CLINICAL STUDY PROTOCOL

A PHASE 1 MULTIPLE ASCENDING DOSE STUDY OF MILADEMETAN, AN ORAL MDM2 INHIBITOR, IN SUBJECTS WITH ADVANCED SOLID TUMORS OR LYMPHOMAS

PROTOCOL NUMBER: DS3032-A-U101

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VERSION 3.0, 29 SEP 2015

VERSION 2.0, 03 MAR 2015

VERSION 1.0, 25 MAR 2013

DAIICHI SANKYO, INC.

211 Mt. Airy Road

Basking Ridge, NJ 07920-2311

United States

INVESTIGATOR AGREEMENT

A PHASE 1 MULTIPLE ASCENDING DOSE STUDY OF MILADEMETAN, AN ORAL MDM2 INHIBITOR, IN SUBJECTS WITH ADVANCED SOLID TUMORS OR LYMPHOMAS

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo, Inc. (DSI) representative listed below.

PPD	PPD
Print Name	Signature
Senior Director Clinical Development Oncology	12 Feb 2020
Title	Date (DD MMM YYYY)

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from DSI. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives, and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	Signature
Title	Date (DD MMM YYYY)

SUMMARY OF CHANGES

Amendment Rationale:

This amendment was prepared to allow evaluation of less frequent dosing schedules of once daily for 7 out of 28 days (QD 7/28) and QD for 3 out of 14 days (QD 3/14) repeated twice in a 28-day cycle; remove restrictions on the timing of meal relative to the drug administration, remove the restriction of concomitant use of medications that are strong inhibitors of cytochrome P450 (CYP) 3A.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Changes to the Protocol:

Please refer to the comparison document for protocol Version 4.0 (dated, 04 Feb 2020) vs. protocol Version 3.0 (dated, 29 Sep 2015) for actual changes in-text. The summary of changes below is a top-line summary of major changes in the current DS3032-A-U101 clinical study protocol (Version 4.0) by section.

CONVENTIONS USED IN THIS SUMMARY OF CHANGES		
All locations (Section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in this Summary of Changes.		
Minor edits, such as updates to language that do not alter original meaning, update to version numbering, formatting, change in font color, corrections to typographical errors, use of abbreviations, moving verbiage within a section or table, change in style, or changes in case, are not noted in the table below.		
Section # and Title	**Description of Change**	**Brief Rationale**
General	Changed DS-3032b to milademetan.	International nonproprietary name provided.
Cover Page	Company name and address changed.	Company name changed and moved to new location.
Sponsor Approval	Approver changed to Prasanna Kumar, PhD.	Change in personnel.
Protocol Synopsis (Part 1 Secondary Objectives) Section 3.1.2.1 Part 1 (Dose Escalation)	Part 1 Secondary Objectives: moved from exploratory to secondary objective: To evaluate the response of solid tumors and lymphoma and their subtypes to milademetan using the Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 or International Working Group (IWG) criteria.	To include efficacy signals as one of the criteria to select the most optimal dosing schedule during dose escalation.

Section # and Title	Description of Change	Brief Rationale
Protocol Synopsis (Part 1 Exploratory Objectives) Protocol Synopsis (Part 2 Dose Expansion, Exploratory Objectives) Section 3.1.3.1 Part 1 (Dose Escalation) Section 3.1.3.2 Part 2 (Dose Expansion)	Added assessment of blood and tumor samples for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) analysis.	For molecular analysis of tumor DNA and RNA and circulating free DNA to identify predictors of response, resistance and toxicity to milademetan.
Protocol Synopsis (Part 1 Exploratory Objectives) Protocol Synopsis (Part 2 Dose Expansion, Exploratory Objectives) Section 3.1.3.1 Part 1 (Dose Escalation) Section 3.1.3.2 Part 2 (Dose Expansion)	Deleted specifics of assessing pharmacodynamic (PDy) effect on reticulocyte and absolute neutrophil count and added if samples are available.	Language edited for flexibility, since post-treatment tumor samples are not always available.
Protocol Synopsis (Part 2 Dose Expansion, Secondary Objectives) Section 3.1.2.2 Part 2 (Dose Expansion)	Deleted evaluation of relationship of tumor response to milademetan and predictive biomarkers.	Moved to exploratory objective because validated predictive biomarkers are not available yet.
Protocol Synopsis (Part 2 Dose Expansion, Exploratory Objectives) Protocol Synopsis (Study Design) Protocol Synopsis (Study Design-Part 2 Dose Expansion in Subjects with Advanced Melanoma or DLBCL) Figure 2: Flow Diagram of Food SubStudy Part 2 Section 3.1.3.2 Part 2 (Dose Expansion) Section 7.3.2.2. Part 2 (Dose Expansion), Cycle 1/Day 1) Section 7.3.2.7. Part 2 (Dose Expansion), Cycle 2/Day 1) Section 7.3.2.8. Part 2 (Dose Expansion), Cycle 2/Day 2)	Deleted food effect component of study; deleted from objective, study design.	A separate food effect study on milademetan pharmacokinetic (PK) (DS3032-A-U115) has been completed.
Protocol Synopsis (Part 2 Dose Expansion, Exploratory Objectives)	Added evaluation of relationship between tumor response to milademetan and predictive	Moved from secondary objective to exploratory objective; the biomarkers are

Section # and Title	Description of Change	Brief Rationale
Section 3.1.3.2 Part 2 (Dose Expansion)	biomarkers in tumor samples.	still under exploration.
Protocol Synopsis (Primary and Secondary outcome measure) Section 3.2 Outcome Measures Section 3.2.1 Primary Outcome Measures Section 3.2.2 Secondary Outcome Measures	Added outcome measures and corresponding details for each; timeframe from start of study for approximately 6 years for all; end differs as detailed). Outcome measures are: Primary: number of subjects with treatment-emergent adverse events (TEAEs) during study until last subject last visit, maximum tolerated dose until final data base lock, number of subjects with dose-limiting toxicities (DLTs) until the DLT evaluation of the last subject in dose escalation part, response rates in melanoma and diffuse large B-cell lymphoma (DLBCL) in dose expansion cohorts until last subject last tumor assessment in Dose Expansion. Secondary: PK parameters and pharmacodynamic effect of milademetan until final database lock.	New Daiichi Sankyo, Inc. requirement to comply with CTgov and EudraCT disclosure guidelines.
Protocol Synopsis (Study Design)	Added schedule for dose escalation: (eg, QD 28/28, QD 7/28, QD 3/14 × 2).	Clarification.
Protocol Synopsis (Study Design-Part 1 Dose Escalation)	Revised maximum tolerated dose (MTD) model: removed modified continuous reassessment method (mCRM) throughout; kept Bayesian logistic regression model (BLRM). Replaced mCRM with BLRM throughout.	Clarification that the escalation is essentially based on BLRM.

Section # and Title	Description of Change	Brief Rationale
Protocol Synopsis (Study Design-Part 1 Dose Escalation-Dose escalation using alternative drug administration schedule) Section 4.1.2.1 Part 1 (Dose Escalation)	Added less frequent dosing schedule to be evaluated with a starting dose of 120 mg that was the MTD determined in the QD × 21/28-day schedule: QD for 7 out of 28 days (QD × 7/28 days) QD for 3 out of 14 days (QD × 3/14 days) repeated twice in a 28-day cycle	Alternative less frequent dosing schedule to optimize milademetan treatment in dose escalation.
Protocol Synopsis (Study Design-Part 2 Dose Expansion in Subjects with Advanced Melanoma or DLBCL) Section 4.1.2.2 Part 2 (Dose Expansion in Subjects With Advanced Melanoma or DLBCL)	Revised text for definition of when dose expansion will begin to the establishment of MTD/tentative recommended Phase 2 dose (RP2D) and drug administration schedule in Part 1. Revised text from PDy response to PDy signals. Added assessment will be in approximately 20 subjects and added that tumors tested positive for wild type gene encoding p53 (TP53) genotype.	Clarification.
Protocol Synopsis (Study Design-Part 2 Dose Expansion in Subjects with Advanced Melanoma or DLBCL) Section 4.1.2.2 Part 2 (Dose Expansion in Subjects With Advanced Melanoma or DLBCL)	Modified sentence: If the incidence of adverse events fulfilling the criteria of a DLT has exceeded that predicted by the escalation with overdose control (EWOC) principle, after the initial 4 DLT-evaluable subjects or after further enrollment, no further testing at the MTD/tentative RP2D level established in Part 1 will be done and dose de-escalation or treatment at alternative dose schedules may be considered for further evaluation of safety and efficacy.	Clarification.
Protocol Synopsis (Study Design-Part 2 Dose Expansion in Subjects with Advanced Melanoma or DLBCL)	Edited the language to clarify that 20 subjects each of melanoma and DLBCL with wild type TP53 will be enrolled in Part 2 classifier criteria.	Clarification.
Protocol Synopsis (Study Design-	Added to include dose expansion.	Clarified who needs to be

Section # and Title	Description of Change	Brief Rationale
Part 2 Dose Expansion TP53 genotyping, subject enrollment and early discontinuation criteria)-	Modified language that only the investigator will be informed if the test confirms the presence of inactivating TP53 mutations. Removed allowing subject to continue if genotyping indeterminate. Removed details of methodology of TP53 genotyping, specifications of type of samples, handling of results, and re-testing.	informed and the result that should be shared with the investigator as it pertains to the study conduct.
Protocol Synopsis (Part 2 [Dose Expansion in Subjects with Advanced Melanoma or DLBCL]) Section 4.1.2.2. Part 2 (Dose Expansion in Subjects With Advanced Melanoma or DLBCL)	Added to end of section: "for further evaluation of safety and efficacy."	Clarification.
Protocol Synopsis (Dose-Limiting Toxicity Definition) Section 4.1.5.2 Dose-limiting Toxicities	Deleted Grade ≥ 3 for febrile neutropenia.	Febrile neutropenia is already Grade ≥ 3.
Protocol Synopsis (Study Design-Part 2 Dose Expansion TP53 genotyping, subject enrollment, and early discontinuation criteria)- Protocol Synopsis (Subject Eligibility Criteria) Section 5.1.2 Exclusion Criteria Section 5.2 Removal of Subjects from Therapy Section 5.2.1 Reasons for Withdrawal/Early Discontinuation Section 9.2.1. TP53 Status	In synopsis: deleted redundant text and added inclusion criterion 14, applicable to Part 2 only: subject willing to undergo pre-treatment tumor biopsies. Exclusion criteria header revised to indicate criteria apply to both Part 1 and Part 2. Deleted "contains a nonsynonymous mutation" Added "contains an inactivating mutation" Added "contains an inactivating mutation" to Part 1 and Part 2 exclusion criteria. Added clarification that whenever subject withdraws, they will be followed for 30 days or beyond until resolution of toxicity.	"Containing an inactivating mutation" or "contain an inactivating mutation" added for further clarity.
Protocol Synopsis (Study Duration)	Changed from 3 to 6 years.	Update of study duration.
Protocol Synopsis (Study Sites	Modified that 5 sites to be used	Clarification that the same sites

Section # and Title	Description of Change	Brief Rationale
and Location)	for both escalation and expansion.	to be used for both parts.
Protocol Synopsis (Planned Sample Size)	Changed text to potentially evaluate multiple dosing schedules. Added that sample size is not known because of the multiple dosing schedules to be evaluated to determine the most optimal schedule. Defined subject population further as advanced melanoma and DLBCL. Removed details on obtaining 10 biomarker positive subjects.	Update on sample size
Protocol Synopsis (Planned Sample Size) Section 12.10 Sample size Determination	Removed: "with biomarker-positive tumors" from paragraph: For the Dose Expansion phase (Part 2), approximately 20 subjects (each of subjects with advanced melanoma and DLBCL) will be enrolled.	Clarification.
Protocol Synopsis (Subject Eligibility Criteria) Section 5.1.1 Inclusion Criteria	For Part 2 Inclusion Criteria, removed text indicating additional inclusion criteria for solid tumor/lymphoma expansion; revised to melanoma/DLBCL. For Part 1 and Part 2: Added bullet under criteria 1 that subjects with certain tumor types (eg, well-differentiated (WD)/dedifferentiated (DD) liposarcoma) may be preferentially enrolled in Part 1.	Clarification.
Protocol Synopsis (Statistical Analysis)	Added for tumor response that additional efficacy analyses, including progression free survival and spider plots, will be detailed in the statistical analysis plan (SAP).	Clarification.
Section 2.1.1.5. Nonclinical Studies	Deleted nonclinical sections for pharmacology, safety pharmacology, absorption, distribution, metabolism,	Clinical data are now available and this information moved to the current Investigator's Brochure (IB).

Section # and Title	Description of Change	Brief Rationale
	excretion, toxicokinetics, toxicology, and phototoxicity.	
Section 2.1.1.5.1 Human Starting Dose Section 2.1.1.6 Clinical Experience Section 2.3.1 Potential Risks Associated with Milademetan 2.3.2 Potential Risk of Drug-Drug Interaction	Text added for reader to refer to current IB.	Clinical data are now available in the current IB.
Protocol Synopsis (Dosage Form, Dose and Route of Administration) Section 2.4 Population, Route, Dosage, Dosage Regimen, Treatment Period Section 6.1 Investigational Products	Two other capsule strengths of 30 and 100 mg added.	Additional strengths now available.
2.3.2 Potential Risk of Drug-Drug Interaction	Data added detailing completed Phase 1 study in healthy subjects evaluating the effect of co-administration of strong CYP3A4 inhibitors and instructing the investigator to reduce dose of milademetan to half when concomitantly administered with strong CYP3A4 inhibitors.	Important safety data for CYP3A4 inhibitors available and the summary needed to be highlighted in the protocol.
Section 3.3 Study Hypothesis	Revised to solid tumors and lymphomas vs. melanoma and DLBCL.	Clarification.
Section 4.1.1 Study Type	New header and text added describing study and number of sites.	New template.
Section 4.1.2 Treatment Groups	Section revised. Text added that safety and tolerability will be determined by the PDy response in tumor samples and preliminary efficacy will be determined in advanced melanoma or DLBCL. Dosing schedule specified as QD × 21/28 days but option based on results to use an alternative dosing schedule if there is clinical benefit.	Clarification.

Section # and Title	Description of Change	Brief Rationale
Section 4.1.2.1 Part 1 (Dose Escalation)	Added text that the MTD will be guided by a BLRM following EWOC principle after an initial accelerated titration design (ATD) and that this will minimize the number of subject treated at sub-therapeutic doses. Toxicity levels for decision making for enrollment of next dose and defining DLT for the ATD were specified. EWOC principle requirements for BLRM recommended dose for the next cohort of subjects added. Identification of Sponsor's clinical team and investigators as determining the selection of the dose to be tested in the next cohort of subjects. Defined that safety, PK and PDy data collected using QD × 21/28-day schedule determines the alternative drug administration schedule. Also added that if the alternative dosing schedule provides less toxicity and more benefit, this alternative dosing schedule will be used in lieu of or in parallel with the QD × 21/28-day schedule. Scenarios defining the situations where this would apply were defined; Case 1 (starting dose less frequent than QD × 21/28-day schedule) added. For Case 3, added that the first cohort to be evaluated will begin treatment with milademetan at 90 mg QD × 21/28 days, preferentially in subjects with liposarcoma. Added criteria for dose reduction in the case of platelet decrease or thrombocytopenia. Added less frequent dosing schedules to be considered if the	Clarification.

Section # and Title	Description of Change	Brief Rationale
	starting dose of 120 mg is the MTD. Both the original QD × 21/28 days and alternative dosing schedules are explored in parallel. The final MTD for each dosing schedule will be decided based on considerations of the respective MTDs estimated by the BLRM, and on an overall assessment of safety data from subsequent cycles and PK/PDy information collected at all different doses tested. Upon determining the final MTD of the original QD × 21/28 days and/or alternative dosing schedules, one dosing regimen will be selected for further evaluation in Part 2 (Dose Expansion) and as the tentative RP2D.	
Section 4.1.2.2 Part 2 (Dose Expansion in Subjects With Advanced Melanoma or DLBCL)	Added: Upon establishing MTD/tentative RP2D and drug administration schedule in Part 1, the Dose Expansion part will begin with the intention of confirming the safety and tolerability of milademetan, determining the PDy signals in tumor samples, and evaluating preliminary efficacy of milademetan in approximately 20 subjects each with advanced melanoma and DLBCL whose tumors are tested positive for wild-type TP53 genotype.	Clarification.
Section 4.1.2.2 Part 2 (Dose Expansion in Subjects With Advanced Melanoma or DLBCL)	Tumor re-biopsy added: To search for possible mechanisms of acquired resistance to milademetan, an optional tumor re biopsy may be performed within 30 days following the last dose of milademetan treatment for subjects who have achieved an	Clarification.

Section # and Title	Description of Change	Brief Rationale
	initial complete response (CR)/partial response (PR) or stable disease for at least 6 months by standard response criteria but later developed progressive disease (PD) while on therapy (both in Dose Escalation and Dose Expansion), preferably prior to initiating new therapy.	
Section 4.1.2.2 Part 2 (Dose Expansion in Subjects With Advanced Melanoma or DLBCL) Section 9.2.1. TP53 Status	Added to TP53 genotyping, subject enrollment, and early discontinuation criteria: During Dose Escalation and Dose Expansion, tumor TP53 genotyping will be performed in archived formalin-fixed paraffin-embedded and, if available, fresh tumor biopsies in all enrolled subjects. Confirmation of TP53 wild-type status is NOT required prior to milademetan dosing. The investigator will be informed if the genotyping confirms the presence of inactivating TP53 mutations: testing result shows that a subject's malignant cells contain an inactivating mutation, insertion, or deletion in the TP53 gene. If study treatment has already begun, the subject may choose to discontinue study drug or continue study drug as long as clinical benefit is noted per the investigator's judgment.	Deleted text as there is not an established sensitive gene expression signature, nor do all TP53 wild type represent a sensitive population.
Section.9.2.1. TP53 Status	Revised during dose expansion that tumor samples may be analyzed for DNAseq and by RNAseq.	
Protocol Synopsis Section.9.2.1. TP53 Status	Deleted "Nonmutant PT53 genotype and/or presence of a sensitive gene expression signature constitute the "biomarker positive" population.	
Section 5.2.2 Withdrawal Procedures	Deleted: Protocol-specified withdrawal procedures are the same as those to be performed at	Clarification.

Section # and Title	Description of Change	Brief Rationale
	the End-of-Treatment Visit.	
Section 5.2.4 Subject Re-Screening Procedures	Added to end of paragraph: … re-screened subjects, except for those that were not repeated during re-screening (eg, tumor biopsies) or other tests that are still valid within the screening window per the medical monitor	Clarification.
Section 6.2.1. Prohibited Concomitant Medications/Activities	Added that if drugs that are strong inhibitors of CYP3A need to be taken concomitantly, then milademetan dose must be reduced to half the assigned dose. Added Seville oranges as prohibited.	Clarification.
Section 7.3.1.5. Part 1 (Dose Escalation), Cycle 1/Days 18 to 21	Added: (For subjects enrolled in the QD × 7/28 days schedule, this visit is needed only if there are unresolved Grade ≥ 3 adverse events (AEs) or Grade ≥ 2 thrombocytopenia on Day 15 that need follow up).	Clarification (because there is no drug administration or other assessments at this time point in the QD × 7/28 day schedule)
Section 7.3.1.11. Part 1 (Dose Escalation), Cycle 4 and All Subsequent Cycles, Day 1	Added: For Cycle 4 Day 1 and beyond: subjects who completed more than 1 year of treatment with continued clinical benefit and no ongoing Grade ≥ 3 TEAEs or risk thereof in the judgment of the investigator are allowed to continue on with the subsequent visits at every other cycle, and may have additional visits as clinically needed.	To allow less frequent visits for subjects after confirmation of safety, tolerance, and benefit for more than 1 year on treatment.
Section 7.3.2.12. Part 2 (Dose Expansion), Cycle 4 and All Subsequent Cycles, Day 1	Added: For Cycle 4 Day 1 and beyond: subjects who completed more than 1 year of treatment with continued clinical benefit and no ongoing Grade ≥ 3 TEAEs or risk thereof in the judgment of the investigator are allowed to continue on with the subsequent visits at every other cycle, and	To allow less frequent visits for subjects after confirmation of safety, tolerance, and benefit for more than 1 year on treatment.

Section # and Title	Description of Change	Brief Rationale
	may have additional visits as clinically needed.	
Section 7.3.1.5. Part 1 (Dose Escalation), Cycle 1/Days 18 to 21	Added: (For subjects receiving study drug under the QD 7/28 days or QD 3/14 days schedules, the blood sample collection [exploratory blood samples, PK samples, ad macrophage inhibitory cytokine-1 (MIC-1) induction] on Cycle 1 Days 18 to 21 is not required)	Clarification that the sample collection in the said schedules are not need at this time point due to time lag after the last dose.
Section 8.1. Efficacy Variable(s)	Added: As a complementary approach to the exploratory objective #2 in Part 1 (Section 3.1.3.1), particularly in WD/DD liposarcoma that are preferentially enrolled in the study due to high prevalence of murine double minute 2 amplification, the growth rates of the target tumors before starting milademetan versus on-treatment with milademetan may be analyzed by capturing the target tumor measurements by local reading in 2 or more prior scans from the medical records, if available. Additionally, a digital or electronic copy of the computed tomography (CT)/magnetic resonance imaging (MRI) scans performed for RECIST v 1.1 assessment may be collected by the sponsor for centralized analysis by sponsor-appointed radiologist(s) as a post-hoc exploration of the effect of milademetan on specific tumor histologies (eg, WD/DD liposarcoma). Deleted: If feasible, multiple pre-screening CT/MRI scans may be collected and included in the analysis to	Additional exploratory analysis of the tumor responses in solid tumor subpopulations (WD/DD liposarcoma).

Section # and Title	Description of Change	Brief Rationale
	compare the progression rate before milademetan treatment vs tumor response after starting milademetan. Any additional results will also be data protected for privacy.	
Section 9.1 Pharmacokinetic Assessment(s)	Revised blood samples collected for PK analysis of milademetan. Added table Description of PK parameter analyses moved to Section 12.5.1.	Clarification of the PK sample collections for the different dosing schedules with a table and footnotes.
Section 9.2.1. TP53 Status	Revised to DNAseq and RNAseq vs sensitive gene expression signature.	Revised to the exploratory analysis by DNAseq and RNAseq, because a sensitivity gene expression signature was not available.
Section 10.4.3 Grade Assessment	Added National Cancer Institute Common Terminology Criteria for Adverse Events guidelines for certain AEs and clarification that for each episode, the highest severity grade attained should be reported. Life-threatening definition modified to include urgent intervention indicated.	Clarification.
Section 12.2. 3 Biomarker Positive Analysis Set	Deleted.	Deleted because of the absence of a validated sensitivity biomarker.
Section 12.2.4. Dose-Limiting Toxicity Evaluable Set	Added to further define as milademetan doses during the first 3 weeks (21 days).	Clarification.
Section 12.2.6. Pharmacokinetic Analysis Set	Added that subjects in this analysis set had any amount of milademetan and had measurable plasma concentrations of DS-3032a (the free form of milademetan).	Clarification.
Section 12.2.7. Biomarker Analysis Set	New text: The PDy biomarker analysis set will include all subjects in the enrolled analysis set who received any amount of milademetan and who had the baseline assessment	Definition of PDy biomarker analysis set added.

Section # and Title	Description of Change	Brief Rationale
	and where applicable, at least 1 post-baseline assessment for biomarkers.	
Section 12.4.1. Primary Efficacy Analyses	Added: Change in tumor size comparing to pretreatment/historical data will be presented graphically. Additional details will be presented in the SAP.	Additional exploratory analysis of tumor response.
Section 12.4.2. Secondary Efficacy Analyses	Added: In addition, the growth rates of the target tumors before starting milademetan based on prior scans from subjects' medical records versus on-treatment with milademetan may be summarized. Additional analyses will be described in the SAP.	Additional exploratory analysis of tumor response.
Section 12.5.1. Pharmacokinetic Analyses	Revised section that plasma concentration data will be summarized using descriptive statistics, and a table was added for the parameters to be analyzed in the dose escalation and expansion phases using non-compartmental analyses. Added that Population pharmacokinetic (PopPK) and exposure response may be developed but will be provided separately along with results.	Clarification with the table and footnotes to explain the PK sample collections for the different dosing schedules.
Protocol Synopsis (Predictive Biomarker Parameters) Section 9.2.3. Exploratory Biomarker Analysis Section 12.5.3. Biomarker and Exploratory Analyses	Added that pre-treatment, on-treatment, and end-of-treatment tumor samples will be examined. Deleted: "in the form of multi-gene and/or protein signature " and p14, p16, and CDKN2A.	Clarified the biomarker analysis of tumor samples and removed the multigene and/or protein signature that is not available yet.
Section 12.11. Specification of Bayesian Logistic Regression Model with Escalation with Overdose Control	Removed mCRM throughout.	Clarification by replacing mCRM with BLRM.
Table 18.2 Schedule of Events Part 1 (Dose Escalation)	Added to sampling for exploratory blood samples, PK	Updates of the schedule of events and footnotes for all the

Section # and Title	Description of Change	Brief Rationale
	collection and MIC-1 induction, that these samples are not required of subjects receiving study drug under the QD 7/28 days or QD 3/14 days schedules, the blood sample collection on Cycle 1 Days 18 to 21.	different dosing schedules.
Table 18.2 Schedule of Events Part 1 (Dose Escalation) Table 18.3 Schedule of Events Part 2 (Dose Expansion)	Abbreviations added and updated. Text added to electrocardiogram footnote regarding subjects enrolled per Case 3. PK sampling schedule updated.	Updated to match updates in text.
Table 18.4 Schedule of Events (Extension Phase)	New footnote added: For subjects who completed more than 1 year of study drug with continued clinical benefit and no ongoing clinically significant TEAEs or at risk of clinically significant TEAEs in the judgment of the investigator, the subsequent visits every other cycle, and additional visits as clinically indicated, is allowed. Footnote modified from every other cycle to every 3 cycles and as clinically indicated.	To allow less frequent visits for subjects after confirmation of safety, tolerance, and benefit for more than 1 year on treatment.

