Title Page

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Protocol Title: A Phase 2 Study to Evaluate the Efficacy and Safety of MK-1026 in Participants with Hematologic Malignancies

Protocol Number: 003-00

Compound Number: MK-1026

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

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Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	133989
EudraCT Number	2020-002324-36

Approval Date: **Will be added by RCM at PA**

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
Original Protocol		Not applicable

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2 Study to Evaluate the Efficacy and Safety of MK-1026 in Participants with Hematologic Malignancies

Short Title: Phase 2 Study of MK-1026 in Participants with Hematologic Malignancies

Acronym: MK1026-003

Hypotheses, Objectives, and Endpoints:

Formal hypothesis testing will not be performed in this protocol.

This study will be performed in 2 parts: Dose Escalation and Confirmation (Part 1) and Cohort Expansion (Part 2) in male and female participants at least 18 years of age with various hematological malignancies (Cohorts as defined in Sections 1.2 and 4.1) who have either relapsed following or are refractory to available therapies.

Primary Objectives	Primary Endpoints
- Part 1: To determine the safety and tolerability and to establish a recommended Phase 2 dose (RP2D) of MK-1026.	- Dose-limiting toxicity (DLT). - Adverse Event (AE). - Discontinuing study intervention due to an AE.
- Part 2: Cohorts A to C (chronic Lymphocytic Leukemia [CLL]/Small Lymphocytic Leukemia [SLL]): To evaluate the objective response rate (ORR) of MK-1026 per International Workshop on CLL (iwCLL) criteria 2018 as assessed by independent central review (ICR).	- Objective response (OR): complete response (CR), or complete response with incomplete bone marrow recovery (CRi), or partial response (PR).
- Part 2: Cohorts D to G (Richter's Transformation [RT], Mantle cell Lymphoma [MCL], Marginal zone Lymphoma [MZL], Follicular Lymphoma [FL]): To evaluate the ORR of MK-1026 per the Lugano criteria 2014 as assessed by ICR.	- OR: CR or PR.
- Part 2: Cohort H (Waldenstrom's Macroglobulinemia [WM]): To evaluate the ORR of MK-1026 per International	- OR: CR, very good partial response (VGPR) or PR.

Workshop on WM (IWWM) 2014 as assessed by ICR.	
- Part 2: Cohort I (chronic Graft Versus Host Disease [cGVHD]): To evaluate the cGVHD response rate of MK-1026 per cGVHD Consensus Panel 2015 as assessed by investigator review.	- Objective cGVHD response: National Institute of Health (NIH)-defined CR or PR.
Secondary Objectives	Secondary Endpoints
- Part 1: To characterize the pharmacokinetic (PK) profile of MK-1026.	- PK parameters including area under the curve (AUC), minimum concentration (Cmin), and maximum concentration (Cmax).
- Part 1: To evaluate the ORR and duration of response (DOR) of MK-1026 for CLL/SLL participants per iwCLL criteria 2018 as assessed by ICR.	- OR: CR, CRi, or PR. - DOR, defined as the time from the first documented evidence of at least PR that led to response until disease progression or death due to any cause, whichever occurs first.
- Part 1: To evaluate the ORR and DOR of MK-1026 for lymphoma participants per the Lugano criteria 2014 as assessed by ICR.	- OR: CR or PR. - DOR.
- Part 1: To evaluate the ORR and DOR of MK-1026 for WM participants per IWWM 2014 as assessed by ICR.	- OR: CR, VGPR, or PR. - DOR.
- Part 2: All Cohorts: To determine the safety and tolerability of MK-1026.	- AE. - Discontinuing study intervention due to an AE.
- Part 2: All Cohorts: To characterize the PK profile of MK-1026.	- PK parameters including AUC, Cmin, and Cmax.
- Part 2: Cohorts A to C (CLL/SLL): To evaluate DOR of MK-1026 per iwCLL criteria 2018 as assessed by ICR.	- DOR.
- Part 2: Cohorts D to G: (RT, MCL, MZL, FL): To evaluate the DOR of MK-1026 per	- DOR.

the Lugano criteria 2014 as assessed by ICR.	
- Part 2: Cohort H (WM): To evaluate the DOR of MK-1026 per IWWM 2014 as assessed by ICR.	- DOR.
- Part 2: Cohort I (cGVHD): To evaluate the durability of response of MK-1026 per cGVHD Consensus Panel 2015 as assessed by investigator.	- Sustained response, defined as NIH-defined CR or PR that was sustained for at least 20 weeks.

