Official Protocol Title:	Protocol/Amendment No.: 002-05 A Phase 1b Study to Evaluate the Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of MK0482 in Participants with Relapsed or Refractory Acute Myeloid Leukemia or Chronic Myelomonocytic Leukemia
NCT number:	NCT05038800
Document Date:	02-OCT-2023

TITLE PAGE

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Protocol Title: A Phase 1b Study to Evaluate the Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of MK-0482 in Participants with Relapsed or Refractory Acute Myeloid Leukemia or Chronic Myelomonocytic Leukemia

Protocol Number: 002-05

Compound Number: MK-0482

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

EudraCT	2022-003740-27
IND	154224
EU CT	2023-503580-42

Approval Date: 02 October 2023

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 5	02-OCT-2023	To add the EU CT number to the list of Regulatory Agency Identifying Numbers
Amendment 4	22-MAY-2023	To add a new dose strength 750 mg/vial for MK-0482
Amendment 3	07-DEC-2022	To add the Eudra CT number to the list of Regulatory Agency Identifying Numbers
Amendment 2	11-JUL-2022	To allow participants with relapsed/refractory CMML to participate in the dose escalation part of the study
Amendment 1	09-JUN-2021	Revisions based on FDA feedback
Original Protocol	02-APR-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendment:

To add the EU CT number to the list of Regulatory Agency Identifying Numbers.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Title Page	Updated Regulatory Agency Identifying Numbers	This change was made to address new regulatory guidance.

Section Number and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Not applicable.	Not applicable.	Not applicable.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1b Study to Evaluate the Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of MK-0482 in Participants with Relapsed or Refractory Acute Myeloid Leukemia or Chronic Myelomonocytic Leukemia

Short Title: Phase 1b study to evaluate MK-0482 for Relapsed/Refractory AML/CMML

Acronym:

Hypotheses, Objectives, and Endpoints:

In the participant population with relapsed and refractory AML/CMML subtypes of acute and chronic myelomonocytic leukemia or acute monoblastic/monocytic leukemia:

Primary Objective	**Primary Endpoint**
To determine the safety and tolerability and to determine a preliminary recommended Phase 2 dose of MK-0482 monotherapy	Dose-limiting toxicity Adverse Events (AEs) Discontinuing study intervention due to an AE
Secondary Objectives	**Secondary Endpoints**
To characterize the pharmacokinetic (PK) profile of MK-0482 monotherapy	Noncompartmental PK parameters
To evaluate antileukemia activity of MK-0482 monotherapy in acute myeloid leukemia (AML)	The following response endpoints will be assessed per 2017 European Leukemia Net (ELN) AML response criteria: Complete remission (CR), Composite CR: CR + CR with incomplete recovery (CR_i) Objective response: CR + CR_i + partial remission (PR)

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Acute myeloid leukaemia
Population	Relapsed/refractory acute myeloid leukemia with subtypes of acute myelomonocytic leukemia or acute monoblastic/monocytic leukemia, and relapsed/refractory chronic myelomonocytic leukemia
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 3 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 30 to 35 participants will be allocated as described in Section 9.9.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Part 1	MK-0482	100 mg/vial 750 mg/vial	7.5 mg, 25 mg, 75 mg, 225 mg, 750 mg or higher if needed	IV Infusion	Q3W up to 35 cycles	Test Product
Part 2	MK-0482	100 mg/vial 750 mg/vial	RP2D	IV Infusion	Q3W up to 35 cycles	Test Product

Total Number of Intervention Groups/Arms	1
Duration of Participation	Each participant will participate in the study for approximately 2 years from the time the participant provides documented informed consent through the final contact. After a screening phase of 21 days, each participant will receive assigned intervention for approximately 2 years. After the end of treatment each participant will be followed for 30 days for the occurrence of AEs and spontaneously reported pregnancy, as described in Section 8.4. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or end of the study.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Steering Committee	No

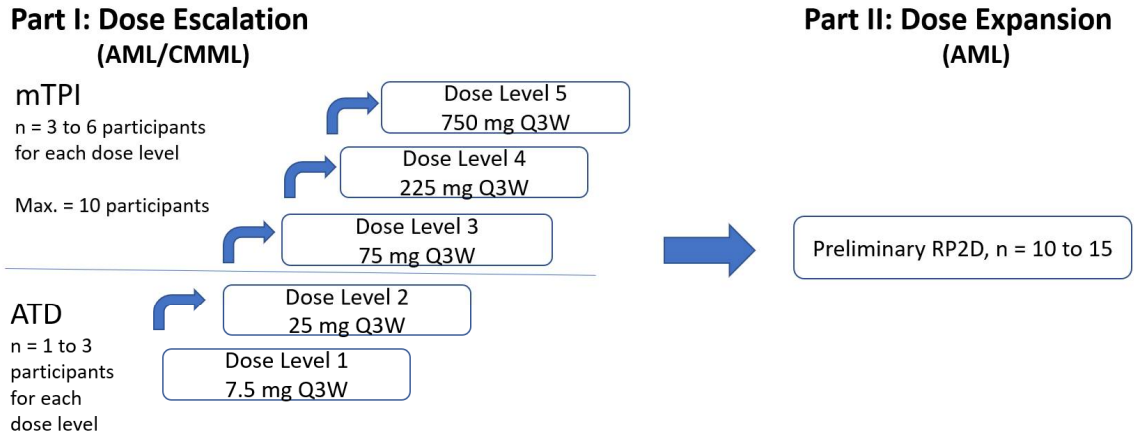
Study governance considerations are outlined in Appendix 1.

Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 11.

1.2 Schema

Figure 1 Part 1 and Part 2 Study Schema



AML=acute myeloid leukemia; ATD=accelerated titration design; CMML=chronic myelomonocytic leukemia; mTPI=modified toxicity probability interval; n=number of participants; RP2D=recommended Phase 2 dose; Q3W=every 3 weeks.
Note: Intermediate or higher dose levels may be evaluated. The maximum treatment duration is 35 cycles (~ 24 months).
Intraparticipant dose escalation is allowed for participants enrolled to ATD dose levels to up to 75mg dose.

1.3 Schedule of Activities

1.3.1 Dose Escalation and Expansion

Study Period	**Screening**	**Intervention**										**EOT/ Discon.**	**Safety FU**	**Survi-val FU**	**Notes**
Treatment Cycle		**1**					**2**		**3**		**4 to 35**				
Scheduled Day per Cycle	**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**1**	**8**	**1**	**At time of treatment discon.**	**30 days after last dose**	**Q12W**	
Scheduling Window (Days):		**-**	**+1**	**+1**	**±3**	**±3**	**±3**	**± 3**	**±3**	**± 3**	**±3**		**+7**	**±14**	
Administrative Procedures															
Informed Consent	X														
Informed Consent for Future Biomedical Research	X														If the participant (or their legally acceptable representative) provides documented informed consent for FBR, any leftover sample/tissue that would ordinarily be discarded will be retained for FBR. Participation in FBR is optional. See Section 8.9.
Inclusion/Exclusion Criteria	X														
Participant Identification Card	X	X													Update on C1D1.
Demographic and Medical History	X														
Prior Oncology Treatment History	X														

Study Period	**Screening**	**Intervention**										**EOT/ Discon.**	**Safety FU**	**Survival FU**	**Notes**
Treatment Cycle		**1**					**2**		**3**		**4 to 35**				
Scheduled Day per Cycle	**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**1**	**8**	**1**	**At time of treatment discon.**	**30 days after last dose**	**Q12W**	
Scheduling Window (Days):		**-**	**+1**	**+1**	**±3**	**±3**	**±3**	**± 3**	**±3**	**± 3**	**±3**		**+7**	**±14**	
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X		Prior medications – Record all medications taken within 30 days of the first dose of study treatment. Concomitant medications – Enter new medications started during the study through 30 days after the last dose of study treatment. See Section 8.1.6.
MK-0482 Administration		X					X		X		X				Study treatment administered on Day 1 of each cycle after all procedures/ assessments have been completed. A 24-hour or longer observation period may be mandated, if clinically indicated. See Section 8.1.9.
Survival Status		X	X	X	X	X	X	X	X	X	X	X	X	X	Survival FU begins after investigator-determined disease progression or start of new anticancer treatment. In addition, on Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Posttreatment Anticancer Therapy Status													X	X	Enter new medications and procedures for cancer therapy started after the EOT through Survival FU.

Study Period	**Screening**	**Intervention**										**EOT/ Discon.**	**Safety FU**	**Survi-val FU**	**Notes**
Treatment Cycle		**1**					**2**		**3**		**4 to 35**				
Scheduled Day per Cycle	**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**1**	**8**	**1**	**At time of treatment discon.**	**30 days after last dose**	**Q12W**	
Scheduling Window (Days):		**-**	**+1**	**+1**	**±3**	**±3**	**±3**	**± 3**	**±3**	**± 3**	**±3**		**+7**	**±14**	
Disease Assessments and Safety Procedures															
Full Physical Examination and Height[a]	X	X[b]													To be performed by the investigator or qualified designee.
Directed Physical Examination			X	X	X	X	X		X		X	X	X		Symptom directed as needed. May be performed on Day 1 of Cycles 2 to 4 and every third cycle thereafter (ie, Cycle 7, Cycle 10, Cycle 13).
Weight, Vital Signs (including oxygen saturation)	X	X	X	X	X	X	X		X		X	X	X		Weight to be measured at Screening and predose on Day 1 of each cycle. Vital signs and oxygen saturation to be collected predose and 10, 30, and 60 minutes after MK-0482 infusion. For Cycle 1, vital signs and oxygen saturation may also be collected approximately 24 hours after the end of the MK-0482 infusion (see Section 8.3.2 for details).
12-lead ECG	X	----------If clinically indicated----------													Additional ECGs may be performed as clinically indicated.
Chest X-Ray	X	----------If clinically indicated----------													For baseline and symptomatic evaluation of chest disease

Study Period	**Screening**	**Intervention**										**EOT/ Discon.**	**Safety FU**	**Survi-val FU**	**Notes**
Treatment Cycle		**1**					**2**		**3**		**4 to 35**				
Scheduled Day per Cycle	**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**1**	**8**	**1**	**At time of treatment discon.**	**30 days after last dose**	**Q12W**	
Scheduling Window (Days):		**-**	**+1**	**+1**	**±3**	**±3**	**±3**	**± 3**	**±3**	**± 3**	**±3**		**+7**	**±14**	
Urine or Serum hCG Pregnancy Test (WOCBP only) – as per local SOP	X	X					(x)		(x)		(x)		X		Perform at Screening and within 72 hours prior to the start of study treatment. (x) Additional tests may also be performed if clinically warranted, or as defined by local regulations (Appendix 5). If urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
Hematology (see also Table 8)	X	X	X	X	X	X	X	X	X	X	X	X	X		- Hematology is also part of efficacy evaluation in conjunction with bone marrow evaluation and in addition to CBC with differential. Immunoprofiling with AML and monocytic panels will be performed at screening and at visits when bone marrow evaluation is performed, when feasible. - Screening samples must be collected within 72 hours prior to the start of study treatment (24 hours for hematological values). If screening tests are performed within 72 hours prior to study treatment, C1D1 can be skipped with exception of hematology and
Urinalysis	X	X	X	X	X	X	X		X		X	X	X		
Chemistry (includes ALT, AST, bilirubin, LDH, also see Table 8)	X	X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation tests (PT/INR and aPTT/PTT)	X	X			X	X	X					X	X		

Study Period	**Screening**	**Intervention**										**EOT/ Discon.**	**Safety FU**	**Survival FU**	**Notes**
Treatment Cycle		**1**					**2**		**3**		**4 to 35**				
Scheduled Day per Cycle	**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**1**	**8**	**1**	**At time of treatment discon.**	**30 days after last dose**	**Q12W**	
Scheduling Window (Days):		**-**	**+1**	**+1**	**±3**	**±3**	**±3**	**± 3**	**±3**	**± 3**	**±3**		**+7**	**±14**	
															coagulation tests. These tests must be repeated on C1D1 and participant meet eligibility prior to dosing. - On subsequent Day 1 visits when dosing occurs, all laboratory tests must be performed within 72 hours prior to dosing. - Laboratory testing for monitoring of TLS on C1D2 and C1D4 should be performed as appropriate. Please also refer to Appendix 10 for details. - PTT may be performed if the local laboratory is unable to perform aPTT. Also refer to Table 8.