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

IND Number:	118125
Protocol Number:	DS3032-A-U101
Investigational Product:	Milademetan (DS-3032b)
Active Ingredient(s)/INN:	(3'R,4'S,5'R)-N-[(3R,6S)-6-Carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate
Study Title:	A Phase 1 Multiple Ascending Dose Study of Milademetan, an Oral MDM2 Inhibitor, in Subjects with Advanced Solid Tumors or Lymphomas
Study Phase:	Phase 1
Indication Under Investigation:	Milademetan will be evaluated in subjects with advanced solid tumors or lymphomas that are refractory to standard therapy or for which no standard therapy is available.
Study Objectives:	**Part 1 (Dose Escalation)** Primary Objectives: To assess the safety and tolerability of milademetan in subjects with advanced solid tumors or lymphomas who have relapsed from or are refractory to standard therapy or for whom no standard therapy is available. To determine the maximum tolerated dose (MTD) or tentative recommended Phase 2 dose (RP2D) of milademetan in subjects with advanced solid tumors or lymphomas. Secondary Objectives: 1. To determine the plasma pharmacokinetics (PK) of DS-3032a (the free form of milademetan). 2. To determine the pharmacodynamic (PDy) effect of milademetan on macrophage inhibitory cytokine-1 (MIC-1) levels in serum. 3. To evaluate the response of solid tumors and lymphoma

and their subtypes to milademetan using the corresponding standard response criteria (Response Evaluation Criteria in Solid Tumors [RECIST] v 1.1 or revised International Working Group [IWG] criteria, respectively).

Exploratory Objectives:

1. To compare progression free survival (PFS) between that observed with milademetan treatment and that observed from the most recent therapeutic regimen.
2. To bank blood samples for deoxyribonucleic acid (DNA) analysis for the assessment of potential biomarkers (eg, murine double minute 2 [MDM2] single-nucleotide polymorphism [SNP] 309) that may be predictive of benefit or toxicity from milademetan.
3. To assess blood and tumor samples for DNA or ribonucleic acid (RNA) analysis that may be predictive of benefit or toxicity from milademetan.
4. To evaluate the relationship between tumor response to milademetan and potential predictive biomarkers studied in archived tumor samples, pre-treatment tumor biopsies, if available, and/or blood samples.
5. To assess the PDy effect of milademetan on the expression levels of p53, p21, MDM2, murine double minute 4 (MDM4), Ki67, apoptosis markers, and/or other biomarkers in pre- and post-treatment solid tumor/lymphoma samples, if available.
6. To characterize the plasma metabolites of DS-3032a.

Part 2 (Dose Expansion)

Primary Objectives:

1. To confirm the safety and tolerability of milademetan at the MTD/tentative RP2D in subjects with advanced melanoma or diffuse large B-cell lymphoma (DLBCL) who have relapsed from or are refractory to standard therapy or for whom no standard therapy is available.
2. To assess tumor response in subjects with melanoma using RECIST v 1.1 and in subjects with DLBCL using the revised IWG criteria.

Secondary Objectives:

1. To determine the PK profile of DS-3032a at the

MTD/tentative RP2D.

To determine the PDy effect of milademetan on MIC-1 levels in serum.

Exploratory Objectives:

1. To compare PFS between that observed with milademetan treatment and that observed from the most recent therapeutic regimen.
2. To bank blood samples for DNA analysis for the assessment of potential biomarkers (eg, MDM2 SNP 309) that may be predictive of benefit or toxicity from milademetan.
3. To assess blood and tumor samples for DNA or RNA analysis that may be predictive of benefit or toxicity from milademetan.
4. To assess the PDy effect of milademetan on the expression levels of p53, p21, MDM2, MDM4, Ki67, apoptosis markers, and/or other biomarkers in pre- and post-treatment solid tumor/lymphoma samples, if available.
5. To characterize the plasma metabolites of DS-3032a.
6. To evaluate the relationship between tumor response to milademetan and biomarkers studied in archived tumor samples and pretreatment, on-treatment, and end-of-treatment tumor biopsies.

Primary Outcome Measure

Title: Number of subjects with treatment-emergent adverse events (TEAEs) during the study

Details: Number of subjects with TEAEs by frequency and grade in each cohort of dose and dosing schedule and the total number of subjects with the TEAEs

Timeframe: From start of study until last subject last visit (approximately 6 years).

Title: Maximum tolerated dose(s)

Details: MTD(s) identified at different dosing schedules

Time frame: From start of study until final database lock (approximately 6 years)

	Title: Number of subjects with dose-limiting toxicities (DLTs) **Details:** Number of subjects with DLTs at each dose [level /cohort] and the total number of subjects with DLTs **Time frame:** From start of study until the DLT evaluation of the last subject in dose escalation part (approximately 6 years or less) **Title:** Response rates in melanoma and DLBCL in dose expansion cohorts **Details:** Number and percentage of subjects with melanoma and DLBCL in dose expansion cohorts who achieved objective response per RECIST v 1.1 and IWG, respectively **Time frame:** From start of study until last subject last tumor assessment in Dose Expansion (approximately 6 years) **Secondary Outcome Measure** **Title:** PK parameters of milademetan **Details:** Determination of milademetan PK parameters (maximum plasma concentration [Cmax], time to reach maximum plasma concentration [Tmax], AUC, apparent clearance [CL/F], and half-life [T1/2]). **Timeframe:** From start of study until final database lock (approximately 6 years) **Title:** Pharmacodynamic effect of milademetan **Details:** Pharmacodynamic effect of milademetan assessed by increase in serum MIC-1 levels over baseline. **Time frame:** From start of study until final database lock (approximately 6 years)
Study Design	This will be a Phase 1, open-label study of milademetan to assess its safety and tolerability, identify an MTD/tentative RP2D, and assess its PK/PDy properties in subjects with advanced solid tumors or lymphomas. Dose regimen Milademetan will be administered once daily on Days 1 to 21 of a 28-day cycle (once a day [QD] × 21/28 days). An

alternative drug administration schedule for dose escalation may be considered based on safety, PK, and PDy data collected during Dose Escalation using the above schedule, and upon review by the Principal Investigators and Sponsor (eg, QD 28/28, QD 7/28, QD 3/14 × 2).

Part 1 (Dose Escalation)

Dose escalation of milademetan to determine the MTD will be guided by a Bayesian logistic regression model (BLRM) following escalation with overdose control (EWOC) principle following an initial accelerated titration design (ATD).

Accelerated titration design for determining initial dose for escalation by BLRM with EWOC.

Before starting BLRM, initial dose escalation will proceed following an ATD in order to minimize the number of subjects treated at sub-therapeutic doses of the drug. The proposed human starting dose of milademetan is 15 mg/day. Single subjects will be enrolled into sequential dose levels with a dose increment of 100% from the previous dose. Over-enrollment in ATD up to 3 subjects per cohort is permitted. The dose for ending ATD will be the dose level in which one of the following occurs:

- One Grade 2 or higher milademetan-related toxicity according to National Cancer Institute Common Terminology Criteria for Adverse Events v 4 (NCI-CTCAE v4) during Cycle 1, 3 to 6 subjects will be enrolled at the next dose level, which will be guided by BLRM[1]; or
- If a DLT is observed during Cycle 1, the cohort will first be expanded to 3 DLT-evaluable subjects and the next 2 subjects in the expanded cohort will receive milademetan treatment starting at least 1 week apart. If no further DLT is reported, the cohort will be expanded to include up to 3 additional DLT-evaluable subjects prior to initiation of BLRM in the next dose level.

The information from the accelerated titration stage will be included in the Bayesian model for dose escalation.

Dose level increment during dose escalation by BLRM with

[1] For isolated NCI-CTCAE v4 Grade ≥ 2 laboratory abnormalities that are not associated with signs or symptoms, transition from ATD to BLRM will be at the discretion of the Investigator.

EWOC

The dose increment during BLRM will be as follows:

- The dose level increment should be no less than 30% in order to have distinction among dose levels considering the inter-subject variability in exposure, but flexibility may be applied in selecting the dose to accommodate the available dosage form strengths.
- The dose level increment should be no more than 100% even if the model suggested a higher dose than 100% for the next cohort.
- In the event of a DLT, the next 2 subjects in the expanded cohort will receive milademetan treatment starting at least 1 week apart.

The dose escalation will be based on a BLRM with EWOC principle. The logistic regression model for the dose-toxicity (DLT rate) relationships will include 2 parameters: the intercept and the slope. After the first 3 subjects of each cohort complete DLT evaluation during Cycle 1, the posterior distributions of the DLT rate will be derived for all dose levels based on the BLRM using the DLT outcome data from all assessed exposure levels and a pre-specified prior distribution for the model parameters. The posterior probability of the DLT rate in the following 4 intervals at each dose level: [0%, 16%] as the DLT rate interval for under-dosing, [16%, 33%] as the target DLT rate interval, [33%, 60%] as the DLT rate interval for excessive toxicity, and [60%, 100%] as the DLT rate interval for unacceptable toxicity will then be calculated, and used for dose recommendation for the next cohort according to the EWOC principle.

The EWOC principle requires that the BLRM recommended dose for the next cohort of subjects is the one with the highest posterior probability of the DLT rate in the target DLT rate interval of [16%, 33%] among all dose levels fulfilling the overdose control constraint: there is less than 25% of probability for the DLT rate > 33% (probability for excessive or unacceptable toxicity).

The dose to be tested in the next cohort of subjects chosen by the Sponsor's clinical team and the investigator(s) involved in the clinical study will be based on the dose recommended by the BLRM, clinical assessment of toxicity profiles, and PK/PDy information observed thus far.

Cohorts of 3 to 6 subjects will be enrolled and assessed for

DLT before escalation to a new higher dose. As an exception, the model will be reevaluated before enrollment of any additional subjects to the cohort if 2 evaluable subjects in the cohort experience DLT before the enrollment of the next subject. Enrollment of subjects to a new cohort requires completion of DLT evaluation of at least 3 subjects treated in the current cohort. Subjects who have neither completed DLT evaluation nor experienced DLT will be censored and not included in the BLRM update. In the event that subjects in the previous cohort experience DLT after the enrollment of subjects to a new cohort has begun, dose level assignment of the next subject in the new cohort will be based on an updated BLRM using DLT outcome data from all assessed doses.

For a subject to be considered evaluable for dose escalation decisions, the subject must have received 75% of the doses (ie, 16 days) during Cycle 1, or experienced a DLT in Cycle 1. The final MTD will be decided based on considerations of the respective MTD estimated by the BLRM, and on an overall assessment of safety data from subsequent cycles and PK/PDy information collected at all different doses tested. For dose determination, the following stopping rules will be implemented for the Dose Escalation part: (a) at least 6 evaluable subjects at MTD level with at least 21 evaluable subjects in total enrolled in the Dose Escalation part, or (b) at least 9 evaluable subjects have been enrolled at a dose level that is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity is at least 50%, or (c) dose level -1 is too toxic.

Cohorts may be expanded at any dose level or at the MTD for further elaboration of safety, PK, or PDy parameters as required.

<u>Dose escalation using alternative drug administration schedule</u>

Based on safety, PK, and PDy data collected during Dose Escalation using the QD × 21/28-day schedule of milademetan, an alternative drug administration schedule for dose escalation may be considered following review by the Principal Investigators and Sponsor. Modeling and simulation will be performed to evaluate DS-3032a exposure relationship to PDy and toxicity. If the results indicate that using an alternative dosing schedule may provide less toxicity (eg, myelosuppression) while offering pharmacodynamic benefits based on available biomarkers or a better PK profile, dose escalation using this recommended alternative dosing schedule will be performed in lieu of, or in parallel with the

QD × 21/28-day schedule. For example:

- Case 1: If the recommended dosing schedule is less frequent than QD × 21/28 days, the starting daily dose of the new schedule will be same as the highest daily dose tested for the QD × 21/28-day schedule that showed DLT in less than one-third of evaluable subjects.
- Case 2: If the recommended dosing schedule is more frequent than QD × 21/28 days (eg, QD continuous × 28 days), the starting daily dose will be ≤ 75% of the highest daily dose tested for the QD × 21/28-day schedule that showed DLT in less than one-third of evaluable subjects. This starting dose of the new schedule will provide the same 4-week cumulative dose while reducing daily exposure by ≥ 25%.
- Case 3: If additional testing is suggested to optimize the dosing regimen (to maintain sufficient dose density over time without requiring frequent dose interruptions as a result of delayed toxicities) after the MTD is identified, then dosing may initiate at a dose level lower than MTD in that dosing regimen. Subject enrollment may be limited to one or a small number of cancer types or molecular sub-types depending on available clinical data for milademetan with the dosing regimen and investigator experience with this class of compound. Up to 15 subjects may be enrolled in the cohort and enrollment may be conducted in parallel with Part 2 of the study.

  The first cohort to be evaluated will begin treatment with milademetan at 90 mg QD × 21/28 days, preferentially in subjects with liposarcoma considering the existing data in this patient population at 120 mg QD × 21/28 days and 90 mg QD × 28/28 days for comparison of safety.

  The dose of 90 mg QD × 21/28 days is evaluated to define a hematologically safe and tolerable regimen based on the safety data at the doses previously evaluated (15 mg through 30, 60, 120, 160 and 240 mg QD × 21/28 days, with the determination of MTD at 120 mg) in this dosing schedule. Most DLTs arose from myelosuppression, particularly thrombocytopenia, which also resulted in dose delays and dose reductions in the subjects who continued in Cycle 2 and subsequent cycles. Therefore to reduce the risk of progressing to more severe bone marrow toxicities and dose interruptions during continued treatment, the following dose adjustment rules will be followed for

Cycle 2 and subsequent cycles:

- If platelets decrease to < 50% of baseline (the platelets measured at Cycle 1 Day 1) or Grade ≥ 2 thrombocytopenia (Platelets < 75×10^9/L) at the end of Cycle 1, then:
  - If platelets decrease by > 50% from baseline, but are ≥ 75×10^9/L, do not interrupt milademetan dosing, but reduce the dose of milademetan to 60 mg QD × 21/28 days.
  - If Grade ≥ 2 thrombocytopenia, hold dosing of milademetan. When the platelets recover to ≥ 75×10^9/L, resume milademetan at a reduced dose of 60 mg QD × 21/28 days.
- Dose interruptions and further dose reductions due to toxicity will be allowed.

After an initial cohort of 3 subjects has completed treatment in Cycle 1, the dose may be adjusted based on the safety results and discussion between the investigators and the Sponsor.

In addition to the above dose dense schedules, the following less frequent dosing schedules will be evaluated in dose escalation with a starting dose of 120 mg that was the MTD determined in the QD × 21/28 days schedule:

- QD for 7 out of 28 days (QD × 7/28 days)
- QD for 3 out of 14 days (QD × 3/14 days) repeated twice in a 28-day cycle

Both the original QD × 21/28 days and alternative dosing schedules are explored in parallel.

The final MTD for each dosing schedule will be decided based on considerations of the respective MTDs estimated by the BLRM, and on an overall assessment of safety data from subsequent cycles and PK/PDy information collected at all different doses tested. Upon determining the final MTD of the original QD × 21/28 days and/or alternative dosing schedules, one dosing regimen will be selected for further evaluation in Part 2 (Dose Expansion), which may also be the tentative RP2D.

Dose-Limiting Toxicity Definition

A DLT is defined as any TEAE not attributable to disease or disease-related processes that occurs during the observation period (Cycle 1) in each dose-level cohort and is Grade 3 or higher according to NCI-CTCAE v4, with the exceptions as defined below:

For hematologic events, a DLT is defined as follows:

- Grade 4 neutropenia lasting > 7 days
- Febrile neutropenia
- Grade 4 anemia
- Grade 4 thrombocytopenia or Grade ≥ 3 thrombocytopenia lasting more than 7 days or associated with bleeding
- Dose delay > 7 days secondary to myelosuppression

For elevations in hepatic function enzymes, a DLT is defined as follows:

- Grade 4 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels
- AST/ALT > 5 × upper limit of normal (ULN) lasting > 3 days without liver metastases
- AST/ALT > 5 × ULN if accompanied by ≥ Grade 2 elevation in bilirubin
- AST/ALT > 5 × ULN lasting > 3 days, if the baseline level was ≤ 3 × ULN in subjects with liver metastases
- AST/ALT > 8 × ULN lasting > 3 days, if the baseline level was > 3 × ULN in subjects with liver metastases

The following adverse events are NOT considered DLTs:

- Grade 3 fatigue lasting < 3 days
- Grade 3 nausea or vomiting that has resolved to Grade ≤ 2 within 48 hours after standard antiemetic therapies
- Grade 3 diarrhea that has resolved to Grade ≤ 2 within 48 hours after standard antidiarrheal therapies
- Isolated laboratory findings not associated with signs or symptoms including Grade 3/4 alkaline phosphatase, uric acid, amylase, and lipase elevations, and Grade 3 hyponatremia lasting < 72 hours developed from Grade 1 at baseline

- Grade 3/4 lymphopenia

Subjects who are unable to complete at least 75% of the prescribed dose of milademetan in the first 21 days as a result of nondisease-related ≥ Grade 2 adverse events will be considered to have a DLT.

- A delay of ≥ 1 week in initiating Cycle 2 secondary to a nondisease-related ≥ Grade 2 adverse event will be considered a DLT.

Part 2 (Dose Expansion in Subjects with Advanced Melanoma or DLBCL)

Upon establishing MTD/tentative RP2D and drug administration schedule in Part 1, the Dose Expansion part will begin with the intention of confirming the safety and tolerability of milademetan, determining the PDy signals in tumor samples, and evaluating preliminary efficacy of milademetan in approximately 20 subjects each with advanced melanoma and DLBCL whose tumors are tested positive for wild-type TP53 genotype.

Four subjects of each tumor type will initially be treated. Following the completion of the first cycle, a safety analysis will be conducted to allow the reevaluation of the appropriateness of the dosing level. If the incidence of adverse events fulfilling the criteria of a DLT has exceeded that predicted by the EWOC principle, after the initial 4 DLT-evaluable subjects or after additional enrollment, no further testing at the MTD/tentative RP2D level established in Part 1 will be done, and dose de-escalation or treatment at alternative dose schedules may be considered for further evaluation of safety and efficacy.

Tumor assessment (Part 1 and Part 2)

Tumor assessment will be performed according to the study schedule at baseline, every 2 cycles while the subject remains on study for the first 8 cycles and then every 3 cycles thereafter (start of Cycles 3, 5, 7, and 9, then Cycles 12, 15, etc.).

Tumor re-biopsy

To search for possible mechanisms of acquired resistance to milademetan, an optional tumor re-biopsy may be performed within 30 days following the last dose of milademetan treatment for subjects who have achieved an initial complete response (CR)/partial response (PR) or stable disease for at

	least 6 months by standard response criteria but later developed progressive disease (PD) while on therapy (both in Dose Escalation and Dose Expansion), preferably prior to initiating new therapy. TP53 genotyping, subject enrollment, and early discontinuation criteria • During Dose Escalation and Dose Expansion, tumor TP53 genotyping will be performed in archived formalin-fixed paraffin-embedded (FFPE) and, if available, fresh tumor biopsies in all enrolled subjects. Confirmation of TP53 wild-type status is NOT required prior to milademetan dosing. The investigator will be informed if the genotyping confirms the presence of inactivating TP53 mutations testing result shows that a subject's malignant cells contain an inactivating mutation, insertion, or deletion in the TP53 gene. If study treatment has already begun, the subject may choose to discontinue study drug or continue study drug as long as clinical benefit is noted per the investigator's judgment. TP53 re-testing can be considered.
Study Duration:	The study duration is expected to last approximately 6 years from the time the first subject is enrolled in Part 1 of the study. The number of treatment cycles is not fixed in this study. Subjects who continue to derive clinical benefit from treatment in the absence of withdrawal of subject consent, progression, or unacceptable toxicity may continue treatment. Subjects in Part 1 and Part 2 who are still on study at least 6 months after enrollment is completed in both the parts will be eligible to continue receiving study drug in a separate extension phase of the protocol. Data collected from those subjects may be captured in a separate database.
Study Sites and Location:	Approximately 5 United States sites are planned for Part 1 (Dose Escalation) and for Part 2 (Dose Expansion). The same sites are planned to participate for both parts.
Planned Sample Size:	The Dose Escalation phase of this study (Part 1) consists of an ATD followed by BLRM + EWOC design with at least 3 DLT-evaluable subjects per dose level. At least 21 DLT-evaluable subjects are needed to reach an accurate estimate of the MTD. However, to better define an RP2D that will be clinically beneficial to the subjects as well as hematologically safe and tolerable for prolonged treatment without dose delays, subjects

in additional cohorts and multiple dosing schedules may be added.

Sample size for the dose escalation part of the study is not known because of the multiple dosing schedules to be evaluated to determine the most optimal schedule. No formal statistical assessment has been performed.

For the Dose Expansion part (Part 2), approximately 20 subjects (each of subjects with advanced melanoma and DLBCL) will be enrolled. If response rate is more than 25% (null hypothesis: response rate ≤ 0.25, alternative hypothesis: response rate > 0.25), then the probability of no response out of 10 subjects will be less than 10%. The probability that 4 or more responders out of 10 subjects are observed will be less than 25% under the null hypothesis but more than 80% under alternative hypothesis with response rate = 0.50.

The probability values for the sample size are derived based on binomial distribution using SAS Version 9.2.

Subject Eligibility Criteria:

Inclusion Criteria

1a. Dose Escalation Cohorts (Part 1)

Has a histologically or cytologically documented advanced solid tumor or lymphoma that has relapsed from or is refractory to standard treatment, or for which no standard treatment is available.

- Subjects with melanoma who are ineligible to receive or have declined ipilimumab treatment, or who are refractory or intolerant to ipilimumab may enroll.
- Subjects with certain tumor types such as those with high prevalence of MDM2 amplification or overexpression (eg, well-differentiated (WD)/dedifferentiated (DD) liposarcoma) may be preferentially enrolled in Part 1.

1b. Dose Expansion Cohort (Part 2)

Has a histologically or cytologically documented advanced melanoma or DLBCL, with measurable disease that is refractory to standard treatment or for which no standard treatment is available.

Subjects with melanoma who are ineligible to receive or have declined ipilimumab treatment, or who are refractory or intolerant to ipilimumab may enroll.

Subjects with DLBCL who have failed, been deemed

ineligible for, or refused autologous stem cell transplantation may enroll.

2. Male or female ≥ 18 years old.
3. Has an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.
4. Has adequate bone marrow function, defined as:
   - Platelet count ≥ 100×10^9/L
   - Hemoglobin ≥ 9.0 g/dL
   - Absolute neutrophil count ≥ 1.5×10^9/L
5. Has adequate renal function, defined as:
   - Creatinine clearance ≥ 60 mL/min, as calculated using the modified Cockcroft-Gault equation, ([140 - age (in years)] × weight (in kg) / [serum creatinine (in mg/dL) × 72]; multiply by 0.85 if female), OR
     creatinine ≤ 1.5 × ULN
6. Has adequate hepatic function, defined as:
   - AST/ALT ≤ 3 × ULN (if liver metastases are present, ≤ 5 × ULN)
   - Bilirubin ≤ 1.5 × ULN
7. Has adequate blood clotting function, defined as:
   - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN
8. Subject should be able to provide written informed consent, comply with protocol visits and procedures, be able to take oral medication, and not have any active infection or comorbidity that would interfere with therapy.
9. Subject (male and female) of childbearing/reproductive potential must agree to use double-barrier contraceptive measures or avoid intercourse during the study and for 90 days after the last dose of study drug.
10. Subject must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible side effects) and must sign and date an Institutional Review Board-approved informed consent form (including Health Insurance Portability and Accountability Act authorization, if applicable) before performance of any study-specific procedures or tests.
11. Is willing to provide and there is confirmed availability of

pre-existing diagnostic or resected tumor samples, such as paraffin-embedded sections. Providing fresh tumor biopsy is optional for subjects in Dose Escalation cohorts.

12. Is willing to undergo tumor genotyping for TP53 mutation, insertion, or deletion at screening. Confirmation of TP53 nonmutant status is encouraged, but not required prior to milademetan dosing.
13. Is willing to provide additional archived samples for comprehensive genomic and/or proteomic analyses if the subject has a partial response (PR)/complete response (CR) to milademetan treatment.
14. (Applicable to Part 2 only) Is willing to undergo pre-treatment tumor biopsies (post-treatment biopsies are requested).

Exclusion Criteria

Part 1 and Part 2: Dose Escalation and Dose Expansion

1. Has a tumor that contains an inactivating mutation, insertion, or deletion in the TP53 gene determined previously or at screening.
2. Has a history of primary central nervous system malignancy.
3. Has gastrointestinal conditions that could affect the absorption of milademetan in the opinion of the investigator.
4. Has an uncontrolled infection requiring intravenous antibiotics, antivirals, or antifungals, known human immunodeficiency virus infection, or active hepatitis B or C infection.
5. Has received an allogeneic bone marrow or allogeneic stem cell transplant.
6. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the investigator or Sponsor.
7. Has clinically active brain metastases, defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with steroids may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A

minimum of 4 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment (2 weeks for stereotactic radiotherapy).

8. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE v4, Grade ≤ 1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the investigator and Sponsor (eg, Grade 2 chemotherapy-induced neuropathy).
9. Had an autologous transplant within 3 months of starting study drug treatment.
10. Is receiving concomitant treatment with a strong inducer of cytochrome P450 (CYP) 3A.
11. Had systemic treatment with anticancer therapy, antibody-based therapy, retinoid therapy, or hormonal therapy within 3 weeks before study drug treatment; or treatment with nitrosoureas or mitomycin C within 6 weeks before study drug treatment; or treatment with small-molecule targeted agents within 2 weeks before study drug treatment. Previous and concurrent use of hormone replacement therapy, the use of gonadotropin-releasing hormone modulators for prostate cancer, and the use of somatostatin analogs for neuroendocrine tumors are permitted if such therapy has not been changed within 8 weeks before study drug treatment.
12. Had therapeutic radiation therapy or major surgery within 4 weeks before study drug treatment or palliative radiation therapy within 2 weeks before study drug treatment.
13. Participated in a clinical study within 3 weeks before study drug treatment, or current participation in other therapeutic investigational procedures.
14. Prolongation of corrected QT interval by Fridericia's method (QT_cF) at rest, where the mean QT_cF interval is > 450 ms for males and > 470 ms for females based on triplicate electrocardiogram (ECG).
15. Pregnant or breastfeeding.
16. Substance abuse or medical, psychological, or social conditions that, in the opinion of the investigator, may interfere with the subject's participation in the clinical

	study or evaluation of the clinical study results. 17. Prior treatment with an MDM2 inhibitor.
Dosage Form, Dose and Route of Administration:	Milademetan will be administered as an oral capsule. It will be supplied in 5, 20, 80, and 200 mg capsules individually packaged in desiccant-embedded aluminum blisters. Two other capsule strengths of 30 and 100 mg will also be supplied in high-density polyethylene bottles.
Study Endpoints:	**Safety Endpoints:** Safety parameters will include serious adverse events, TEAEs, physical examination findings (including ECOG performance status), vital sign measurements, standard clinical laboratory parameters (serum chemistry, hematology, urinalysis), and ECG parameters. Adverse events will be graded according to the NCI-CTCAE v4. Dose escalation will be determined by plasma drug concentrations and rate of DLTs. **Pharmacokinetic and Pharmacodynamic Endpoints:** Plasma PK and standard non-compartmental PK parameters will be assessed. Plasma samples for PK assessments will be taken at multiple time points in the study. Additionally, PK samples may also be obtained outside of the specified time points during the study if deemed clinically necessary. Induction of serum MIC-1 will be the primary PDy biomarker. Whole blood samples will be collected at multiple time points in the study to assess the effect of milademetan treatment on MIC-1 induction. Other exploratory PDy biomarkers including, but not limited to, expression levels of p53, p21, MDM2, MDM4, Ki67, apoptosis markers, and/or other biomarkers will also be assessed, if available. **Efficacy Endpoints:** In solid tumor subjects with measurable disease, tumor response will be evaluated using RECIST v 1.1. In subjects with lymphomas, treatment response will be evaluated using the revised IWG criteria.
Statistical Analyses	The primary analysis will occur either after all subjects in Part 1 and Part 2 have discontinued the study or at least 6 months after enrollment of the last subject. After the primary analysis, the main study will be closed. Subjects in Part 1 and Part 2 who are still on study drug at the time of the primary analysis will be eligible to continue receiving study drug in a separate extension phase of the protocol, and data collected from those subjects

may be captured in a separate database.

Descriptive statistics will be provided for selected demographic, safety, PK, and PDy data by dose and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

Safety Endpoints:

The safety profile will be based on serious adverse events, TEAEs, physical examination findings (including ECOG performance status), vital sign measurements, standard clinical laboratory endpoints (serum chemistry, hematology, urinalysis), and ECG endpoints. All subjects receiving at least 1 dose of milademetan will be included in the safety analyses.

Tumor Response:

Response assessment will be performed according to the Schedule of Events or if disease progression is suspected. Radiographic assessment should include computed tomography (CT) of all affected sites. In addition, subjects with lymphoma should undergo a (^{18}F) fluorodeoxyglucose-positron emission tomography (FDG-PET) scan. Tumor responses will be assessed by the investigator according to RECIST v 1.1 criteria for subjects with solid tumors and revised IWG criteria for subjects with lymphoma. Descriptive statistics for the greatest percent change in the sum of longest dimensions (SLD) of measurable tumors will be provided. A waterfall plot of the greatest percent change from screening in the SLD for each subject will be presented for subjects with advanced solid malignancies and lymphomas. Additional efficacy analyses, including PFS and spider plots, will be detailed in the Statistical Analysis Plan (SAP). In addition, descriptive statistics for FDG-PET scans will be provided for lymphoma subjects according to revised IWG criteria.

Pharmacokinetic Endpoints:

Plasma concentrations of milademetan will be listed and summarized using descriptive statistics by dose cohort at each time point. A non-compartmental analysis will be performed to estimate PK endpoints, which include Cmax, time to Cmax [Tmax], minimum plasma concentration (Cmin), area under the curve until 8 hours [AUC0-8h] and 24 hours [AUC0-24h], accumulation index [AI], as well as any other endpoints deemed appropriate.

A Population pharmacokinetic [PopPK] analysis and exposure-response analysis for various endpoints may be developed. The analysis plan and the Technical Report will be provided separately.

Pharmacodynamic Endpoints:

Changes in MIC-1 levels in serum and other PDy markers, if available, will be listed and summarized using descriptive statistics by dose level cohort.

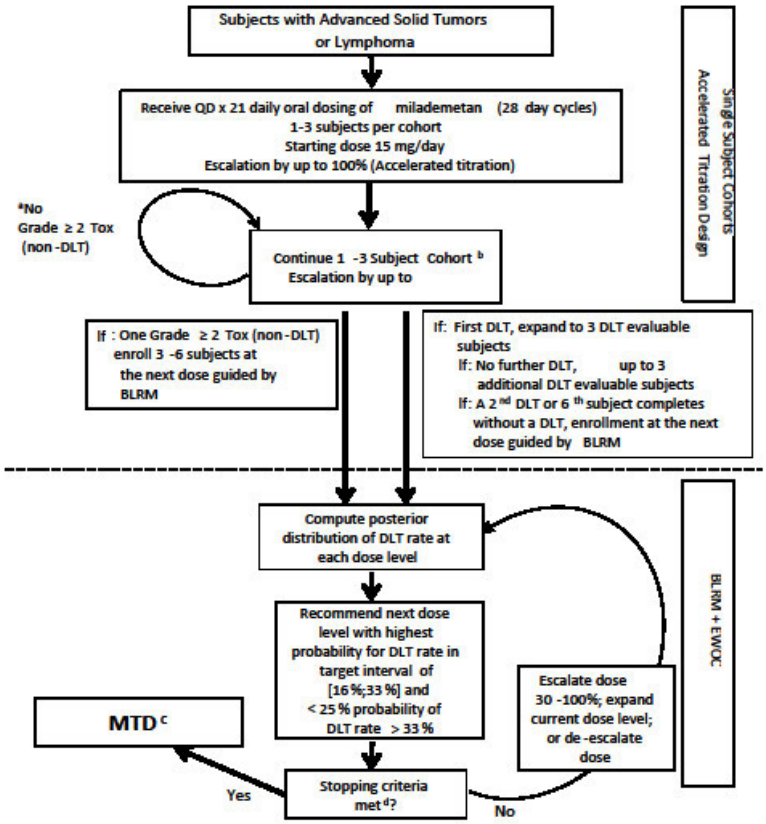
Predictive Biomarker Endpoints:

Archived or pre-treatment, on-treatment, and end-of-treatment biopsied tumor samples will be examined for components of the p53 pathway, which may include, but are not limited to, expression of p53, p21, MDM2, MDM4, and MDM2 copy number, and TP53 mutations. Additional biomarkers outside of the p53 pathway may be included in order to better understand the responsiveness to therapy. These may include protein, metabolite, gene expression, or genetic biomarkers.

Analyses for potential biomarkers that may be predictive of benefit from milademetan will be graphed and/or listed and summarized using descriptive statistics by dose level cohort.

1.2. Study Schema

Figure 1.1: Flow Diagram of Dose Escalation Phase



BLRM = Bayesian logistic regression model; DLT = dose-limiting toxicity; EWOC = escalation with overdose control; MTD = maximum tolerated dose; QD = once daily

[a] Continue single subject cohort, 100% dose escalation until a non-DLT adverse event of Grade ≥ 2 or a DLT is observed.

[b] Over-enrollment in ATD up to 3 subjects per cohort is permitted.

[c] In total, there should be at least 21 DLT-evaluable subjects before claiming the MTD.

[d] Refer to Section 4.1.5.1 for stopping criteria.

Note: Alternative dosing schedules will be evaluated after reaching MTD at QD × 21/28-day schedule

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ABBREVIATION	DEFINITION
AE	Adverse events
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATD	Accelerated titration design
AUC0-8h	Area under the plasma concentration- time curve from time 0 to 8 hours
AUC0-24h	Area under the plasma concentration- time curve from time 0 to 24 hours
BLRM	Bayesian logistic regression model
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CFR	Code of Federal Regulations
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DD	Dedifferentiated
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DNAseq	Deoxyribonucleic acid sequence
DS-3032a	The free form of milademetan
DSI	Daiichi Sankyo, Inc.
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture

ABBREVIATION	DEFINITION
EIU	Exposure in utero
EWOC	Escalation with overdose control
FDG-PET	(^{18}F) fluorodeoxyglucose-positron emission tomography
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
HNSTD	Highest nonseverely toxic dose
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Council of Medical Journal Editors
INR	International normalized ratio
IRB	Institutional Review Board
IWG	International Working Group
MDM2	Murine double minute 2
MDM4	Murine double minute 4
MIC-1	Macrophage inhibitory cytokine-1
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
PD	Progressive disease
PDy	Pharmacodynamic
PFS	Progression free survival
PGx	Pharmacogenomics
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic
PR	Partial response
QD	Once daily
QT_cB	Corrected QT interval using Bazett's formula
QT_cF	Corrected QT interval using Fridericia's formula
RNA	Ribonucleic acid
RNAseq	Ribonucleic acid sequence
RP2D	Recommended phase 2 dose

ABBREVIATION	DEFINITION
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SAVER	Serious adverse event report
SD	Stable disease
SID	Subject identification number
SLD	Sum of longest dimensions
SNP	Single-nucleotide polymorphism
SOC	System Organ Class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse event reaction
t1/2	Terminal elimination half-life
Tmax	Time to reach maximum plasma concentration
TEAE	Treatment-emergent adverse event
TP53	The gene encoding p53
TTR	Time-to-response
ULN	Upper limit of normal
US	United States
WD	Well-differentiated

2. INTRODUCTION AND BACKGROUND INFORMATION

2.1. Data Summary

2.1.1. Investigational Product(s)

2.1.1.1. Name

Milademetan

Chemical Name: (3'R,4'S,5'R)-N-[(3R,6S)-6-Carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate

2.1.1.2. Description

Milademetan is an orally available and highly selective inhibitor of the murine double minute 2 (MDM2)-p53 interaction.

2.1.1.3. Intended Use Under Investigation

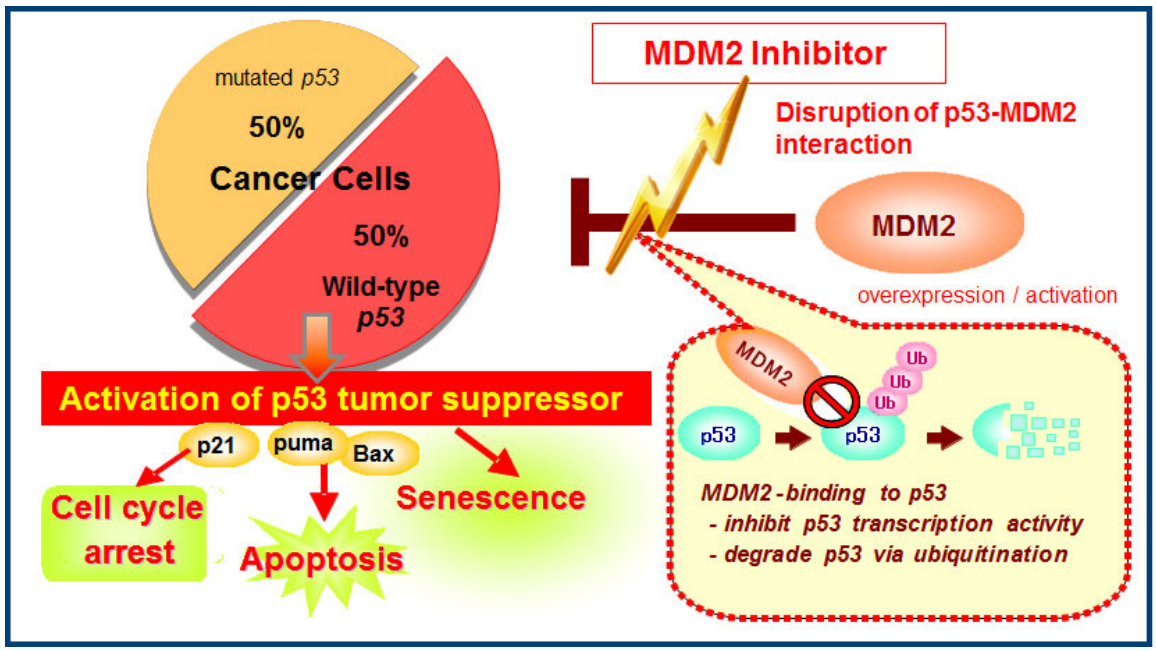
Milademetan will be evaluated in subjects with advanced solid tumors or lymphomas refractory to standard treatment or for which no standard treatment is available.

2.1.1.4. Pharmacological Target(s)

Milademetan, a novel, specific, small-molecule inhibitor of MDM2, disrupts interactions between MDM2 and the tumor suppressor protein p53 in tumor cells and is being developed as an oral drug for the treatment of cancer. The tumor suppressor protein p53 plays an essential role in preventing neoplasia by inducing cell cycle arrest or apoptosis in cells undergoing various types of physiological stress. However, inactivation of p53 by mutation occurs in a significant percentage of human tumors, resulting in a loss of tumor suppressor activity and thereby removing a pivotal barrier to neoplastic development.

The mechanism of action of milademetan is summarized in Figure 2.1.

Figure 2.1: Targeted Mechanism of Milademetan Antitumor Activity



Bax = Bcl-2–associated X protein; MDM2 = murine double minute 2;
p21 = cyclin-dependent kinase inhibitor 1; puma = p53 upregulated modulator of apoptosis; Ub = ubiquitin.
Note: Schematic of p53/MDM2 interactions and impact on cell signaling pathways altered in certain malignancies. Milademetan exerts antitumor activity by inhibiting interactions between MDM2 and p53 and preventing p53 degradation. The resulting increase in wild-type p53 activity activates signal transduction pathways important in inducing cell cycle arrest, apoptosis, and/or senescence in tumor cells.
Source: Data on File

In human tumors that retain wild-type p53 protein, its activity is frequently inhibited by intermolecular interactions between p53 and MDM2. MDM2 and p53 form a regulatory feedback loop in which MDM2 maintains low levels of p53 activity in normal, unstressed cells, by promoting export of p53 out of the nucleus and proteasome-mediated degradation of p53 through its E3 ubiquitinization ligase activity.[1] In the presence of stress, p53 becomes activated and subsequently acts as a transcription factor that modulates the expression of a variety of genes, including MDM2.[2] The MDM2 binding domain on p53 overlaps with the transcriptional activation domain of p53, thereby inhibiting the activity of p53. Thus, in human tumors, disruption of MDM2/p53 balance through overexpression and/or oncogenic activation of MDM2 allows tumorigenesis and tumor growth by preventing p53 function. Pharmacologic inhibition of the interaction between MDM2 and wild-type p53 in tumor cells could result in sustained increases in p53 activity and subsequent antitumor effects.[3,4] Therefore, pharmacologic restoration of the p53 pathway could be an effective strategy for cancer therapy targeting the wide array of human cancers that retain wild-type p53.[5]

2.1.1.5. Nonclinical Studies

Please refer to the current milademetan Investigator's Brochure (IB)[6] for nonclinical data supporting its use in clinical studies.[6]

2.1.1.5.1. Human Starting Dose

Based on the rat and dog repeat-dose toxicity studies, the dog proved to be the most sensitive species to milademetan-induced myelotoxicity. The highest nonseverely toxic dose (HNSTD) in dog was found to be 3 mg/kg/day (60 mg/m^2/day; human equivalent dose 1.62 mg/kg or ~ 100 mg in a 60-kg patient). Applying a safety factor of 6, these data supported a starting dose of 10 mg/m^2 (~15 mg in a 60-kg patient). The nonclinical pharmacology data suggested that pharmacologically active exposures were likely to be achieved through dose escalation. To mitigate the risk of untoward toxicity, the use of a continuous reassessment method coupled with a dose-exposure model is proposed to guide dose escalation. Additional details are provided in the current IB.[6]

2.1.1.6. Clinical Experience

This is the first-in-human study of milademetan. No prior clinical experience of milademetan was available when the study was initiated. Additional details of ongoing clinical studies are provided in the current IB.[6]

2.2. Study Rationale

The tumor suppressor p53 is a transcription factor that plays a central role in preventing tumor development and progression by inducing cell cycle arrest, apoptosis, or senescence. The gene encoding p53 (TP53) suffers disabling somatic mutations or deletions in about 50% of all malignant tumors. In tumors expressing wild-type protein, the tumor suppressor function of p53 may be attenuated by other mechanisms, such as over-expression of MDM2, a negative regulator of p53. MDM2 binds p53 with high affinity and negatively modulates the transcriptional activity and stability of the tumor suppressor. In tumors with functional p53, inhibition of the MDM2-p53 interaction can restore p53 activity and is expected to offer a novel strategy for cancer therapy.

Milademetan is an orally available and highly selective inhibitor of the MDM2-p53 interaction. It shows antitumor efficacy against tumors with wild-type p53 via activation of the tumor suppressor in a variety of cell culture and xenograft models. This ongoing Phase 1 first-in-human study will be conducted to assess the safety and tolerability of milademetan, as well as to determine the pharmacokinetic (PK)/pharmacodynamic (PDy) profile and preliminary efficacy of the drug.

2.3. Risks and Benefits for Study Subjects

2.3.1. Potential Risks Associated with Milademetan

Investigators in the milademetan program must be aware of the potential for hematologic and gastrointestinal toxicities and properly monitor for these toxicities and promptly manage subjects who experience these adverse events (AEs). Please refer to the current IB[6] for updated safety and risk/benefit assessment.

2.3.2. Potential Risk of Drug-Drug Interaction

Nonclinical studies indicate that DS-3032a (the free form of milademetan) is metabolized by cytochrome P450 (CYP) 3A4 and CYP3A5 by using microsomes containing individual recombinant human CYP isoforms. Drugs that are strong inducers of CYP3A may alter the pharmacokinetics of milademetan and, therefore, should be avoided until formal drug-drug interaction studies have been conducted.

A Phase 1 study in healthy subjects was conducted to evaluate the effect of co-administration of the strong CYP3A4 inhibitors (itraconazole and posaconazole) on milademetan PK (Study U107). Co-administration of milademetan 100 mg with itraconazole 200 mg at steady state increased milademetan geometric mean Cmax and AUCinf by 8% and 115%, respectively. Similarly, posaconazole 200 mg at steady state increased milademetan geometric mean Cmax by approximately 19% and AUCinf by approximately 149%. Therefore, dose of milademetan is recommended to be reduced to half when it is concomitantly administered with strong CYP3A4 inhibitors.

Milademetan showed direct inhibition on CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A, but not on CYP1A2 and CYP2E1 (half maximal inhibitory concentration range: 7.8 μM to 27.0 μM). Milademetan also showed metabolism-dependent inhibition on CYP3A (both testosterone 6β-hydroxylase and midazolam 1'-hydroxylase). The concentration required for half maximal inactivation (K_I) and maximal rate of inactivation at saturation (k_{inact}) values were calculated to be 60.5 μM and 0.0619 min^{-1} for CYP3A (midazolam 1'-hydroxylase), respectively. However, these levels of milademetan are much higher than those expected to be achievable in humans. Therefore concomitant use of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A substrates will be permitted. Please refer to the current IB for additional details on drug-drug interactions with milademetan.[6]

2.3.3. Potential Benefit Associated with Milademetan

Milademetan is a novel, specific, small-molecule inhibitor of MDM2 that disrupts interactions between MDM2 and p53 in tumor cells. Nonclinical data demonstrated in human tumor cell lines expressing wild-type p53 that milademetan inhibited cell growth in a concentration-dependent manner and induced apoptosis, and was more potent than the well-characterized MDM2 inhibitor Nutlin-3a. In vivo studies in mouse xenografts demonstrated that multiple doses of milademetan produced statistically significant dose-related antitumor responses. The highest dose of milademetan yielded a 93% tumor reduction relative to the control group. These data demonstrate that in tumors with wild-type p53, inhibition of MDM2-p53 interaction can restore p53 activity and is expected to offer a novel strategy for cancer therapy.

2.4. Population, Route, Dosage, Dosage Regimen, Treatment Period

Milademetan will be administered as an oral capsule. It will be supplied in 5, 20, 80, and 200 mg capsules individually packaged in desiccant-embedded aluminum blisters. Two other capsule strengths of 30 and 100 mg are also supplied in high density polyethylene (HDPE) bottles.

2.4.1. Part 1 (Dose Escalation)

This study will enroll adult subjects with advanced solid tumors or lymphomas that are refractory to standard therapy or for which no standard therapy is available. See Section 5.1.1 and Section 5.1.2 for a detailed description of all inclusion and exclusion criteria, respectively.

2.4.2. Part 2 (Dose Expansion)

Although the subjects in the Dose Escalation and Dose Expansion parts of the study will have common inclusion and exclusion criteria, subjects with advanced melanomas or with diffuse large B-cell lymphomas (DLBCLs) in the Dose Expansion part of the study will have additional inclusion criteria, as described in Section 5.1.1.

See Section 4.1 for a detailed description of the study drug administration schedule, treatment cycle duration, and follow-up after discontinuation.

3. STUDY OBJECTIVES AND HYPOTHESES

3.1. Study Objectives

3.1.1. Primary Objectives

3.1.1.1. Part 1 (Dose Escalation)

The primary objectives are as follows:

1. To assess the safety and tolerability of milademetan in subjects with advanced solid tumors or lymphomas who have relapsed from or are refractory to standard therapy or for whom no standard therapy is available.

To determine the maximum tolerated dose (MTD) or tentative recommended Phase 2 dose (RP2D) of milademetan in subjects with advanced solid tumors or lymphomas.

3.1.1.2. Part 2 (Dose Expansion)

The primary objectives are as follows:

1. To confirm the safety and tolerability of milademetan at the MTD/tentative RP2D in subjects with advanced melanoma or DLBCL who have relapsed from or are refractory to standard therapy or for whom no standard therapy is available.
2. To assess tumor response in subjects with melanoma using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 and in subjects with DLBCL using the revised International Working Group (IWG) criteria.

3.1.2. Secondary Objectives

3.1.2.1. Part 1 (Dose Escalation)

The secondary objectives are as follows:

1. To determine the plasma PK of DS-3032a (the free form of milademetan).
2. To determine the PDy effect of milademetan on macrophage inhibitory cytokine-1 (MIC-1) levels in serum.
3. To evaluate the response of solid tumors and lymphoma and their subtypes to milademetan using the corresponding standard response criteria (Response Evaluation Criteria in Solid Tumors [RECIST] v 1.1 or revised IWG criteria, respectively).

3.1.2.2. Part 2 (Dose Expansion)

The secondary objectives are as follows:

1. To determine the PK profile of DS-3032a at the MTD/tentative RP2D.
2. To determine the PDy effect of milademetan on MIC-1 levels in serum.

3.1.3. Exploratory Objectives

3.1.3.1. Part 1 (Dose Escalation)

The exploratory objectives are as follows:

1. To compare progression free survival (PFS) between that observed with milademetan treatment and that observed from the most recent therapeutic regimen.

To bank blood samples for deoxyribonucleic acid (DNA) analysis for the assessment of potential biomarkers (eg, MDM2 single-nucleotide polymorphism [SNP] 309) that may be predictive of benefit or toxicity from milademetan.

To assess blood and tumor samples for DNA or ribonucleic acid (RNA) analysis that may be predictive of benefit or toxicity from milademetan.

To evaluate the relationship between tumor response to milademetan and potential predictive biomarkers studied in archived tumor samples, pre-treatment tumor biopsies, if available, and/or blood samples.

To assess the PDy effect of milademetan on the expression levels of p53, p21, MDM2, murine double minute 4 (MDM4), Ki67, apoptosis markers, and/or other biomarkers in pre- and post-treatment solid tumor/lymphoma samples, if available.

To characterize the plasma metabolites of DS-3032a.

3.1.3.2. Part 2 (Dose Expansion)

The exploratory objectives are as follows:

1. To compare PFS between that observed with milademetan treatment and that observed from the most recent therapeutic regimen.

