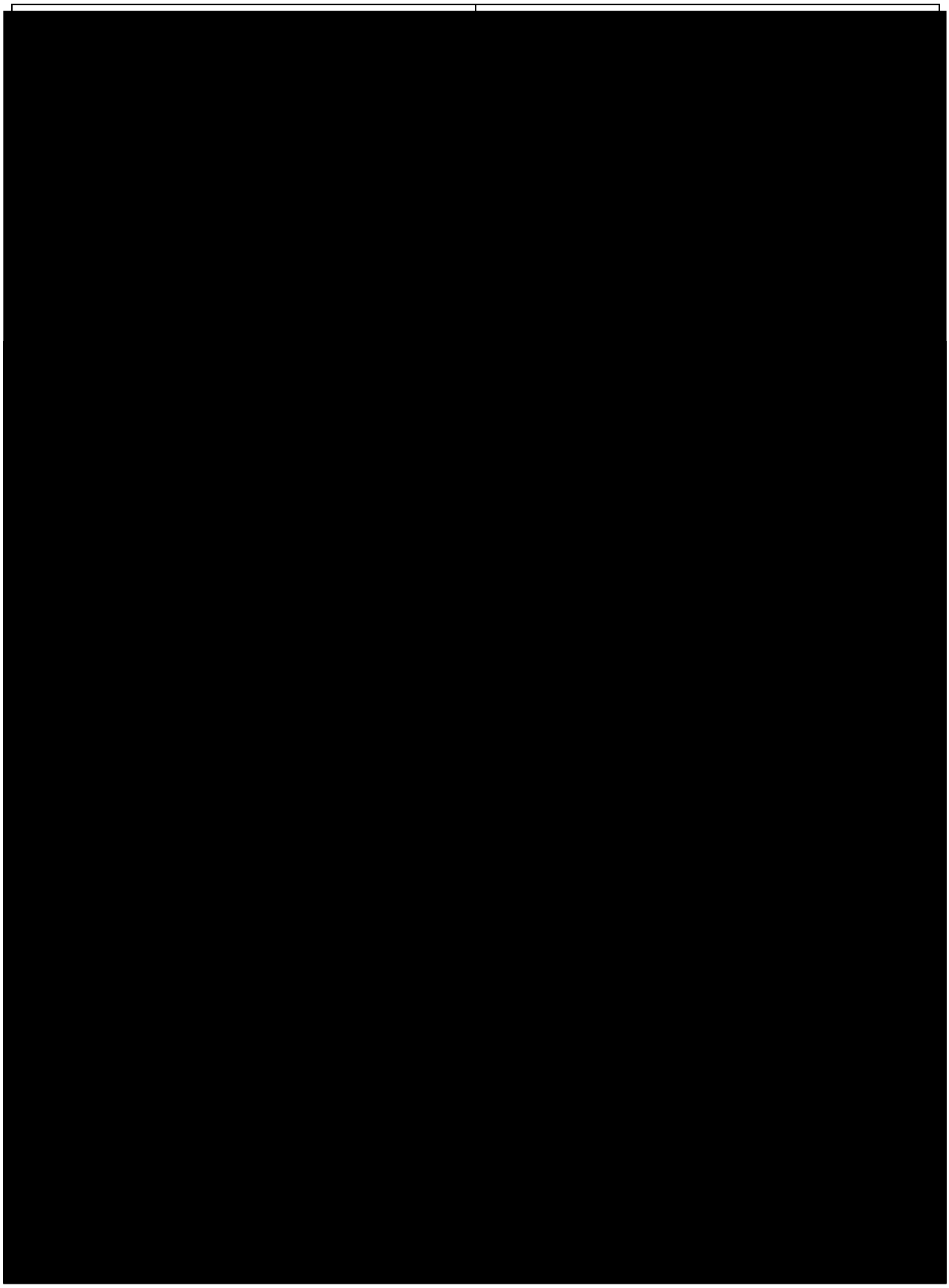
Mladademetan 260 mg QD will administered orally on Days 1 to 3 and Days 15 to 17 of each 28-day cycle. Mladademetan will be administered at the clinical site on the indicated visit days (Cycle 1: Days 1, 3, and 15, Cycles 2 and 3: Days 1 and 15, and Cycles 4+: Day 1 only; Table 1)

[redacted]

6.2.1 Mladademetan Dose Modifications

[redacted]





[redacted]

6.3 Trabectedin Administration

Trabectedin will be administered at 1.5 mg/m^2 BSA as a 24-hour IV infusion, every 3 weeks through a central venous line. Clinical laboratory assessments must be resulted and evaluated prior to administration of study drug on the day of administration.

6.3.1 Trabectedin Dose Calculation

The dose administered will be based on the patient's BSA determined on Day 1 (± 7 days) of each cycle. The DuBois and DuBois formula for BSA calculation is:

$$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$$

Investigational sites are instructed to use the DuBois and DuBois formula but may also use the formula/method in current institutional practice if accurate dose calculation can be assured.

6.3.2 Trabectedin Infusion Duration

Reconstituted, diluted trabectedin solution should be infused over a 24-hour period through a central venous line using an infusion set with a 0.2 micron polyethersulfone in-line filter to reduce the risk of exposure to adventitious pathogens that may be introduced during solution preparation.

Infusion must be completed within 30 hours of initial reconstitution. Discard any unused portion of the reconstituted product or infusion solution.

6.3.3 Trabectedin Dose Modifications

[redacted]

6.4 Premedication

Administer dexamethasone (or equivalent) and antiemetics per institution's standard-of-care 30 minutes before each dose of trabectedin.

6.5 Treatment Beyond Progression

Patients with disease progression who meet the following criteria:

a. Absence of symptoms and signs indicating clinically significant progression of disease.

b. No decline in ECOG or Karnofsky performance status.

c. Absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., symptomatic pleural effusion, spinal cord compression)

may continue to receive study drug if, in the opinion of the Investigator, the patient is still benefiting (e.g., asymptomatic systemic progression or local symptomatic progression) following discussion with and approval by the Medical Monitor (or designee). The Investigator should periodically discuss the ongoing treatment with study drug with the Medical Monitor. Where applicable the IRB/IEC will be notified of any planned treatment beyond progression. Patients may receive palliative radiation to disease sites of progression, including brain metastases, following discussion with and approval by the Medical Monitor (or designee).