Study Period	**Screening**	**Intervention**										**EOT/ Discon.**	**Safety FU**	**Survi-val FU**	**Notes**
Treatment Cycle		**1**					**2**		**3**		**4 to 35**				
Scheduled Day per Cycle	**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**1**	**8**	**1**	**At time of treatment discon.**	**30 days after last dose**	**Q12W**	
Scheduling Window (Days):		**-**	**+1**	**+1**	**±3**	**±3**	**±3**	**± 3**	**±3**	**± 3**	**±3**		**+7**	**±14**	
Bone Marrow Aspirate and Biopsy	X								X		X	X			Screening/baseline sampling to be performed within 14 days prior to C1D1. Postbaseline sampling to be performed prior to C3D1, C5D1, C7D1, and then Day1 visit of every 3 Cycles (to be performed within 7 days of the scheduled visit) until progression or achieving confirmed CR. Bone marrow sampling also can be performed as clinically indicated. Bone marrow assessments should include pathological assessment and immunoprofiling, and other assessments (such as cytogenetic) as appropriate.
ECOG Performance Status	X	X			X	X	X		X		X	X	X		Evaluate within 72 hours prior to the start of study treatment at Screening, pre-treatment on Day 1 of each cycle and on designated days.

Study Period	**Screening**	**Intervention**										**EOT/ Discon.**	**Safety FU**	**Survi-val FU**	**Notes**
Treatment Cycle		**1**					**2**		**3**		**4 to 35**				
Scheduled Day per Cycle	**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**1**	**8**	**1**	**At time of treatment discon.**	**30 days after last dose**	**Q12W**	
Scheduling Window (Days):		**-**	**+1**	**+1**	**±3**	**±3**	**±3**	**± 3**	**±3**	**± 3**	**±3**		**+7**	**±14**	
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X	X		Continuous reporting (see Section 8.4). Record all AEs and ECIs occurring within 30 days after last dose of study treatment and SAEs for 90 days after the EOT or 30 days after EOT if the participant initiates new anticancer therapy (whichever is earlier). Report treatment-related SAEs regardless of when they occur.

Study Period	**Screening**	**Intervention**										**EOT/ Discon.**	**Safety FU**	**Survival FU**	**Notes**
Treatment Cycle		**1**					**2**		**3**		**4 to 35**				
Scheduled Day per Cycle	**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**1**	**8**	**1**	**At time of treatment discon.**	**30 days after last dose**	**Q12W**	
Scheduling Window (Days):		**-**	**+1**	**+1**	**±3**	**±3**	**±3**	**± 3**	**±3**	**± 3**	**±3**		**+7**	**±14**	
Pharmacokinetics/Pharmacodynamics/Future Biomedical Research/Biomarkers															
Serum for MK-0482 PK		X	X	X	X	X	X	X	X	X	X	X			Pre- and posttreatment on C1D1, C2D1, C3D1, C4D1, C6D1, C8D1, and every 4 cycle thereafter. All pretreatment should be drawn within 24 hours prior to start of MK-0482 infusion, and all posttreatment except C1D2 should be drawn within 30 minutes after the end of MK-0482 infusion. Additional posttreatment samples: C1D2 (22-26 hours after C1D1 dosing), C1D4 (± 1 day), C1D8 (± 1 day), C1D15 (± 1 day), C2D8 (± 1 day), and C3D8 (± 1 day) can be drawn anytime in the window. For EOT, PK can be drawn any time of the day. *Note: PK and ADA samples may be used for neutralizing antibody assay development and/or validation.*

Study Period	**Screening**	**Intervention**										**EOT/ Discon.**	**Safety FU**	**Survival FU**	**Notes**
Treatment Cycle		**1**					**2**		**3**		**4 to 35**				
Scheduled Day per Cycle	**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**1**	**8**	**1**	**At time of treatment discon.**	**30 days after last dose**	**Q12W**	
Scheduling Window (Days):		**-**	**+1**	**+1**	**±3**	**±3**	**±3**	**± 3**	**±3**	**± 3**	**±3**		**+7**	**±14**	
Blood for Receptor Occupancy		X	X	X	X	X	X	X	X	X	X	X			Pretreatment on C1D1, C2D1, C3D1, C4D1, C6D1, C8D1, and then every 4 cycle thereafter. Samples can be drawn anytime on C1D2, C1D4, C1D8, C1D15, C2D8, C3D8, and EOT.
Serum for Anti-MK-0482 Antibodies		X					X		X		X	X			Pretreatment on C1D1, C2D1, C3D1, C4D1, C6D1, C8D1, every 4 cycle thereafter, and anytime on EOT.
CCI [redacted]															

AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; C1D1 = Cycle 1 Day 1; CBC = complete blood count; CR = complete remission; ctDNA = circulating tumor deoxyribonucleic acid; ECG = electrocardiogram; ECI = event of clinical interest; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FBR = future biomedical research; FU = follow-up; hCG = beta human chorionic gonadotropin; LDH = lactate dehydrogenase; PK = pharmacokinetic; PT/INR = prothrombin time/international normalized ratio; PTT = partial thromboplastin time; Q12W = every 12 weeks; SAE = serious adverse event; SOP = standard operating procedure; TLS = tumor lysis syndrome; WOCBP = women of childbearing potential.

[a] Height will be measured at Screening only.

[b] Full physical examination at C1D1 to be performed within 72 hours before dosing.

2 INTRODUCTION

AML is a heterogenous hematologic malignancy characterized by the clonal expansion of myeloid blasts in the bone marrow, peripheral blood, and potentially other tissues [Dohner, H., et al 2015]. AML is the most common form of adult acute leukemia in the US [Carter, J. L., et al 2020] with a median age of around 68 years at the initial diagnosis [Shallis, R. M., et al 2019]. In 2021 in the US, the estimated number of new AML cases is ~20,240 and the estimated number of deaths due to AML is ~ 11,400 [Siegel, R. L., et al 2021]. Despite increasing understanding of the underlying biology of AML and the development of several new therapies, the 5-year relative survival rate remains low, at about 26% based on 2021 estimate from SEER [American Cancer Society 2021].

The initial goal of AML treatment is attempting to achieve a CR via chemotherapy (ie, induction), followed by postremission treatment (ie, consolidation). The selection of initial treatment is multifactorial based on a patient's age, comorbidity, performance status, cytogenetic risk category, molecular profiling, and other medical histories etc. The search for a matched sibling or alternative hematopoietic stem cell transplantation donor is an option in addition to participation in a clinical study. Younger and physically fit patients are generally treated with intensive chemotherapy represented by high-dose cytarabine-based regimens; while older and unfit patients will receive therapies with less intensity or opt to receive best supportive care only. In the past few years, several targeted therapies have received regulatory approval and been integrated into AML treatment regimens including tyrosine kinase inhibitors targeting FIL3 mutations, epigenetic modulators targeting IDH1/2 mutations, anti-CD33 mAb drug conjugates, Bcl-2 inhibitors, and liposomal chemotherapy [National Comprehensive Cancer Network 2021]. Even though addition of these new agents has improved clinical benefits in subsets of patients, the rate of refractory to initial induction and rate of relapse within 1 year of remission are still high in both fit and unfit patients. The choice of treatments for refractory and relapsed AML is very limited, which is an area with significant unmet medical need.

CMML is a myeloid neoplasm characterized by dysplasia, abnormal production and accumulation of monocytic cells with an elevated risk of transforming into acute leukemia. It is characterized by 1) persistent monocytosis $>1 \times 10^9$/L in the peripheral blood; monocytes ≥10% of white blood cell count) along with dysplastic features in the bone marrow, lack of Philadelphia chromosome and BCR-ABL 1 fusion gene; 3) no rearrangement of PDGFRA or PDGFRB; 4) fewer than 20% blasts in peripheral blood and bone marrow; and 5) dysplasia involving one or more myeloid lineages [Arber, D. A., et al 2016] [Orazi, A., et al 2008].

Due to renewed evidence demonstrating clinical, morphological and molecular differences, the 2016 WHO classification recommended categorization of CMML into "proliferative" (MPN-CMML) and "dysplastic" (MDS-CMML) subtypes based on a white blood cell count of $\geq 13 \times 10^9$/L for MPN-CMML [Arber, D. A., et al 2016]. In addition, based on peripheral blood and bone marrow blast percentage, CMML can be classified into 3 subcategories; CMML-0, a category for cases with <2% blasts in peripheral blood and <5% blasts in bone marrow; CMML-1 for cases with 2 % to 4 % blasts in peripheral blood and/or 5% to 9% blasts in bone marrow; and CMML-2 for cases with 5% to 19% blasts in peripheral blood,

10% to 19% in bone marrow, and/or when any Auer rods are present [Arber, D. A., et al 2016].

Therapeutic approaches in CMML have generally been the model for treating the other MDS/MPN, with hypomethylating agent treatment for intermediate- and higher-risk patients and using these agents as a bridge to allogeneic HCT for those patients deemed to be transplant eligible [National Comprehensive Cancer Network 2022] [Patnaik, M. M. 2018]. Allogeneic stem cell transplantation remains the only curative option for patients with CMML. This modality is however fraught with complications including, acute and chronic GVHD, nonrelapse mortality and posttransplant disease relapse [Patnaik, M. M. 2018]. Reported median survival time is 20 to 40 months and progression to AML occurs in approximately 15% to 30% [Orazi, A., et al 2017] [Geissler K 2021]. These patients have strong unmet medical need.

2.1 Study Rationale

Immunoglobulin-like transcript 3 (ILT3, also known as LILRB4), belongs to a family of inhibitory cell surface receptors, the LILRBs. The inhibitory ILT members signal via multiple cytoplasmic ITIM leading to negative regulations of immune cell activation [Kang, X., et al 2016] [van der Touw, W., et al 2017].

Expression of ILT3 has been reported on dendritic cells, monocytic myeloid cells, macrophages, progenitor mast cells, endothelial cells and osteoclasts. The expression of ILT3 on myeloid cells and dendritic cells is thought to be involved in immune suppression and antigen-specific immune tolerance and is considered contributing to the immunosuppressive tumor microenvironments in various human cancers [Kang, X., et al 2016].

ILT3 has been found highly expressed in human AML with monocytic differentiations, ie, the M4 and M5 subtypes per French-American-British classification [Dobrowolska, H., et al 2013] [Deng M, Gui X, Kim J, Xie L, Chen W, Li Z, et al. 2018]. An in vivo study using NSG mouse model inoculated with human monocytic AML THP-1 cells and in vitro study using human monocytic AML cell lines THP-1 and MV4-11 showed that ILT3 signaling in monocytic AML cells mediates T-cell suppression and promotes tumor cell tissue infiltration [Deng M, Gui X, Kim J, Xie L, Chen W, Li Z, et al. 2018]. Furthermore, these functional activities of ILT3 could be inhibited by anti-ILT3 antibodies or be abolished in THP-1 and MV4-11 cells with the LILRB4 gene being knocked out. APOE has been identified as an extracellular binding protein of ILT3 [Deng M, Gui X, Kim J, Xie L, Chen W, Li Z, et al. 2018].

Further evaluation by Li et al. [Li, Z., et al 2020] suggested that the intracellular ITIM domain of activated ILT3 recruits SHP-2, which activates NFκB. Activation of NFκB results in regulations of downstream effectors including uPAR and ARG1, leading to inhibition of T-cell proliferation and infiltration of AML cells into tissues. Gui et al. developed a humanized antibody to ILT3 h128-3. Disrupting ILT3/APOE interaction using h128-3 could reverse T-cell suppression and block AML development in mouse models [Gui, X., et al 2019]. This research indicates that ILT3 can be a useful target for monocytic AML.

MK-0482 is a novel humanized IgG4 mAb that binds to ILT3 and, an inhibitory receptor expressed on the surface of myeloid immune cells. Based on the preclinical research from the Sponsor laboratories, the following were observed:

1. In vitro assay showed that anti-ILT3 enhanced interferon gamma production in THP-1 and T-cell coculture assay;

2. In vivo experiment showed that anti-ILT3 mAb (a mice surrogate of MK-0482 clone c52B8) eliminated systemic MV-4-11 growth;

3. Using PBMC from AML patients, clone 52B8 reduced tumor blast cells and modulated T_{reg} in these ILT3 high AML PBMC (unpublished data).