To bank blood samples for DNA analysis for the assessment of potential biomarkers (eg, MDM2 SNP 309) that may be predictive of benefit or toxicity from milademetan.

To assess blood and tumor samples for DNA or RNA analysis that may be predictive of benefit or toxicity from milademetan.

To assess the PDy effect of milademetan on the expression levels of p53, p21, MDM2, MDM4, Ki67, apoptosis markers, and/or other biomarkers in pre- and post-treatment solid tumor/lymphoma samples, if available.

To characterize the plasma metabolites of DS-3032a.

To evaluate the relationship between tumor response to milademetan and biomarkers studied in archived tumor samples and pretreatment, on-treatment, and end-of-treatment tumor biopsies.

3.2. Outcome Measures

3.2.1. Primary Outcome Measure

Title: Number of subjects with TEAEs during the study

Details: Number of subjects with TEAEs by frequency and grade in each cohort of dose and dosing schedule and the total number of subjects with the TEAEs

Timeframe: From start of study until last subject last visit (approximately 6 years)

Title: Maximum tolerated dose(s)

Details: MTD(s) identified at different dosing schedules

Time frame: From start of study until final database lock (approximately 6 years)

Title: Number of subjects with dose-limiting toxicities (DLTs)

Details: Number of subjects with DLTs at each dose [level /cohort] and the total number of subjects with DLTs

Time frame: From start of study until the DLT evaluation of the last subject in dose escalation part (approximately 6 years or less)

Title: Response rates in melanoma and DLBCL in dose expansion cohorts

Details: Number and percentage of subjects with melanoma and DLBCL in dose expansion cohorts who achieved objective response per RECIST v 1.1 and IWG, respectively

Time frame: From start of study until last subject last tumor assessment in Dose Expansion (approximately 6 years)

3.2.2. Secondary Outcome Measure

Title: PK parameters of milademetan

Details: Determination of milademetan PK parameters (Cmax, Tmax, AUC, CL/F, and T½).

Timeframe: From start of study until final database lock (approximately 6 years)

Title: Pharmacodynamic effect of milademetan

Details: Pharmacodynamic effect of milademetan assessed by increase in serum MIC-1 levels over baseline.

Time frame: From start of study until final database lock (approximately 6 years)

3.3. Study Hypothesis

Milademetan will be safe and well tolerated and will exhibit acceptable PK/PDy properties in subjects with advanced solid tumors or lymphomas who have relapsed from or are refractory to standard therapy or for which no standard therapy is available. Milademetan will manifest activity as evidenced by objective response in subjects with solid tumors and lymphomas.

3.4. Study Endpoints

The endpoints for the study include the following:

- Safety endpoints:

Serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), physical examination findings (including Eastern Cooperative Oncology Group [ECOG] performance status), vital signs measurements, standard clinical laboratory parameters (serum chemistry, hematology, urinalysis), and electrocardiogram (ECG) parameters. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4. Dose escalation will be determined by plasma drug concentrations and rate of DLTs.

- Pharmacokinetic and pharmacodynamic endpoints:

Plasma PK and standard non-compartmental PK parameters will be assessed. Plasma samples for PK assessments will be taken at multiple time points in the study. Additionally, a PK sample may also be obtained outside of the specified time points during the study if deemed clinically necessary.

Induction of serum MIC-1 will be the primary PDy biomarker. Whole blood samples will be collected at multiple time points in the study to assess the effect of milademetan treatment on MIC-1 induction. Other exploratory PDy biomarkers including, but not limited to, expression levels of p53, p21, MDM2, MDM4, Ki67, apoptosis markers, and/or other biomarkers will also be assessed, if available.

- Efficacy endpoints:

In solid tumor subjects with measurable disease, tumor response will be evaluated using RECIST v 1.1. In subjects with lymphomas, treatment response will be evaluated using the revised IWG criteria.[7]

4. STUDY DESIGN

4.1. Overall Plan

4.1.1. Study Type

This will be a Phase 1, open-label study of milademetan to assess its safety and tolerability, identify an MTD/tentative RP2D, and assess its PK/PDy properties in subjects with advanced solid tumors or lymphomas.

Approximately 5 United States (US) sites are planned for Part 1 (Dose Escalation) and Part 2 (Dose Expansion). The same sites are planned to participate for both parts.

4.1.2. Treatment Groups

This 2-part study will include both a Dose Escalation portion, to identify the MTD/tentative RP2D, and a Dose Expansion portion, to confirm the safety and tolerability of milademetan, by determining the PDy response in tumor samples and evaluating the preliminary efficacy of milademetan in subjects with advanced melanoma or DLBCL.

Milademetan will be administered once daily on Days 1 to 21 of a 28-day cycle (QD × 21/28 days). An alternative drug administration schedule for dose escalation may be considered to evaluate the DS-3032a exposure relationship to PDy, toxicity, and efficacy. If the results indicate that using an alternative dosing schedule may provide less toxicity (eg, myelosuppression) while offering PDy benefits based on available biomarkers, or better PK profile, dose escalation using this recommended alternative dosing schedule will be performed in lieu of or in parallel with the QD × 21/28-day schedule.

After discontinuation of the study drug, subjects will be contacted for an End-of-Study Follow-up Visit 30 (± 2) days after the last dose of study drug.

4.1.2.1. Part 1 (Dose Escalation)

Dose escalation of milademetan to determine the MTD will be guided by a Bayesian logistic regression model (BLRM) following escalation with overdose control (EWOC) principle following an initial accelerated titration design (ATD).

Accelerated titration design for determining the initial dose for escalation by BLRM with EWOC

Before starting BLRM, initial dose escalation will proceed following an ATD in order to minimize the number of subjects treated at sub-therapeutic doses of the drug. The proposed human starting dose of milademetan is 15 mg/day. Single subjects will be enrolled into sequential dose levels with a dose increment of 100% from the previous dose. Over-enrollment in ATD up to 3 subjects per cohort is permitted. The dose for ending ATD will be the dose level in which one of the following occurs:

- One Grade 2 or higher milademetan-related toxicity according to NCI-CTCAE v4 during Cycle 1, in which case, 3 to 6 subjects will be enrolled at the next dose level, which will be guided by BLRM[2]; or
- If a DLT is observed during Cycle 1, the cohort will first be expanded to 3 DLT-evaluable subjects, and the next 2 subjects in the expanded cohort will receive milademetan treatment starting at least 1 week apart. If no further DLT is reported, the cohort will be expanded to include up to 3 additional DLT-evaluable subjects prior to initiation of BLRM in the next dose level.

The information from the accelerated titration stage will be included in the Bayesian model for dose escalation.

Dose level increment during dose escalation by BLRM with EWOC

The dose increment during the BLRM will be as follows:

- The dose level increment should be no less than 30% in order to have distinction among dose levels considering the inter-subject variability in exposure, but flexibility may be applied in selecting the dose to accommodate the available dosage form strengths.
- The dose level increment should be no more than 100% even if the model suggested a higher dose than 100% for the next cohort.
- In the event of a DLT, the next 2 subjects in the expanded cohort will receive milademetan treatment starting at least 1 week apart.

The dose escalation will be based on a BLRM with EWOC principle. The logistic regression model for the dose-toxicity (DLT rate) relationships will include 2 parameters: the intercept and the slope. After the first 3 subjects of each cohort complete DLT evaluation during Cycle 1, the posterior distributions of the DLT rate will be derived for all dose levels based on the BLRM using the DLT outcome data from all assessed exposure levels and a pre-specified prior distribution for the model parameters. The posterior probability of the DLT rate in the following 4 intervals at each dose level will then be calculated and used for dose recommendation for the next cohort according to the EWOC principle [0%, 16%] as the DLT rate interval for

[2] For isolated NCI-CTCAE v4 Grade ≥ 2 laboratory abnormalities that are not associated with signs or symptoms, transition from ATD to BLRM will be at the discretion of the Investigator.

under-dosing, [16%, 33%] as the target DLT rate interval, [33%, 60%] as the DLT rate interval for excessive toxicity, and [60%, 100%] as the DLT rate interval for unacceptable toxicity.

The EWOC principle requires that the BLRM recommended dose for the next cohort of subjects is the one with the highest posterior probability of the DLT rate in the target DLT rate interval of [16%, 33%] among all dose levels fulfilling the overdose control constraint: there is less than 25% of probability for the DLT rate > 33% (probability for excessive or unacceptable toxicity).

The dose to be tested in the next cohort of subjects chosen by the Sponsor's clinical team and the investigator(s) involved in the clinical study will be based on the dose recommended by the BLRM, clinical assessment of toxicity profiles, and PK/PDy information observed thus far.

Cohorts of 3 to 6 subjects will be enrolled and assessed for DLT before escalation to a new higher dose. As an exception, the model will be reevaluated before enrollment of any additional subjects to the cohort if 2 evaluable subjects in the cohort experience DLT before the enrollment of the next subject. Enrollment of subjects to a new cohort requires completion of DLT evaluation of at least 3 subjects treated in the current cohort. Subjects who have neither completed DLT evaluation nor experienced DLT will be censored and not included in the BLRM update. In the event that subjects in the previous cohort experience a DLT after the enrollment of subjects to a new cohort has begun, dose level assignment of the next subject in the new cohort will be based on an updated BLRM using DLT outcome data from all assessed doses.

Cohorts may be expanded at any dose level or at the MTD for further elaboration of safety, PK, or PDy parameters as required.

Dose escalation using alternative drug administration schedules

Based on safety, PK, and PDy data collected during Dose Escalation using the QD × 21/28-day schedule of milademetan, an alternative drug administration schedule for dose escalation may be considered following review by the Principal Investigators and Sponsor. Modeling and simulation will be performed to evaluate DS-3032a exposure relationship to PDy and toxicity. If the results indicate that using an alternative dosing schedule may provide less toxicity (eg, myelosuppression) while offering pharmacodynamic benefits based on available biomarkers or a better PK profile, dose escalation using this recommended alternative dosing schedule will be performed in lieu of or in parallel with the QD × 21/28-day schedule. For example:

- Case 1: If the recommended dosing schedule is less frequent than QD × 21/28 days, the starting daily dose of the new schedule will be the same as the highest daily dose tested for the QD × 21/28-day schedule that showed DLT in less than one-third of evaluable subjects.
- Case 2: If the recommended dosing schedule is more frequent than QD × 21/28 days (eg, QD continuous × 28 days), the starting daily dose will be ≤ 75% of the highest daily dose tested for the QD × 21/28-day schedule that showed DLT in less than one-third of evaluable subjects. This starting dose of the new schedule will provide the same 4-week cumulative dose while reducing daily exposure by ≥ 25%.
- Case 3: If additional testing is suggested to optimize the dosing regimen (to maintain sufficient dose density over time without requiring frequent dose interruptions as a result of delayed toxicities) after the MTD is identified, then dosing may initiate at a

dose level lower than MTD in that dosing regimen. Subject enrollment may be limited to one or a small number of cancer types or molecular sub-types depending on available clinical data for milademetan with the dosing regimen and investigator experience with this class of compound. Up to 15 subjects may be enrolled in the cohort, and enrollment may be conducted in parallel with Part 2 of the study.

The first cohort to be evaluated will begin treatment with milademetan at 90 mg QD × 21/28 days, preferentially in subjects with liposarcoma considering the existing data in this patient population at 120 mg QD × 21/28 days and 90 mg QD × 28/28 days for comparison of safety.

The dose of 90 mg QD × 21/28 days is evaluated to define a hematologically safe and tolerable regimen based on the safety data at the doses previously evaluated (15 mg through 30, 60, 120, 160, and 240 mg QD × 21/28 days, with the determination of MTD at 120 mg) in this dosing schedule. Most DLTs arose from myelosuppression, particularly thrombocytopenia, which also resulted in dose delays and dose reductions in subjects who continued in Cycle 2 and subsequent cycles. Therefore, to reduce the risk of progressing to more severe bone marrow toxicities and dose interruptions during continued treatment, the following dose adjustment rules will be followed for Cycle 2 and subsequent cycles:

- If platelets decrease to <50% of baseline (the platelets measured at Cycle 1 Day 1) or Grade ≥2 thrombocytopenia (Platelets < 75×10^9/L) at the end of Cycle 1, then:
    - If platelets decrease by >50% from baseline, but are ≥ 75×10^9/L, do not interrupt milademetan dosing, but reduce the dose of milademetan to 60 mg QD × 21/28 days.
    - If Grade ≥2 thrombocytopenia, hold dosing of milademetan. When the platelets recover to ≥ 75×10^9/L, resume milademetan at a reduced dose of 60 mg QD × 21/28 days.
- Dose interruptions and further dose reductions due to toxicity will follow the same guidelines provided in Section 4.1.8.

After an initial cohort of 3 subjects has completed treatment in Cycle 1, the dose may be adjusted based on the safety results and discussion between the investigators and the Sponsor.

In addition to the above dose dense schedules, the following less frequent dosing schedules will be evaluated in dose escalation with a starting dose of 120 mg that was the MTD determined in the QD 21/28-day schedule:

- QD for 7 out of 28 days (QD × 7/28 days)
- QD for 3 out of 14 days (QD × 3/14 days) repeated twice in a 28-day cycle

Notes:

1. The QD 7/28 and QD 3/14 days schedules were initiated by a memo to the institutional review boards (IRBs) by referring to the above section in Protocol v 3.0 allowing alternative dosing schedules.
2. These alternative dose schedules were initiated in dose escalation after the dose expansion in the dose schedule QD 21/28 was evaluated in subjects with melanoma and DLBCL and found that the QD 21/28 schedule was not tolerated well for further development of the drug.

Both the original QD × 21/28 days and alternative dosing schedules can be explored in parallel.

The final MTD for each dosing schedule will be decided based on considerations of the respective MTDs estimated by the BLRM and on an overall assessment of safety data from subsequent cycles and PK/PDy information collected at all different doses tested. Upon determining the final MTD of the original QD × 21/28 days and/or alternative dosing schedules, one dosing regimen will be selected for further evaluation in Part 2 (Dose Expansion) and as the tentative RP2D.

4.1.2.2. Part 2 (Dose Expansion in Subjects With Advanced Melanoma or Diffuse Large B-cell Lymphoma)

Upon establishing the MTD/tentative RP2D and drug administration schedule in Part 1, the Dose Expansion part will begin with the intention of confirming the safety and tolerability of milademetan, determining the PDy signals in tumor samples, and evaluating the preliminary efficacy of milademetan in approximately 20 subjects each with advanced melanoma and DLBCL whose tumors tested positive for wild-type TP53 genotype.

Four subjects of each tumor type will initially be treated. Following the completion of the first cycle, a safety analysis will be conducted to allow the reevaluation of the appropriateness of the dosing level. If the incidence of AEs fulfilling the criteria of a DLT has exceeded that predicted by the EWOC principle after the initial 4 DLT-evaluable subjects or after further enrollment, no further testing at the MTD/tentative RP2D level established in Part 1 will be done, and dose de-escalation or treatment at alternative dose schedules may be considered for further evaluation of safety and efficacy.

Tumor assessment (Part 1 and Part 2)

Tumor assessment will be performed according to the study schedule at baseline, every 2 cycles while the subject remains on study for the first 8 cycles and then every 3 cycles thereafter (start of Cycles 3, 5, 7, and 9, then Cycles 12, 15, etc.).

Tumor re-biopsy

To search for possible mechanisms of acquired resistance to milademetan, an optional tumor re-biopsy may be performed within 30 days following the last dose of milademetan treatment for subjects who have achieved an initial complete response (CR)/partial response (PR) or stable disease (SD) for at least 6 months by standard response criteria but later developed progressive disease (PD) while on therapy (both in Dose Escalation and Dose Expansion), preferably prior to initiating new therapy.

TP53 genotyping, subject enrollment, and early discontinuation criteria

- During Dose Escalation and Dose Expansion, tumor TP53 genotyping will be performed in archived formalin-fixed paraffin-embedded (FFPE) and, if available, fresh tumor biopsies in all enrolled subjects. Confirmation of TP53 wild-type status is NOT required prior to milademetan dosing. The investigator will be informed if the genotyping confirms the presence of inactivating TP53 mutations testing result shows that a subject's malignant cells contain an inactivating mutation, insertion, or deletion in the TP53 gene. If study treatment has already begun, the subject may choose to discontinue study drug or continue study drug as long as clinical benefit is noted per the investigator's judgment. TP53 re-testing can be considered.

4.1.2.3. Intrasubject Dose Escalation

No intrasubject dose escalation will be permitted.

4.1.3. Duration of the Study

The study duration is expected to last approximately 6 years from the time the first subject is enrolled in Part 1 of the study.

4.1.4. Duration of Subject Participation

The number of treatment cycles is not fixed in this study. Subjects who continue to derive clinical benefit from treatment in the absence of withdrawal of subject consent, progression, or unacceptable toxicity may continue treatment. Subjects in Part 1 and Part 2 who are still on study at least 6 months after enrollment is completed in both parts will be eligible to continue receiving study drug in a separate extension phase of the protocol (see Section 18.7). Data collected from those subjects may be captured in a separate database.

4.1.5. Stopping Rules

The study may be terminated at any time at Daiichi Sankyo, Inc.'s (DSI's) discretion.

4.1.5.1. Stopping Rule for Maximum Tolerated Dose Determination

The final MTD will be decided based on considerations of the respective MTD estimated by the BLRM and on an overall assessment of safety data from subsequent cycles and PK/PDy information collected at all different doses tested. For MTD determination, the following stopping rules will be implemented for the Dose Escalation part: (a) at least 6 evaluable subjects at MTD level with at least 21 evaluable subjects in total enrolled in the Dose Escalation part, or (b) at least 9 evaluable subjects have been enrolled at a dose level that is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity is at least 50%, or (c) dose level -1 is too toxic.

Cohorts may be expanded at any dose level or at the MTD for further elaboration of safety, PK, or PDy parameters as required.

4.1.5.2. Dose-limiting Toxicities

A DLT is defined as any TEAE not attributable to disease or disease-related processes that occurs during the observation period (Cycle 1) in each dose-level cohort and is Grade 3 or higher according to NCI-CTCAE, v 4, with the exceptions as defined below:

For hematologic events, a DLT is defined as follows:

- Grade 4 neutropenia lasting > 7 days
- Febrile neutropenia
- Grade 4 anemia
- Grade 4 thrombocytopenia or Grade ≥ 3 thrombocytopenia lasting more than 7 days or associated with bleeding
- Dose delay > 7 days secondary to myelosuppression

For elevations in hepatic function enzymes, a DLT is defined as follows:

- Grade 4 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels
- AST/ALT > 5 × upper limit of normal (ULN) lasting > 3 days without liver metastases
- AST/ALT > 5 × ULN if accompanied by ≥ Grade 2 elevation in bilirubin
- AST/ALT > 5 × ULN lasting > 3 days, if the baseline level was ≤ 3 × ULN in subjects with liver metastases
- AST/ALT > 8 × ULN lasting > 3 days, if the baseline level was > 3 × ULN in subjects with liver metastases

The following adverse events are NOT considered DLTs:

- Grade 3 fatigue lasting < 3 days
- Grade 3 nausea or vomiting that has resolved to Grade ≤ 2 within 48 hours after standard antiemetic therapies
- Grade 3 diarrhea that has resolved to Grade ≤ 2 within 48 hours after standard antidiarrheal therapies
- Isolated laboratory findings not associated with signs or symptoms including Grade 3/4 alkaline phosphatase, uric acid, amylase, and lipase elevations, and Grade 3 hyponatremia lasting < 72 hours developed from Grade 1 at baseline
- Grade 3/4 lymphopenia

Subjects who are unable to complete at least 75% of the prescribed dose of milademetan in the first 21 days as a result of nondisease-related ≥ Grade 2 adverse events will be considered to have a DLT.

- A delay of ≥ 1 week in initiating Cycle 2 secondary to a nondisease-related ≥ Grade 2 adverse event will be considered a DLT.

4.1.6. Maximum Tolerated Dose and Tentative Recommended Phase 2 Dose Definition

Once the stopping criteria are met, the MTD estimated by BLRM + EWOC is the dose with the highest posterior probability of the DLT rate in the target DLT rate interval of [16%, 33%] among all doses fulfilling the overdose control constraint: there is less than 25% probability for the DLT rate > 33% (probability for excessive or unacceptable toxicity) (Section 4.1.2.1). Since an alternative drug administration schedule may be explored in lieu of or in parallel with the original QD × 21/28 days schedule, separate MTDs may be identified for each regimen. The final MTD for each dosing schedule will be decided based on considerations of the respective MTDs estimated by the BLRM and on an overall assessment of safety data from subsequent cycles and PK/PDy information collected at all different doses tested. Upon determining the final MTD of the original QD × 21/28 days and/or alternative dosing schedules, one dosing regimen will be selected for further evaluation in Part 2 (Dose Expansion), which may also be the tentative RP2D.

4.1.7. Management of Subjects with Adverse Events

Treatment-related toxicities meeting the DLT definition (see Section 4.1.5.2 for DLT definitions) occurring after Day 28 (ie, outside the DLT observation period) or occurring in Part 2 of the study will result in interruption and/or discontinuation of therapy. For subjects deriving clinical benefit from treatment, an option to resume the therapy at 1 dose level below that at which the toxicity occurred may be considered after the toxicity returns to NCI-CTCAE v4 Grade ≤ 1 or to baseline values. However, subjects requiring more than 4 weeks to recover from acute toxicities will be withdrawn from the treatment. If a subject experiences NCI-CTCAE v4 Grade 3 or 4 toxicity or an SAE that is unequivocally attributable to the underlying malignancy, milademetan treatment may be postponed until the toxicity has resolved to NCI-CTCAE v4 Grade ≤ 1 or returns to baseline values.

The window for recommencing treatment may be extended to up to 8 weeks, if subject has obtained clinical benefit from milademetan treatment that continued during the recovery period of the AEs.

4.1.8. Guidelines for Dose Delays

Dosing of milademetan should be interrupted if the following adverse events develop any time during treatment:

- Absolute neutrophil count < 1×10^9/L ($1000/mm^3$).
- Platelet count < 75×10^9/L.
- All other NCI-CTCAE v4 Grade ≥ 2 nonhematological, nondisease-related toxicities, except alopecia and Grade ≥ 2 fatigue lasting < 48 hours.
- For other NCI-CTCAE v4 Grade ≥ 2 laboratory abnormalities that are not DLTs, treatment continuation with milademetan will be at the discretion of the investigator.

Commencing rules for milademetan administration are:

- Absolute neutrophil count ≥ 1×10^9/L ($1000/mm^3$).
- Platelet count ≥ 75×10^9/L.

- All other NCI-CTCAE v4 Grade ≥ 2 nonhematological toxicities (excluding alopecia) must have resolved to Grade ≤ 1 or baseline values.

These parameters should be seen as guidelines and are not intended to supersede the clinical judgment of the treating physician. All adjustments should be made in consultation with the Sponsor's Medical Monitor.

In the event of a dose delay occurring prior to completion of the PK/PDy sampling in the study, investigators should contact DSI for guidance regarding rescheduling these procedures.

In the event of a dose delay due to noncompliance, the study site should notify DSI at the earliest possible time. Subjects missing more than 25% of the scheduled doses in Cycle 1 for nontoxicity-related reasons may be removed from the study.

4.2. Selection of Doses

4.2.1. Experimental Treatments

4.2.1.1. Part 1 (Dose Escalation)

The study will enroll subjects into cohorts with dose escalation by BLRM with EWOC principle as outlined in Section 4.1.2.1. The starting dose will be 15 mg/day (see Section 2.1.1.5.1 for justification of the human starting dose). In the event of a DLT, the next 2 subjects in the expanded cohort will receive milademetan treatment starting at least 1 week apart.

Upon completion of Part 1 (Dose Escalation) and determination of the MTD/tentative RP2D, Part 2 (Dose Expansion) will immediately begin. Subjects will receive milademetan at the MTD/tentative RP2D defined in Section 4.1.2.1.

4.2.1.2. For the Study

Please see Section 2.2 for further details.

4.2.1.3. For Individual Subjects

Please see Section 2.4 for further details.

4.2.2. Control Treatments

Not applicable.

5. STUDY POPULATION

The study population will comprise male and female subjects aged 18 years and older with a pathologically documented advanced solid tumor or lymphoma that has relapsed from or is refractory to standard treatment, or for which no standard treatment is available. Specific inclusion and exclusion criteria are available in Section 5.1.1 and Section 5.1.2.

5.1. Enrollment

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects (initials, age, sex), date, and outcome of screening process (eg, enroll in the study, reason for ineligibility, refused to participate).

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects who have been allocated to a subject identification number (SID) upon enrolling in the study allows the investigator to reveal the identity of any subject when necessary.

Each subject or legally acceptable representative will be provided with information about the study, will have all questions answered to their satisfaction, and will sign and date an informed consent form (ICF). This will be completed before any study-specific procedures are performed. Additional information about informed consent procedures is provided in Section 16.3.

A subject is considered enrolled in the study upon the Investigator or designee obtaining written informed consent from the subject or the subject's legally acceptable representative (Section 16.3) and upon determination that all inclusion and exclusion criteria have been satisfied. After assigning a SID to each subject at the timing of screening, investigators will assess the eligibility of a subject based on the inclusion and exclusion criteria after obtaining written informed consent from the subject. After assessment by investigators, the inclusion criteria/exclusion criteria form will be completed for registration. The Sponsor will perform registration after verifying that the subject meets the inclusion/exclusion criteria provided by the Investigator. If the Sponsor has any questions regarding the information sent by the investigator, he or she will immediately contact the investigator to check the details. Directly after registration, the Sponsor will forward the results of registration to the investigator. At this time, the subject will be assigned to study drug treatment.