At the time of radiographic progression of disease, patients should be informed of treatments with known clinical benefit they may be foregoing in order to continue receiving the investigational product.

6.6 Compliance

Investigators are required to conduct the study in compliance with the protocol. Compliance with the protocol will be closely monitored. Important aspects of compliance with this clinical study include:

- Eligibility
- Study drug administration, including:
  - Dose calculation, for the trabectedin arm
  - Dose modification
  - Infusion duration, for the trabectedin arm
- Performance of protocol-specified assessments
- ECG monitoring
- AE reporting

Protocol deviations are defined as any departure from the protocol or associated instructions and will be monitored. Deviations from the protocol, including violations of inclusion/exclusion criteria, will be assessed as "minor" or "major". Protocol deviations at investigational sites will be discussed with the Investigator and additional training will be provided as needed to secure Investigator compliance.

Study staff will receive additional training as needed to prevent noncompliance.

6.7 Study Visits

Protocol-required assessments scheduled for each study visit are summarized in the Schedule of Events (Table 1 [milademetan arm] and Table 4 [trabectedin arm]) and described below. In exceptional circumstances with prior Sponsor approval, study visits may be performed by local provider.

6.7.1 Screening Period/Baseline Assessments

Patients may be screened anytime during the 21 days prior to randomization. Unless otherwise specified, baseline assessments may be done anytime following consent and prior to randomization. Patients who are determined not to meet eligibility criteria at any time prior to randomization will not be enrolled. The following will be assessed or measured at screening/baseline:

- Informed consent
- Eligibility (including tumor assessment)
- Medical/Disease history including all anticancer treatment
- Demographics
- Physical examination and vital signs, including height and weight
- ECOG
- ECG (12-lead) in triplicate

- Collect blood samples for laboratory assessments (see Table 2 [milademetan arm] and Table 5 [trabectedin arm]); ensure a serum pregnancy test is collected within 21 days of Cycle 1 Day 1 for WOCBP
- Patient-reported outcome questionnaire (EORTC QLQ-C30)
- Tumor tissue
  - Formalin-fixed paraffin embedded (FFPE) block from newly obtained biopsy or archival tissue of approximately 25 FFPE sections. Two sections will be used for eligibility confirmation after enrollment (enrollment is based on local pathology). The remaining 23 sections will be used for future genetic testing.

[redacted]

- In patients who provide consent to the optional procedure:
  - Tumor biopsy consisting of sufficient tissue to generate an FFPE block of approximately 25 sections. Refer to the study Laboratory Manual for details.
- Concomitant medications
  - Record all concomitant medications used after 21 days prior to Cycle 1 Day 1
  - Special attention should be accorded to medications that are known to cause prolongation of QTc or deplete potassium
- Baseline physical and radiographic tumor assessment
  - Perform physical examination and radiological assessments per RECIST version 1.1; include a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis, unless otherwise clinically indicated. The baseline radiographic tumor assessment is required within 28 days (± 1week window [7 days]) prior to the first dose of study drug.

6.7.2 Treatment Period

See the Schedule of Events for the timing of procedures during the Treatment Period (Table 1 [milademetan arm] and Table 4 [trabectedin arm]). Blood samples will be collected at the time points indicated in Table 2 (milademetan arm) and Table 5 (trabectedin arm). If screening laboratory assessments were performed within 72 hours of Cycle 1 Day 1 dosing, these screening laboratory assessments can be used as Cycle 1 Day 1 safety laboratory assessments.

Physical and radiographic tumor assessments will be performed at the end of Week 8, Week 16, Week 24, and Week 32; and then every 12 weeks (± 1 week [7 days]) until treatment discontinuation, and any other time during the study as clinically indicated. In accordance with RECIST version 1.1, response (PR and CR) must be confirmed by a subsequent tumor assessment at least 4 weeks after the initial observed response. The same imaging modality used for baseline imaging (i.e., CT or MRI) must be used for subsequent radiographic tumor

assessments. Any dose interruption after starting study treatment will not cause adjustment to the tumor assessment schedule. Additional tumor assessments may be performed as clinically indicated (e.g., if disease progression is suspected).

6.7.3 End-of-Treatment Visit

The EOT Visit should take place 30 days (± 7 days) after the last study drug administration or before starting new anticancer treatment. If the patient begins another form of anticancer therapy before the end of the 30-day period, every effort will be made to complete all EOT assessments before commencing the new therapy. If there is an AE in need of monitoring beyond the EOT Visit, patients will be followed until resolution or confirmed stability of the AE. The following will be performed at the EOT Visit:

- Collect blood samples for laboratory assessments (see Table 2 [milademetan arm] and Table 5 [trabectedin arm]
- Urine pregnancy test in WOCBP
- ECOG
- Physical examination and vital signs, including height and weight
- Record AEs
- Record concomitant medications
- Patient-reported outcomes questionnaire (EORTC QLQ-C30)
- In patients who provide consent to these optional procedures: tumor biopsy consisting of sufficient tissue to generate an FFPE block of approximately 25 sections. Refer to the study Laboratory Manual for details.

6.7.4 Long-Term Follow-Up

Once a patient has completed the EOT Visit, they will enter the follow-up phase. 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 first dose of study drug of the last patient enrolled, whichever comes first.