In non-AML cells, in vitro studies of MK-0482 provide evidence that ILT3 blockade leads to dendritic cell activation, T-cell activation in combination with pembrolizumab, and reduction of the suppressive function of MDSCs (MK-0482 IB).

Based on research from the Sponsor and others on the role of ILT3 in monocytic AMLs, MK-0482 may play a role as a treatment for the monocytic subtypes of AML.

As for the CMML, it is a myeloid neoplasm characterized by dysplasia, abnormal production and accumulation of monocytic cells with ~ 30% to 40% risk of transforming into AML. Expression of ILT3 and role in CMML and MDS are unknown. However, Chien et al [Chien, K. S., et al 2020] recently investigated LILRB4 expression in 19 CMML, 27 MDS patients, and a few healthy volunteers. The study team found that LILRB4 RNA expression was increased in CMML patients when compared with MDS patients and healthy controls and slightly increased in patients who responded to hypomethylating agents. This study also showed that interferon gamma response and CTLA4 signaling genes positively correlated with LILRB4 expression in CMML patients. Given that there are no effective treatments available for CMML patients with refractory or relapsed disease, exploring clinical effects of anti-ILT3 mAb MK-0482 in this this myeloid malignancy is justified.

2.2 Background

Refer to the IB for detailed background information on MK-0482.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 MK-0482 Pharmaceutical and Therapeutic Background

MK-0482 is a novel, first-in-class, humanized IgG4 mAb with high specificity of binding to ILT3, an inhibitory receptor expressed on the surface of myeloid immune cells. Based on in vitro data, MK-0482 has high affinity for ILT3, is selective for ILT3 versus other ILT family members, and is a potent antagonist of ILT3. MK-0482 has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced solid tumors, to be used as monotherapy or in combination with pembrolizumab to increase antitumor efficacy in participants with various tumor indications.

The ILT family of proteins, also called the leukocyte immunoglobulin-like receptor family, contains both activating and inhibitory signaling domains with varying cellular expression profiles.

In humans, ILT3 is only expressed in the monocytic myeloid lineage of the immune system [Brown, D., et al 2004] [Kang, X., et al 2016] [Cella, M., et al 1997]. Internal mRNA data confirm this expression at both the tissue and immune cell level.

In organ transplant studies, expression of ILT3 on DCs is associated with induction of antigen-specific tolerance [Chang, C. C., et al 2002] [Brenk, M., et al 2009] [Vlad, G., et al 2008] [Suciu-Foca, N., et al 2007] [Svajger, U., et al 2008] [Brown, D. P., et al 2009] [Kim-Schulze, S., et al 2006] [Steinbrink, K., et al 2002] [Penna, G., et al 2005] [Manavalan, J. S., et al 2004] [Manavalan, J. S., et al 2003]. Antibody blockade of ILT3 has been shown to rescue the T-cell priming capacity of otherwise tolerogenic DCs [Manavalan, J. S., et al 2003] [Brenk, M., et al 2009] and block the action of allo-specific CD8+ T suppressor cells [Chang, C. C., et al 2002].

Elevated levels of a sILT3 has been detected in the serum of patients with NSCLC, melanoma, colorectal, and pancreatic cancer compared with healthy controls [Suciu-Foca, N., et al 2007] [de Goeje, P. L., et al 2015]. Using a validated sandwich ELISA, internal data shows increased sILT3 levels in patient serum samples in the following cancer cohorts: multiple myeloma, NSCLC, pancreatic cancer, and colon cancer. It is hypothesized that ILT3 is overexpressed in MDSCs infiltrating these types of tumors and is shed from the surface of these cells into the blood stream.

ILT3 in myeloid cell-driven immune suppression in the tumor microenvironment

MDSCs are recognized as critical players in the tumor microenvironment [Marvel, D. 2015]. Numerous studies have documented the infiltration of tumors with myeloid cells and an association of that feature with immunosuppression and resistance to checkpoint inhibitors [Kumar V, Patel S, Tcyganov E, Gabrilovich DI. 2016] [Solito, S., et al 2014] [Messmer, M. N., et al 2015]. Similarly, elevated numbers of immature “MDSCs” in the peripheral blood of cancer patients has been widely reported. Indeed, in patients with previously treated metastatic bladder cancer, a high baseline circulating monocytic MDSC count was associated with a shorter OS after treatment with nivolumab compared with patients with a low MDSC count [Sharma, P., et al 2017]. A role for myeloid cells in the molecular epidemiology of resistance to checkpoint inhibitors, including pembrolizumab, has been reported, and ILT3 is strongly associated with that myeloid signature. Furthermore, De Goeje et al. have observed an inverse correlation between the level of ILT3 expression on circulating MDSCs and patient survival in NSCLC [de Goeje, P. L., et al 2015].

Nonclinical studies of an analog of MK-0482 in NOD scid gamma humanized mouse model systems reveal its ability to reduce tumor burden and shift cellular phenotypes to a more activated state.

Study MK-0482-002 will be the first clinical study to evaluate MK-0482 in an AML population. Data from in-house preclinical studies have shown the following:

1. In an in vivo MV-4-11 model, luciferase labeled MV-4-11 cells were injected intravenously in female NSG mice and tumor growth was assessed via whole body bioluminescence (of note, MV-4-11 is a human monocytic AML cell line). In this experiment, mice treated with anti-ILT3 antibody clone c52B8, the parental clone of MK-0482, produced significant tumor growth inhibition compared with mice treated with a huIgG4 isotype. In the same experiment setting, MV-4-11 cells and human PBMCs were injected together in the mice. Mice treated with anti-ILT3 mAb c52B8 also showed significant tumor growth inhibition compared with mice treated with the huIgG4 isotype. These results indicated that there is likely a direct effect of tumor cell growth inhibition by anti-ILT3 on MV-4-11 cells.

4. In an in vitro assay, human PBMC samples from patient with monocytic AML were treated with anti-ILT3 mAb c52B8 and huIgG4. C52B8 reduced tumor blasts and Treg in these ILT3 high AML PBMC compared with samples treated with huIgG4.

Based on in-house preclinical data and those that were published from others (see Section 2 Introduction), we hypothesized that MK-0482 may have direct effect to control the growth of monocytic AML cells.

2.2.2 Preclinical and Clinical Studies

See the MK-0482 IB.

2.2.3 Ongoing Clinical Studies

MK-0482 is currently being evaluated in Study MK-0482-001, an ongoing FIH, Phase 1 clinical study that includes a dose escalation and confirmation phase in participants with advanced solid tumors of any type and a cohort expansion part in participants with select tumor types. Study objectives during dose escalation and confirmation include assessing the safety, tolerability, PK, and pharmacodynamics, and identifying a preliminary RP2D for MK-0482 when used as monotherapy and in combination with the anti PD-1 mAb pembrolizumab.

Based on preliminary data from the Part I dose escalation in study MK-0482-001 (data cutoff 20-JAN-2021), MK-0482 monotherapy is well tolerated up to doses of 2250 mg Q3W with no drug-related Grade 4 or 5 adverse events and no DLTs observed. Of 29 participants who received at least 1 dose of MK-0482 monotherapy, 9 participants (31.0%) experienced at least 1 treatment-related AE. Most of these AEs were Grade 1 or Grade 2. The treatment-related AE of pyrexia was observed in 3 of 29 participants (10.3%), the only treatment-related AE with an incidence ≥5%. No CRS or TLS has been reported for participants who have received either MK-0482 as monotherapy or in combination with pembrolizumab.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

MK-0482 is being studied in study MK-0482-001 in solid tumors as monotherapy and in combination with pembrolizumab. MK-0482 monotherapy up to 2250 mg Q3W dosing has been well tolerated based on data from 29 participants with advanced solid tumor and no clinically significant safety concerns.

MK-0482-002 is the first study of MK-0482 in the refractory/relapsed AML subpopulation with monocytic differentiations or refractory/relapsed CMML. Based on preclinical data, blocking ILT3 in monocytic AML cells via anti-ILT3 mAb could control monocytic AML cell growth, prevent tissue infiltration and reverse suppression of T-cell activity. Therefore, there is potential benefit. Given CMML is a myeloid neoplasm with high accumulation of monocytic cells, it may also benefit from an anti-ILT3 agent like MK-0482. The safety profile of MK-0482 in the monocytic AML or CMML population may be different from that in the advanced solid tumor population. Therefore, the initial dose in the MK-0482 002 dose escalation is considerably lower, at 7.5 mg. Safety of participants will be closely monitored via clinical visits with physical examinations and laboratory tests. Due to the nature of this disease, participants are also monitored clinically for the occurrence of TLS and CRS.

Since effective treatment for refractory and relapsed AML or CMML is very limited, patients are encouraged to participate in clinical studies for novel therapies. Participation in this study is justified. Benefit and risk will be further evaluated.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In the participant population with relapsed and refractory AML/CMML subtypes of acute and chronic myelomonocytic leukemia or acute monoblastic/monocytic leukemia:

Primary Objective	**Primary Endpoint**
To determine the safety and tolerability and to determine a preliminary recommended Phase 2 dose of MK-0482 monotherapy	Dose-limiting toxicity Adverse Events (AEs) Discontinuing study intervention due to an AE
Secondary Objectives	**Secondary Endpoints**
To characterize the pharmacokinetic (PK) profile of MK-0482 monotherapy	Noncompartmental PK parameters
To evaluate antileukemia activity of MK-0482 monotherapy in acute myeloid leukemia (AML)	The following response endpoints will be assessed per 2017 European Leukemia Net (ELN) AML response criteria: Complete remission (CR), Composite CR: CR + CR with incomplete recovery (CR_i) Objective response: CR + CR_i + partial remission (PR)
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
CCI [redacted]	

To evaluate antileukemia activity of MK-0482 monotherapy in chronic myelomonocytic leukemia (CMML)	Response criteria for CMML: evaluated per 2015 International Consortium Proposal of Uniform Response Criteria for Myelodysplastic Syndromes (MDS)/Myeloproliferative Neoplasms (MPN) in Adults with endpoints including CR, PR, complete cytogenetic remission, marrow response and clinical benefit as appropriate
To evaluate the duration of response (DOR)	For participants who demonstrate CR, CR_i, or PR, DOR is defined as the time from the first documented evidence of CR, CR_i, or PR until disease progression or death due to any cause, whichever occurs first

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter, open-label, Phase 1b study to evaluate safety, tolerability, PK and pharmacodynamics of MK-0482 in participants with relapsed/refractory AML or CMML.

There are 2 parts in this study: Dose Escalation (Part 1) and Dose Expansion (Part 2).

For Part 1, initial dose escalation will follow an ATD to evaluate 2 low DLs: DL1 of 7.5 mg and DL2 of 25 mg, with each group enrolling 1 to 3 participants. Once the study passes DL2, further dose escalation will follow the mTPI design [Ji, Y. and Wang, S.-J. 2013] to evaluate dose levels of 75 mg, 225 mg, and 750 mg MK-0482, respectively, in accordance with dose levels evaluated in the MK-0482-001 study. During this study, a higher dose level up to 2250 mg may be explored depending on the combined safety, PK, and pharmacodynamics data available. Each dose level under mTPI will enroll 3 to 6 participants initially (with at least 2 participants with AML) with potential expansion to a maximum of 10 participants (with at least 5 participants with AML).

Progression from one DL to the next higher DL is based on the evaluation of DLT. The ATD cohort will end early if a Grade 2 or higher treatment-related toxicity occurs. In that situation, the dose level will be evaluated per mTPI. During dose escalation, a higher dose level cannot be initiated until the previous lower dose level has cleared DLT.

Dose finding in Part 1 will end after 10 participants have been treated at any dose level. The pool-adjacent-violators algorithm [Ji, Y. and Wang, S.-J. 2013] will be used to estimate the DLT rates across doses in each treatment arm under the assumption of monotonicity between DLT rates and dose levels. The totality of the data including safety events that occur within or beyond the DLT window, tolerability, preliminary antitumor activity, PK, and pharmacodynamics across all the dose levels will be considered before deciding a preliminary RP2D for carrying forward to Part 2. Approximately 20 participants will be enrolled in Part 1.