The Investigator must not prescribe or administer the study drug until the subject has completed registration. If the Sponsor disqualifies a subject from participation in the clinical study, the investigator will be notified. The investigator will then explain this outcome to the relevant subject.

Data for all study visits will be recorded on the electronic case report form (eCRF) for subjects who receive study drug treatment. Only minimal data (ie, demography and reason for withdrawal) will be recorded on the eCRF for subjects who fail the inclusion/exclusion criteria and/or do not receive study drug. Further data, such as adverse events, will not be collected from subjects once they are considered screen failures or have decided to withdraw prior to receiving study drug.

5.1.1. Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study:

1a. Dose Escalation Cohorts (Part 1)

Has a histologically or cytologically documented advanced solid tumor or lymphoma that has relapsed from or is refractory to standard treatment, or for which no standard treatment is available.

- Subjects with melanoma who are ineligible to receive or have declined ipilimumab treatment or who are refractory or intolerant to ipilimumab may enroll.
- Subjects with certain tumor types such as those with high prevalence of MDM2 amplification or overexpression (eg, well-differentiated [WD]/dedifferentiated [DD] liposarcoma) may be preferentially enrolled in Part 1.

1b. Dose Expansion Cohort (Part 2)

Has a histologically or cytologically documented advanced melanoma or DLBCL, with measurable disease that is refractory to standard treatment or for which no standard treatment is available.

- Subjects with melanoma who are ineligible to receive or have declined ipilimumab treatment or who are refractory or intolerant to ipilimumab may enroll.
- Subjects with DLBCL who have failed, been deemed ineligible for, or refused autologous stem cell transplantation may enroll.

2. Male or female ≥ 18 years old.
3. Has an ECOG performance status of 0 to 1.
4. Has adequate bone marrow function, defined as:
   - Platelet count ≥ 100×10^9/L
   - Hemoglobin ≥ 9.0 g/dL
   - Absolute neutrophil count ≥ 1.5×10^9/L.
5. Has adequate renal function, defined as:
   - Creatinine clearance ≥ 60 mL/min, as calculated using the modified Cockcroft-Gault equation, ([140 - age (in years)] × weight (in kg) / [serum creatinine (in mg/dL) × 72]; multiply by 0.85 if female), OR creatinine ≤ 1.5 × ULN.
6. Has adequate hepatic function, defined as:
   - AST/ALT levels ≤ 3 × ULN (if liver metastases are present, ≤ 5 × ULN)
   - Bilirubin ≤ 1.5 × ULN.
7. Has adequate blood clotting function, defined as:
   - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN.

8. Subject should be able to provide written informed consent, comply with protocol visits and procedures, be able to take oral medication, and not have any active infection or comorbidity that would interfere with therapy.
9. Subject (male and female) of childbearing/reproductive potential must agree to use double-barrier contraceptive measures or avoid intercourse during the study and for 90 days after the last dose of study drug.
10. Subject must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible side effects) and must sign and date an IRB-approved ICF (including Health Insurance Portability and Accountability Act authorization, if applicable) before performance of any study-specific procedures or tests.
11. Is willing to provide and there is confirmed availability of pre-existing diagnostic or resected tumor samples, such as paraffin-embedded sections. Providing fresh tumor biopsy is optional for subjects in Dose Escalation cohorts.
12. Is willing to undergo tumor genotyping for TP53 mutation, insertion, or deletion at screening. Confirmation of TP53 nonmutant status is encouraged but not required prior to milademetan dosing.
13. Is willing to provide additional archived samples for comprehensive genomic and/or proteomic analyses if the subject has a PR/CR to milademetan treatment.
14. (Applicable to Part 2 only) Is willing to undergo pre-treatment tumor biopsies (post-treatment biopsies are requested).

5.1.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Has a tumor that contains an inactivating mutation, insertion, or deletion in the TP53 gene determined previously or at screening.
2. Has a history of primary central nervous system malignancy.
3. Has gastrointestinal conditions that could affect the absorption of milademetan in the opinion of the investigator.
4. Has an uncontrolled infection requiring intravenous antibiotics, antivirals, or antifungals, known human immunodeficiency virus infection, or active hepatitis B or C infection.
5. Has received an allogeneic bone marrow or allogeneic stem cell transplant.
6. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the investigator or Sponsor.
7. Has clinically active brain metastases, defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with steroids may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 4 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment (2 weeks for stereotactic radiotherapy).

8. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE v4, Grade ≤ 1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the investigator and Sponsor (eg, Grade 2 chemotherapy-induced neuropathy).
9. Had an autologous transplant within 3 months of starting study drug treatment.
10. Is receiving concomitant treatment with a strong inducer of CYP3A.
11. Had systemic treatment with anticancer therapy, antibody-based therapy, retinoid therapy, or hormonal therapy within 3 weeks before study drug treatment; or treatment with nitrosoureas or mitomycin C within 6 weeks before study drug treatment; or treatment with small-molecule targeted agents within 2 weeks before study drug treatment. Previous and concurrent use of hormone replacement therapy, use of gonadotropin-releasing hormone modulators for prostate cancer, and use of somatostatin analogs for neuroendocrine tumors are permitted if such therapy has not been changed within 8 weeks before study drug treatment.
12. Had therapeutic radiation therapy or major surgery within 4 weeks before study drug treatment or palliative radiation therapy within 2 weeks before study drug treatment.
13. Participated in a clinical study within 3 weeks before study drug treatment or current participation in other therapeutic investigational procedures.
14. Prolongation of corrected QT interval by Fridericia's method (QT_cF) at rest, where the mean QT_cF interval is > 450 milliseconds (ms) for males and > 470 ms for females based on triplicate ECG.
15. Pregnant or breastfeeding.
16. Substance abuse or medical, psychological, or social conditions that, in the opinion of the investigator, may interfere with the subject's participation in the clinical study or evaluation of the clinical study results.
17. Prior treatment with an MDM2 inhibitor.

5.2. Removal of Subjects from Therapy

Any subject may withdraw from the treatment or study at any time. Subjects will be followed for a 30-day safety follow-up or beyond if there are unresolved drug-related toxicities.

5.2.1. Reasons for Withdrawal/Early Discontinuation

Any subject who discontinues from the study drug for any reason will have their study drug discontinuation recorded.

Subjects may be withdrawn from the study after signing informed consent for the following reasons:

- Adverse event
- Lost to follow-up
- Death

- Protocol violation
- Withdrawal of consent by subject
- TP53 contain an inactivating mutation, insertion, or deletion detected
- Study terminated by Sponsor
- PD (radiographic progression)
- Other (eg, discretion of the investigator or clinical progression or start of new therapy)

If a subject withdraws from the study, the investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn due to an adverse event, the investigator will follow the subject until the adverse event has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures (Section 5.2.2).

5.2.2. Withdrawal Procedures

Protocol-specified withdrawal procedures will involve an End-of-Treatment Visit and an End-of-Study Follow-up Visit 30 (± 2) days later (Sections 7.3.1.12 and Section 7.3.1.13).

5.2.3. Subject Replacement

During Part 1 of the study, any subject who discontinues study participation before completing the first cycle of treatment and is not evaluable for DLT may be replaced. See Section 4.1.5.2 for definitions of DLTs.

5.2.4. Subject Re-screening Procedures

The study will allow re-screening for any subject who failed to meet eligibility criteria upon initial screening. The Principal Investigator will consult with the Sponsor before making the re-screen decision. For both Parts 1 and 2, the SID must remain the same at the time of re-screening. The initial screening information and the reason why the subject is ineligible for the initial evaluation will be recorded on the Screening Log. No data from the initial evaluation will be entered into the clinical database for re-screened subjects, except for those that were not repeated during re-screening (eg, tumor biopsies) or other tests that are still valid within the screening window per the medical monitor.

6. TREATMENTS ADMINISTERED

6.1. Investigational Products

The investigator must ensure that the investigational product will be used only in accordance with the protocol.

Milademetan will be administered as an oral capsule. It will be supplied in 5, 20, 80, and 200 mg capsules individually packaged in desiccant-embedded aluminum blisters. Two other capsule strengths of 30 and 100 mg will also be supplied in HDPE bottles.

6.1.1. Method of Assigning Subjects to Treatments and Blinding

6.1.1.1. Randomization

Not applicable because this is a single-arm study.

6.1.1.2. Blinding

Both parts of the study are open label, and no blinding will be performed.

6.1.2. Method of Assessing Treatment Compliance

The following measures will be employed to ensure treatment compliance during dosing at the clinical site:

- Milademetan only to subjects participating in the study and complying with the instructions from the clinical study personnel.
- Doses on the visit days of Cycle 1 should be administered to subjects under the supervision of clinical study personnel at the site. A mouth and hand check of all subjects should be completed to ensure that all capsules have been swallowed.
- Milademetan may be dispensed in amounts exceeding the minimum amount required for the period of time until the next visit. Subjects will be instructed to return all unused milademetan at the next visit. Alternatively, to ensure compliance, the site personnel may choose to dispense only the adequate amount of study drug required until the next scheduled visit. Compliance with the study drug regimen will be determined by counting unused capsules and needs to be ≥ 75% in the DLT evaluation period.
- Milademetan administration that occurs at clinic visits will be supervised by a member of the site staff.

6.1.3. Labeling and Packaging

Milademetan will be supplied in individually packaged desiccant-embedded aluminum blisters.

The clinical site will dispense take-home medication with labels and instructions.

6.1.4. Preparation

Procedures for proper handling and disposal of anticancer drugs should be followed in accordance with the standard operating procedures (SOPs) of the study site.

6.1.5. Storage

Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions listed below:

- Stored at 2°C to 8°C (36°F to 46°F).

If storage conditions are not maintained per specified requirements, Medpace or DSI should be contacted.

6.1.6. Drug Accountability

When a drug shipment is received, the investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label and drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be faxed as instructed on the form. The original will be retained at the site. In addition, the investigator or designee shall contact DSI as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the investigational product. The record must be kept current and should contain the dates and quantities of drug received, subject (identification number and/or initials or supply number as applicable) for whom the investigational product was dispensed, the date and quantity of investigational product dispensed and remaining, if from individual subject drug units, as well as the initials of the dispenser.

At the end of the study, or as directed, all milademetan capsules including unused, partially used, or empty containers will be returned to a designee as instructed by DSI. Investigational product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of investigational product must be documented and the documentation included in the shipment. At the end of the study, a final investigational product reconciliation statement must be completed by the investigator or designee and provided to the Sponsor. Unused drug supplies may be destroyed by the investigator when approved in writing by DSI/delegate, and DSI/delegate has received copies of the site's drug handling and disposition SOPs.

All investigational product inventory forms must be made available for inspection by a DSI authorized representative or designee and regulatory agency inspectors. The investigator is responsible for the accountability of all used and unused study supplies at the site.

6.1.7. Retention Samples

Not applicable.

6.2. Concomitant Medications

Medications used within 30 days before screening will be recorded. All concomitant medications will be recorded on the eCRF.

6.2.1. Prohibited Concomitant Medications/Activities

The following medications and products will be prohibited:

- Other anticancer therapy, including cytotoxic, antibody, retinoid, or hormonal treatment and small-molecule tyrosine kinase inhibitors. Concurrent use of hormone replacement therapy, the use of gonadotropin releasing hormone modulators for prostate cancer, and the use of somatostatin analogs for neuroendocrine tumors are permitted if such therapy has not been changed within 8 weeks before study drug treatment. Megestrol acetate as supportive care is also permitted.
- Other investigational agents.
- Nonclinical studies indicate that milademetan is metabolized by CYP3A. Drugs that are strong inducers of these enzymes may alter the PK of milademetan and should therefore be avoided (Section 18.5). If drugs that are strong inhibitors of CYP3A need to be taken concomitantly, then milademetan dose must be reduced to half the assigned dose.
- Milademetan is metabolized by CYP3A. St. John's Wort (hypericin) therefore will not be permitted for 30 days before and during participation in the study.
- Because milademetan is a substrate for CYP3A and grapefruit juice and Seville oranges contain CYP3A inhibitors, foods or beverages containing grapefruit or Seville oranges should be avoided within 48 hours before initial dose of study drug and throughout the duration of the study.

7. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Section 18.6.

7.1. Screening

7.1.1. Part 1 (Dose Escalation), Screening (Pre-cycle)

The screening (Pre-cycle) period occurs within 14 days prior to starting study therapy.

The following procedures will be performed during the Part 1 screening period:

- Obtain written (ie, signed and dated) informed consent.
- Assign an SID number.
- Record demographic, medical history information including PFS post the most recent prior therapy, and prior medication history information for cancer.
- Perform a complete physical examination and record weight and height.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain blood samples for safety laboratories (Section 10.8).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.
- Obtain a urine sample for urinalysis (Section 10.8).
- Perform a 12-lead ECG in triplicate:
  - For subjects enrolled per Case 3 (Section 4.1.2.1), 4 sets of triplicate ECGs should each be taken approximately 1 hour apart.
- Record concomitant medications.
- Assess subjects for adverse events.
- Obtain archived tumor samples for TP53 testing (approximately 25 FFPE sections or blocks) (Section 9.2.1).
- Perform a tumor biopsy (optional) within 21 days prior to the first dose of study drug (Section 9.2).
- Perform a tumor assessment within 4 weeks before the administration of the first dose of study drug (Section 8.1).
  - For all subjects with lymphoma, perform a (^{18}F) fluorodeoxyglucose-positron emission tomography (FDG-PET) scan under fasting conditions at baseline. Assess bone marrow by aspirate and/or biopsy per investigator decision.

- Complete the Inclusion/Exclusion Criteria Form for subject registration.
  - The Sponsor will perform registration after verifying that the subject meets the inclusion/exclusion criteria (Section 5.1) provided by the investigator. If the Sponsor has any questions regarding the information sent by the investigator, he or she will immediately contact the investigator to check the details. Directly after registration, the Sponsor will forward the results of registration to the investigator. At this time, the subject will be assigned to study drug treatment.
  - The investigator must not prescribe or administer the study drug until the subject has completed registration. If the Sponsor disqualifies a subject from participation in the clinical study, the investigator will be notified. The investigator will then explain this outcome to the relevant subject.

7.2. Randomization

Not applicable because this is a single-arm study.

7.3. Treatment Period

7.3.1. Treatment Period, Part 1 (Dose Escalation)

Unless otherwise stated, an activity occurs before drug administration.

7.3.1.1. Part 1 (Dose Escalation), Cycle 1/Day 1

The following procedures will be completed predose during the Part 1, Cycle 1/Day 1 visit. If the screening visit for Part 1 is completed within 24 hours of Cycle 1/Day 1, the assessments do not need to be repeated.

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry) both before administration of study drug and at 2 hours postdose.
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain blood samples for safety laboratories (Section 10.8).
- Obtain a PK blood sample.
- Obtain a blood sample for tumor markers as appropriate for the tumor type.
- Obtain a blood sample for pharmacogenomics (PGx). Instructions for handling and shipping the PGx blood sample are included in the Study Manual.
- Obtain MIC-1 serum sample.
- Obtain blood samples for exploratory analysis (Section 10.8).
- Obtain a urine sample for urinalysis (Section 10.8).
- Perform a 12-lead ECG in triplicate.

- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).

The following procedures will be completed postdose during the Part 1, Cycle 1/Day 1 visit:

- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry) at 2 hours postdose.
- Obtain PK blood samples at the following time points: 0.5, 1, 2, 3, and 6 to 8 hours postdose.
- Obtain MIC-1 serum samples 6 to 8 hours postdose.
- Obtain blood samples for exploratory analyses 6 to 8 hours postdose (Section 10.8).
- Perform a 12-lead ECG at 2 hours postdose in triplicate:
  - For subjects enrolled per Case 3 (Section 4.1.2.1), triplicate ECGs will be taken at predose, 0.5, 1, 2, 3, and 8 hours postdose, corresponding to the PK time points. The time points for the ECG and PK sample collection should be as close as possible within a 10-minute window.

7.3.1.2. Part 1 (Dose Escalation), Cycle 1/Day 2

The following procedures will be performed during the Part 1, Cycle 1/Day 2 visit.

- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain a predose PK blood sample.
- Obtain a predose MIC-1 serum sample.
- Perform a 12-lead ECG in triplicate.
  - For subjects enrolled per Case 3 (Section 4.1.2.1), triplicate ECGs will be taken at predose, corresponding to the PK time point. The time point for the ECG and PK sample collection should be as close as possible within a 10-minute window.
- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense a pill diary with dose administration instructions to assess treatment compliance.

7.3.1.3. Part 1 (Dose Escalation), Cycle 1/Day 8

The following procedures will be performed during the Part 1, Cycle 1/Day 8 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain a predose PK blood sample.
- Obtain a predose MIC-1 serum sample.
- Obtain a predose urine sample for urinalysis (Section 10.8).
- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for adverse events.
- Obtain an optional tumor biopsy 6 hours postdose.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.1.4. Part 1 (Dose Escalation), Cycle 1/Day 15

The following procedures will be performed during the Part 1, Cycle 1/Day 15 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain a predose PK blood sample.
- Obtain a predose MIC-1 serum sample.
- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.1.5. Part 1 (Dose Escalation), Cycle 1/Days 18 to 21

The following procedures will be completed predose during the Part 1, Cycle 1/Days 18 to 21 visit:

(For subjects enrolled in the QD × 7/28 days schedule, this visit is needed only if there are unresolved Grade ≥3 AEs or Grade ≥2 thrombocytopenia on Day 15 that need follow up).

(For subjects receiving study drug under the QD 7/28 days or QD 3/14 days schedules, the blood sample collection [exploratory blood samples, PK samples, ad MIC-1 induction] on Cycle 1 Days 18 to 21 is not required)

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain PK blood samples at the following time points: predose, 0.5, 1, 2, 3, and 6 to 8 hours postdose.
- Obtain a predose MIC-1 serum sample.
- Obtain predose blood samples for exploratory analysis (Section 10.8).
- Obtain a predose urine sample for urinalysis (Section 10.8).
- For subjects enrolled per Case 3 (Section 4.1.2.1), perform a 12-lead ECG in triplicate.
  - Triplicate ECGs will be taken at predose and 3 hours postdose, corresponding to the PK time points. The time points for the ECG and PK sample collection should be as close as possible within a 10-minute window.
- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Review pill diary to assess treatment compliance.

7.3.1.6. Part 1 (Dose Escalation), Cycle 2/Day 1

The following procedures will be performed during the Part 1, Cycle 2/Day 1 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry) before administration of study drug.
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).

- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain PK blood samples at the following time points: predose and at 1, 3, and 6 to 8 hours postdose.
- For subjects enrolled per Case 3 (Section 4.1.2.1), obtain a predose MIC-1 serum sample.
- Obtain a blood sample for tumor markers as appropriate for the tumor type.
- Obtain a predose urine sample for urinalysis (Section 10.8).
- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.1.7. Part 1 (Dose Escalation), Cycle 2/Day 8

The following procedures will be performed at the Part 1, Cycle 2/Day 8 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.1.8. Part 1 (Dose Escalation), Cycle 2/Day 15

The following procedures will be performed at the Part 1, Cycle 2/Day 15 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).

- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.1.9. Part 1 (Dose Escalation), Cycle 3/Day 1

The following procedures will be performed at the Part 1, Cycle 3/Day 1 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.
- Obtain a blood sample for tumor markers as appropriate for the tumor type.
- Obtain a predose urine sample for urinalysis (Section 10.8).
- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for adverse events.
- Perform a tumor assessment (Section 8.1).
  - If the subject has a lymphoma that is FDG-PET avid, post-treatment FDG-PET scans will be performed under fasting conditions. If baseline bone marrow aspirate and/or biopsy was positive, it may be repeated at this time.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.1.10. Part 1 (Dose Escalation), Cycle 3/Day 15

The following procedures will be performed at the Part 1, Cycle 3/Day 15 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).

- Obtain predose blood samples for safety laboratories (Section 10.8).
- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.1.11. Part 1 (Dose Escalation), Cycle 4 and All Subsequent Cycles, Day 1

The following procedures will be performed at the Part 1, Cycle 4/Day 1 visit and all additional Cycle Day 1 visits:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain a blood sample for tumor markers as appropriate for the tumor type.
- Record concomitant medications.
- Assess subjects for adverse events.
- Perform a tumor assessment at the time points outlined in the Schedule of Events; every 2 cycles of treatment for the first 8 cycles and then every 3 cycles thereafter (ie, at start of Cycles 3, 5, 7, and 9, then Cycles 12, 15, etc.). (Section 8.1).
  - If the subject has a lymphoma that is FDG-PET avid, post-treatment FDG-PET scans will be performed under fasting conditions. If baseline bone marrow aspirate and/or biopsy was positive, it may be repeated at the same time as subsequent tumor assessments.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

For Cycle 4 Day 1 and beyond: subjects who completed more than 1 year of treatment with continued clinical benefit and no ongoing Grade ≥3 TEAEs or risk thereof in the judgment of the investigator are allowed to continue on with the subsequent visits at every other cycle and may have additional visits as clinically needed.

7.3.1.12. Part 1 (Dose Escalation), End-of-Treatment (Post-cycle)

This End-of-Treatment Visit should occur at the earliest day possible within 30 (± 2) days after the last administration of milademetan but before beginning any other form of anticancer

therapy. The same procedures will be performed when subjects roll over to the Extension Phase (Section 18.7).

The following assessments will be performed at this visit:

- Perform a complete physical examination and record weight and height.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain blood samples for safety laboratories (Section 10.8).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.
- Obtain a blood sample for tumor markers as appropriate for the tumor type.
- Obtain PK blood sample.
- Obtain blood samples for exploratory analyses (Section 10.8).
- Obtain a urine sample for urinalysis (Section 10.8).
- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for adverse events.
- Review pill diary to assess treatment compliance.
- Record reason for treatment discontinuation.
- Tumor re-biopsy (optional) (Section 7.3.1.14).

7.3.1.13. Part 1 (Dose Escalation) End-of-Study Follow-up

The End-of-Study Follow-up should occur 30 (± 2) days after the last administration of milademetan. Follow-up information will be collected via a phone call or site visit. If the subject begins another form of anticancer therapy before the end of the 30 (± 2)-day period, every effort will be made to complete all the End-of-Study assessments prior to commencing the new therapy. The investigator should follow subjects with adverse events until the event has resolved or the condition has stabilized. In case of unresolved adverse events, including significant abnormal laboratory values at the End-of-Treatment assessment, these events will be followed up until resolution or until they become clinically irrelevant.

The following information will be collected at this follow-up:

- Assessment of adverse events
- Current medications
- Subject survival status

If the End-of-Study Follow-up is not performed (ie, due to death, lost to follow-up, etc.), record the reason.

7.3.1.14. Part 1 (Dose Escalation) Tumor Re-biopsy

To search for possible mechanisms of acquired resistance to milademetan, an optional tumor re-biopsy may be performed in subjects who have achieved an initial CR/PR or SD for at least 6 months by RECIST v 1.1 or revised IWG criteria to milademetan but later develop PD while on therapy. Tumor re-biopsy would be performed within 30 days following the last dose of milademetan treatment, preferably prior to initiating new therapy.

7.3.2. Treatment Period, Part 2 (Dose Expansion)

Unless otherwise stated, an activity occurs before study drug administration.

7.3.2.1. Part 2 (Dose Expansion), Screening (Pre-cycle)

The screening (Pre-cycle) period is within 14 days before starting study therapy.

The following assessments will be performed during the Part 2 screening period:

- Obtain written (ie, signed and dated) informed consent.
- Record demographic, medical history information including PFS post the most recent prior therapy, and prior medication history information for cancer.
- Perform a complete physical examination and record weight and height.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain blood samples for safety laboratories (Section 10.8).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.
- Obtain a urine sample for urinalysis (Section 10.8).
- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for adverse events.
- Obtain archived tumor samples for TP53 testing (approximately 25 FFPE sections or blocks) (Section 9.2.1).
- Perform a pre-treatment tumor biopsy (Section 9.2).
- Perform a tumor assessment within 4 weeks before the administration of the first dose of study drug (Section 8.1).
  - For all subjects with DLBCL, perform a FDG-PET scan under fasting conditions at baseline. Assess bone marrow by aspirate and/or biopsy per investigator decision.
- Complete the Inclusion/Exclusion Criteria Form for subject registration.

- The Sponsor will perform registration after verifying that the subject meets the inclusion/exclusion criteria provided by the investigator. If the Sponsor has any questions regarding the information sent by the investigator, he or she will immediately contact the investigator to check the details. Directly after registration, the Sponsor will forward the results of registration to the investigator. At this time, the subject will be assigned to study drug treatment.
- The investigator must not prescribe the study drug until the subject has completed registration. If the Sponsor disqualifies a subject from participation in the clinical study, the investigator will be notified. The investigator will then explain this outcome to the relevant subject.

7.3.2.2. Part 2 (Dose Expansion), Cycle 1/Day 1

The following will be completed during the Part 2, Cycle 1/Day 1 visit. If the screening visit for Part 2 is completed within 24 hours of Cycle 1/Day 1, the assessments do not need to be repeated.