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Treatment of participants with hematologic malignancies
Population	Participants with CLL, lymphoma, WM, and cGVHD
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 78 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 465 participants with various hematological malignancies and cGVHD will be treated in the dose escalation and confirmation (Part 1) and cohort expansion (Part 2) of

the study. In Part 1 approximately 25 participants, a minimum of 3 participants with the potential to treat up to a maximum of 10 participants depending on dose decisions, will be enrolled at each dose level. In Part 2, approximately 450 participants (a minimum of 30 to a maximum of 100 participants per cohort) will be enrolled.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
MK-1026	MK-1026	80 mg (DL 1)	QD	Oral	Until progressive disease or discontinuation	Exp
MK-1026	MK-1026	100 mg (DL 2)	QD	Oral	Until progressive disease or discontinuation	Exp
MK-1026	MK-1026	120 mg (DL 3)	QD	Oral	Until progressive disease or discontinuation	Exp
MK-1026	MK-1026	65 mg [a]	QD	Oral	Until progressive disease or discontinuation	Exp

Abbreviations: DL=dose level; Exp=experimental; QD=once daily.
[a] In the event of sufficient DLTs observed at 80 mg, the 65 mg dose will be used in Part 2.

Other current or former name(s) or alias(es) for study intervention(s) are as follows: MK-1026 was formerly known as ARQ 531.

Total Number of Intervention Groups/ Arms

This is a single arm study in which participants will be treated with MK-1026.

Duration of Participation

Each participant will participate in the study from the time of signing the Informed Consent Form through to the final contact. After a screening phase of 28 days, each participant will receive the assigned intervention until disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, or administrative reasons requiring cessation of treatment. Participants who discontinue for reasons other than disease

	progression will have post-treatment follow-up response assessments until disease progression is documented, the start of a new anti-cancer treatment, withdrawal of consent, pregnancy, death, or loss to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