Once a preliminary RP2D is identified in Part 1, approximately 10 to 15 additional participants with R/R AML will be enrolled at the RP2D for Part 2. The study will enroll approximately 30 to 35 participants in total.

Study will include a screening period of maximum of 21 days. Eligible participants will receive study treatment and be monitored carefully via physical examinations and laboratory tests for safety. AEs will be evaluated by the investigator per NCI CTCAE 5.0.

Clinical activities will be evaluated for the changes in AML blasts in bone marrow as well as in peripheral blood in accordance with ELN 2017 response criteria (Appendix 8). Clinical activities for CMML will be evaluated per 2015 International Consortium Proposal of Uniform Response Criteria for MDS/MPN in Adults (Appendix 9).

Clinical PK, receptor occupancy, and biomarker sampling will be performed per the schedules outlined in the SoA.

Intraparticipant dose escalation is allowed for participants who are enrolled into the first 2 dose levels of Part 1 once they have completed DLT evaluation and once a higher dose level has been cleared for DLT if the participants have not progressed. The definition of DLTs and criteria for dose modification of MK-0482 are outlined in Section 4.3.1.3 and Section 6.6.

MK-0482 will be administered via IV infusion in a 3-week cycle. Participants will be treated until progressive disease, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, participant withdrawal of consent, pregnancy of the participant, noncompliance with study intervention or procedure requirements, participant completes treatment, or administrative reasons requiring cessation of treatment. Participants may receive study treatment for up to 35 cycles (24 months). In addition, if a participant has not achieved a PR or CR after 6 months of study treatment, the investigator should discuss the lack of response to the study treatment and other treatment options with the participant. If other alternative treatments with potential clinical benefits are available for the participant at that time, study treatment should be discontinued.

Participants who discontinue treatment for reasons other than confirmed progressive disease will be followed for disease status until disease progression, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow-up.

After confirmed progressive disease, each participant will be contacted by telephone every 12 weeks (84 ± 14 days) for survival follow-up until withdrawal of consent to participate in the study, becoming lost to follow-up, death, or end of the study, whichever occurs first.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Since this is a Phase 1b study, clinical responses are included for efficacy evaluations as secondary endpoints, including rate of CR, rate of composite CR (CR + CR_i) and objective response rate (CR + CR_i and PR). The response criteria for AML as defined in the 2017 ELN international expert panel recommendations (Appendix 8) are well adapted in the clinical field worldwide, which also include response parameters suitable for clinical studies such as definition of stable disease, progressive disease, and relapse, etc. The assessments of these parameters are developed in accordance with the 2016 WHO classification of myeloid neoplasms and acute leukemia [Arber, D. A., et al 2016]. The response criteria for CMML will be evaluated per 2015 International Consortium Proposal of Uniform Response Criteria for MDS/MPN in Adults as outlined in Appendix 9.

4.2.1.2 Safety Endpoints

The primary objective of this study is to characterize the safety and tolerability of MK-0482 as monotherapy. The primary safety analysis will be based on participants who experience toxicities as defined by NCI CTCAE 5.0 criteria. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by participants who have received MK-0482 as monotherapy.

For AEs, attribution to drug, time of onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs that will be analyzed include, but are not limited to, all AEs, SAEs, fatal AEs, and laboratory changes.

4.2.1.3 Pharmacokinetic Endpoints

A secondary objective of this study is to characterize the PK profile of MK-0482 after administration as a single agent. The serum concentration of this agent will serve as the primary readout for the PK, and these data will be used to derive PK parameters of the agent. Furthermore, the results of these analyses will be used in conjunction with the pharmacodynamics, and safety and exploratory endpoint data to help assess future dosing strategies for MK-0482.

4.2.1.4 Antidrug Antibodies

Formation of ADA can potentially confound drug exposures at therapeutic doses and prime for subsequent infusion-related toxicity. Antidrug antibody response at the beginning of each cycle will be determined to understand drug metabolism, exposure, and safety. The incidence of ADA and neutralizing ADA will be evaluated and summarized over time by dose. Correlations between the presence/absence of positivity for ADAs and PK and pharmacodynamic markers, activity, and safety of MK-0482 will be explored.

4.2.1.5 Pharmacodynamic Endpoints

CCI

[redacted]

4.2.1.6 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely

understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include, but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations.

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes called a ‘hyper-mutated’ state) may generate neoantigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor cells and blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in AML and CMML cells, cells from bone marrow, and in blood may be performed to define gene signatures that correlate to clinical response to treatment with MK-0482 or other immunotherapies. Specific immune-related gene sets (ie, those capturing interferon gamma transcriptional pathways, or signatures of genes associated with populations of immune cells) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling. In addition, genomic translocations, rearrangements, and deletions may be assessed, as some of these types of genomic alterations are prognostic markers in AML and CMML, and would be important to assess to determine the genomic complexity of the disease.

CCI [redacted]

4.2.1.7 Future Biomedical Research

CCI [redacted]

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

4.3.1.1 Rationale for Starting and Maximum Dose of MK-0482

MK-0482 Q3W has been evaluated in advanced solid tumors as monotherapy at dose levels ranging from 0.2 mg to 2250 mg; and in combination with pembrolizumab 200 mg Q3W in dose levels ranging from 7.5 mg to 2250 mg during MK-0482-001. MK-0482 was well tolerated in all the dose levels in monotherapy and had an acceptable safety profile in combination with pembrolizumab.

Preliminary PK data show target mediated drug disposition at lower MK-0482 doses while linear PK was observed at tested doses ≥75 mg. Near complete receptor occupancy was also observed in blood samples from participants treated with MK-0482 at dose levels ≥75 mg. Even with stringent assumptions, 750 mg MK-0482 Q3W is likely to maintain complete receptor occupancy in the tumor. The terminal $t_{1/2}$ of MK-0482 at the 750 mg MK-0482 dose was 19.5 days when given as monotherapy and 13.7 days when given in combination with 200 mg pembrolizumab.

While ADA was observed in 16 of 62 participants with evaluable data treated with MK-0482 doses between 0.2 mg and 750 mg, there was no clear impact of ADA on PK or receptor occupancy. A dose-dependent increase in total soluble ILT3 concentration was seen in blood samples; however, based on internal investigations, there was no confirmed immunosuppressive activity for soluble ILT3.

ILT3 target expression levels in AML/CMML patient blood, relative to patients in other solid tumors is unknown. In AML/CMML patients, the safety profile resulting from ILT3 target binding is also unknown as this point. Therefore, dose escalation will start at 7.5 mg to rule out any unforeseen AEs. In patients with solid tumors, this dose yields minimal target engagement in blood at trough concentration (~ 20%). The study will enroll 3 to 6 participants initially for each cohort at 75 mg, 225 mg, and 750 mg dose levels and will increase up to 10 participants as needed per mTPI design (see Table 1). Trough target engagement increases substantially between 7.5 and 75 mg in patients with solid tumors, and thus safety evaluations in more participants is warranted beyond 25 mg.

Based on the collective evaluation of data from safety, PK, and receptor occupancy, the 750 mg dose of MK-0482 was selected as the RP2D in combination with pembrolizumab for further evaluation in advanced solid tumors. Complete target engagement is expected to be achieved by this dose; however, based on actual data from the dose escalation, a higher dose level may be evaluated, if warranted.

4.3.1.2 Rationale for Dose Interval and Escalation Increments

Once complete target engagement is achieved, MK-0482 exhibits a PK profile that is consistent with that of other monoclonal antibodies. Preliminary data from MK-0482-001 suggests that MK-0482 has a half-life of approximately 17 days. A 3-week dose interval is

expected to be adequate to maintain complete target engagement at trough in AML/CMML patients. A 3-week dosing interval is also being explored in MK-0482-001.

Approximately 3-fold dose escalation increments will be used. While the extent of population variability in exposure in AML/CMML patients is not known, a 3-fold difference between doses is expected to produce nonoverlapping exposures across doses. The 3-fold escalation increments are also being used in MK-0482-001.

4.3.1.3 Accelerated Titration Design

The initial dose escalation will follow an ATD to minimize the number of participants treated at potentially subtherapeutic doses of MK-0482. Single participants will be enrolled sequentially into the escalating dose levels 7.5 mg and 25 mg, respectively. The transition from ATD to mTPI is planned at the next dose level of 75 mg.

Intraparticipant dose escalation will be allowed for participants in the ATD. Participants may undergo dose escalation up to the 75 mg dose level. Intermediate dose levels may be evaluated, if warranted. The dose to be tested in each group of participants will be communicated to the investigators or designees after the dose-escalation decision meeting for the previous dose. Enrollment of up to 3 participants per dose level at ATD is permitted on approval by the Sponsor's medical monitor or designee provided that the first 2 participants will receive MK-0482 treatment at least 3 days apart. All participants enrolled at each dose level must complete the DLT period before the next dose level is initiated.

The ATD will end when at least 1 of the following occurs:

- The highest dose level (up to 75 mg) has completed the DLT evaluation period and MK-0482 has been determined to be safe and well tolerated in this cohort.
- Occurrence of a Grade 2 or higher treatment-related toxicity according to NCI CTCAE 5.0 during Cycle 1 (ATD ends at that current dose level).

Any time a DLT occurs in the ATD phase, the dose level in which the DLT occurred will be expanded at this dose per mTPI guidelines below. If no DLT occurs in the ATD phase, then the ATD phase will proceed to the mTPI phase once 1 of the above triggers is met.

4.3.1.4 Dose Finding Using a Modified Toxicity Probability Interval Design

Further dose finding will follow the mTPI design [Ji, Y., et al 2007] with a target DLT rate of 25%. Dose-escalation and deescalation decisions are based on the mTPI design and depend on the number of participants enrolled and number of DLTs observed at the current dose level.

A minimum of 3 participants are required at each dose. However, depending on the accrual rate, 3 to 6 participants may be enrolled to an open dose level providing that the first 2 participants receive the first dose at least 3 days apart. In Table 1, the columns indicate the numbers of participants treated at the current dose level, and the rows indicate the numbers of participants experiencing DLT. The entries of the table are the dose-finding decisions: E, S,

D, and DU represent escalating the dose, staying at the same dose, deescalating the dose, and excluding the dose from the study due to unacceptable toxicity, respectively. For example, if 0 of 3 participants at a given dose level develop a DLT, then the dose can escalate to the next level. If 2 participants of 3 develop a DLT, the dose will be deescalated to the next lower dose level. If 3 of 3 participants develop a DLT, this indicates an unacceptable toxicity at this dose. The dose should be deescalated and the current dose will not be explored further. If 1 of 3 participants at a given dose level develop a DLT, then additional participants should be enrolled at that dose level following the rules below.

When adding participants to a dose level in response to a "stay" decision, the number of additional participants to be enrolled is capped to minimize the exposure to a dose that may be unacceptably toxic (denoted as DU in Table 1). Second, to determine how many more participants can be enrolled at the dose level, one can count steps in a diagonal direction (down and to the right) from the current cell to the first cell marked DU. For example, if 1 of 3 participants experienced a DLT at a given dose level, no more than an additional 3 participants should be enrolled at this dose level until additional DLT data are available. This dose level would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (ie, 4/6 participants with DLT in Table 1). The same principles will be applied whether 3, 4, 5, or 6 participants are initially enrolled at that dose level.

A D or DU decision at the lowest dose level will stop the study. An E decision at the highest dose level will result in staying at that level. During dose finding, it may be acceptable to deescalate to an intermediate dose that was not predefined and not previously studied if evaluation of toxicity at such a dose is desired. If this approach is taken, 3 to 6 new participants may be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

After 10 participants have been enrolled at any of the tested doses (including intermediate doses), dose finding will stop if the mTPI table indicates "S" for staying at current dose. Otherwise, up to 10 new participants may be enrolled at a lower dose if "D" or "DU" is indicated, or at a higher dose if "E" is indicated.

The pool-adjacent-violators algorithm [Ji, Y. and Wang, S.-J. 2013] will be used to estimate the DLT rates across doses. The dose with an estimated DLT rate closest to 25% will be treated as a preliminary MTD. However, the totality of the data will be considered before deciding on the dose to carry forward to Part 2, and the escalation schedule may be adjusted based on pharmacodynamic, PK, and safety data emerging throughout the study.