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry) both before administration of study drug and at 2 hours postdose.
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain a blood sample for tumor markers as appropriate for the tumor type.
- Obtain PK blood samples at the following time points: predose, and then at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose. All samples should be collected within ±5 minutes of specified time points.
- Obtain a blood sample for PGx. Instructions for handling and shipping the PGx blood sample are included in the Study Manual.
- Obtain MIC-1 serum samples predose and another sample between 6 and 8 hours postdose.
- Obtain blood samples for exploratory analyses predose and at 8 hours postdose (Section 10.8).
- Obtain a predose urine sample for urinalysis (Section 10.8).
- Perform a 12-lead ECG both predose and at 2 hours postdose in triplicate.
- Administer mildemetan per protocol (at the site).
- Record concomitant medications.
- Assess subjects for adverse events.

7.3.2.3. Part 2 (Dose Expansion), Cycle 1/Day 2

The following procedures will be performed during the Part 2, Cycle 1/Day 2 visit:

- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain a predose PK blood sample.
- Obtain a predose MIC-1 serum sample.
- Perform a 12-lead ECG predose and 2 hours postdose in triplicate.
- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense a pill diary with dose administration instructions to assess treatment compliance.

7.3.2.4. Part 2 (Dose Expansion), Cycle 1/Day 8

The following procedures will be performed during the Part 2, Cycle 1/Day 8 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain a predose PK blood sample.
- Obtain a predose MIC-1 serum sample.
- Obtain a predose urine sample for urinalysis (Section 10.8).
- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for adverse events.
- Perform a tumor biopsy (requested) 6 hours postdose (optional).
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.2.5. Part 2 (Dose Expansion), Cycle 1/Day 15

The following procedures will be performed during the Part 2, Cycle 1/Day 15 visit:

- Perform a complete physical examination and record weight.

- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain a predose PK blood sample.
- Obtain a predose MIC-1 serum sample.
- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.2.6. Part 2 (Dose Expansion), Cycle 1/Days 18 to 21

The following procedures will be performed during the Part 2, Cycle 1/Days 18 to 21 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain PK blood samples at the following time points: predose, 0.5, 1, 2, 3, 4, 6, and 8 hours postdose. All samples should be collected within ± 5 minutes of specified time points.
- Obtain a predose MIC-1 serum sample.
- Obtain predose blood samples for exploratory analyses (Section 10.8).
- Obtain a predose urine sample for urinalysis (Section 10.8).
- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Review pill diary to assess treatment compliance.

7.3.2.7. Part 2 (Dose Expansion), Cycle 2/Day 1

The following procedures will be performed during the Part 2, Cycle 2/Day 1 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry) before administration of study drug.
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).

- Obtain a blood sample for tumor markers as appropriate for the tumor type.
- Obtain a predose urine sample for urinalysis (Section 10.8).
- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for adverse events.
- Obtain PK blood samples at the following time points: predose, and then at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose.
- Administer mildemetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.2.8. Part 2 (Dose Expansion), Cycle 2/Day 8

The following procedures will be performed during the Part 2, Cycle 2/Day 8 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.2.9. Part 2 (Dose Expansion), Cycle 2/Day 15

The following procedures will be performed during the Part 2, Cycle 2/Day 15 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.2.10. Part 2 (Dose Expansion), Cycle 3/Day 1

The following procedures will be performed at the Part 2, Cycle 3/Day 1 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.
- Obtain a blood sample for tumor markers as appropriate for the tumor type.
- Obtain a predose urine sample for urinalysis (Section 10.8).
- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for adverse events.
- Perform a tumor assessment (Section 8.1).
  - If the subject has DLBCL that is FDG-PET avid, post-treatment FDG-PET scans will be performed under fasting conditions. If baseline bone marrow aspirate and/or biopsy was positive, it may be repeated at this time.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.2.11. Part 2 (Dose Expansion), Cycle 3/Day 15

The following procedures will be performed during the Part 2, Cycle 3/Day 15 visit:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Record concomitant medications.
- Assess subjects for adverse events.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

7.3.2.12. Part 2 (Dose Expansion), Cycle 4 and All Subsequent Cycles, Day 1

The following procedures will be performed at the Part 2, Cycle 4/Day 1 visit and all additional Cycle Day 1 visits:

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain predose blood samples for safety laboratories (Section 10.8).
- Obtain a blood sample for tumor markers as appropriate for the tumor type.
- Record concomitant medications.
- Assess subjects for adverse events.
- Perform a tumor assessment at the time points outlined in the Schedule of Events; every 2 cycles of treatment for the first 8 cycles and then every 3 cycles thereafter (ie, at start of Cycles 3, 5, 7, and 9, then Cycles 12, 15, etc.). (Section 8.1).
  - If the subject has DLBCL that is FDG-PET avid, post-treatment FDG-PET scans will be performed under fasting conditions. If baseline bone marrow aspirate and/or biopsy was positive, it may be repeated at the same time as subsequent tumor assessments.
- Administer milademetan per protocol (at the site).
- Dispense milademetan per protocol (to take home).
- Dispense and review pill diary to assess treatment compliance.

For Cycle 4 Day 1 and beyond: subjects who completed more than 1 year of treatment with continued clinical benefit and no ongoing Grade ≥ 3 TEAEs or risk thereof in the judgment of the investigator are allowed to continue on with the subsequent visits at every other cycle and may have additional visits as clinically needed.

7.3.2.13. Part 2 (Dose Expansion), End-of-Treatment (Post-Cycle)

This End-of-Treatment Visit should occur at the earliest day possible within 30 (±2) days after the last administration of milademetan, but before beginning any other form of anticancer therapy. The same procedures will be performed when subjects roll over to the Extension Phase (Section 18.7).

The following assessments will be performed at this visit:

- Perform a complete physical examination and record weight and height.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry).
- Assess functional status using the ECOG Performance Status Scale (Section 18.1).
- Obtain blood samples for safety laboratories (Section 10.8).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.

- Obtain a blood sample for tumor markers as appropriate for the tumor type.
- Obtain blood samples for exploratory analyses (Section 10.8).
- Obtain a urine sample for urinalysis (Section 10.8).
- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for adverse events.
- Review pill diary to assess treatment compliance.
- Record reason for treatment discontinuation.
- Tumor re-biopsy (optional) (Section 7.3.2.15).

7.3.2.14. Part 2 (Dose Expansion) End-of-Study Follow-up

The End-of-Study Follow-up should occur 30 (± 2) days after the last administration of milademetan. Follow-up information will be collected via a phone call or site visit. If the subject begins another form of anticancer therapy before the end of the 30 (± 2)-day period, every effort will be made to complete all the End-of-Study assessments prior to commencing the new therapy. The investigator should follow subjects with adverse events until the event has resolved or the condition has stabilized. In case of unresolved adverse events, including significant abnormal laboratory values at the End-of-Treatment assessment, these events will be followed up until resolution or until they become clinically not relevant.

The following information will be collected at this follow-up:

- Assessment of adverse events
- Current medications
- Subject survival status

If the End-of-Study Follow-up is not performed (ie, due to death, lost to follow-up, etc.), record the reason.

7.3.2.15. Part 2 (Dose Expansion) Tumor Re-biopsy

Please see Section 7.3.1.14 for details regarding performing tumor re-biopsy in Part 2. Re-biopsy in Part 2 will follow the same procedures used in Part 1.

8. EFFICACY ASSESSMENTS

8.1. Efficacy Variable(s)

Efficacy assessments will be based on tumor assessments to be performed at screening and every 2 cycles of treatment for the first 8 cycles and then every 3 cycles thereafter (ie, at start of Cycles 3, 5, 7, and 9, then Cycles 12, 15, etc.) while the subject remains on study drug. The clinical activity of milademetan will be assessed by evaluating tumor response. In subjects with solid tumors, tumor response will be evaluated using RECIST v 1.1 (Section 18.3). In subjects with lymphomas, tumor response will be evaluated using the revised IWG criteria (Section 18.4).[7]

Computed tomography (CT) and/or magnetic resonance imaging (MRI) (spiral CT or MRI with ≤ 5 mm cuts) of the chest, abdomen, and pelvis should be used for tumor assessment unless another modality of disease assessment is necessary for the lesions. Every effort should be made to use the same assessment modality for all assessments for each subject.

Subjects with lymphoma require an FDG-PET scan at baseline. Subjects with lymphoma who are FDG-PET avid require FDG-PET scanning at each tumor assessment. Bone marrow will be assessed at baseline by aspirate and/or biopsy per the investigator's decision. If positive, bone marrow assessments may be repeated with subsequent tumor assessments.

As a complementary approach to the exploratory objective #2 in Part 1 (Section 3.1.3.1), particularly in WD/DD liposarcoma that are preferentially enrolled in the study due to the high prevalence of MDM2 amplification, the growth rates of the target tumors before starting milademetan versus on-treatment with milademetan may be analyzed by capturing the target tumor measurements by local reading in 2 or more prior scans from the medical records, if available.

Additionally, a digital or electronic copy of the CT/MRI scans performed for RECIST v 1.1 assessment may be collected by the sponsor for centralized analysis by sponsor-appointed radiologist(s) as a post-hoc exploration of the effect of milademetan on specific tumor histologies (eg, WD/DD liposarcoma).

9. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

9.1. Pharmacokinetic Assessment(s)

Blood samples for PK analyses will be collected for the measurement of plasma concentrations of milademetan as shown in Table 9.1. Additionally, PK samples may be obtained at any time during the study if deemed clinically necessary. At each time point, approximately 5 mL of blood will be collected for DS-3032a analysis. Instructions for the handling of blood samples and shipping of plasma samples for PK analyses are included in a separate document (eg, laboratory manual). The actual time of study drug administration and the exact time of blood sampling for PK analysis must be recorded on the case report form (CRF).

The PK samples will be shipped to a central laboratory for forwarding to a Sponsor-designated bioanalytical laboratory. Plasma concentrations of DS-3032a will be measured using a validated assay at the bioanalytical laboratory.

The PK parameters (eg, Cmax, area under the plasma concentration-time curve from time 0 to 24 hours [AUC0-24h], etc.) will be estimated by non-compartmental analysis as described in Section 12.5.1.

Table 9.1: Blood Sample Collection for Milademetan Pharmacokinetics

Part	**Dose Escalation**									
Cycle/Days	**Cycle 1/ Days 1, 18 to 21 and Cycle 2/ Day 1[e]**								**Cycle 1/ Days 2, 8, 15**	**End-of-Treatment**
Hour	0[a,d]	0.5[b]	1[b]	2[b]	3[b]	6 to 8[c]			0[a]	0[a]
Part	**Dose Expansion**									
Cycle/Days	**Cycle 1/ Days 1, 18 to 21 and Cycle 2/ Day 1**								**Cycle 1/ Days 2, 8, 15**	**End-of-Treatment**
Hour	0[a,d]	0.5[b]	1[b]	2[b]	3[b]	4[b]	6[b]	8[b]	0[a]	0[a]

eCRF = electronic case report form; PK = pharmacokinetics; QD = once daily
[a] Predose within 2 hours prior to drug administration.
[b] ± 15% of nominal time.
[c] PK sample will be collected between time window of 6 and 8 hours postdose. Actual time of sample collection must be recorded in eCRF.
[d] 24-hour PK on Cycle 1 Days 18 to 21 and Cycle 2 Day 1 will be imputed to its predose PK.
[e] Cycle 1 Days 18 to 21 PK sample collection is not needed for subjects in QD x 7/28 days and QD 3/14 days dose schedules.

9.2. Pharmacodynamic/Predictive Biomarker Variable(s)

9.2.1. TP53 Status

- During Dose Escalation, tumor TP53 genotyping will be performed in archived FFPE and, if available, fresh tumor biopsies in all enrolled subjects. Confirmation of TP53 wild-type status is NOT required prior to milademetan dosing. The investigator will be informed if the genotyping confirms the presence of inactivating TP53 mutations (ie, if the testing result shows that a subject's malignant cells contain an inactivating mutation, insertion, or deletion in the TP53). If the testing result shows that a subject's tumor contains an inactivating mutation, insertion, or deletion in the TP53 gene after milademetan has begun, the subject may choose to discontinue from the study or continue treatment as long as the subject is deriving clinical benefit (SD or objective response) in the absence of unacceptable toxicities per investigator assessment. TP53 re-testing can be considered.
- During Dose Expansion, TP53 genotyping will be performed in both fresh pre-treatment tumor biopsies and archived samples from subjects with sarcoma and DLBCL. In addition to TP53 genotyping, tumor samples may be analyzed for DNAseq and RNAseq. Confirmation of TP53 wild-type status is NOT required prior to milademetan dosing, but the investigator will be informed if the genotyping confirms the presence of inactivating TP53 mutations. If the testing result shows that a subject's tumor contains an inactivating mutation, insertion, or deletion in the TP53 gene after milademetan has begun, the subject may choose to discontinue from the study or continue treatment as long as the subject is deriving clinical benefit (SD or objective response) in the absence of unacceptable toxicities per investigator assessment. TP53 re-testing can be considered.

9.2.2. Pharmacodynamic Variables

Induction of serum MIC-1 will be the primary PDy biomarker. Serum samples will be collected at multiple time points in the study to assess the effect of milademetan treatment on MIC-1 induction. Other exploratory PDy biomarkers including, but not limited to, expression levels of p53, p21, MDM2, MDM4, Ki67, apoptosis markers, and/or other biomarkers will also be assessed, if available.

9.2.3. Exploratory Biomarker Analysis

Archived or pre-treatment, on-treatment, and end-of-treatment biopsied tumor samples will be examined for components of the p53 pathway, which may include, but are not limited to, expression of p53, p21, MDM2, MDM4, and MDM2 copy number, and TP53 mutations. Additional biomarkers outside of the p53 pathway may be included in order to better understand the responsiveness to therapy. These may include protein, metabolite, gene expression, or genetic biomarkers.

Subjects should be willing to provide archived tumor samples. During Part 1 (Dose Escalation), subjects will have the option to provide pre- and post-treatment biopsies (baseline and 6 hours postdose [± 2 hours] on Cycle 1 Day 8 [± 2 days]). During Part 2 (Dose Expansion), subjects are

required to provide a pre-treatment biopsy (baseline). Post-treatment tumor biopsies will be requested to be obtained 6 hours postdose [± 2 hours] on Cycle 1 Day 8. Tumor biopsies may be obtained by skin punch biopsies (for melanoma), Tru-cut technique, or core needle biopsies under imaging guidance.

Optional tumor re-biopsy will be performed within 30 days of the last dose of milademetan in subjects who have achieved an initial CR/PR or SD for at least 6 months to milademetan but later developed PD while on therapy.

9.3. Pharmacogenomics

As part of this study, a blood sample will also be banked for possible future PGx analysis in DNA. All participants should be presented with the PGx ICF at screening. Participation in this portion of the study is optional for all subjects. Thus, those who choose not to provide a sample for PGx analysis may still participate in the main portion of the study.

In all parts of the study, on Day 1 of Cycle 1 prior to study drug administration, the blood PGx sample should be collected for subjects who sign the PGx ICF. This sample may be analyzed only for genes suspected to contribute to the safety and efficacy of the study drug (milademetan).

Results will provide information on how individuals metabolize and/or react to the study drug or help to identify subjects who are more likely or less likely to benefit from the study drug. The information may be useful in increasing the knowledge of differences among individuals in the way they metabolize the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

Because emerging information regarding the safety and efficacy of milademetan may become available in the future, samples will be retained for possible future analysis. Samples will be retained until the DNA has been exhausted or until the Sponsor instructs the genotyping contractor to destroy the sample (in accordance with laboratory procedures). During the period of storage, the DNA sample will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time.

The samples will be shipped to a central laboratory for forwarding to Gentris Clinical Genetics, Inc., which has been contracted by the Sponsor to process these blood samples.

To ensure subject confidentiality, sample tubes will be identified only by a barcode label. This barcode will be linked to the subject's SID number.

Refer to a separate document for instructions for sample collection, preparation, handling, storage, and shipment.

10. SAFETY EVALUATION AND REPORTING

10.1. Adverse Event Collection and Reporting

All clinical adverse events occurring after the subject signs the ICF and up to 30 (±2) days after the last dose of study drug, whether observed by the investigator or reported by the subject, will be recorded on the adverse event eCRF page. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history. All SAEs are to be reported according to the procedures in Section 10.5. Investigators should report diagnosis as the adverse event or SAE term; when the diagnosis is unavailable, they should report signs and symptoms as individual entries of adverse event or SAE until the diagnosis becomes available. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an adverse event or SAE, but the reason for the procedure may be an adverse event or SAE. Pre-planned (prior to signing the ICF) procedure or treatment requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 10.4.2 for definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression is a study endpoint and consequently should not be reported as an adverse event/SAE. However, when a subject dies from disease progression with no other immediate causes, “disease progression” should be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the investigator assesses as related to study drug should also be reported and managed as an SAE.

At each visit, the investigator will determine whether any adverse events have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject, or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. All laboratory values must be appraised by the investigator as to clinical significance. All post-baseline abnormal laboratory values considered clinically significant by the investigator must be recorded as an adverse event on the eCRF and, if serious, reported as an SAE following the procedures in Section 10.5.

The investigator should follow subjects with adverse events until the event has resolved or the condition has stabilized. In case of unresolved adverse events including significant abnormal laboratory values at the End-of-Treatment assessment, these events will be followed up until resolution or until they become clinically irrelevant.

10.2. Safety Endpoints

Safety endpoints include SAEs, TEAEs, physical examination findings (including ECOG performance status), vital signs measurements, standard clinical laboratory parameters (serum chemistry, hematology, urinalysis), and ECG parameters.

10.3. Adverse Events of Special Interest

Not applicable.

10.4. Adverse Event

10.4.1. Definition of Adverse Event

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (International Council for Harmonisation [ICH] E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

It is the responsibility of investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings that should be considered adverse events.

10.4.2. Serious Adverse Event

Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias, or development of drug dependency or drug abuse.

Note:

- A procedure is not an adverse event or SAE, but the reason for the procedure may be an adverse event.
- Pre-planned (prior to signing the ICF) procedures or treatment requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

10.4.3. Grade Assessment

The severity of AEs will be graded using NCI-CTCAE, v 4.0. For each episode, the highest severity grade attained should be reported.

The NCI-CTCAE guidelines do not allow certain grades for certain AEs. For example, pain can be Grade 1 to 3 only (ie, cannot be life-threatening or fatal), whereas sepsis can only be Grade 4 or 5 (ie, can only be life-threatening or fatal). In addition, alopecia can only be Grade 1 or 2. The NCI-CTCAE guidelines should be followed closely.

- Grade 1 Mild adverse event
- Grade 2 Moderate adverse event
- Grade 3 Severe adverse event
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to adverse event

Severity vs. Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on subject/event outcome at the time of the event. For example, the NCI-CTCAE Grade 4 (life-threatening or disabling adverse event) is assessed based on unique clinical descriptions of severity for each adverse event, and these criteria may be different from those used for the assessment of adverse event seriousness. An adverse event assessed as Grade 4 based on the NCI-CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

10.4.4. Causality Assessment

The investigator should assess causal relationship between an adverse event and milademetan on the basis or his/her clinical judgment and the following definitions. The causality assessment should be made based on the available information and can be updated as new information becomes available.

- 1 = Related:
  - The adverse event follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

    Or

  - The adverse event follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its chemical group or is predicted by known pharmacology.

- 2 = Not Related:
  - The adverse event does not follow a reasonable sequence from study product administration or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

10.4.5. Action Taken Regarding the Study Product

- 1 = Dose Not Changed: No change in study drug dosage was made.
- 2 = Drug Withdrawn: The study drug was permanently stopped.
- 3 = Dose Reduced: The dosage of study drug was reduced.
- 4 = Drug Interrupted: The study drug was temporarily stopped.
- 5 = Dose Increased: The dosage of study drug was increased.

10.4.6. Other Action Taken for Event

- None
  - No treatment was required
- Medication required
  - Prescription and/or over-the counter (OTC) medication was required to treat the adverse event.
- Hospitalization or prolongation of hospitalization required
- Other

10.4.7. Adverse Event Outcome

- 1 = Recovered/Resolved
  - The subject fully recovered from the adverse event with no residual effect observed.
- 2 = Recovered/Resolved with Sequelae
  - The residual effects of the adverse event are still present and observable.
  - Include sequelae/residual effects.
- 3 = Not Recovered/Not Resolved
  - The adverse event itself is still present and observable.
- 4 = Fatal
  - Fatal should be used when death is a direct outcome of the adverse event.
- 5 = Unknown

10.5. Serious Adverse Event Reporting Procedure For Investigators

All AEs and SAEs will be reported in the eCRF. Additionally, SAEs should be reported by the investigator on a serious adverse event report (SAVER) form within 24 hours of awareness.

Call Medpace study personnel immediately once notified of an SAE.

Medpace SAE hotline - USA:
Phone: PPD
Fax: PPD
E-mail: PPD

All events (serious and non-serious) must be reported with the investigator's assessment of the event's seriousness, severity, and causality to the study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome, should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Source documents (including medical reports) will be retained at the study site and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.6. Notifying Regulatory Authorities, Investigators, IRB, and Competent Authorities

DSI and/or Medpace will inform investigators, IRBs, and regulatory authorities of any suspected unexpected serious adverse event reactions (SUSARs) occurring in other study sites or other DSI studies of the investigational product, as appropriate per local reporting requirements.

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the study drug, unless delegated to the Sponsor, it is the investigator's responsibility to inform the IRB per Sponsor's instruction.

10.7. Exposure In Utero During Clinical Studies

DSI must be notified of any subject who becomes pregnant while receiving study drug or up to the End-of-Study Follow-up (at least 30 [± 2] days after the last administration of study drug) or withdrawal from the study, whichever occurs later.

Although pregnancy is not technically an adverse event, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the investigator, or designee, to report any pregnancy in a subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE

(ie, post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs as outlined in Section 10.5.

The potential for milademetan to affect fertility and embryo-fetal development has not been tested. Women of childbearing potential should be informed of the potential risk, have periodic pregnancy tests, and use highly effective methods of birth control during treatment and for an additional 90 days after the end of treatment. Women should not breastfeed during the study and for an additional 90 days after the end of treatment.

The potential of milademetan to be transferred by semen and its effect on sperm is unknown. Male subjects with partners of childbearing potential should inform their partners of their participation in the clinical study and use highly effective methods of birth control during treatment and for an additional 90 days after the end of treatment.

10.8. Clinical Laboratory Evaluations

The following clinical laboratory tests will be measured. For clinical laboratory parameters, the reference range of the institution that performs the measurements will be used.

Information will be entered in the eCRF on whether or not measured, date of measurement, and measurement results for the following items.

- Hematology tests
  - red blood cell count, hemoglobin, hematocrit, platelet count, and white blood cell count with 5-part differential, including absolute neutrophil count and reticulocyte count.
- Serum chemistry tests
  - sodium, potassium, bicarbonate, chloride, calcium, phosphorus, albumin, glucose, serum creatinine, uric acid, total protein, blood urea nitrogen, AST, ALT, alkaline phosphatase, and total and direct bilirubin.
- Urinalysis
  - Creatinine clearance (screening only), protein, glucose, blood, microscopy assessments, and specific gravity.
- Coagulation: INR and aPTT.
- Serum or urine beta-human chorionic gonadotropin pregnancy test.
- Tumor markers.

All laboratory values must be appraised by the investigator as to clinical significance. All abnormal laboratory values considered clinically significant by the investigator must be recorded in the adverse event page of the eCRF. Abnormal laboratory values (NCI-CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

10.9. Vital Signs

Vital sign measurements will include systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, body temperature, and pulse oximetry.

Blood pressure and pulse rate will be measured after the subject has rested in a recumbent position for 5 minutes or more.

Whether or not measured, information will be entered in the eCRF on date of measurement and measurement results for the following items: systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature, and pulse oximetry.

10.10. Electrocardiograms

Twelve-lead ECGs (in triplicate) will be measured after the subject has rested in a recumbent position for 5 minutes or more. Whether or not measured, date performed, results, and findings will be recorded in the eCRF.

Standard supine 12-lead ECGs will be performed by qualified technicians in triplicate as noted in the schedule of events. ECGs will be reviewed at the site for treatment of any urgent issues. The clinical significance of any ECG change must be assessed by the investigator in the context of the subject's medical history, physical examination, and concomitant medications. The investigator or delegated physician will review, sign, and date all ECGs. Please refer to Table 18.2 and Table 18.3 for timing of ECG assessments and specific instructions for subjects enrolled per Case 3 (Section 4.1.2.1).

10.11. Physical Examinations

Physical examinations will evaluate the following body systems/organs: general appearance; dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; genitourinary (optional); lymphatic; musculoskeletal/extremities; and neurological. Weight and height will also be recorded in kilograms and centimeters, respectively, and BMI calculated. Clinically significant changes from baseline must be reported as AEs. ECOG performance status will also be assessed as part of the physical examinations.

10.12. Other Safety Assessments

Not applicable.

11. OTHER ASSESSMENTS

Not applicable.

12. STATISTICAL METHODS

12.1. General Statistical Considerations

The primary analysis is to summarize DLT during the Dose Escalation part; efficacy in the Dose Expansion part; and safety, PK, and PDy data in both study parts.

The primary analysis will occur either after all subjects in Part 1 and Part 2 have discontinued the study or at least 6 months after enrollment of the last subject. After the primary analysis, the main study will be closed. Subjects in Part 1 and Part 2 who are still on study drug at the time of the primary analysis may be eligible to continue receiving study drug in a separate extension phase of the protocol (see Section 18.7), and data collected from those subjects may be captured in a separate database.

Descriptive statistics will be provided for selected demographic, safety, PK, and PDy data by dose and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

Assessments of change from baseline to post-treatment or the ratio of post-treatment to baseline will include only those subjects with both baseline and post-treatment measurements. The last nonmissing value of a variable taken before the first dose of study drug will be used as the baseline value, unless otherwise specified. In general, missing or dropout data will not be imputed for the purpose of data analysis, unless otherwise specified.