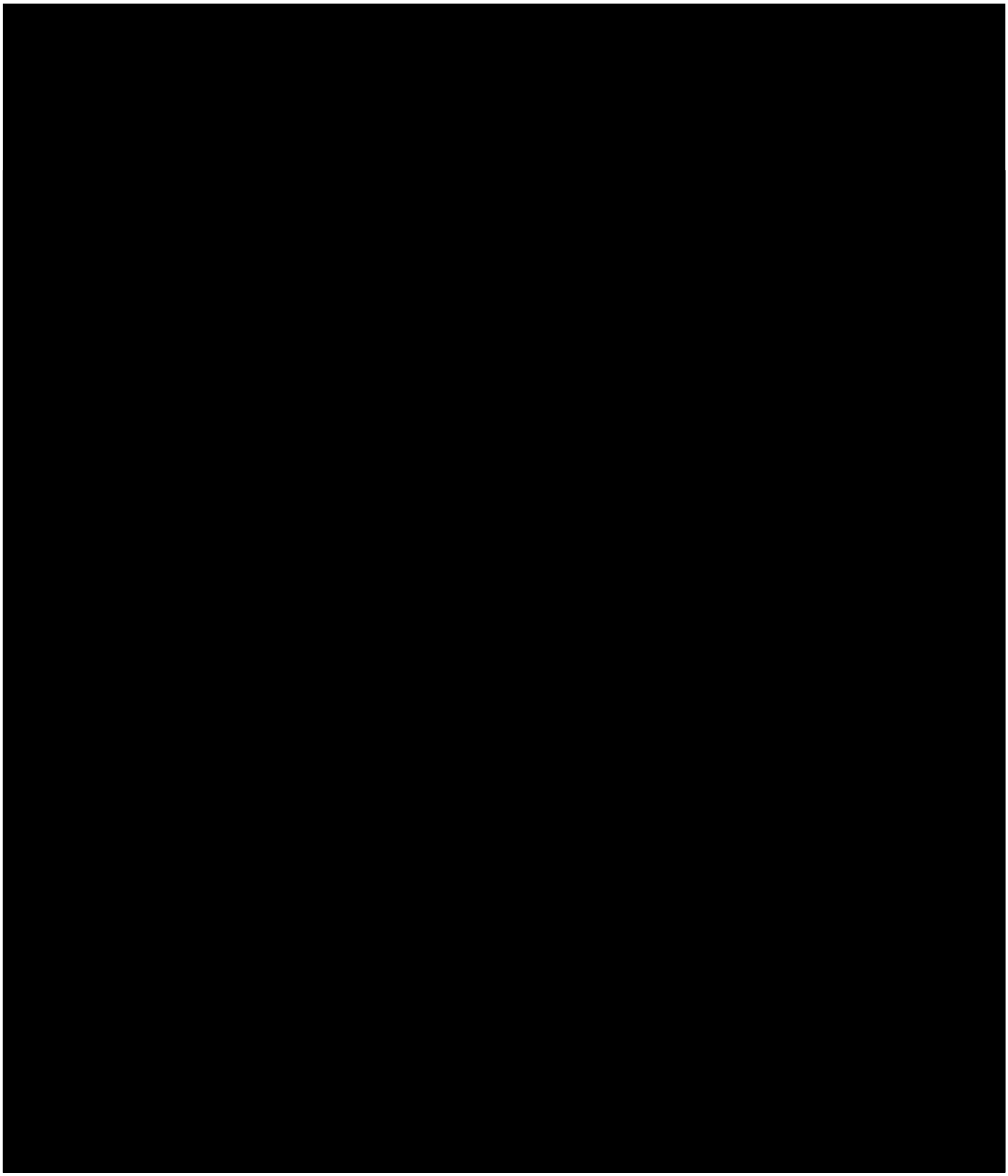
6.8 Concomitant Medications and Treatments

All concomitant medications (prescription and over -the -counter) and blood products taken from the Screening Visit until the EOT Visit will be recorded. The reason(s) for treatment, dose, and dates of treatment will be recorded. In addition, concomitant medications used to treat AEs occurring up to 30 days after the last dose of study drug will be recorded.

See Appendix A for a list of prohibited medications and those medications that are permitted but should be used with caution during the study. Supportive care should be provided as appropriate

to each patient to manage disease-related symptoms (e.g., antiemetics, antibiotics, transfusions, nutritional support, and pain control) according to institutional guidelines.

6.8.1 Prohibited Medications



7. ASSESSMENT OF EFFICACY

Tumor assessments via imaging (CT scans or MRIs) will be performed by both the Investigator and a blinded central review committee; the evaluation of tumor response will be based on RECIST version 1.1. The primary efficacy objective is to compare PFS, as determined by BICR, between patients receiving milademetan versus trabectedin. However, the decision to discontinue study drug for disease progression will be determined locally by the Investigator.

Tumor response evaluations will be performed at screening; at the end of Week 8, Week 16, Week 24, and Week 32; and then every 12 weeks (± 1 week [7 days]) while the patient remains on study drug, and any other time during the study as clinically indicated.

In accordance with RECIST version 1.1, response (PR and CR) must be confirmed by a subsequent tumor assessment at least 4 weeks after the initial observed response. The scheduling of subsequent tumor assessments may be adjusted based on the date of the most recent imaging. Investigators are instructed to ensure that original images (or high-quality copies) of all baseline and on-study scans are filed and available for transmission to the Sponsor (or designee) for central reading.

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, as determined by BICR.

7.2 Secondary Efficacy Endpoints

Secondary efficacy variables include:

- OS
- DCR by BICR and Investigator assessment
- ORR by BICR and Investigator assessment
- DOR by BICR and Investigator assessment
- PFS by Investigator assessment
- HRQoL evaluations:
    - EORTC QLQ-C30

8. ASSESSMENT OF SAFETY AND EXPLORATORY VARIABLES

8.1 Definitions

8.1.1 Adverse Event Definitions

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

8.1.1.1 Events Not Considered to be Adverse Events

AEs do not include the following events:

- Medical procedures, such as surgery, endoscopy, tooth extraction, or transfusion; however, the condition that led to the procedure may be an AE and must be reported
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the Screening visit that do not worsen after the initiation of study drug
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery or social and/or convenience admissions)
- Overdose without clinical sequelae, as overdose is a special situation that should be reported using the Special Situation Report Form
- Any medical condition or clinically significant laboratory abnormality with an onset date of on or after the informed consent form is signed but before the first dose of study drug and not related to a protocol-associated procedure. In this case, the condition or clinically significant laboratory abnormality is not an AE but should be considered preexisting and should be documented as medical history.
- An event that is part of the natural course of the disease under study (i.e., disease progression, death due to disease progression) should not be recorded as an AE or SAE; however, signs and symptoms of clinical sequelae resulting from disease progression will be reported if they fulfill the definition of AE or SAE. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

8.1.1.2 Serious Adverse Events

An AE is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening (immediate risk at the time of the event)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

Any other important medical event, as defined as an AE that may jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed above, based upon appropriate medical judgement, should be reported as an SAE. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2 Adverse Events Reporting

8.2.1 Adverse Event Collection Period

After signing the informed consent, but before the initiation of study drug, an event must be collected and entered on the AE case report form (CRF), **IF** it is related to protocol-required procedures (e.g., biopsy); otherwise, the event must be reported as medical history.

Following initiation of study drug, all AEs, regardless of causality, will be collected and entered on the AE CRF until 30 days after the last administration of study drug or until initiation of another anticancer therapy, whichever comes first.