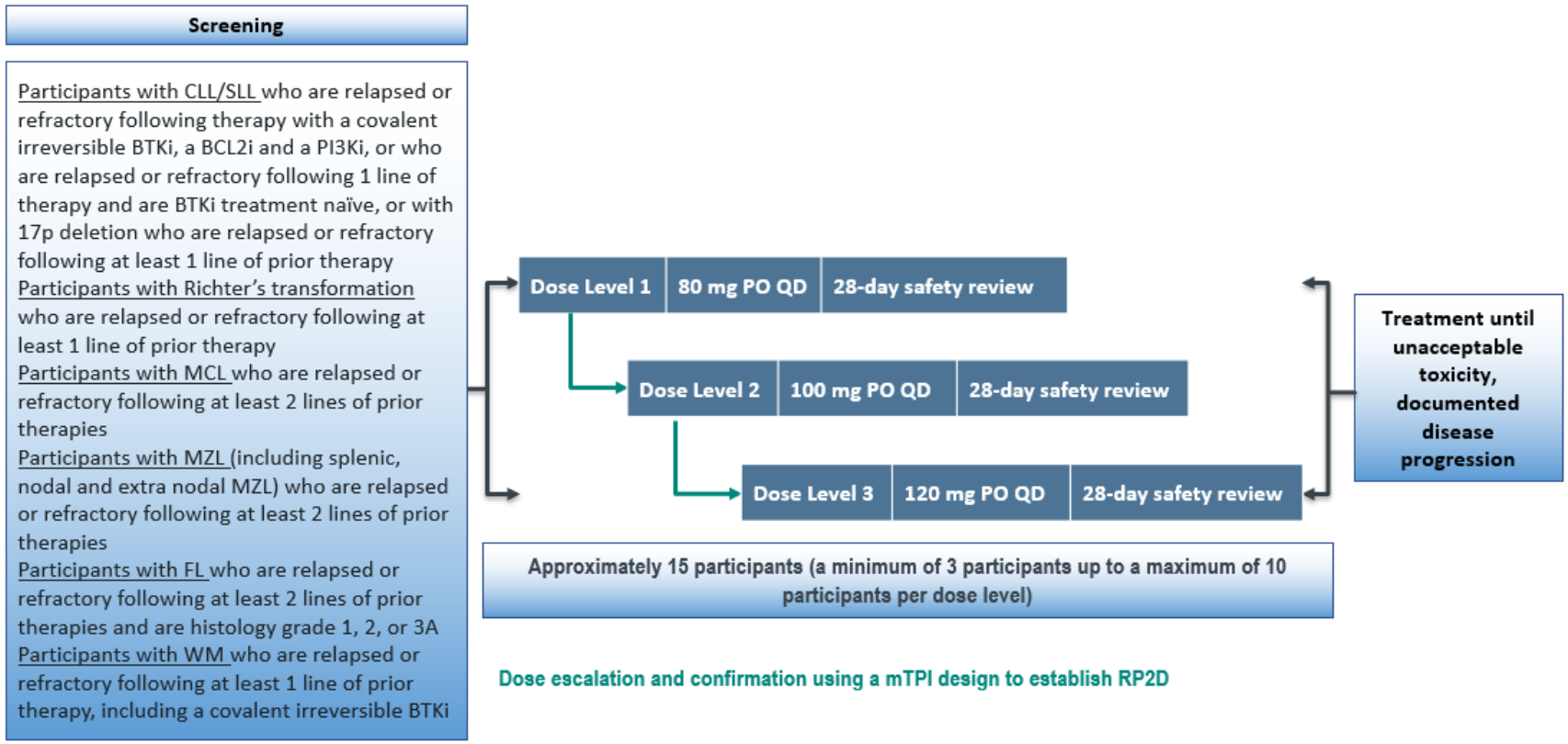
Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Insert Other Oversight Committee	No

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 14.