Note that although 25% was the target toxicity rate used to generate the guidelines in Table 1, the observed rates of participants with DLTs at the MTD may be slightly above or below 25%.

Table 1 Dose-finding Rules per mTPI Design

Number of Participants With At Least 1 DLT	**Number of Participants Evaluable for DLT at Current Dose**							
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**
0	E	E	E	E	E	E	E	E
1	S	S	S	S	E	E	E	E
2	D	S	S	S	S	S	S	S
3	DU	DU	DU	D	S	S	S	S
4		DU	DU	DU	DU	DU	D	S
5			DU	DU	DU	DU	DU	DU
6				DU	DU	DU	DU	DU
7					DU	DU	DU	DU
8						DU	DU	DU
9							DU	DU
10								DU

D=Deescalate to the next lower dose; DLT=dose-limiting toxicity; DU=The current dose is unacceptably toxic; E=Escalate to the next higher dose; mTPI=modified toxicity probability interval; S=Stay at the current dose.
Target toxicity rate = 25%
Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.03[Ji, Y., et al 2007] [Ji, Y. and Wang, S.-J. 2013] [Ji, Y., et al 2010].

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

4.4.1 Clinical Criteria for Early Study Termination

Recruitment in the study or at a particular study site may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems, or if the number of discontinuations for administrative reasons is too high.

Early study termination will be the result of the criteria specified below:

1. Incidence or severity of adverse drug reactions in this or other studies suggest a potential health hazard to participants
5. Plans to modify or discontinue the development of the study intervention

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-0482.

5 STUDY POPULATION

Male/female participants at least 18 years of age with relapsed or refractory AML or CMML will be enrolled in this study.

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Has confirmed diagnosis of AML with myelomonocytic or monoblastic/monocytic differentiation per WHO 2016 criteria[Arber, D. A., et al 2016] and with confirmed refractory or relapsed disease (ie, ≥5% blast in bone marrow or in peripheral blood) after treatment with available therapies known to benefit participant's AML subtypes.

   OR

   Has known diagnosis of CMML per WHO criteria [Orazi, A., et al 2017] with confirmed refractory or relapsed disease after treatment with available therapies known to be active for CMML.
6. Has a WBC count ≤20 × 10^9/L within 24 hours prior to the first dose of study treatment. Note: Hydroxyurea should be used to keep the WBC count maintained ≤20 × 10^9/L until the first dose of study treatment, to the extent that this is possible.
7. Has ECOG performance status of 0 to 2 as assessed within 72 hours prior to the first dose of study treatment.
8. Has adequate organ function as defined in Table 2 and as assessed within 72 hours prior to the first dose of study treatment.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Renal	
Measured or calculated[a] CrCl (GFR can also be used in place of CrCl)	≥40 mL/min
Hepatic	
Total bilirubin	≤1.5 × ULN or direct bilirubin ≤ULN or ≤3 × ULN if deemed elevated due to Gilbert's disease or leukemia
AST (SGOT) and ALT (SGPT)	≤3 × ULN or ≤5 × ULN if deemed elevated due to leukemia

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CrCl = creatinine clearance; GFR = glomerular filtration rate; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; ULN = upper limit of normal.

a CrCl should be calculated per Cockcroft-Gault formula, as below:
CrCl (male) = ([140-age in years] × weight in kg)/(serum creatinine in mg/dL × 72)
CrCl (female) = CrCl (male) × 0.85

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

Demographics

9. Is male or female, at least 18 years at the time of providing the informed consent.

Female Participants

10. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Not a WOCBP
  OR
- A WOCBP and:
  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 90 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- Has a negative highly sensitive pregnancy test (urine as required by local regulations) within 72 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.
- Abstains from breastfeeding during the study intervention period and for at least 90 days after study intervention MK-0482.
- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

11. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

12. A bone marrow aspirate and biopsy sample will be performed within 14 days of treatment start date. Details pertaining to bone marrow biopsy submission can be found in the Laboratory Manual.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has active CNS leukemia.
   Note: Participants with clinical signs of CNS involvement or with suspected CNS involvement must have CSF testing to confirm leukemic involvement.
13. Has isolated extramedullary disease, ie, no leukemic involvement in bone marrow or peripheral blood.
14. Has diagnosis of acute promyelocytic leukemia or participants with known Ph+ AML.
15. Has received previous allogeneic stem cell transplant or organ transplant within 60 days of the start of study treatment.
    Note: Participants with relapsed AML or CMML after allogeneic SCT, including those who have received donor lymphocyte infusions, are eligible if they have no active GVHD and are off immunosuppression therapy or are taking a maintenance dose of <10 mg daily prednisone or equivalent.
    Note: Receipt of previous autologous transplant for AML or non-AML condition is allowed.

16. Has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 1 year.
    Note: The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, or carcinoma in situ (eg, breast cancer in situ, cervical cancer in situ).
17. Has a history of any of the following cardiovascular conditions within 6 months of screening: myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic attack, coronary artery bypass graft, or pulmonary embolism; has NYHA Class III or IV congestive heart failure.
18. Has had a severe hypersensitivity reaction to treatment a mAB and or any components of the study intervention, MK-0482.
19. Has an active uncontrolled infection requiring directed therapy.
20. Has immediately life-threatening, severe complications of leukemia such as uncontrolled bleeding, pneumonia with hypoxia or shock, or disseminated intravascular coagulation.
21. Has known HIV and/or hepatitis B or C infections or is known to be positive for HBsAg/HBV DNA or hepatitis C antibody or RNA. Active hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.
22. Has known psychiatric or substance abuse disorders (verbally reported) that would interfere with the participant's ability to cooperate with the requirements of the study.
23. Is pregnant or breast feeding or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 120 days after the last dose of study intervention.

Prior/Concomitant Therapy

24. Has received systemic anticancer therapy, radiotherapy, or surgery within 2 weeks before the start of study treatment.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline.
25. Has received hematopoietic cytokines (G-CSF, GM-CSF, or erythropoietin) within 2 weeks prior to start of study treatment.
26. Has received a live or live attenuated vaccine within 30 days before the first dose of study medication.

    Note: Killed vaccines are allowed. Refer to Section 6.5 for information on COVID-19 vaccines.
27. Has received prior treatment(s) with another agent targeting ILT3.

Prior/Concurrent Clinical Study Experience

28. Is currently participating and receiving study intervention in a study of an investigational agent or has participated and received study intervention in a study of an investigational agent or has used an investigational device within 14 days of administration of MK-0482.

    Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 2 weeks since the last dose of the previous investigational agent.

Diagnostic Assessments

29. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study medication.

    Note: Participants who require intermittent use of nonsystemic steroids such as ocular, inhaled, intranasal, topical steroids, or local steroid injections are not excluded from the study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

There are no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity Restrictions

There are no activity restrictions during participation in this study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

To adequately evaluate the safety of the doses administered in this study, all participants enrolled must meet the criteria for evaluability for Cycle 1. Participants are considered non-evaluable for DLT evaluation if:

- They are allocated, but not treated.
- They discontinue from the study before completing all the safety evaluations for reasons other than treatment-related AEs.
- They receive <75% of the total MK-0482 infusion in Cycle 1 (eg, if the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT.

Participants who are non-evaluable for DLT evaluation will be replaced unless accrual at the dose level has stopped. Non-evaluable participants will not be counted toward the total number of participants at the dose level for DLT evaluation.

If a participant experiences a DLT in Cycle 1, study intervention may be discontinued; however, if the participant is deriving clinical benefit from the study intervention, the participant may be allowed to continue after discussion with and approval by the Sponsor.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in Table 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Part 1	Experimental	MK-0482	Biological/Vaccine	Solution	100 mg/vial 750 mg/vial	7.5 mg, 25 mg, 75 mg, 225 mg, 750 mg or higher if needed	IV Infusion	Q3W up to 35 cycles	Test Product	IMP	Provided centrally by the Sponsor
Part 2	Experimental	MK-0482	Biological/Vaccine	Solution	100 mg/vial 750 mg/vial	RP2D	IV Infusion	Q3W up to 35 cycles	Test Product	IMP	Provided centrally by the Sponsor

EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP =noninvestigational/auxiliary medicinal product; Q3W=every 3 weeks; RP2D=recommended Phase 2 dose.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP/NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 3 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 8.1.9 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of MK-0482 are provided in the appropriate Pharmacy Manual.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

In Part 1 of the study, treatment will be allocated by nonrandom assignment using an IVRS/IWRS based on the dose level evaluated at the time. C1D1 treatment for the first and second enrolled participants should be at least 3 days apart. A new dose level group will not start until the previous dose level group has been evaluated for DLT and is indicated for dose escalation. Part 2 enrollment will be initiated after the RP2D dose is determined and treatment will be allocated by nonrandom assignment using an IVRS/IWRS.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.4 for dose modification and toxicity management for irAEs associated with MK-0482 and for other allowed dose interruption of MK-0482.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician; however, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

6.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care except for those that are prohibited as described in Section 6.5.2. All concomitant medication will be recorded on the CRF including all prescription, OTC, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. If participants experience an SAE or ECI, all concomitant medications administered after 30 days after the last dose of study intervention are to be recorded as defined in Section 8.4.

6.5.2 Prohibited Concomitant Medications

- Participants are prohibited from receiving the following therapies during the screening and treatment phases of this study:
- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion with Sponsor consultation after the DLT observation period for the participant to be considered evaluable for DLT.
- Live or attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study. Examples of live vaccines include, but are not limited to the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be discontinued from study intervention. Participants may receive other medications that the investigator deems to be medically necessary.

6.5.3 Rescue Medications and Supportive Care

6.5.3.1 General Supportive Care

Supportive care for managing AML should be given as needed per institution standard such as transfusion of leukocyte-depleted blood products (eg, RBC, platelets), prophylaxis and treatment for infections. Hydroxyurea can be given in an attempt to maintain WBC to

≤20 × 10^9/L. Growth factors (GM-CSF, G-CSF) may be considered as a part of supportive care for postremission therapy; however, it may confound bone marrow evaluation and therefore should be off for a minimum of 7 days before obtaining bone marrow for evaluation.

6.5.3.2 Tumor Lysis Prophylaxis

Participants with risk for developing TLS should receive prophylaxis treatment, such as with allopurinol, extra hydration, and diuretics, etc. per institution standard as clinically indicated. Hydroxyurea can be given in an attempt to maintain WBC to <20 × 109/L during treatment (see Section 6.5.3.1 and Appendix 10).

6.6 Dose Modification

6.6.1 Definition of Dose-limiting Toxicity

All toxicities will be graded using NCI CTCAE 5.0 based on the investigator assessment.

The DLT window of observation will be 21 days since the first dose of study intervention (ie, during Cycle 1).

The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study intervention administration.

1. Grade 4 nonhematologic toxicity (not laboratory).
30. Any Grade 3 nonhematologic toxicity.

Exceptions to the DLT definition:

- Grade 3 fatigue lasting ≤3 days
- Grade 3 diarrhea, nausea, or vomiting without requiring tube feeding, total parenteral nutrition, or prolonged hospitalization
- Grade 3 hypersensitivity reaction that is successfully managed and resolved within 72 hours

31. Any Grade 3 or Grade 4 nonhematologic laboratory value if:
    - Clinically significant medical intervention is required to treat the participant, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week, or
    - Electrolyte imbalances lasting more than 48 hours despite optimal therapy, or
    - The abnormality results in a DILI (see Section 8.4.7 for criteria).

    Exceptions to the DLT definition: Grade 3 or Grade 4 isolated abnormalities without clinical consequences that is resolved with or without intervention to less than Grade 2 in <72 hours.

32. Grade 4 neutropenia and/or thrombocytopenia, in the absence of active leukemia, lasting for more than 14 days.
33. Prolonged delay (>2 weeks) in initiating Cycle 2 due to intervention-related toxicity.
34. Any intervention-related toxicity that causes the participant to discontinue intervention during Cycle 1.
35. Missing >25% of MK-0482 dose as a result of drug-related AEs during the first cycle.
36. Grade 5 toxicity.