All AEs should be followed until resolution or until the AE is stable, if possible. The Sponsor may request that certain AEs be followed beyond the protocol-defined follow-up period.

8.2.2 Adverse Event Term

AEs must be reported using standard medical terminology. The use of abbreviations (standard and nonstandard) should be avoided to help ensure a clear understanding of the event. An example of a standard abbreviation that may have several meanings is "MI" which could mean "myocardial infarction" or "mitral insufficiency." All AE terms will be coded using a standardized dictionary (i.e., Medical Dictionary for Regulatory Activities [MedDRA]). Generally, when reporting a well-known and understood condition, it is preferable to report the overall diagnosis rather than the individual signs and symptoms. The term "intermittent" should be avoided as the duration and incidence of events helps in understanding the safety profile of the study drug.

8.2.3 Adverse Event Severity

AEs will be reported at the highest experienced severity. AE severity will be graded according to NCI CTCAE version 5.0. A copy of the document will be provided to investigational sites and an electronic version is available at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to the NCI CTCAE); the event itself may be of relatively minor medical significance (e.g., severe headache without any further findings).

Events not listed in NCI CTCAE will be graded according to the criteria described in Table 133.

Table 13: Severity Grading Guideline for Adverse Events Not Listed in NCI CTCAE

Adverse Events Not Listed in NCI CTCAE Version 5.0	
Grade	**Description**
1	• Mild • Asymptomatic or mild symptoms • Clinical or diagnostic observations only • Intervention not indicated
2	• Moderate • Minimal, local or noninvasive intervention indicated • Limiting age-appropriate instrumental activities of daily living[a]
3	• Severe or medically significant but not immediately life-threatening • Hospitalization or prolongation of hospitalization indicated • Disabling • Limiting self-care activities of daily living[b]
4	• Life-threatening consequences • Urgent intervention indicated
5	• Death related to adverse event

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events
[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care activities of daily living refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Note: A semicolon indicates "or" within the description of the grade.

8.2.4 Adverse Event Duration

The start date (the date that the event was first noticed) and the end date (the date that the event had completely resolved, returned to baseline, or improved in severity grade) will be recorded. If the exact date is not known, the best estimate should be reported.

8.2.5 Adverse Event Causality

Where the determination of the relationship of the AE to study drug rests on medical judgment, the determination must be made with the appropriate involvement of the Investigator, or, if the Investigator is not a physician, a designated Sub-investigator who is a physician.

Using the following criteria, Investigators will assess whether there is a reasonable possibility that the study drug caused or contributed to the AE.

Related (Possibly, Probably, or Definitely Related)

- The time sequence between the onset of the AE and study drug administration is consistent with the event being related to study drug; and/or

- There is a possible biologic mechanism for study drug causing or contributing to the AE; and the AE may or may not be attributed to concurrent/underlying illness, other drugs, or procedures.

Not Related (Unlikely Related)

- Another cause of the AE is most likely; and/or
- The time sequence between the onset of the AE and study drug administration is inconsistent with a causal relationship; and/or
- A causal relationship is considered biologically unlikely.

8.3 Serious Adverse Events Reporting

Error! Reference source not found. Investigators must report all SAEs regardless of causality immediately (within 24 hours of learning of the event without undue delay) on the AE CRF. If the EDC system is unavailable, SAEs must be reported by completing the back-up paper on the SAE report form and emailing the completed form to:

[redacted]

An event that results in hospitalization or prolongs an existing hospitalization will not be considered an SAE, if the only reason for that hospitalization or prolongation is:

- To administer study drug
- To conduct protocol-specified study procedures
- For placement of permanent IV catheter
- Hospice placement due to PD
- Respite care

[redacted]

Table 14: Severity Grading Guideline for Infusion-Related Reactions

Infusion-Related Reactions	
Grade	**Description**
1	• Mild transient reaction; • Infusion interruption not indicated; • Intervention not indicated
2	• Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, and intravenous fluids); • Prophylactic medications indicated for ≤ 24 hours
3	• Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); • Recurrence of symptoms following initial improvement; • Hospitalization indicated for clinical sequelae
4	• Life-threatening consequences; • Urgent intervention indicated
5	• Death

Adapted from National Cancer Institute Common Terminology Criteria for Adverse Events v5.0
Note: A semicolon indicates "or" within the description of the grade.

8.5 Reporting Disease Progression and Death

PD, also referred to as disease progression, and death due to any cause are study endpoints and information related to these events will be collected in eCRFs specifically designed to collect these data. These events will not be reported as AE/SAEs unless the Investigator feels that they are accelerated, atypical, or related to study drug. All deaths must be communicated as soon as possible to the appropriate IRB/IEC and/or reported in accordance with local laws and regulations.

If an autopsy is performed, a copy of the report will be requested and provided to the Sponsor, if available.

8.6 Special Situation Reporting

Special situations may require immediate reporting and/or safety evaluations, and these situations must be reported without undue delay. These include, but are not limited to:

- Overdose of any study drug – administration of a quantity of study drug above the recommended dose according to the protocol. In cases of a discrepancy in the drug accountability, overdose is established only when it is clear that the patient has taken additional doses or the Investigator has a reason to suspect that the patient has taken additional doses.
- Abuse – persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

- Misuse of a study drug – situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- Medication error – unintentional error in the prescribing, dispensing, or administration of the medicinal product.
- Product complaint – any written, electronic, or oral communication alleging deficiencies related to the identity, quality, durability, reliability, safety, or effectiveness of a drug after it is released for distribution. This situation should be reported by completing the specific Product Complaint Form (See Pharmacy Manual forms for details). If also associated with an AE, report the AE on the AE CRF.

All special situations must be reported by completing the Special Situation Report Form except for a product complaint (see above). The completed form should be sent via email to: [redacted] If the special situation is associated with an AE, the AE must also be recorded on the AE CRF.

8.7 Electrocardiogram Monitoring

Standard 12-lead ECGs will be performed locally using a calibrated digital ECG machine capable of providing automated measurements. All ECG tracings will be acquired with the patient in the supine position after the patient has been resting for at least approximately 10 minutes. ECG tracings will be measured and interpreted locally by a cardiologist or other qualified health care professional in accordance with institutional standard-of-care.