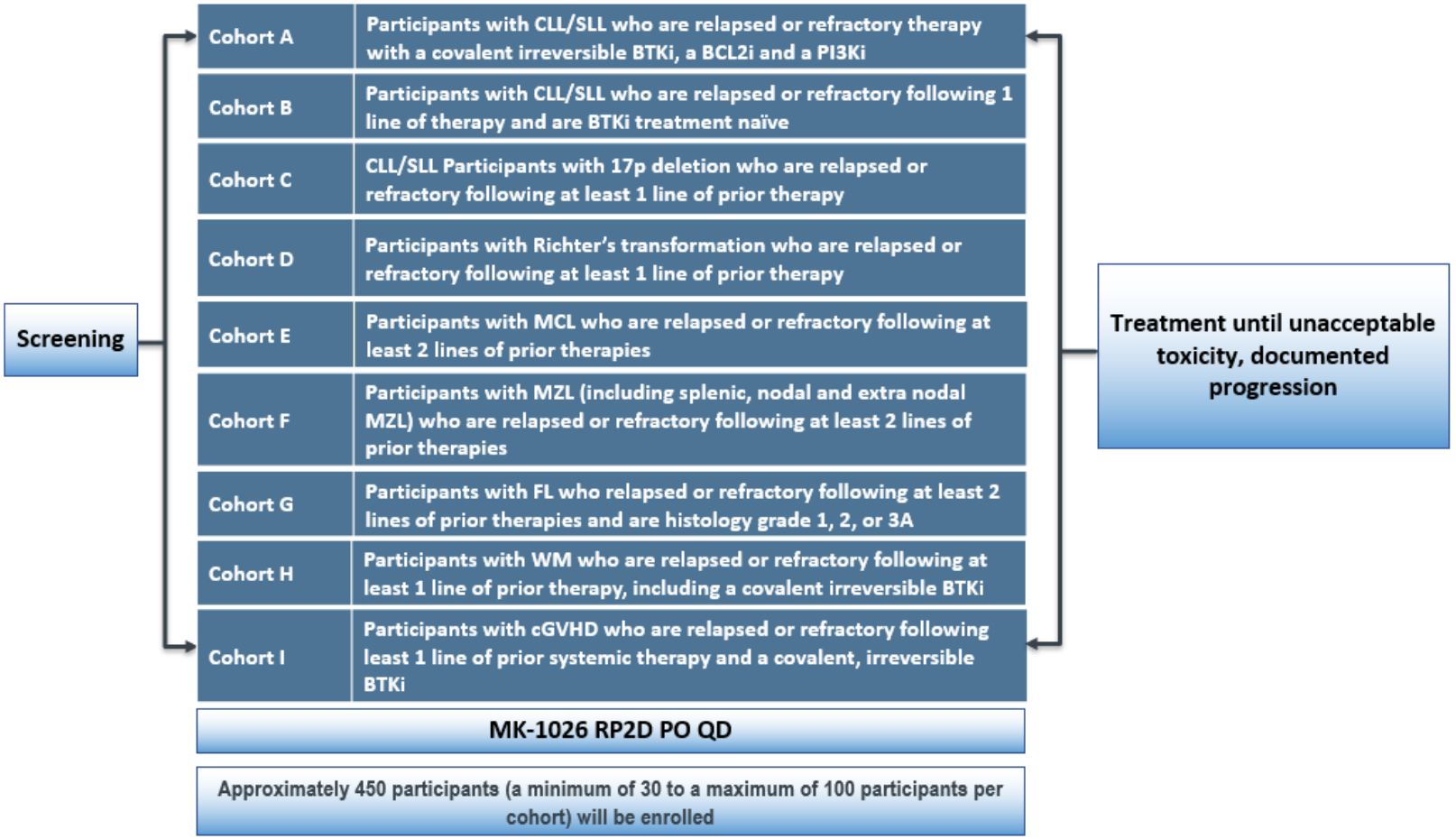
1.2 Schema

Figure 1 Dose Escalation and Confirmation (Part 1)



Abbreviations: BCL2i=B-cell lymphoma 2 inhibitor; BTKi=Bruton's tyrosine kinase inhibitor; cGVHD=chronic graft versus host disease; CLL=chronic lymphocytic leukemia; FL=follicular lymphoma; MCL=mantle cell lymphoma; MZL=marginal zone lymphoma; PI3Ki=phosphoinositide-3 kinase inhibitor; PO=per os (orally); QD=once a day; SLL=small lymphocytic lymphoma; WM=Waldenström's macroglobulinemia.

Figure 2 Cohort Expansion (Part 2)



Abbreviations: BCL2i=B-cell lymphoma 2 inhibitor; BTKi=Bruton's tyrosine kinase inhibitor; cGVHD=chronic graft versus host disease; CLL=chronic lymphocytic leukemia; FL=follicular lymphoma; MCL=mantle cell lymphoma; MZL=marginal zone lymphoma; PI3Ki=phosphoinositide-3 kinase inhibitor; PO=per oral; QD=daily; RP2D=recommended Phase 2 dose; SLL=small lymphocytic lymphoma; WM=Waldenström's macroglobulinemia.