6.6.2 Dose Expansion

In Part 2 of the study, approximately 10 additional participants with AML will be enrolled with preliminary RP2D identified from Part 1.

6.6.3 Timing of Dose Administration

MK-0482 will be administered Q3W as an IV infusion. The reason for any variability in administration of MK-0482 outside the protocol-specified window should be documented in the participant's medical record and recorded on the eCRFs.

Every effort should be made to begin the first dose of study intervention on the day of allocation or within 3 days of allocation. Subsequent doses will be administered on Day 1 of each cycle with a window of ± 3 days. Study intervention should be administered after all predose study procedures and assessments have been completed as detailed in Section 1.3.

The Pharmacy Manual contains specific instructions for MK-0482 dose calculation, reconstitution, preparation, and administration.

6.6.4 Guidelines for Dose Modification due to Adverse Events

6.6.4.1 Dose Modification for MK-0482

The NCI CTCAE 5.0 must be used to grade the severity of AEs. The investigator may attribute each toxicity event to MK-0482 and modify the dose according to Table 4. If a participant experiences several toxicities and there are conflicting recommendations, follow the most conservative recommendations. Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

Table 4 MK-0482 Dose Modification and Treatment Discontinuation Guidelines for Drug-related Adverse Events

	Hold/Discontinue Treatment	**Criteria for Restarting Treatment**	**Toxicity Management**
Hematological Toxicities:			
• Any Grade 4 neutropenia or thrombocytopenia, in the absence of active leukemia, lasting for more than 14 days	Discontinue	N/A	Symptomatic treatment and supportive care at investigator's discretion
Nonhematological Toxicities:			
• Any Grade 1 nonhematological toxicity	No	N/A	N/A
• Any Grade 2 intolerant nonhematological toxicity except Grade 2 fatigue	Dose interrupt	If treatment held, may be restarted when AE resolves back to baseline or to Grade 1	Symptomatic treatment at investigator's discretion
• Any Grade 3 nonhematological toxicity, clinically significant Grade 3 or 4 laboratory	Dose interrupt	Treatment may be restarted when AE resolves back to baseline or to Grade 1 and after Sponsor consultation	Symptomatic treatment at investigator's discretion
• Any Grade 4, or recurrent Grade 3 nonhematological toxicity	Discontinue	N/A	Symptomatic treatment at investigator's discretion
AE=adverse event; N/A = not applicable			

Participants with dose interruption of more than 2 cycles (>6 weeks + 3 days) should be discontinued from study treatment, unless otherwise approved by the Sponsor.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.1.10 unless the participant has withdrawn from the study as specified in Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.4, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Unacceptable adverse experiences as described in Section 8.4.
- Progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Lack of response (ie, no PR or CR), after 6 months of study treatment.

  Note: The investigator should discuss the lack of response to study treatment with the Sponsor and the alternative options. If other alternative treatments with potential clinical benefits are available for the participant at that time, treatment with MK-0482 should be discontinued.

- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.
- Investigator's decision to discontinue treatment.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

  Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will be defined in the Procedure Manual and will not exceed what is recommended by regulatory agencies, IRBs or ethical committees.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically important by the investigator. Details regarding the disease for which the participant has enrolled in the study will be recorded separately and not listed as medical history.

8.1.5 AML or CMML-related Medical History

Detailed medical history related to the participant's AML or CMML should be obtained, including, but not limited to date of initial diagnosis, AML or CMML subtype at initial diagnosis, identified cytogenetic and molecular genetic aberrations, risk category, initial and subsequent treatments for AML or CMML (including history of hematopoietic stem cell transplant) and outcomes, date of most recent relapse, etc.

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 30 days before the first dose of study intervention.

8.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.4.

All new anticancer therapy initiated after the study start must be recorded in the eCRF. If a participant initiates another anticancer therapy other than the assigned study intervention, the study intervention should be discontinued and the participant will move into the Survival Follow-up Phase; if a participant initiates a new anticancer therapy within 30 days after the last dose of the study intervention, the 30-day Safety Follow-up Visit should occur before the first dose of the new therapy.

8.1.7 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention. Each participant will

be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.10.1.

8.1.8 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

In a situation where rerandomization of the participants is planned (eg, study extension periods), the rerandomization will be based on a new randomization schedule; however, each participant will retain his/her original treatment/randomization number. Only the study intervention regimen associated with the rerandomization period or phase may change.

8.1.9 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual.

Allocation by nonrandom assignment will be done using an IVRS/IWRS.

Administration of study medication will be witnessed by the investigator and/or study staff.

The total volume of study intervention infused will be compared with the total volume prepared to determine compliance with each dose administered.

Refer to Section 6 for dose and treatment details.

8.1.9.1 Timing of Dose Administration

Dosing and schedules are described in Section 6.1.

After the first cycle, study intervention may be administered up to 3 days before or after the scheduled dosing date for each infusion due to administrative reasons.

On Day 1 of each cycle, MK-0482 will be administered Q3W at the assigned dose level. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. Given the variability of infusion pumps form site to site, a window of minus (-) 5 minutes and plus (+) 10 minutes is allowed (ie, infusion time is 30 minutes, -5 min/+10 min).

Details on the preparation and administration of MK-0482 is provided in the Pharmacy Manual.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Disease Assessments

8.2.1.1 AML or CMML Disease Assessments at Screening/ Baseline

Disease status of participant's AML/CMML will be assessed by the investigator based on local laboratory reports. At screening/baseline, bone marrow aspirate and biopsy, peripheral blood samples will be collected for CBC and differentials, histopathology evaluation, and immunophenotyping (primarily focusing on acute myeloid and monocytic leukemic or CMML panels per institutional standard).

Participants with AML must have ≥5% blasts in bone marrow or peripheral blood at baseline to be eligible for the study. Blasts count will include myeloblasts, monoblasts, promonocytes, and/or megakaryoblasts per WHO criteria for AML [Dohner, H., et al 2017].

Extramedullary disease should be evaluated as clinically indicated per institutional guideline. Participants with CNS leukemia or isolated extramedullary lesion (ie, without bone marrow or peripheral disease as required per-protocol) should be excluded. For eligible participants, locations of extramedullary lesions should be recorded in the CRF.

8.2.1.2 AML or CMML Disease Assessments During Study Treatments

Disease status during the study treatment period will be evaluated by the investigator based on local laboratory reports of bone marrow and peripheral blood assessments. Extramedullary disease will be evaluated or followed as clinically indicated. Response evaluation criteria for AML and CMML as provided in Appendix 8 and Appendix 9, respectively will be followed for evaluating disease status at each protocol-specified timepoint or as clinically indicated. Details in disease assessment will be recorded in the CRF.

8.2.2 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status at screening, before the administration of each dose of study intervention on the day of study treatment, and during the follow-up period as specified in the SoA (Section 1.3).

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Section 8.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard during the screening period. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.1.2 Directed Physical Examination

For cycles that do not required a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at screening, before the administration of each dose of study intervention, and during the follow-up period as specified in the SoA. Vital signs include temperature, resting pulse, resting respiratory rate, weight, oxygen saturation, and blood pressure. Height will be measured at Visit 1 only.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECGs is specified in the SoA. Clinically significant abnormal findings should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal

laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.4.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

Laboratory tests for screening should be performed within 3 days before the first dose of study intervention. After Cycle 1, predose laboratory safety tests can be conducted up to 72 hours before dosing (24 hours for hematological values) unless otherwise noted on the flow charts.

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable before administration of each dose of study intervention. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory tests within the normal range do not need to be repeated after the end of treatment.

8.3.5 Pregnancy Testing

- Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing ([urine] as required by local regulations) should be conducted within 72 hours of each cycle of study intervention and 30 days posttreatment during intervention.
- If a urine test is positive or not evaluable, a serum test will be required.
- Pregnancy testing ([urine] as required by local regulations) should be conducted at the end of relevant systemic exposure.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
  - Participants must be excluded/discontinued from the study in the event of a positive or borderline-positive test result.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through 120 days after cessation of study intervention, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.
2. An elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow-up to an ECI, that occurs to any participant must be reported within 24 hours to the Sponsor if it causes the participant to be excluded from the study or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

For the time period beginning at study intervention allocation through 30 days after cessation of study intervention, any ECI, or follow-up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry

guidelines. Paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for MK-0482 by ≥20% of the indicated dose. No specific information is available on the treatment of overdose of MK-0482. In the event of overdose, MK-0482 may be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

To further evaluate MK-0482 immunogenicity and exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of ADA and PK are currently planned as shown in Section 1.3. Blood samples will be obtained to measure PK of serum MK-0482. The MK-0482 serum C_{max} and C_{trough} at planned visits and times will be summarized.

8.6.1 Blood Collection for Plasma MK-0482

Sample collection, storage, and shipment instructions for plasma samples will be provided in the Laboratory Manual.

Pharmacokinetic samples should be drawn according to the PK collection schedule for all participants.

8.6.2 Blood Collection for Antidrug Antibodies

Sample collection, storage, and shipment instructions for serum samples will be provided in the Laboratory Manual. Anti-MK-0482 samples should be drawn according to the ADA collection schedule for all participants (Section 1.3). Simultaneous PK sampling is required for interpretation of ADA analysis.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be in the Laboratory Manual.

8.8 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Blood for serum biomarker analysis
- Blood for receptor occupancy

- Blood for exploratory immune cell analyses
- Blood for genetic analysis
- Blood for ctDNA analysis
- Bone marrow aspirate

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be in the Laboratory Manual.

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the Laboratory Manual. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/IEC does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for FBR only if participant signs the FBR consent.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover DNA for future research
- Leftover RNA for future research
- Leftover blood/serum/plasma
- Leftover bone marrow

8.10 Health Economics

Health economics are not evaluated in this study.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Screening

Approximately 21 days before treatment allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 3 days before the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 72 hours before the first dose of study intervention, with the exception of CBC with differential, which must be collected within 24 hours prior to the first dose of study treatment.
- Evaluation of ECOG is to be performed within 72 hours before the first dose of study intervention.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours before the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study-site laboratory).
- A bone marrow aspirate and biopsy sample will be performed within 14 days of treatment start date. Details pertaining to bone marrow biopsy submission can be found in the Laboratory Manual.

8.11.2 Study Intervention Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.

8.11.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in Section 1.3. Additional details regarding participant withdrawal and discontinuation are presented in Section 7.

8.11.3.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first.

All AEs that occur before the Safety Follow-up Visit should be recorded (up to 30 days after the end of treatment).

8.11.3.2 Survival Follow-up Visits

Participants who experience confirmed disease progression or start a new anticancer therapy will move into the Survival Follow-up Phase and should be contacted by telephone every 12 weeks (± 14 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The Sponsor may request survival status be assessed at additional time points during the course of the study. For example, these additional time points may be requested before an efficacy interim analysis, and/or final analysis. All participants who are not known to have died before the request for these additional survival status time points will be contacted at that time.

8.11.4 Survival Status

To ensure current and complete survival data are available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to, but not limited to an eDMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategies and procedures for the primary and secondary analyses of the study. Exploratory and other nonconfirmatory analyses will be outlined in a separate sSAP.

If, after the study has begun, changes are made to primary and/or secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before the conduct of any analyses, will be documented in the sSAP as needed and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

A summary of the SAP is provided in Table 6. Full details are in the SAP, Section 9.2 to 9.12.

Table 6 Statistical Analysis Plan Summary

Study Design Overview	Phase 1b study to evaluate the safety, tolerability, and pharmacokinetics/pharmacodynamics of MK-0482 in participants with relapsed or refractory acute myeloid leukemia or chronic myelomonocytic leukemia. The study applies an accelerated titration design followed with a mTPI design for dose finding.
Intervention Assignment	Participants will be allocated centrally through IRT by nonrandom assignment.
Analysis Populations	Safety (Primary): All Participants as Treated (APaT) PK (Secondary): Per-Protocol (PP) Efficacy (Secondary): Full Analysis Set (FAS)
Primary Endpoint(s)	• DLTs • AEs • Discontinuations of study intervention due to an AE
Secondary Endpoints	• Noncompartmental PK parameters • CR rate, composite CR rate, ORR in AML
Statistical Methods for Efficacy/Immunogenicity/ Pharmacokinetic Analyses	PK parameters of study medicines will be summarized by planned visit and time for each dose separately. Point estimates and the corresponding 95% CIs will be provided for CR rate, composite CR rate, and ORR using the Clopper and Pearson method [Clopper, C. J. 1934]. Exploratory efficacy analyses are documented in the sSAP.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate. The pool-adjacent-violators algorithm [Ji, Y., et al 2007] will be used to estimate the DLT rates across doses. The estimate of the DLT rate among participants treated at RP2D of MK-0482 and the 80% Bayesian credible intervals for the estimate will be provided.