ECGs will be performed at the time points indicated in the Schedule of Events (Table 1 [milademetan arm] and Table 4 [trabectedin arm]). Screening ECGs should be performed in triplicate in all patients.

8.7.1 Subgroup of Patients Undergoing Intensive Electrocardiogram Monitoring at Selected Study Centers

A subset of milademetan-treated patients (see Section 4.2.1) will undergo intensive ECG and PK assessments. ECGs will be collected digitally using an ECG continuous 12-lead digital recorder on the day of dosing. Holter monitoring will commence 60 minutes before the administration of milademetan and will continue through 24 hours following the administration of milademetan on Day 1 and Day 3 of Cycle 1. The Holter flash cards will be sent to an established clinical research organization with ECG experience (hereafter referred to as the "ECG core laboratory") where replicate ECGs will be extracted at time points matching the PK sample collection schedule. Each ECG will be extracted from a supine rest period of at least 10 minutes of supine rest; PK sample collection will be performed immediately following the ECG supine rest periods. Triplicate ECGs and plasma concentration will be sampled before dosing (3 sets of triplicate ECGs collected before dosing on Cycle Day 1 at -45, -30, and -15 minutes to serve as baseline (e.g., 3 supine resting windows in the hour before dosing); and 1 set of predose ECGs will be collected on Day 3). Triplicate ECGs will be extracted at 1, 2, 3, 4, 6, 8, and 24 hours after dosing on Cycle 1 Days 1 and 3 (last treatment of first 3 doses) during Cycle 1. Safety ECGs will be reviewed by the Investigator, and continuous ECG recordings will be uploaded to

the ECG core laboratory for cardiologist over-reading. ECGs will be measured and have cardiologist evaluation in a blinded manner using the ECG core laboratory's validated data management system (Table 3).

All clinically significant ECG readings should be manually verified by a qualified individual. If the Investigator has any question regarding the local automated read, a local cardiologist should be consulted.

8.8 Vital Sign Assessments

The following vital signs will be assessed after the patient has been sitting for approximately 5 minutes. Vital signs will be obtained at each visit indicated in the Schedule of Events (Table 1 [milademetan arm] and Table 4 [trabectedin arm]). Vital signs to be measured include:

- Blood pressure (systolic and diastolic; mmHg)
- Heart rate (beats per minute)
- Body temperature (°C)
- Respiration rate (breaths per minute)

8.9 Clinical Laboratory Assessments

Clinical laboratory assessments will be performed by each institution's local laboratory and must be resulted and evaluated prior to administration of study drug on the day of administration. The following laboratory variables (Table 155) will be collected at the time points indicated in Table 2 (milademetan arm) and Table 5 (trabectedin arm).

Table 15: Clinical Laboratory Assessments

Serum Chemistry[a]:	Sodium Potassium Chloride Bicarbonate Calcium Magnesium Phosphorous Glucose	Blood urea nitrogen Bilirubin Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Albumin Total protein Creatinine
Hematology:	Red blood cell count with differential and reticulocyte count Hemoglobin Hematocrit Platelet count Reticulocyte count White blood cell count with differential (reported as absolute counts) • Total neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
Coagulation:	International normalized ratio Activated partial thromboplastin time	
Pregnancy Test:	In women with childbearing potential only: serum β-human chorionic gonadotropin pregnancy test, urine, or urine dipstick	

[a] If screening laboratory assessments were performed within 72 hours of Cycle 1 Day 1 dosing, the same screening laboratory assessments can be used as Cycle 1 Day 1 safety laboratory assessments. If the site cannot perform serum chemistry analysis, then the test may be performed with plasma (blood).

All clinically significant unscheduled laboratory results will be recorded and all clinically significant laboratory results (scheduled and unscheduled) obtained during the study period will be reported as AEs (e.g., Grade ≥ 2 aspartate aminotransferase, alanine aminotransferase, or serum bilirubin).

8.10 Contraception and Pregnancy Testing and Reporting

Patients who are WOCBP will have a serum pregnancy test performed at Screening and a urine pregnancy test performed on Day 1 (before dosing) of every cycle and at the EOT Visit. If a patient's serum pregnancy test at screening is within 72 hours of their first dose of study drug, a negative urine pregnancy test on Cycle 1 Day 1 is not required. Additional pregnancy testing may be performed according to institutional practice.

Patients who are WOCBP and male patients whose partners are WOCBP will be counseled on the importance of avoiding pregnancy during the study and after the final dose of study drug.

WOCBP must use a highly effective method of contraception during the study and for at least 3 months after the last dose of study drug. Highly effective contraceptive measures include, but are not limited to the following:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, etc.) associated with inhibition of ovulation
- Progestogen-only hormonal contraception (oral, etc.) associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner

[redacted] For this study, male abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Periodic abstinence, withdrawal (coitus interruptus), or the use of spermicides only are not acceptable methods of contraception.

All patients will be instructed to report any suspected pregnancies in themselves or their female partners during the study. The Investigator must report the pregnancy by completing the EIU form and emailing the completed form to [redacted] within 24 hours of awareness.

If a female patient becomes pregnant, she should immediately discontinue the study drug and receive appropriate monitoring and care until the conclusion of the pregnancy.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons. However, the pregnancy should be followed until the outcome is known. Once the outcome of the pregnancy is known, the EIU form should be completed within 24 hours of awareness and emailed to [redacted]

If the pregnancy outcome is spontaneous abortion, stillbirth, neonatal death, infant with congenital anomaly, or a postpartum complication, the Investigator must also report the outcome as an SAE by completing the required information on the AE CRF.

8.11 Physical Examinations

Complete physical examinations, including a review of all body systems, will be performed at the visits indicated in the Schedule of Events (Table 1 [milademetan arm] and Table 4 [trabectedin arm]). Height and weight will be recorded at the Screening and EOT Visits. Weight will be recorded at all other visits. Clinically significant findings observed during the physical examination will be reported as medical history (pretreatment) or AEs (post-treatment).

8.12 Eastern Cooperative Oncology Group

All patients will be assessed at screening, Day 1 of each Cycle, and EOT using the ECOG Performance Status Scale (Table 166). An ECOG performance score of 0 to 1 is required for study entry but is not a criterion for retreatment or study drug discontinuation.