Safety analyses will be performed based on the safety analysis set. Analysis of PK parameters will be based on the PK analysis sets, and biomarker analyses will be based on the PDy biomarker analysis sets. Efficacy endpoints will be analyzed based on the full analysis set and the primary analysis set. Data from the Dose Escalation part will be summarized by dose level and overall.

A detailed SAP describing the methodology to be used in the final analysis will be prepared and finalized before database lock. Statistical methods described within this document may be changed based on advances in research.

12.2. Analysis Sets

12.2.1. Enrolled Analysis Set

The enrolled analysis set will include all subjects who signed an ICF and were enrolled in either the Dose Escalation part or the Dose Expansion part of the study.

12.2.2. Full Analysis Set

The full analysis set will include all subjects enrolled in the Dose Escalation part or the Dose Expansion part who received any amount of milademetan.

12.2.3. Biomarker Positive Analysis Set

The Biomarker Positive analysis set will include all subjects in the full analysis set who were biomarker positive.

12.2.4. Dose-Limiting Toxicity Evaluable Set

The DLT-evaluable set will include all subjects enrolled in the Dose Escalation part who had a DLT within the first 4 weeks (28 days) on study, or without DLT but received at least 75% of scheduled Cycle 1 (28 days) milademetan doses and completed Cycle 1 safety assessments.

12.2.5. Safety Analysis Set

The safety analysis set will include all subjects enrolled who received any amount of milademetan. Subjects will be summarized according to treatment actually received.

Three groups of subjects will be identified within the safety analysis set: (1) subjects in the Dose Escalation part, (2) subjects in the Dose Expansion part, and (3) all subjects in the study.

12.2.6. Pharmacokinetic Analysis Set

The PK analysis set will include all subjects in the enrolled analysis set who received any amount of milademetan and had measurable plasma concentrations of milademetan.

12.2.7. Biomarker Analysis Set

The PDy biomarker analysis set will include all subjects in the enrolled analysis set who received any amount of milademetan and who had the baseline assessment and, where applicable, at least 1 post-baseline assessment for biomarkers.

12.3. Study Population Data

Disposition and reasons for ending the treatment and discontinuing from the study will be summarized and listed for subjects in the enrolled analysis sets.

Demographic and baseline characteristics such as age, sex, race, baseline ECOG performance status, histology, cancer stage, best response to prior chemotherapy, lines of prior regimens, and prior treatment type will be summarized for the enrolled analysis sets, full analysis sets, primary analysis sets, and safety analysis sets. If 2 analysis sets within a part of the study are identical to each other, the table will be presented only once.

Study drug exposure, treatment duration, and compliance with study therapy will be summarized using descriptive statistics for the safety analysis sets.

12.4. Efficacy Analyses

12.4.1. Primary Efficacy Analyses

Not applicable for Part 1.

For Part 2 (Dose Expansion), primary efficacy variables will include objective response rate (the sum of CR and PR rates); disease control rate (DCR) (the sum of CR rate, PR rate, and SD rate

for a minimum of 8 weeks from the first dosing date), response duration, duration of SD, and time-to-response (TTR), using RECIST v 1.1 or the revised IWG criteria.

The primary efficacy variables will be listed and summarized using descriptive statistics based on the full analysis set and the primary analysis set for the Dose Expansion part of the study. For both objective response rate and DCR, point estimates and 95% exact binomial confidence intervals will be provided. Time to event variables including PFS, response duration, and duration of SD will be summarized descriptively using the Kaplan-Meier method. PFS is defined as the time from the date of the first dose to the earlier of the dates of the first objective documentation of radiographic disease progression, death due to any cause, or the last radiographic assessment if no progression assessment occurs. Censoring rules for the PFS analysis will be specified in the SAP.

In addition to the above analysis, descriptive statistics for the percent change in the sum of longest dimensions (SLD) in measurable tumors will be provided for solid tumors. A waterfall plot of the greatest percent decreases from screening in the SLD will be presented for each subject with an advanced solid malignancy. In addition, the percent change in the SLD at each of the first 3 post-baseline assessments will be presented. Change in tumor size comparing to pretreatment/historical data will be presented graphically. Additional details will be presented in the SAP.

12.4.2. Secondary Efficacy Analyses

For Part 1 (if feasible), objective response rate, DCR, response duration, duration of SD, TTR, PFS, and percent change in SLD of measurable tumors may also be analyzed using the same method as described above for the primary efficacy analyses.

In addition, the growth rates of the target tumors before starting milademetan based on prior scans from subjects' medical records versus on-treatment with milademetan may be summarized.

Additional analyses will be described in the SAP.

12.4.3. Exploratory Efficacy Analyses

For both Part 1 and Part 2, the growth modulation indices (the intrasubject ratio of PFS post-study drug versus PFS post the most recent prior therapeutic regimen) will be summarized by dose level.

12.5. Pharmacokinetic/Pharmacodynamic Analyses

12.5.1. Pharmacokinetic Analyses

Plasma concentration data for milademetan will be summarized using descriptive statistics (number of subjects [n], mean, coefficient of variance [CV%], standard deviation, median, geometric mean, geometric CV%, minimum and maximum) by dose cohort at each time point. The last PK time point for Cycle 1 Day 1 (24 hr) is the predose sample for Cycle 1 Day 2.

For Dose Escalation and Dose Expansion, the PK parameters listed in Table 12.1 will be summarized descriptively by dose and cancer type calculated using non-compartmental analysis. The PK parameters will be listed and summarized using descriptive statistics (same as above) by

dose cohort and visit, except Tmax, where only n, median, minimum, and maximum will be presented.

Table 12.1: Pharmacokinetic Parameters for Non-Compartmental Analysis

PK Parameter	Definition of PK Parameter
Cmax	Maximum plasma concentration
Cmin	minimum plasma concentration
Tmax	Time to reach maximum plasma concentration
t1/2	Terminal elimination half-life
t1/2,eff	Effective half-life[a]
AUCinf	Area under the plasma concentration-time curve up to infinity
AUC0-8h	Area under the plasma concentration-time curve from time 0 to 8 hours
AUC0-24h	Area under the plasma concentration-time curve from time 0 to 24 hours
AUClast	Area under the plasma concentration-time curve up to the last recorded time point
CL/F	Apparent clearance
Vd/F	Apparent volume of distribution
AI	Accumulation index[a]

[a] AI and steady-state exposures will be calculated using the PK data from the 21/28- and 28/28-day dosing schedules.

The dose proportionality of milademetan will be assessed for Cmax, area under the plasma concentration-time curve from time 0 to 8 hours (AUC0-8h), and AUC0-24h on Cycle 1 Day 1.

A PopPK analysis and exposure-response analysis for various endpoints may be developed. The analysis plan and the technical report will be provided separately.

12.5.2. Pharmacodynamic Analyses

Increase in MIC-1 levels over baseline in serum will be listed and summarized using descriptive statistics by dose level cohort.

12.5.3. Biomarker and Exploratory Analyses

Archived or pre-treatment, on-treatment, and end-of-treatment biopsied tumor samples will be examined for components of the p53 pathway, which may include, but are not limited to, expression of p53, p21, MDM2, MDM4, and MDM2 copy number, and TP53 mutations. Additional biomarkers outside of the p53 pathway maybe included in order to better understand the responsiveness to therapy. These may include protein, metabolite, gene expression, or genetic biomarkers.

Analyses for potential biomarkers that may be predictive of benefit from milademetan will be graphed and/or listed and summarized using descriptive statistics by dose level cohort.

Change in post-treatment biomarker expression from pre-treatment expression will be summarized by dose and cancer type if data warrant.

12.6. Safety Analyses

Safety parameters will include SAEs, TEAEs, physical examination findings (including ECOG performance status), vital sign measurements, standard clinical laboratory parameters (serum chemistry, hematology, urinalysis), and ECG parameters. Adverse events will be graded according to the NCI-CTCAE v4. In the Dose Escalation part, the incidence of DLTs will also be evaluated.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. In the Dose Escalation part, the number of DLTs identified among the DLT-evaluable subjects in the DLT-evaluable set will be listed and summarized for each dose of milademetan.

12.6.1. Adverse Event Analyses

A TEAE is defined as an adverse event that emerges during the treatment period (from first dose date until 30 days after the last dosing date), having been absent at pre-treatment; or reemerges during treatment, having been present at baseline but stopped prior to treatment; or worsens in severity after starting treatment relative to the pre-treatment state, when the adverse event is continuous.

The number and percentage of subjects reporting TEAEs will be tabulated by the worst NCI-CTCAE grade, system organ class (SOC), and preferred term.

Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs/SAEs considered related to milademetan.

A by-subject adverse event (including TEAE) data listing will be provided, including, but not limited to, verbatim term, preferred term, SOC, NCI-CTCAE grade, and relationship to study drug.

Deaths, other SAEs, and other significant AEs, including those leading to permanent discontinuation from milademetan, will be listed.

12.6.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for selected clinical laboratory test results (hematology and blood chemistry) and changes from baseline by scheduled time of evaluation, including the End-of-Treatment Visit, maximum post-treatment value, and minimum post-treatment value.

Abnormal laboratory results will be graded according to NCI-CTCAE, v4, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. Abnormal clinical laboratory test results that are deemed of clinical significance or of Grade 3 or 4 will be listed.

12.6.3. Vital Signs Analyses

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation, including the End-of-Treatment Visit and the maximum and minimum post-treatment values.

12.6.4. Electrocardiogram Analyses

ECG parameters (PR, RR, QRS, QT, corrected QT interval using Bazett's formula [QT_cB], and QT_cF) will be summarized using descriptive statistics for actual values and for changes from baseline by scheduled time of evaluation, including the End-of-Treatment Visit and the maximum post-treatment value. The corrected QT intervals using Bazett's and Fridericia's formula will be calculated as follows: $QT_cB = QT/(RR)^{1/2}$ and $QT_cF = QT/(RR)^{1/3}$.

The incidence of notable ECG changes in maximum absolute QT, QT_cF, and QT_cB intervals (> 450, > 480, and > 500 ms) over all post-treatment evaluations, as well as in QT, QT_cF, and QT_cB maximum changes from baseline (> 30 and > 60 ms) over all post-treatment evaluations will be summarized. A listing of ECG data will be provided.

The concentration-delta QTc relationship will be characterized by a linear mixed-effect model, and the slope and 90% CI will be estimated.

12.6.5. Physical Finding Analyses

Physical examination findings will be listed for the safety analysis sets.

12.6.6. Other Safety Analyses

The ECOG performance status at baseline will be summarized for the safety analysis sets. A shift table, presenting the 2-way frequency tabulation for baseline and End-of-Treatment Visit, will be provided for ECOG performance status.

12.7. Other Analyses

Not applicable.

12.8. Interim Analyses

No formal interim analysis is planned, except for the assessment of the MTD after each escalation cohort in the Dose Escalation part.

12.9. Data and Safety Monitoring Board

Not applicable.

12.10. Sample Size Determination

Cohorts of 3 to 6 subjects will be enrolled and assessed for DLT before escalation to a new higher dose. As an exception, the model will be reevaluated before enrollment of any additional subjects to the cohort if 2 evaluable subjects in the cohort experience a DLT before the enrollment of the next subject. For a subject to be considered evaluable for dose escalation decisions, the subject must have received 75% of the prescribed doses within the DLT observation period in Cycle 1 or experienced a DLT in Cycle 1. Subjects who are unable to complete at least 75% of the prescribed doses of milademetan within the DLT observation period as a result of unequivocal progression of disease may be replaced.

In total, there should be (a) at least 6 evaluable subjects at the MTD dose level with at least 21 evaluable subjects in total enrolled in the Dose Escalation part, or (b) at least 9 evaluable subjects have been enrolled at a dose level that is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity is at least 50%, or (c) dose level -1 is too toxic. At least 21 DLT-evaluable subjects are needed to reach an accurate estimate of the MTD.[8,9,10] However, to better define an RP2D that will be clinically beneficial to the subjects as well as hematologically safe and tolerable for prolonged treatment without dose delays, subjects in additional cohorts and multiple dosing schedules may be added.

For the Dose Expansion part (Part 2), approximately 20 subjects (each for advanced melanoma and DLBCL) will be enrolled. If the response rate is more than 25% (null hypothesis: response rate ≤ 0.25, alternative hypothesis: response rate > 0.25), then the probability of no response out of 10 subjects will be less than 10%. The probability that 4 or more responders out of 10 subjects are observed will be less than 25% under the null hypothesis but more than 80% under alternative hypothesis with response rate = 0.50.

The probability values for the sample size are derived based on binomial distribution using SAS v 9.2.

12.11. Specification of Bayesian Logistic Regression Model with Escalation with Overdose Control

12.11.1. Bayesian Logistic Regression Model for Modified Continuous Reassessment Method

The dose-toxicity relationship for BLRM with EWOC principle will be described by a 2-parameter BLRM:

$\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*), \quad \alpha>0, \beta>0$

where $\text{logit}(\pi(d))= \ln(\pi(d)/(1-\pi(d)))$, $\pi(d)$ is the probability of a DLT or the DLT rate at dosed. Doses are rescaled as d/d^* with the reference dose $d^* = 90$ mg/day. As a consequence, α is equal to the odds of toxicity at d^*. Note that for a dose equal to zero, the probability of toxicity is zero.

12.11.2. Prior Specification for Bayesian Logistic Regression Model Parameters

The Bayesian approach requires the specification of a prior distribution for the BLRM parameters. A minimally informative bivariate normal prior[11] for the model parameters ($\log(\alpha)$, $\log(\beta)$) is obtained as follows:

- Based on extrapolation of nonclinical toxicology studies in dogs, the MTD is projected to be greater than 90 mg/day in humans (the HNSTD of dogs is 3 mg/kg/day [60 mg/m^2/day], and assuming humans and dogs are equally sensitive, the MTD is projected to be greater than 90 mg/day in humans). The median prior probabilities of DLT are set to be approximately 8.0% and 24.5% at 15 mg/day (10 mg/m^2/day) (projected starting dose for dose escalation using BLRM) and at 90 mg/day (60 mg/m^2/day), respectively.
- For the remaining doses, the prior medians of probability of DLT are assumed linear in log-dose on the logit-scale.

- Based on the above medians for the probability of DLT at each dose and wide prior credible intervals (obtained from minimally informative Beta distributions[11]), the optimal parameters of the bivariate normal distribution can be obtained as follows:

Parameters	Means	Standard Deviations	Correlation
log(α), log(β)	(-1.1286, -0.4947)	(2.0244, 1.0595)	-0.4831

12.11.3. Escalation with Overdose Control Principle

Dose recommendation for the next cohort will be based on summaries of the posterior probability of the DLT rate for provisional doses: 15, 30, 60, 90, 130, 200, 300, 440, 680, and 900 mg/day. After each cohort of subjects completes DLT evaluation during Cycle 1, the posterior distributions of the DLT rate are derived for all provisional dose levels based on the BLRM using the DLT outcome data from all assessed doses and a prespecified prior distribution for the model parameters. The posterior probability of the DLT rate in the following 4 intervals at each dose level: [0%, 16%] as the DLT rate interval for underdosing, [16%, 33%] as the target DLT rate interval, [33%, 60%] as the DLT rate interval for excessive toxicity, and [60%, 100%] as the DLT rate interval for unacceptable toxicity will then be calculated and used for dose recommendation for the next cohort according to the EWOC principle. The above provisional doses are based on an initial estimate of the human MTD of 90 mg/day using the HNSTD of dogs in nonclinical toxicology studies (3 mg/kg/day). Of note, the HNSTD of rats was considerably higher (1000 mg/kg/day), and dog bone marrow cells were approximately 6-fold to 7-fold more sensitive to milademetan-induced myelotoxicity than human in the colony-forming unit-granulocyte/macrophage assay (see current IB). It is therefore conceivable that the posterior probability of DLT rate for dose recommendation may be generated using alternative provisional doses as long as the predicted exposure increments are between 30% and 100% (Section 4.1.2.1).

The EWOC principle requires that the BLRM recommended dose for the next cohort of subjects is the one with the highest posterior probability of the DLT rate in the target DLT rate interval of [16%, 33%] among all doses fulfilling the overdose control constraint: there is less than 25% of probability for the DLT rate > 33% (probability for excessive or unacceptable toxicity).

13. DATA INTEGRITY AND QUALITY ASSURANCE

13.1. Monitoring and Inspections

The DSI and Medpace monitor and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, eCRFs, source data, and other pertinent documents).

Verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH Good Clinical Practice (GCP) and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each study site. The monitor is responsible for visiting site(s) at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, GCP, and applicable regulations to the investigator and will ensure that appropriate action(s) designed to prevent recurrence of the detected deviations is taken and documented.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Audit of study site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator should respond to audit findings. In the event that a regulatory authority informs the investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

13.2. Data Collection

An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedure. If a subject is not treated, the reason must be recorded on the eCRF.

All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF, and any corrections made will be automatically documented via an "audit trail."

The eCRF should be kept current to enable the monitor to review the subject's status throughout the course of the study. Upon completion of the subject's eCRF, it will be reviewed and signed off by the investigator via the electronic data capture (EDC) system's electronic signature. This

signature will indicate that the investigator reviewed the data in the eCRF, the data queries, and the site notifications, and agrees with the eCRF content. Instructions for completion of the eCRFs will be provided. Corrections to electronic forms will be automatically documented by using the software's "audit trail."

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

The extent or frequency of data collection during the extension period of the study may be the same as during the main period of the study or may be reduced at the Sponsor's discretion considering the number of PFS and OS events, the number of subjects on study drug, and the value of additional data collection for evaluation of study endpoints.

Refer to Schedule of Assessments, Extension Phase, for details (Table 18.4).

13.3. Data Management

This is an open-label study. Each subject will be identified in the database by a unique subject identifier as defined by DSI.

To ensure the quality of clinical data across all subjects and sites, a Clinical Data Management review will be performed on subject data according to specifications given to Sponsor/or designee.

Each subject will be identified in the database by a unique subject identifier as defined by the sponsor.

To ensure the quality of clinical data across all subjects and study sites, a Clinical Data Management review will be performed on subject data according to specifications given to Sponsor/or designee. Data will be vetted both electronically and manually for eCRFs, and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the Clinical Data Management review process, eCRF queries will be raised and resolved within the EDC application.

Data received from external sources such as central labs will be reconciled to the clinical database.

SAEs in the clinical database will be reconciled with the safety database.

All prior cancer therapy and prior/concomitant medications entered into the database will be coded by using the latest version of World Health Organization Drug Dictionary. All adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities.

13.4. Study Documentation and Storage

The investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB/ethics committee (EC) correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

13.5. Record Keeping

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed eCRFs, ICFs, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the EC/IRB and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at study site, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

13.6. Product Complaints

A product complaint is any dissatisfaction with a product that may be attributed to the identity, quality, durability, reliability, or safety of the product. Individuals who identify a potential product complaint situation should immediately report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a quality representative form from the Sponsor. For product complaints, refer to the Study Manual for instructions and details.

14. FINANCING AND INSURANCE

14.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with DSI. This agreement will include the financial information agreed upon by the parties.

14.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

15. PUBLICATION POLICY

The Sponsor is committed to meeting the highest standards of publication and public disclosure of information arising from clinical studies sponsored by the company. The Sponsor will comply with US, European Union, and Japanese policies for public disclosure of the clinical study protocol and clinical study results and for sharing of clinical study data. The Sponsor will follow the principles set forward in "Good Publication Practice for Communicating Company- Sponsored Medical Research (GPP3)", and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Council of Medical Journal Editors (ICMJE).

In order to ensure compliance with the public disclosure policies and the ICMJE recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be reviewed and approved in writing by the Sponsor prior to submission.

16. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

16.1. Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- US Food and Drug Administration GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56, and 312, as appropriate, and
- other applicable local regulations.

16.2. Subject Confidentiality

The investigators and the Sponsor, DSI, will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted to DSI or the contract research organization (CRO), subjects should be identified by a unique subject identifier as designated by DSI. Documents that are not for submission to DSI and/or Medpace (eg, signed ICFs) should be kept in strict confidence by the investigator.

In compliance with ICH GCP guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. The investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the subject.

16.3. Informed Consent

Before a subject's participation in the study, it is the investigator's responsibility to obtain freely given consent, in writing, from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries, and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IRB prior to being provided to potential subjects.

The subject's written informed consent should be obtained prior to his/her participation in the study and should be documented in the subject's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion (not

necessarily the investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject. The date and time (if applicable) that informed consent was given should be recorded on the eCRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject or the legally acceptable representative and that informed consent was freely given by the subject.

Suggested model text for the ICF for the study and any applicable subparts (genomic, pharmacokinetic, etc) and assent forms for pediatric subjects (if applicable) are provided in the DSI ICF template for the investigator to prepare the documents to be used at his or her site. Updates to applicable forms will be communicated via letter from the Sponsor.

The consent for PGx sampling for banking and tumor biopsies should be documented in the subject's written informed consent. The consent form should be signed and personally dated by the subject or the subject's legal representative prior to his/her participation in the study. Participation for PGx sampling for banking is optional for all subjects. Participation for pre- and post-treatment tumor biopsies is optional for all subjects in Part 1, but for pre-treatment is mandatory in Part 2. Participation for tumor re-biopsy upon progression is optional for all subjects. Those subjects who choose not to provide a sample for PGx sampling for banking or optional tumor biopsies may still participate in the main portion of the study.

16.4. Regulatory Compliance

The study protocol, subject information and consent form, the investigator Brochure, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the investigator's qualifications should be submitted to the IRB for ethical review and approval according to local regulations prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the Statistical Analysis Plan (SAP).

In addition, the investigator will inform the Sponsor immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard and of any suspected/actual serious GCP non-compliance that the investigator becomes aware of.

16.5. Protocol Deviations

The investigator should conduct the study in compliance with the protocol agreed to by DSI and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRBs/ECs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. The Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or investigational treatment, and had at least 1 administration of investigational product, data should be collected for safety purposes.

The investigator should notify the IRB of deviations from the protocol in accordance with local procedures.

16.6. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all investigators involved in the clinical study, IRBs/ECs, and regulatory authorities of such information, and, when needed, will amend the protocol and/or subject information.

The investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IRB/EC. The investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICFs.

16.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the investigator by DSI. Also, the Sponsor will ensure the timely submission of amendments to regulatory authorities.

A global protocol amendment will affect study conduct at all study sites in all regions of the world. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented in a Summary of Changes document. These protocol amendments will undergo the same review and approval process as the original protocol.

A local protocol amendment will affect study conduct at a particular study site(s) and/or in a particular region/country. Sponsor approval of local amendments will be clearly documented.

A protocol amendment may be implemented after it has been approved by the IRB/EC and by regulatory authorities where appropriate, unless immediate implementation of the change is necessary for subject safety.

16.8. Study Termination

The Sponsor has the right to terminate the study at any time, and the study termination may also be requested by (a) competent authority/ies.

Stopping criteria are noted in Section 5.2.1.

16.9. Data and Safety Monitoring Board

Not applicable.

16.10. Address List

A list of key study personnel (including personnel at the sponsor, CRO, laboratories, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and updated in study reference materials.

17. REFERENCES

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18. APPENDICES

18.1. Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.[12]

18.2. National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When 2 different criteria grades might be applicable for rating a particular toxicity, or similar toxicities, the more severe grade should be used.
3. Any toxicity resulting in death is defined as Grade 5.
4. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
5. For links to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4, please refer to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

18.3. Response Evaluation Criteria in Solid Tumors, Version 1.1

18.3.1. Measurability of Tumor at Baseline

18.3.1.1. Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as follows:

Measurable

- Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by computed tomography (CT) scan (CT scan slice thickness no greater than 5 mm)
  - 10-mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
  - 20 mm by chest X-ray
- Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline (ie, screening for this study) and in follow-up (ie, all measurements past screening for this study), only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and nontarget lesions" for information on lymph node measurement

Nonmeasurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

18.3.1.1.1. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment.

Bone Lesions

- Bone scan, positron emission tomography scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT

or magnetic resonance imaging (MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are nonmeasurable.

Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

18.3.1.2. Specifications by Methods of Measurements

18.3.1.2.1. Measurement of Lesions

All measurements should be recorded in metric notation using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 4 weeks before the beginning of the treatment.

18.3.1.2.2. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. An MRI is also acceptable in certain situations (eg, for body scans).

18.3.2. Tumor Response Evaluation

18.3.2.1. Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. In this study, only subjects with measurable disease at baseline should be included in the study.

18.3.2.2. Baseline Documentation of "Target" and "Nontarget" Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (representative of all involved organs) should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

18.3.2.3. Response Criteria

This section provides the definitions of the criteria used to determine the objective tumor response for target lesions.

18.3.2.3.1. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

18.3.2.3.2. Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5-mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially nonreproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

18.3.2.3.3. Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).

NonCR/NonPD: Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing nontarget lesions (Note: the appearance of 1 or more new lesions is also considered progression).

18.3.2.3.4. Special Notes on Assessment of Progression of Nontarget Disease

The concept of progression of nontarget disease requires additional explanation as follows, when the subject also has measurable disease. In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more nontarget lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

18.3.2.3.5. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (eg, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered that reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example, because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

18.3.2.4. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug until the end of treatment. No confirmatory measurement for CR, PR, or SD is required in the study.

The subject's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions.