Interim Analyses	There are no planned interim analyses for this study.
Multiplicity	No multiplicity adjustment is planned in this Phase 1 study.
Sample Size and Power	The overall sample size for this study depends on the observed DLT profiles of MK-0482. A target sample size of 30 to 35 participants will be used for study planning purposes.
APaT = All Participants as Treated; CI = confidence interval; DLT = Dose-Limiting Toxicity; FAS = Full Analysis Set; PP = Per-Protocol; sSAP = supplemental Statistical Analysis Plan.	

9.2 Responsibility for Analyses/In-house Blinding

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

The study is open-label, ie, participants, investigators, and Sponsor personnel will be aware of participant intervention assignment after each participant is enrolled and treatment is assigned. Participants will be allocated by nonrandom assignment.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

For AML participants, complete remission rate, composite CR rate, and ORR as evaluated by investigator per 2017 ELN AML response criteria (Appendix 8) are the secondary efficacy endpoints. A composite CR is a CR or CR with CR_i. An objective response is a CR, CRi, or PR. For CMML participants, CR rate, PR rate, marrow response, cytogenetic remission, and clinical benefit as evaluated by investigator per 2015 International Consortium Proposal of Uniform Response Criteria for MDS/MPN in Adults (Appendix 9) are exploratory efficacy endpoints.

PK endpoints include serum concentrations of MK-0482, as well as derived PK parameters.

9.4.2 Safety Endpoints

The primary safety endpoint is the incidence of DLTs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

A description of safety measures is provided in Section 8.3.

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all participants who received at least 1 dose of study intervention.

The DLT evaluable population includes APaT participants in Part 1 (dose escalation) that meet the criteria for DLT evaluability (eg, finished Cycle 1 without a DLT or experienced a DLT in Cycle 1). See Section 6.6 for details.

At least 1 laboratory or vital sign measurement obtained after at least 1 dose of study intervention is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.5.2 Pharmacokinetic Analysis Populations

The per-protocol population will be used for the analysis of PK and target engagement data in this study. The per-protocol population consists of the subset of participants who complied with the protocol sufficiently to ensure that their data will be likely to show the effects of treatment, according to the underlying scientific model. Compliance includes such considerations as exposure to treatment, availability of measurements, and the absence of major protocol violations. Any participants or data values excluded from the analyses will be identified, along with the reasons for exclusion, in the CSR. At the end of the study, all participants who were compliant with the study procedures and have available data from at least 1 treatment will be included in the per-protocol analysis dataset.

9.5.3 Efficacy Analysis Populations

The FAS population will be used for the analyses of efficacy data in this study. It consists of all participants with a baseline assessment, and who were administered at least 1 dose of study intervention in the dose expansion part. Participants who were treated at the determined RP2D from the dose-escalation part will be included in the analysis population. Efficacy for AML and CMML participants will be summarized separately.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory endpoints will be described in the sSAP.

9.6.1 Statistical Methods for Efficacy Analysis

CR rate, composite CR rate, and ORR estimates will be reported along with the 95% CI using the Clopper and Pearson method [Clopper, C. J. 1934].

9.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory tests, vital signs, and physical examinations.

AEs will be summarized by counts and frequencies for each dose level. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

DLTs will be listed and summarized by dose level. The pool-adjacent-violators algorithm [Ji, Y., et al 2007], which forces the DLT rate estimates to be nondecreasing with increasing dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The estimate of the DLT rate among participants treated at the RP2D and the 80% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized.

9.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

Peripheral blood ILT3 receptor occupancy and noncompartmental PK parameters will be summarized by planned visit and time for each dose separately.

PK and pharmacodynamics modeling analyses will be documented in the sSAP.

9.7 Interim Analyses

An interim analysis may be conducted to enable future study planning at the Sponsor's discretion and data will be examined on a continuous basis to allow for dose-finding decisions.

9.8 Multiplicity

There will be no multiplicity control in this study.

9.9 Sample Size and Power Calculations

With approximately 2 to 6 total participants in the ATD stage and approximately 3 to 6 participants with a maximum of 10 participants at each dose level in the mTPI stage, the sample size in the dose-escalation part is expected to be approximately 20 AML and CMML participants. The dose expansion part will enroll an additional 10 to 15 AML participants at the determined RP2D. Thus, the total sample size for the study is approximately 30 to 35 participants. The actual sample size depends on the safety profiles and number of doses studied.

The 20 AML participants treated at the RP2D will be available for efficacy analysis. Table 7 presents confidence intervals for different observed response rates.

Table 7 Confidence Intervals for Different Observed Response Rates

Total Sample Size per Group	Observed # of Responses	Observed Response Rate	95% CI
20	4	20%	(6%, 44%)
20	6	30%	(12%, 54%)
20	9	45%	(23%, 68%)
CI = confidence interval			

9.10 Subgroup Analyses

Subgroup analyses of efficacy endpoints will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

Drug accountability data for study intervention will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease-related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support

clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study

completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 8 Protocol-required Clinical Laboratory Assessments

Hematology	Comprehensive Chemistry Panel	Urinalysis	Other
Hematocrit Hemoglobin Platelet count RBC **WBC (total and differential)** Myeloblasts Monoblasts Megakaryoblasts Promyelocytes Myelocytes Metamyelocytes Promonocytes Prolymphocytes Segmented neutrophils Band neutrophils Lymphocytes Monocytes Eosinophil Basophil Plasma cells Absolute lymphocyte count [b] Absolute neutrophil count [b] Total blasts [c] **Coagulation** PT or INR aPTT/PTT Fibrinogen [d]	Albumin Alkaline phosphatase ALT AST Bicarbonate BUN Calcium Chloride Creatinine Glucose (nonfasting) LDH Phosphorus Potassium Sodium Magnesium Total bilirubin (Note: Direct bilirubin is required if total bilirubin is elevated above 2 × ULN) Total protein Uric acid	Blood Glucose Protein Specific gravity Microscopic examination if abnormal results are noted [d]	Pregnancy test (serum or urine) [a]

Hematology	Comprehensive Chemistry Panel	Urinalysis	Other
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = Prothrombin time; PTT = partial thromboplastin time; RBC=red blood cell; ULN = upper limit of normal; WBC=white blood cell. a Perform on women of childbearing potential only 72 hours before Day 1 of Cycle 1. Additional tests may also be performed if clinically warranted, or as defined by local regulations. b Report % and absolute results, as necessary. Report the results in the same manner throughout the study. When neutrophils are reported separately as segmented and band neutrophils, absolute neutrophils should be the sum of the two. c Total blasts (in percentage) should include the following cell types: monoblasts, myeloblasts, megakaryoblasts and promonocytes. d As clinically indicated.			

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions, but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE 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 participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a new cancer (that is not the cancer under study) as noted in Section 8.4.1.
- Is associated with an overdose.

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of causality

- Did the Sponsor's product cause the AE?
- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:
  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.

  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant reexposed to the Sponsor's product in this study?
  - If yes, did the AE recur or worsen?
  - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- Consistency with study intervention profile: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

The recording and follow-up procedures described in this protocol apply to all medical devices as described below. For purposes of this section, medical devices in scope for device information collection include devices intended to be used by a study participant according to the study protocol that are manufactured by the Sponsor or for the Sponsor by a third party, licensed by the Sponsor for human use and/or drug-device combination products as listed in Section 6.1.1. Product Quality Complaints/Malfunctions must be reported to the Sponsor.

10.4.1 Definitions

Combination Product – A product comprised of 2 or more regulated components (ie, a drug and a device; a biologic and device; a biologic and a drug; or a drug, a device, and a biologic). Combination products can be single entity, copackaged, or colabeled.

Complaint – Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. This would include PQC, AE, and customer feedback.

A complaint does not necessarily need to involve a user or any other person.

Constituent Part – A drug, device, or biological product that is part of a combination product.

Customer Feedback – A report that does not allege a PQC or defect and has no relevant safety information/untoward event associated with it (eg, goodwill or courtesy replacement, consumer preference or suggestion, remark that may suggest an improvement in the functionality or quality of a medical device, or device like features of a drug delivery system).

Malfunction – The failure of a device to meet its performance specifications or otherwise perform as intended.

Medical Device – Any instrument, apparatus, appliance, material, or other article, whether used alone or in combination, including the software necessary for its proper application intended by the MANUFACTURER to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment, or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for an injury or handicap,
- investigation, replacement, or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means.

PQC – Any communication that describes a potential defect related to the identity, strength, quality, purity, or performance of a product identified by external customers. This includes potential device or device component malfunctions. Note: A report of Lack or Limited Efficacy is considered an AE rather than a PQC.

Serious Injury – An injury or illness that:

1. Is life-threatening,
2. Results in permanent impairment of a body function or permanent damage to a body structure, or
3. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

10.4.2 Recording, Assessing Causality, and Follow-up of PQCs/Malfunctions

Recording

When a complaint including PQC/malfunction occurs it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

Events occurring during the study will be recorded in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate CRF (paper or electronic) as per instructions provided in the data entry guidelines. Medical device/device constituent part of drug-device combination product information will be collected and reported to the Sponsor in the same time frame as SAEs as per Section 8.4.1 via CRF (paper or electronic). PQCs/malfunctions must be reported to the Sponsor.

Assessing Causality

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship.

The investigator will use clinical judgment to determine the relationship.

Alternative causes such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration should be considered and investigated.

Follow-up

The investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the event as complete as possible.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c, d] • IUS[c,e] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] Male condoms must be used in addition to female participant hormonal contraception. [d] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. • Male condom with cap, diaphragm, or sponge with spermicide. • Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Response Criteria for AML (Modified ELN 2017)

Category	Definition	Comment
Response		
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 × 10^9/L (1000/μL); platelet count ≥100 × 10^9/L (100,000/μL)	MRD+ or unknown
CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia (<1.0 × 10^9/L [1000/μL]) or thrombocytopenia (<100 × 10^9/L [100,000/μL])	
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of Phase 1-2 clinical trials
Treatment Failure		
Primary Refractory Disease	No CR or CR_i after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine are generally considered as the best option for patients not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
Death in aplasia	Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia	
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	

Category	Definition	Comment
Response criteria for clinical trials only		
Stable disease	Absence of CR, CR_i, PR, MLFS; and criteria for Progressive Disease not met	Period of stable disease should last at least 3 months.
Progressive disease (PD)[a,b]	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:	Category mainly applies for older participants given low-intensity or single-agent "targeted therapies" in clinical trials
	• >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline); or persistent marrow blast percentage of >70% over at least 3 months.; without at least a 100% improvement in ANC to an absolute level (>0.5 × 10^9/L [500/µL], and/or platelet count to >50 × 10^9/L [50,000/µL] nontransfused) or	In general, at least 2 cycles of a novel agent should be administered
	• >50% increase in peripheral blasts (WBC × % blasts) to >25 × 10^9/L (>25,000/µL) (in the absence of differentiation syndrome)[b] or	Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 weeks apart; the date of progression should then be defined as of the first observation date
	• New extramedullary disease	Some protocols may allow transient addition of hydroxyurea to lower blast counts
		Progressive disease is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms
Relapse	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extra medullary disease.	

ANC = absolute neutrophil count; CR = complete remission; CRi = complete remission without hematologic recovery; IDH = isocitrate dehydrogenase; MLFS = morphologic leukemia-free state; PR = partial remission; WBC = white blood cell.

[a] The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

[b] Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate progression of disease.