Table 16: ECOG Performance Status Scale

ECOG Performance Status Scale	
Grade	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group
Source: Oken 1982

8.13 Pharmacokinetics

[redacted]

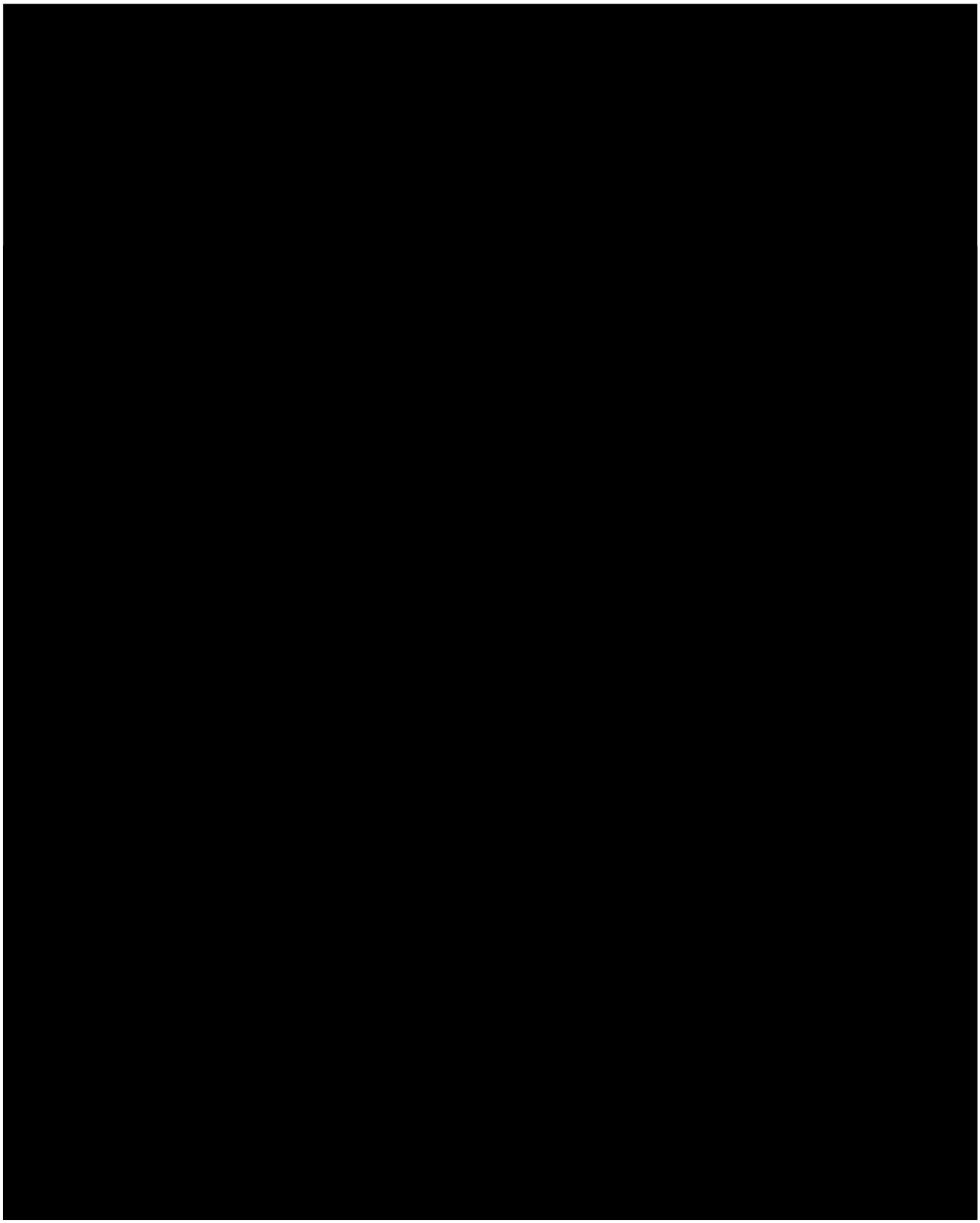
8.13.1 Subgroup of Patients Undergoing Intensive Pharmacokinetic Assessments at Selected Study Centers

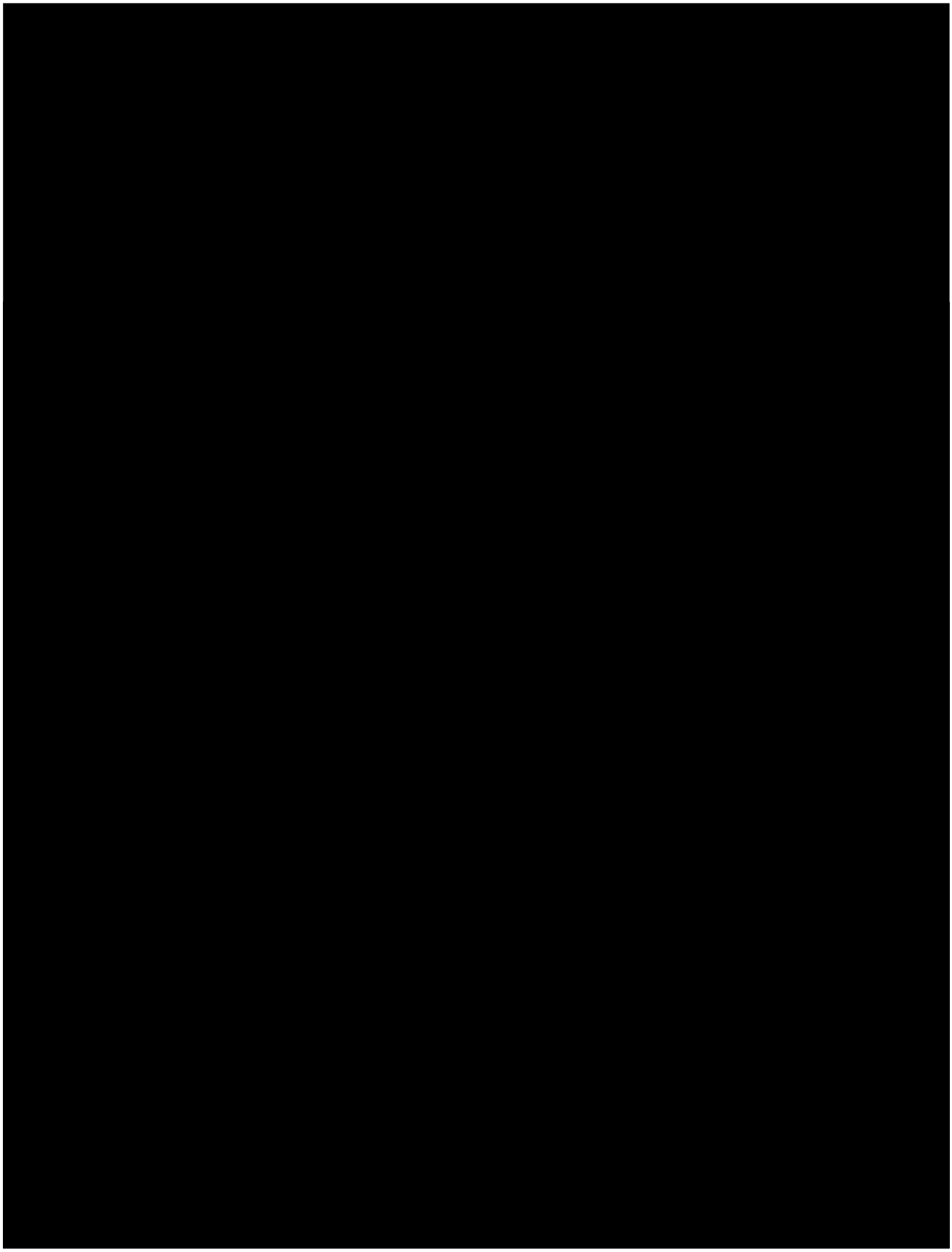
[redacted]