18.3.2.4.1. Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 18.1 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Table 18.1: Overall Response

Time point Response: Subjects with Target (± Nontarget) Disease			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	NonCR/NonPD	No	PR
CR	Not evaluated	No	PR
PR	NonPD or not all evaluated	No	PR
SD	NonPD or not all evaluated	No	SD
Not all evaluated	NonPD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

18.3.2.4.2. Missing Assessments and Inevaluable Designation

When no imaging/measurement is performed at all at a particular time point, the subject is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

18.3.2.4.3. Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject are known.

Best response determination in studies where confirmation of CR or PR IS NOT required: Best response in these studies is defined as the best response across all time points (eg, a subject who

has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline, 6 weeks. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second, and does not meet minimum duration for SD will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

18.3.2.4.4. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the eCRF.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and nontarget disease.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

18.3.2.5. Frequency of Tumor Reevaluation

In this study, tumor measurement will be conducted every 2 cycles while the subject remains on study for the first 8 cycles and then every 3 cycles thereafter (start of Cycles 3, 5, 7, and 9, then Cycles 12, 15, etc.) until progression of disease, withdrawal of consent, death, or loss to follow-up. Scan dates should not be adjusted or rescheduled due to dose interruption of any type.

Baseline tumor assessments must be performed within 4 weeks (28 days) prior to the first dose of treatment.

All efforts should be made to ensure consistency between the baseline measurements and all subsequent measurements in reference to utilization of scanning method, equipment, technique (including slice thickness and field of view), and radiographic interpreter.

The radiographic evaluation must include CT or MRI scanning of the chest, abdomen, and pelvis. Any additional suspected sites of disease should also be imaged. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

All target and nontarget sites are evaluated at each time point of tumor assessment.

18.4. International Working Group Criteria

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunchistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Source: Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579-586.[7]

18.5. Cytokine P450 3A Inducers and Inhibitors

This table is created using information from the hyperlinked source below. Please refer to those sites for additional information.

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

CYP3A Inhibitors	**CYP3A Inducers**
HIV Antivirals: Indinavir[a] Nelfinavir[a] Ritonavir[a] Boceprevir[a] Clarithromycin[a] Conivaptan[a] Grapefruit Juice[a] Itraconazole[a] Ketoconazole[a] Lopinavir[a] Nefazodone[a]	HIV Antivirals: Efavirenz[e] Nevirapine Avasimibe[d] Carbamazepine[d] Phenytoin[d] Rifampin[d] St. John's Wort[d] Bosentan[e] Etravirine[e] Modafinil[e]

CYP3A Inhibitors	CYP3A Inducers
Posaconazole[a]	Nafcillin[e]
Saquinavir[a]	
Telaprevir[a]	Amprenavir[f]
Telithromycin[a]	Aprepitant[f]
	Armodafinil[f]
Voriconazole[a]	Clobazamechinacea[f]
Amprenavir[b]	Pioglitazone[f]
Aprepitant[b]	Prednisone[f]
Atazanavir[b]	Rufinamide[f]
Ciprofloxacin[b]	Vemurafenib[f]
Crizotinib[b]	
Darunavir[b]	Barbiturates
Dilitiazem[b]	Glucocorticoids
Erythromycin[b]	Modafinil
Fluconazole[b]	Oxcarbazepine
Fosamprenavir[b]	Phenobarbital
Grapefruit Juice[b]	Rifabutin
Imatinib[b]	Troglitazone
Verapamil[b]	
Alprazolam[c]	
Amiodarone[c]	
Amlodipine[c]	
Atorvastatin[c]	
Bicalutamide[c]	
Cilostazol[c]	
Cimetidine[c]	
Cyclosporine[c]	
Fluoxetine[c]	
Fluvoxamine[c]	
Ginkgo[c]	
Goldenseal[c]	
Isoniazid[c]	
Lapatinib[c]	
Nilotinib[c]	
Oral Contraceptives[c]	
Pazopanib[c]	
Ranitidine[c]	
Ranolazine[c]	

CYP3A Inhibitors	CYP3A Inducers
Tipranavir[c]	
Ticagrelor[c]	
Zileuton[c]	
Not Azithromycin	
Chloramphenicol	
Delavirdine	
Diethyl-Dithiocarbamate	
Gestodene	
Mibefradil	
Mifepristone	
Norfloxacin	
Norfluoxetine	
Starfruit	

AUC = area under the plasma concentration-time curve; CYP = cytochrome P450; HIV = human immunodeficiency virus

[a] Strong inhibitor: causes a ≥ 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
[b] Moderate inhibitor: causes a ≥ 2-fold increase in the plasma AUC values or 50% to 80% decrease in clearance.
[c] Weak inhibitor: causes a ≥ 1.25-fold but < 2-fold increase in the plasma AUC values or 20% to 50% decrease in clearance.
[d] Strong inducer: causes a ≥ 80% decrease in the plasma AUC values.
[e] Moderate inducer: causes a 50% to 80% decrease in the plasma AUC values.
[f] Weak inducer: causes a 20% to 50% decrease in the plasma AUC value.

18.6. Schedule of Events

Table 18.2: Schedule of Events Part 1 (Dose Escalation)

Cycle[a]	**Pre-Cycle**	**1**									**2**												**3**		**4 and Beyond**	**Post-Cycle**
Visit Number	**1**	**2**						**3**	**4**	**5**	**6**						**7**				**8**	**9**	**10**	**11**	**12 and Beyond**	**TBD**
Visit Description	**Screen-ing**	**Exam and 1st Dose**						**Exam**	**Exam**	**Exam**	**Exam**						**Exam**				**Exam**	**Exam**	**Exam**	**Exam**	**Exam**	**EOT**[b]
Cycle Day(s)	**-14 to 0**	**1**						**2**	**8**	**15**	**18-21**						**1**				**8**	**15**	**1**	**15**	**1**	**ND**
Visit Window (days)									**± 2**	**± 2**	**0**						**± 2**				**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Time Postdose (hours)		**Pre dose**	**0.5**	**1**	**2**	**3**	**6-8**				**Pre dose**	**0.5**	**1**	**2**	**3**	**6-8**	**Pred ose**	**1**	**3**	**6-8**						
Informed consent	X																									
Demographics	X																									
Medical history	X																									
Archive tumor sample	X																									
Inclusion/exclusion criteria	X																									
Pregnancy test[c]	X																						X			X
Adverse events	X	X						X	X	X	X						X				X	X	X	X	X	X
Concomitant medications	X	X						X	X	X	X						X				X	X	X	X	X	X
ECOG	X	X							X	X	X						X				X	X	X	X	X	X
Physical examination and vital signs[d]	X	X			@			@	X	X	X						X				X	X	X	X	X	X
Safety laboratory[e]	X	X						X	X	X	X						X				X	X	X	X	X	X
Urinalysis[f]	X	X							X		X						X						X			X
Tumor markers[g]		X															X						X		X	X
ECG (12-lead)[h]	X	X			X			X	X		X				X		X						X			X
Tumor assessment[i]	X																						X		X	
Tumor biopsy (optional)[j]	X								X																	
PGx blood sample[k]		X																								

Table 18.2: Schedule of Events Part 1 (Dose Escalation) (Continued)

Cycle[a]	Pre-Cycle	1									2											3		4 and beyond	Post-Cycle
Visit Number	1	2						3	4	5	6						7				8	9	10	11	12 and beyond	TBD
Visit Description	Screen-ing	Exam and 1st Dose						Exam	Exam	Exam	Exam						Exam				Exam	Exam	Exam	Exam	Exam	EOT[b]
Cycle Day(s)	-14 to 0	1						2	8	15	18-21						1				8	15	1	15	1	ND
Visit Window (days)									± 2	± 2	0						± 2				± 2	± 2	± 2	± 2	± 2	± 2
Time Postdose (hours)		Pre dose	0.5	1	2	3	6-8				Pre dose	0.5	1	2	3	6-8	Pred ose	1	3	6-8						
Exploratory blood sample[l]		X					X				X															X
Milademetan administration[m]		X						X	X	X	X						X				X	X	X	X	X	
PK blood sample[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						X
MIC-1 serum sample[o]		X					X	X	X	X	X						Xp									
Dispense milademetan								X	X	X							X				X	X	X	X	X	
Pill diaries dispensed/reviewed								X	X	X	X						X				X	X	X	X	X	X
Optional tumor re-biopsy[q]																										X

DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FDG-PET = (18F) fluorodeoxyglucose-positron emission tomography; IWG = International Working Group; MIC-1 = macrophage inhibitory cytokine-1; ND = not determined; PGx = pharmacogenomic; PK = pharmacokinetic(s); QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors Version 1.1; TBD = to be determined

Note: The End-of-Study Follow-up will occur 30 (±2) days after the last administration of milademetan. If the subject begins another form of anticancer therapy before the end of the 30 (±2)-day period, every effort will be made to complete all the End-of-Study assessments prior to commencing the new therapy.

[a] Each cycle will last 28 days. Cohort safety assessment for DLTs will be performed after Day 28 of Cycle 1.

[b] The EOT Visit will occur 30 (± 2) days after the last administration of milademetan. If the subject begins another form of anticancer therapy before the end of the 30 (±2)-day period, every effort will be made to complete all the EOT assessments prior to commencing the new therapy. If there is an abnormality in need of monitoring beyond the EOT Visit, subjects will be followed until resolution or confirmed stability of the abnormality.

[c] Pregnancy test (urine or serum) will be performed in female subjects of childbearing potential at screening, Cycle 3 Day 1, and EOT Visit.

[d] Physical examination including vital signs will be performed on visit days indicated by X. Height and weight will be recorded at Screening and EOT Visits. Weight will be recorded at all other visits. Vital signs will be performed on visit days indicated by X or @.

[e] Safety laboratory samples for Day 1 predose (complete blood count with differential and reticulocyte count, serum chemistry, urinalysis, and coagulation profile) can be collected within 72 hours before the first dose. Creatinine clearance will be performed at screening.

[f] Urinalysis will be performed for the indicated visits up to Cycle 3 Day 1 and at EOT Visit.

[g] Tumor markers will be obtained as appropriate for the tumor type at each cycle.

[h] Twelve-lead ECGs (in triplicate) will be measured after the subject has rested in a recumbent position for 5 minutes or more. ECGs will be performed predose except at additional 2 hours postdose on Day 1. Procedure window is ± 1 hour. For subjects enrolled per Case 3 (Section 4.1.2.1), at Screening 4 sets of triplicate ECGs should each be taken approximately 1 hour apart, then triplicate ECGs will be taken at predose, 0.5, 1, 2, 3, 8, and 24 hours on Cycle 1 Days 1 to 2, and at predose and 3 hours post-dose on Days 18 to 21, corresponding to the PK time points on Day 1, Day 2, and Days 18-21, respectively. The time points for the ECG and PK sample collection should be as close as possible within a 10-minute window.

[i] Tumor assessment by physical examination and RECIST v 1.1 or revised IWG criteria will be performed at baseline within 4 weeks of the first dose of milademetan and after every 2 cycles of treatment for the first 8 cycles and then every 3 cycles thereafter (ie, at start of Cycles 3, 5, 7, and 9, then Cycles 12, 15, etc.). Pre-treatment FDG-PET scans will be performed in all subjects with lymphoma under fasting conditions at baseline within 4 weeks of the first dose of milademetan. In subjects with lymphoma that are FDG-PET avid, FDG-PET scans will be performed every 2 cycles of treatment for the first 8 cycles and then every 3 cycles thereafter (ie, at start of Cycles 3, 5, 7, and 9, then Cycles 12, 15, etc.). Bone marrow will be assessed at baseline by aspirate and/or biopsy per the investigator's decision. If positive, bone marrow assessments may be repeated with the subsequent tumor assessment.

[j] Optional paired tumor biopsies will be obtained by skin punch biopsies (for melanoma), Tru-cut technique, or core needle biopsies under imaging guidance.

[k] Informed consent specifically allowing optional PGx testing must be obtained before collecting sample.

[l] Exploratory blood samples drawn at Cycle 1 Day 1 predose and 6-8 hours postdose, Cycle 1 Days 18-21 predose, and EOT Visit for future analysis of circulating biomarkers. For subjects receiving study drug under the QD 7/28 days or QD 3/14 days schedules, the blood sample collection on Cycle 1 Days 18-21 is not required.

[m] Milademetan is administered per protocol at the clinical site at the indicated visit days. Subjects in the alternative dosing schedules will receive milademetan according to their assigned schedule (QD 7/28 days or QD 3/14 days).

[n] Pharmacokinetic samples will be collected predose at the indicated visit days (Cycle 1 Days 1, 2, 8, 15, 18-21 and Cycle 2 Day 1) and as detailed in Table 9.1. Subjects will be instructed not to take their dose until after sample has been collected on clinic days. Additional PK samples will be collected at the indicated time points. On Cycle 1 Day 8, a predose PK sample will be collected, and if tumor biopsy is performed, one additional PK sample will be taken right before (-1 hour) the tumor biopsy. For subjects receiving study drug under the QD 7/28 days or QD 3/14 days schedules, PK sample collection on Cycle 1 Days 18-21 is not required. The window for PK sample collection will be ± 15% unless otherwise specified in Section 9.1. Based on the PK profile established from the initial subjects treated in the study, PK sample collection time points may be modified upon notification by the Sponsor.

[o] Serum for MIC-1 induction will be obtained at the indicated time points (predose on Cycle 1 Days 1, 2, 8, 15, and 18 to 21). For subjects receiving study drug under the QD 7/28 days or QD 3/14 days schedules, MIC-1 sample collection on Cycle 1 Days 18-21 is not required.

[p] For subjects enrolled per Case 3 (Section 4.1.2.1), an additional sample at Cycle 2 Day 1 predose will be collected.

[q] An optional tumor re-biopsy may be performed within 30 days of the last dose of milademetan in subjects who have achieved an initial complete response/partial response or stable disease for at least 6 months by RECIST v 1.1 or revised IWG criteria to milademetan but later developed progressive disease while on therapy.

Table 18.3: Schedule of Events Part 2 (Dose Expansion)

Cycle[a]	**Pre-Cycle**	**1**																		**2**												**3**		**4 and Beyond**	**Post-Cycle**
Visit Number	**1**	**2**								**3**	**4**	**5**	**6**							**7**								**7b**	**8**	**9**	**10**	**11**	**12 and Beyond**	**TBD**
Visit Description	**Screening**	**Exam and 1st Dose**								**Exam**	**Exam**	**Exam**	**Exam**							**Exam**								**Exam**	**Exam**	**Exam**	**Exam**	**Exam**	**Exam**	**EOT**[b]
Cycle Day(s)	**-14 to 0**	**1**								**2**	**8**	**15**	**18-21**							**1**								**2**	**8**	**15**	**1**	**15**	**1**	**ND**
Visit Window (days)											**± 2**	**± 2**	**0**							**± 2**									**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Time Postdose (hours)		**Predose**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**				**Predose**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**Predose**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**							
Informed consent	X																																	
Demographics	X																																	
Medical history	X																																	
Archive tumor sample	X																																	
Inclusion/exclusion criteria	X																																	
Pregnancy test[c]	X																														X			X
Adverse events	X	X								X	X	X	X							X									X	X	X	X	X	X
Concomitant medications	X	X								X	X	X	X							X									X	X	X	X	X	X
ECOG	X	X									X	X	X							X									X	X	X	X	X	X
Physical examination and vital signs[d]	X	X			@					@	X	X	X							X									X	X	X	X	X	X
Safety laboratory[e]	X	X								X	X	X	X							X									X	X	X	X	X	X
Urinalysis[f]	X	X									X		X							X											X			X
Tumor markers[g]		X																		X											X		X	X
ECG (12-lead)[h]	X	X			X					X	X									X											X			X
Tumor assessment[i]	X																														X		X	

Table 18.3: Schedule of Events Part 2 (Dose Expansion) (Continued)

Cycle[a]	Pre-Cycle	1																		2												3		4 and beyond	Post-Cycle
Visit Number	1	2								3	4	5	6							7							7b	8	9	10	11	12 and beyond	TBD
Visit Description	Screening	Exam and 1st Dose								Exam	Exam	Exam	Exam							Exam							Exam	Exam	Exam	Exam	Exam	Exam	EOT[b]
Cycle Day(s)	-14 to 0	1								2	8	15	18-21							1							2	8	15	1	15	1	ND
Visit Window (days)											± 2	± 2	0							± 2								± 2	± 2	± 2	± 2	± 2	± 2
Time postdose (hours)		Predose	0.5	1	2	3	4	6	8				Predose	0.5	1	2	3	4	6	8	Predose	0.5	1	2	3	4	6	8							
Tumor biopsy[j]	X																																	
PGx blood sample[k]		X																																
Exploratory blood sample[l]		X							X				X																					X
Milademetan administration in clinic[m]		X								X	X	X	X							X								X	X	X	X	X	
PK blood sample[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[p]						
MIC-1 serum sample[o]		X						X		X	X	X	X																					
Dispense milademetan										X	X	X								X								X	X	X	X	X	
Pill diaries dispensed/reviewed										X	X	X	X							X								X	X	X	X	X	X
Optional tumor re-biopsy											X[q]																							X[t]

DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FDG-PET = (^{18}F) fluorodeoxyglucose-positron emission tomography; IWG = International Working Group; MIC-1 = macrophage inhibitory cytokine-1; ND = not determined; PGx = pharmacogenomic; PK = pharmacokinetic(s); QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; TBD = to be determined

Note: The End-of-Study Follow-up will occur 30 (± 2) days after the last administration of milademetan. If the subject begins another form of anticancer therapy before the end of the 30 (±2)-day period, every effort will be made to complete all the End-of-Study assessments prior to commencing the new therapy.

[a] Each cycle will last 28 days. Cohort safety assessment for DLTs will be performed after Day 28 of Cycle 1.

[b] End-of-Treatment Visit will occur 30 (± 2) days after the last administration of milademetan. If the subject begins another form of anticancer therapy before the end of the 30 (±2)-day period, every effort will be made to complete all the End-of-Treatment assessments prior to commencing the new therapy. If there is an abnormality in need of monitoring beyond the End-of-Treatment Visit, subjects will be followed until resolution or confirmed stability of the abnormality.

[c] Pregnancy test will be performed in female subjects of childbearing potential at screening, Cycle 3 Day 1, and End-of-Treatment Visit.

[d] Physical examination including vital signs will be performed on visit days indicated by X. Height and weight will be recorded at Screening and End-of-Treatment Visits. Weight will be recorded at all other visits. Vital signs will be performed on visit days indicated by X or @.

[e] Safety laboratory samples for Day 1 predose (complete blood count with differential and reticulocyte counts, serum chemistry, urinalysis, and coagulation profile) can be collected within 72 hours before the first dose. Creatinine clearance will be calculated at screening.

[f] Urinalysis will be performed for the indicated visits up to Cycle 3 Day 1 and at End-of-Treatment Visit.

[g] Tumor markers will be obtained as appropriate for the tumor type at each cycle.

[h] Twelve-lead ECGs (in triplicate) will be measured after the subject has rested in a recumbent position for 5 minutes or more. ECGs will be performed predose except at additional 2 hours postdose on Day 1 and Day 2. Procedure window is ± 1 hour.

[i] Tumor assessment by physical examination and RECIST v 1.1 or revised IWG criteria will be performed at baseline within 4 weeks of the first dose of milademetan, and after every 2 cycles of treatment for the first 8 cycles and then every 3 cycles thereafter (ie, at start of Cycles 3, 5, 7, and 9, then Cycles 12, 15, etc.). Pre-treatment FDG-PET scans will be performed in all subjects with DLBCL under fasting conditions at baseline within 4 weeks of the first dose of milademetan. In subjects with DLBCL that are FDG-PET avid, FDG-PET scans will be performed every 2 cycles of treatment for the first 8 cycles and then every 3 cycles thereafter (ie, at start of Cycles 3, 5, 7, and 9, then Cycles 12, 15, etc.). Bone marrow will be assessed at baseline by aspirate and/or biopsy per the investigator's decision. If positive, bone marrow assessments may be repeated with the subsequent tumor assessment.

[j] Mandatory pre-treatment tumor biopsies will be obtained by skin punch biopsies (for melanoma), Tru-cut technique, or core needle biopsies under imaging guidance at baseline.

[k] Informed consent specifically allowing optional PGx testing must be obtained before collecting sample.

[l] Exploratory blood samples drawn at Cycle 1 Day 1 predose and 6-8 hours postdose, Cycle 1 Days 18-21 predose, and End-of-Treatment Visit for future analysis of circulating biomarkers.

[m] Milademetan is administered per protocol at the clinical site at the indicated visit days. If an alternative dosing schedule than QD 21/28 is used for dose expansion, the subjects will receive milademetan according to their assigned schedule (eg, QD 3/14 days).

[n] Pharmacokinetic samples will be collected predose at the indicated visits (Cycle 1 Days 1, 2, 8, 15, 18-21 and Cycle 2 Day 1) and as detailed in Table 9.1. Subjects will be instructed not to take their dose until after sample has been collected on clinic days. Additional PK samples will be collected at the indicated time points. On Cycle 1 Day 8, a predose PK sample will be collected, and if tumor biopsy is performed, one additional PK sample will be taken right before (-1 hour) the tumor biopsy. The window for PK sample collection will be ± 15% unless otherwise specified in Section 9.1. Based on the PK profile established from the initial subjects treated in the study, PK sample collection time points may be modified upon notification by the Sponsor.

[o] Serum for MIC-1 induction will be obtained at the indicated time points (predose on Cycle 1 Days 2, 8, 15, and 18-21).

[p] Cycle 1 Day 8 (± 2 days) requested post-treatment re-biopsy should be obtained 6 hours postdose (± 2 h).

[q] An optional tumor re-biopsy may be performed within 30 days of the last dose of milademetan in subjects who have achieved an initial complete response/partial response or stable disease for at least 6 months by RECIST v 1.1 or revised IWG criteria to milademetan but later developed progressive disease while on therapy.

18.7. Extension Phase

18.7.1. Extension Phase Synopsis

Objective of the Extension Phase:	The primary objective of the Extension Phase is to allow continuation of milademetan treatment for those subjects in the milademetan Phase 1 study who have tolerated the drug and whose disease has not progressed (ie, stable disease [SD] or better) at least 6 months after enrollment is completed in both parts.
Design of the Extension Phase:	This is an open-label, nonrandomized extension phase of the main study phase, which is designed to allow subjects who have tolerated milademetan and demonstrated clinical benefit (SD or better) at the time of study closure during the main study phase to continue with milademetan monotherapy. Subjects will continue with the same dose of milademetan monotherapy treatment as in the main study phase until they commence new cancer therapy, experience unacceptable toxicity, withdraw consent, or have progressive disease. If study drug is withheld for toxicity, periodic visits should continue to occur as clinically indicated. These visits should include any procedures needed to ensure subject safety. Subjects enrolled in the Extension Phase will be assessed as outlined in Table 18.4. Data collected will be recorded in the individual, subject-specific electronic case report form (eCRF). The extent or frequency of data collection into the eCRFs may be reduced for the Extension Phase.
Duration of the Extension Phase:	The start of the Extension Phase is at least 6 months after enrollment is completed in both Part 1 and Part 2. Subjects who are receiving clinical benefit (SD or better) and have tolerated milademetan will continue to receive the drug. It is not possible to predict the duration of the Extension Phase because subjects may continue treatment until disease progression, unacceptable toxicity, starting of new cancer therapy, or withdrawal of consent.
Subject Eligibility:	Subjects must have tolerated milademetan and demonstrated clinical benefit (SD or better) at the time of closure of the main study phase (Part 1 and Part 2) in order to be eligible for this extended use phase of the study.

Safety Evaluations:	Safety evaluations include adverse events, serious adverse events, clinical laboratory evaluations, physical examinations, vital signs, as needed. ECGs may be done at investigator discretion, as clinically indicated.
Dose:	Subjects who participate in the Extension Phase will continue to take milademetan at the same dose as was taken in the main study phase.
Statistical Analyses:	Data collected during the Extension Phase will be listed and appended to the Clinical Study Report.

Table 18.4: Schedule of Events (Extension Phase)

Assessment	All Cycles, Day 1[a]	End-of-Treatment Visit[b]
Visit Window (Days)	**28 Days ± 3 Days from Day 1 of Previous Cycle[c]**	**30 to 45 Days After Last Dose**
Physical examination	X	X
Vital signs[d]	X	X
Adverse events	X	X
CBC (with differential and platelet count)	X[d]	X
Serum chemistries	X[d]	X
Milademetan administration[e]	X	
Tumor assessment	X[f]	

CBC = complete blood count; TEAE = treatment-emergent adverse event

[a] Assessments and laboratory tests indicated on Day 1 will occur before administration of milademetan.

[b] End-of-Treatment Visit will occur 30 to 45 days after the last administration of milademetan in the Extension Phase. If there is a clinically significant laboratory abnormality in need of monitoring beyond the End-of-Treatment Visit, subjects will be followed until resolution of the abnormality or until it is considered stable.

[c] For subjects who completed more than 1 year of study drug with continued clinical benefit and no ongoing clinically significant TEAEs or at risk of clinically significant TEAEs in the judgment of the investigator, the subsequent visits every 3 cycles and additional visits as clinically indicated are allowed.

[d] Clinical safety laboratory tests include hematology, chemistry, CBC, and platelet count. The tests described in Section 10.8 will be conducted on Day 1 of all cycles and as clinically indicated by the investigator. The subject's weight will be recorded as part of the vital signs assessment

[e] Milademetan is to be administered at the same dosing schedule that the individual subject was using as during the main study phase.

[f] Tumor assessment will be performed every 3 cycles.