1.3 Schedule of Activities

1.3.1 Dose Escalation and Confirmation (Part 1)

Table 1 Schedule of Assessments for Part 1: Screening and Treatment

Study Period:	**Screening**	**Treatment**												**Notes**
		C1/D1 (W0)	**C1/D8 (W1)**	**C1/D15 (W2)**	**C1/D22 (W3)**	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	Each cycle consists of 4weeks (28 calendar days).
Visit Number/Frequency:	**1**	**2**	**4**	**5**	**6**	**7**	**9**	**10**	**11**	**12**	**13**	**Every cycle**	**Every 3 cycles (Q12W)**	
Window (days):	**-28 to 1**	**0**	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Administrative Procedures														
Informed Consent	X													Informed consent must be obtained prior to any protocol-specific procedures.
Informed Consent for Future Biomedical Research	X													
Inclusion/Exclusion Criteria	X													
Participant Identification Card	X	X												At Visit 2, site personnel should add the allocation number to the participant ID card.
Demography and Medical History	X													Data collection should follow local regulations where applicable.
Prior /Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	
MK-1026 Dispensing		X	X	X	X	X	X	X	X	X	X	X	X	MK-1026 tablets will be administered QD by mouth under fasted condition (either 1 hour prior to, or 2 hours after the meal). Participants should be instructed NOT to take their dose of MK-1026 on study visit days.
MK-1026 Return						X	X	X	X	X	X	X	X	

Study Period:	**Screening**	**Treatment**												**Notes**
		C1/D1 (W0)	**C1/D8 (W1)**	**C1/D15 (W2)**	**C1/D22 (W3)**	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	
Visit Number/Frequency:	**1**	**2**	**4**	**5**	**6**	**7**	**9**	**10**	**11**	**12**	**13**	**Every cycle**	**Every 3 cycles (Q12W)**	Each cycle consists of 4weeks (28 calendar days).
Window (days):	**-28 to 1**	**0**	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Compliance														
Disease Sample Collection														
Optional Archival or Newly obtained tissue collection	X													Tissue collection should only be performed once all other eligibility criteria have been collected and reviewed ≤60 days relative to the date of submission to central laboratory A lymph node sample is optional. If a lymph node sample is considered medically unsafe to perform other appropriate tissue may be submitted (eg, bone marrow).
Efficacy Assessments														
Treatment Response Assessments		Q12W (±7 day window for scans)												Imaging and treatment response assessments are required every 12 weeks and should follow calendar days from C1D1. If dosing is delayed, treatment response assessments should continue as scheduled. Unscheduled imaging can be performed as clinically indicated.
CLL/SLL Participants	X	Q12W												Using IWCLL 2018 criteria (Appendix 10) assessed by ICR and investigator. Assessments to include symptoms, biomarker/cytogenetics, staging, PE, blood sample, CT, bone marrow aspirate + biopsy at screening and in the event of CR, as defined in Section 8.2.1.1.

Study Period:	**Screening**	**Treatment**											**Notes**
		C1/D1 (W0)	**C1/D8 (W1)**	**C1/D15 (W2)**	**C1/D22 (W3)**	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	
Visit Number/Frequency:	**1**	**2**	**4**	**5**	**6**	**7**	**9**	**10**	**11**	**12**	**13**	**Every cycle**	**Every 3 cycles (Q12W)**	Each cycle consists of 4weeks (28 calendar days).
Window (days):	**-28 to 1**	**0**	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
MRD (CLL/SLL who achieve a CR only)		Q12W only when participant achieves CR ◄----------►												MRD to be obtained Q12W from CR confirmation until progression. Local testing is acceptable.
RT. Fl, MZL, MCL Participants	X	Q12W ◄----------►												Using Lugano 2014 criteria, assessed by ICR and investigator. Cheson 2007 criteria assessed by ICR (Appendix 10) Assessments to include disease burden and symptoms, staging, PET-CT, PE, bone marrow aspirate + biopsy at screening and in the event of CR, as defined in Section 8.2.1.2. No further PET scans are required for lymphomas which are not FDG-avid at baseline, unless clinically indicated. For FDG-avid lymphomas, PET is required at baseline, weeks 12 and 24, to confirm CR or as clinically indicated.
WM Participants	X	Q12W ◄----------►												IWWM 2014 criteria (Appendix 10) assessed by ICR and investigator Assessments will include pathognomonic symptoms, IgM, CT, PE and bone marrow aspirate/trephine in the event of CR, as defined in Section 8.2.1.3.
Cryoglobulins (WM participants only)	X	Q12W ◄----------►												To be performed at each response assessment visit and if clinically indicated.
Assessment of B Symptoms	X	Q12W ◄----------►												