[redacted]

8.14 Tumor Tissue

[redacted]





10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Data Quality Assurance

The Sponsor (or designee) will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of the responsibilities and procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded in the electronic data capture (EDC) system for this study must be consistent with the patients' source documentation (i.e., medical records).

10.1.1 Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study center using an EDC system. Data from external sources, such as laboratory data, will be entered into the database. Once the EDC clinical data have been submitted to the central server at the

independent data center, corrections to the data fields will be captured in an audit trail. The reason for the change and name of the person who performed the change, together with the time and date, will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the EDC.

The specific procedures to be used for data entry and query resolution using the EDC system will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system.

11. ETHICS

11.1 Informed Consent

Before each patient is admitted to the study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. This consent form must be signed, dated, and retained by the Investigator or designee (designee must be listed on the Delegation of Authority Log) as part of the study records. The Investigator will not undertake any study-specific procedures until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the EDC system. A copy of each signed informed consent form must be provided to the patient at the time it is signed by the patient.

Patients may elect to provide optional tumor biopsies. These samples will be collected only if the patient provides additional consent.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

11.2 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor (or designee) must ensure that all ethical and legal requirements have been met before the first patient provides consent to participate in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written and approvals received from the appropriate personnel and IRB/IEC/Competent Authority before implementation (if appropriate).

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients with appropriate instructions.

11.3 Duration of the Study

The total study duration is estimated to be 4 years, including approximately 12 months for accrual of patients, up to 12 months of treatment for each patient, and up to 24 months of long-term follow-up following the first dose of study drug of the last patient enrolled. The end of the study is defined as the last patient visit or contact, including telephone contacts, for collection of any study-related data.

11.4 Premature Termination of the Study

If the Investigator, Sponsor, or Medical Monitor become aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure to enroll patients at an acceptable rate
- A decision on the part of the Sponsor to suspend or discontinue development of the drug

11.5 Confidentiality

All goods, materials, information (oral or written), and unpublished documentation provided to the Investigator (or any company acting on their behalf), inclusive of this protocol; the patient eCRFs; and the milademetan Investigator's Brochure are the exclusive property of the Sponsor. Documents and information provided to the Investigator by the Sponsor may not be given or disclosed by the Investigator or by any person within his authority in part or in totality to any unauthorized person without the prior written formal consent of the Sponsor.

It is specified that the submission of this protocol and other necessary documentation to the IRB or IEC is expressly permitted, with the IRB or IEC members having the same obligation of confidentiality.

The Investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced during the study, other than that information to be disclosed to a third party mandated by applicable law.

Any language relating to these issues appearing in the Clinical Trial Agreement will supersede that outlined in this section.

The anonymity of participating patients must be maintained. Patients will be identified in the EDC system and other documents submitted to the Sponsor (or designee) by their patient number, initials, and/or birth date, not by name. Documents not to be submitted to the Sponsor

(or designee) that identify the patient (e.g., the signed informed consent form) must be maintained in confidence by the Investigator.

Information on maintaining patient confidentiality in accordance with individual local and national patient privacy regulations must be provided to each patient as part of the informed consent process either as part of the informed consent form or as a separate signed document (for example, in the US, a site-specific Health Insurance Portability and Accountability Act of 1996 consent may be used). The Investigator or designee must explain to each patient that for the evaluation of study results, the patient's protected health information obtained during the study may be shared with the Sponsor and its designees, regulatory agencies, and IRBs/research ethics boards/IECs. The study Sponsor will not use the patient's protected health information or disclose it to a third party without applicable authorization. It is the Investigators or designee's responsibility to obtain written permission to use protected health information from each patient. If a patient withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the patient and to ensure that no further data will be collected from the patient. Any data collected on the patient before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the patient will be respected with strict adherence to professional standards and regulations.

12. DATA HANDLING AND RECORD KEEPING

12.1 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the EDC system promptly. All source documents from which EDC entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments, ECG recordings, CT scans, MRI, and X-rays. EDC entries may be checked against source documents at the study site or remotely by the Sponsor (or designee) site monitor. After review by the site monitor, completed EDC entries will be uploaded and forwarded to the Sponsor (or designee). Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

The specific procedures to be used for data entry and query resolution using the EDC system will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system.

12.1.1 Data Collection

The Investigators (and appropriately authorized staff) will be given access to an online web-based EDC system which is compliant with the International Council for Harmonisation guidelines on Good Clinical Practice (ICH E6). This system is specifically designed for the collection of the clinical data in electronic format. Access and right to the EDC system will be carefully controlled and configured according to everyone's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each patient included in the study and reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or immediately after the patient's visit or assessment. The Investigator must verify that all data entries in the eCRF are accurate and correct.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on-line directly by the Investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the Investigator will be required to electronically sign off the clinical data.

Data about all study drug dispensed or administered to the patient and any dosage changes will be tracked on the eCRF.