Source: [Dohner, H., et al 2017]

Outcome measures for clinical studies in AML

Category	Definition
Overall survival	Defined for all participants of a trial measured from the date of entry into a clinical trial or from the date of diagnosis (eg, for correlative science studies) to the date of death from any cause, patients not known to have died at last follow-up are censored on the date they were last known to be alive

Source: [Dohner, H., et al 2017]

10.9 Appendix 9: Response Criteria for CMML

Criteria for measurement of treatment response in adult MDS/MPN
CR (presence of all of the following improvements)[a]
Bone marrow: ≤5% myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity[a]
Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤Grade 1 fibrosis)[b]
Peripheral blood[c]
WBC ≤10 × 10^9 cells/L
Hgb ≥11 g/dL
Platelets ≥100 × 10^9/L; ≤450 × 10^9/L
Neutrophils ≥1.0 × 10^9/L
Blasts 0%
Neutrophil precursors reduced to ≤2%
Monocytes ≤1 × 10^9/L
Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly
Provisional category of CR with resolution of symptoms:[c] CR as described above, and complete resolution of disease-related symptoms as noted by the MPN-SAF TSS
Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia[a]
Complete cytogenetic remission
Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic, syndrome myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal of 20 metaphases or FISH[d]
Partial remission
Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity except in cases of MDS/MPN with ≤5% bone marrow blasts at baseline
Marrow response
Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above
Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity, or reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 months apart
Clinical benefit
Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response (cord blood response must be verified at ≥8 wk) to be considered a clinical benefit
Erythroid response
Hgb increase by ≥2.0 g/dL
TI for ≥ 8wk for patients requiring at least 4 packed red blood cell transfusions in the previous 8 wk
Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤8.5 g/dL will count in the red blood cell TI response evaluation[e]
Platelet response
Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 wk
Pretreatment ≤20 × 10^9/L: increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100%
Pretreatment >20 × 10^9/L but ≤ 100 × 10^9/L: absolute increase of ≥30 × 10^9/L[e]
Neutrophil response
Pretreatment ≤0.5 × 10^9/L at least 100% increase and an absolute increase ≥0.5 × 10^9/L
Pretreatment, >0.5 × 10^9/L and ≤1.0 × 10^9/L At least 50% increase and an absolute increase ≥0.5 × 10^9/L[e]

Criteria for measurement of treatment response in adult MDS/MPN
Spleen response Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable Symptom response Improvement in symptoms as noted by decrease of ≥50% as per the MPN-SAF TSS scoring <20 were not considered eligible for measuring clinical benefit.[f]

CMML=chronic myelomonocytic leukemia; CR=complete response; FISH= fluorescence in situ hybridization; Hgb=hemoglobin; MDS/MPN=myelodysplastic syndromes/myeloproliferative neoplasms; MPN-SAF=myeloproliferative neoplasm symptom assessment form; TI=transfusion independence; TSS=total symptom score; WBC=white blood cell; wk=weeks

a. Presence of dysplastic changes, which may be interpreted within the scope of normal range of dysplastic changes, may still exist in the presence of CR as allowed in MDS IWG. Marrow should show age-adjusted normocellularity in CR.
b. If there is no significant fibrosis present on the initial bone marrow biopsy, a second biopsy is not required to prove resolution of fibrosis. Grading of fibrosis in measurement of treatment response should be according to the European Consensus System.
c. Given the current lack of a validated tool to assess complete resolution of symptoms in MDS/MPN, "CR with resolution of symptoms" (a complete resolution of disease-related symptoms as noted by the MPN-SAF TSS in presence of CR) will be a provisional category of disease response.
d. Loss of cytogenetic burden of disease by (via FISH or classic karyotyping) known to adversely affect prognosis is required to reach complete cytogenetic remission. Decrease in the cytogenetic burden of disease must be by ≥50% (via FISH or classic karyotyping) to be indicative of a partial cytogenetic response. Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on the performance characteristics of the specific probes used.
e. Resolution of abnormal peripheral blood counts must persist for at least 2 separate analyses over at least 8 wk. In the case of proliferative MDS/MPN, CR will include resolution of thrombocytosis to a normal platelet count (150-450 × 109/L) and resolution of leukocytosis to WBC ≤10 × 109 cells/L but ≥1.5 × 109/L. Hgb should be maintained >11 g/dL and platelets ≥100 × 109/L without the support of transfusions. Clinical benefit may occur when these changes occur in absence of other changes required for CR or marrow response. Platelet and packed red blood cell TI would be considered for clinical benefit, and duration of TI should be monitored. Reduction in myeloid precursors (promyelocytes, myelocytes, metamyelocytes, nucleated red blood cells) to less than appreciable levels (≤2-3%) and/or 1 × 109/L monocytosis in the absence of infection, cytokine treatment, or other reactive causes.
f. MPN-SAF TSS validation among patients with MDS/MPN is currently under way (R.A. Mesa, personal communication, 2014).

Source: Adapted from [Savona, M. R., et al 2015]

Criteria for measurement of treatment response in adult MDS/MPN
Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from list
Major criteria
Increase in blast count[a]
<5% blasts: ≥50% increase and to >5% blasts
5-10% blasts: ≥50% increase and to >10% blasts
10-20% blasts: ≥50% increase and to >20% blasts
20-30% blasts: ≥50% increase and to >30% blasts[b]
Evidence of cytogenetic evolution[c]
Appearance of a previously present or new cytogenetic abnormality in complete cytogenetic remission via FISH or classic karyotyping
Increase in cytogenetic burden of disease by ≥50% in partial cytogenetic remission via FISH or classic karyotyping
New extramedullary disease
Worsening splenomegaly
Progressive splenomegaly that is defined by IWG-MRT: the appearance of a previously absent splenomegaly that is palpable at >5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of >10 cm
Extramedullary disease outside the spleen
To include new/worsening hepatomegaly, granulocytic sarcoma, skin lesions, etc.
Minor criteria
Transfusion dependence[d]
Significant loss of maximal response on cytopenias ≥50% decrement from maximum remission/response in granulocytes or platelets
Reduction in Hgb by ≥1.5 g/dL from best response or from baseline as noted on complete blood count
Increasing symptoms as noted by increase in ≥50% as per the MPN-SAF TSS[e]
Evidence of clonal evolution (molecular)[f]

FISH=fluorescence in situ hybridization; Hgb=hemoglobin; IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; MDS/MPN=myelodysplastic syndromes/myeloproliferative neoplasms; MPN-SAF=myeloproliferative neoplasm symptom assessment form; TSS=total symptom score

a. Blasts as measured from the bone marrow.
b. Patients with development of acute myeloid leukemia from MDS/MPN; 20-30% blasts may be allowed on some clinical trials for patients with MDS/MPN.
c. Increase in cytogenetic burden of disease by ≥50% (via FISH or classic karyotyping). Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on specific probes used.
d. Transfusion dependency is defined by a history of at least 2 U of red blood cell transfusions in the past month for a hemoglobin level <8.5 g/dL that was not associated with clinically overt bleeding. Cytopenias resulting from therapy should not be considered in assessment of progression.
e. MPN-SAF TSS validation among patients with MDS/MPN is currently under way (R.A. Mesa, personal communication, 2014).
f. The identification of new abnormalities using single nucleotide polymorphism arrays or sequencing or a clearly significant increase in mutational burden of a previously detected abnormality. Precise criteria for defining new abnormalities and what exactly constitutes a significant increase in mutational burden are open to interpretation; we suggest that this criterion should be used conservatively based on current evidence.

Source: Adapted from [Savona, M. R., et al 2015]

10.10 Appendix 10: Classification of Tumor Lysis Syndrome

Metabolic Abnormality	Laboratory TLS Classification Criteria[a]	Clinical TLS Classification Criteria[b]
Hyperuricemia	Uric acid ≥8 mg/dL	N/A
Hyperkalemia	Potassium ≥6 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hyperphosphatemia	Phosphorous ≥4.5 mg/dL	N/A
Hypocalcemia	Corrected calcium ≤7.0 mg/dL or ionized calcium <1.12 mg/dL[c]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesia, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute Kidney Injury[d]	N/A	Increase in the serum creatinine level of 0.3 mg/dL or the presence of oliguria (average urine output of <0.5 mL/kg/h over a 6-hour period)

N/A = not available; TLS = tumor lysis syndrome

a. Laboratory TLS requires 2 or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward.
b. Clinical TLS requires the presence of Laboratory TLS plus one or more findings from the Clinical TLS column.
c. Corrected calcium = measured calcium level in mg/dL + 0.8 × (4 – albumin in g/dL).
d. Acute kidney injury, unless attributable to another cause, represents clinical TLS even if criteria for laboratory TLS are not satisfied.

Source: [Howard, S. C., et al 2011]

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APaT	All-Participants-as-Treated
APL	acute promyelocytic leukemia
APOE	apolipoprotein E
aPTT	activated partial thromboplastin time
AR	adverse reaction
AST	aspartate aminotransferase
ATD	accelerated titration design
ATP	adenosine triphosphate
AUC	area under the curve
BCG	*Bacillus* Calmette–Guérin
bid	twice daily
BMI	body mass index
BP	blood pressure
C1D1	Cycle 1 Day 1
CAC	Clinical Adjudication Committee
CBC	complete blood count
CD	cluster of differentiation
CG	Cockcroft-Gault
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CML	chronic myelogenous leukemia

Abbreviation	Expanded Term
CMML	chronic myelomonocytic leukemia
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CrCl	creatinine clearance
CR	complete remission
CRF	Case Report Form
CR_i	complete remission with incomplete recovery
CRS	Cytokine Release Syndrome
CRU	clinical research unit
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor deoxyribonucleic acid
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTMS	Clinical Trial Management System
C_{trough}	trough plasma concentration
CYP	cytochrome P450
DC	dendritic cell
DILI	drug-induced liver injury
DL	dose level
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application

Abbreviation	Expanded Term
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
eDMC	external Data Monitoring Committee
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ELN	European Leukemia Net
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOT	end of treatment
FDA	Food and Drug Administration
FAS	Full Analysis Set
FBR	future biomedical research
FFPE	formalin-fixed, paraffin embedded
FIH	first in human
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GM-CSF	granulocyte-macrophage colony stimulating factor
GVHD	graft versus host disease
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCT	hematopoietic cell transplantation
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure

Abbreviation	Expanded Term
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDH	isocitrate dehydrogenase
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
ILT3	immunoglobulin-like transcript 3
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IO	immune-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
IRT	interactive response technology
ITIM	immunoreceptor tyrosine based inhibitory motifs
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IVRS	interactive voice response system
IWG	International Working Group
IWRS	integrated web response system
KPS	Karnofsky performance status
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
LILRB	leukocyte immunoglobulin-like receptor Bs
LLN	lower limit of normal
LLOQ	lower limit of quantitation

Abbreviation	Expanded Term
mAb	monoclonal antibody
MAD	maximum administered dose
MDS	myelodysplastic syndromes
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia-free state
MPN	myeloproliferative neoplasms
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCS	not clinically significant
NSCLC	non–small cell lung cancer
NDA	New Drug Application
NOAEL	no observed adverse effect level
NOD	nonobese diabetic
NSG	NOD scid gamma
NYHA	New York Heart Association
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PB	peripheral blood
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based PK
PD-1	programmed cell death 1 protein
PDGFRA	platelet-derived growth factor receptor A

Abbreviation	Expanded Term
PDGFRB	platelet-derived growth factor receptor B
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
Ph+	Philadelphia chromosome positive
PK	pharmacokinetic
PKCθ	protein kinase C-theta
po	orally
PP	per-protocol
PQC	product quality complaint
PR	partial remission
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin
Q2W	every 2 weeks
Q3W	every 3 weeks
QoL	quality of life
QP2	Department of Quantitative Pharmacology and Pharmacometrics
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
R/R	relapsed/refractory
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCT	stem cell transplant
scid	severe combined immunodeficient
SD	standard deviation
sILT3	soluble inactive form of ILT3
SLAB	supplemental laboratory test(s)

Abbreviation	Expanded Term
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TEA	Treatment Eligibility Assessment (form)
TIL	tumor infiltrating lymphocytes
TLS	Tumor Lysis Syndrome
T_{max}	Time to maximum plasma concentration
TME	tumor microenvironment
TPI	Toxicity Probability Interval
$t_{1/2}$	half-life
UDS	urine drug screen
ULN	upper limit of normal
Vd	volume of distribution
VS	vital signs
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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