12.2 Access to Source Data

Patients are informed who may have access to their medical records and study data. During the study, a monitor will make site visits or conduct remote monitoring to review protocol compliance, compare EDC entries with individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements. EDC entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Appropriate access controls will be in place to ensure that access to confidential research information is restricted to those who need access.

Checking of the EDC entries for completeness and clarity and cross-checking with source documents will be required to monitor the progress of the study. Moreover, Regulatory Authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor (or designee) the necessary access at all times.

12.3 Data Processing

All data will be entered by site personnel into the EDC system. The data -review and data -handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data -handling rules for obvious data errors. Query/correction sheets for unresolved queries will be sent to the study monitors for resolution with the Investigator. The database will be updated based on signed corrections.

Concomitant medications will be coded using the WHODrug Global dictionary, which employs the ATC classification system. Medical history including all anticancer treatment, current medical conditions, and AEs will be coded using MedDRA terminology. The versions of the

coding dictionaries will be provided in the clinical study report. When personal data is transferred electronically, data will be encrypted during transfer.

12.4 Archiving Study Records

Per 21 CFR 312.62(c), Investigators shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. However, documents may be retained for a longer period if required by the applicable legal requirements.

The Sponsor will maintain archive copies of all records for a period of no less than 25 years.

13. PUBLICATION POLICY

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without discussion with and approval by the Sponsor.

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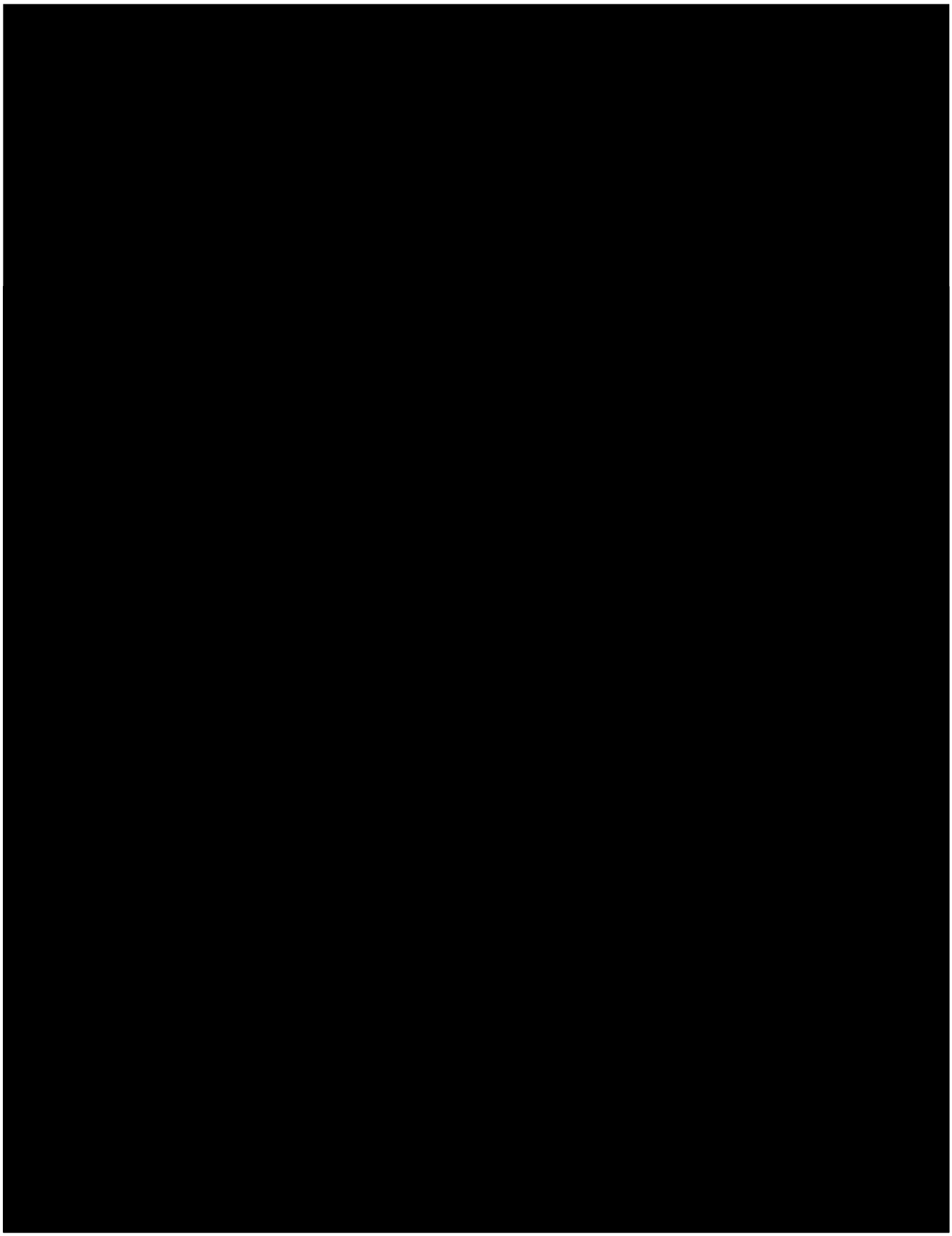

DECLARATION OF THE INVESTIGATOR

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, milademetan Investigator's Brochure, electronic data capture system, and other scientific data. I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol, including the following statements:

- I will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of patients.
- I will personally, conduct or supervise the described investigation.
- I will inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and approval provided in the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (ICH E6) and local requirements are met.
- I will report to the Sponsor adverse experiences that occur in the course of the investigation(s) in accordance with ICH E6 and local requirements. I have read and understand the information in the protocol and milademetan Investigator's Brochure, including the potential risks and side effects of the drug.
- I will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- I will maintain adequate and accurate records in accordance with the ICH E6 and local requirements including making these records available for inspection.
- I will ensure that an IRB/IEC that complies with ICH E6 and local requirements will be responsible for the initial and continuing review and approval of the clinical investigation. I will also promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risks to patients or others. Additionally, I will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to patients.
- I will comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in accordance with ICH E6 and local requirements.

I understand that before I publish any findings from this study in scientific journals or present these at scientific meetings, I must first provide the Sponsor with ample opportunity to review the intended use of the study data. The Sponsor must authorize the disclosure of study data for any proposed abstract, manuscript, or meeting materials prior to their submission.

Responsible Investigator

Signature	Date
Name (Printed)	
Title (Printed)	