Study Period:	**Screening**	**Treatment**												**Notes**
		C1/D1 (W0)	**C1/D8 (W1)**	**C1/D15 (W2)**	**C1/D22 (W3)**	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	
Visit Number/Frequency:	**1**	**2**	**4**	**5**	**6**	**7**	**9**	**10**	**11**	**12**	**13**	**Every cycle**	**Every 3 cycles (Q12W)**	Each cycle consists of 4weeks (28 calendar days).
Window (days):	**-28 to 1**	**0**	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
EORTC QLQ-C30		X	X	X	X	X	X	X	X	X	X	Q4W for Cycles 8 (Wk28), 9 (Wk32), 10 (Wk36), 11 (Wk40), 12 (Wk44), & 13 (Wk48). Q12W for Cycles 16 (Wk60), 19 (Wk72), 22 (Wk84), 25 (Wk96), 28 (Wk108)	Q24W for remaining cycles (eg, Cycles 34 (Wk132), 40 (Wk156), 46 (Wk180), 52 (Wk 228) etc)	PROs should be performed at the scheduled study visit until treatment discontinuation. PROs are to be administered by trained study personnel and completed electronically by participants. PROs should be completed prior to all other study procedures and receiving results of any tests (including disease status). PROs should be administered in the following order: EORTC QLQ-C30 and EQ-5D-5L.
EQ-5D-5L		X	X	X	X	X	X	X	X	X	X			
Safety Assessments														
Full Physical Examination	X													Physical examination must include liver and/or spleen size. Other system-based examinations should be included if clinically indicated.
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	Review of new clinically significant abnormal findings. Neurological/skin examinations should be included if clinically indicated.
Height	X													
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X	X	Screening assessment to be performed within 7 days of treatment allocation.
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	Temperature, respiration rate, pulse, and blood pressure.

Study Period:	**Screening**	**Treatment**											**Notes**
		C1/D1 (W0)	**C1/D8 (W1)**	**C1/D15 (W2)**	**C1/D22 (W3)**	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	
Visit Number/Frequency:	**1**	**2**	**4**	**5**	**6**	**7**	**9**	**10**	**11**	**12**	**13**	**Every cycle**	**Every 3 cycles (Q12W)**	Each cycle consists of 4weeks (28 calendar days).
Window (days):	**-28 to 1**	**0**	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
12-lead ECG	X	See Table 2												After Cycle 3, ECG is only required where clinically indicated. Triplicate 12-lead ECG will be measured and sent for central reading
AE/SAE review		X	X	X	X	X	X	X	X	X	X	X	X	Record all AEs occurring within 30 days after last dose of trial treatment. After 30 days, record all SAEs occurring up to 90 days after last dose of trial treatment or 30 days following last dose if the subject initiates new anticancer therapy, whichever comes first. Any treatment related SAEs must be reported regardless of time they occur.
Laboratory Procedures														Local laboratories.
Hematology, Serum Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	Screening samples must be taken within 7 days of allocation. See Appendix 2 for parameters.
Urinalysis	X													Post screening sample only required if clinically indicated.
Pregnancy Test (WOCBP only)	X	X				X	X	X	X	X	X	X	X	WOCBP require negative test prior to allocation. If more than 72 hours have elapsed prior to first dose of study intervention, another pregnancy test is required prior to starting study intervention. Pregnancy tests should be performed at every study visit as per local regulations.
B2 Microglobulin	X	X				X	X	X	X	X	X	X	X	
Serum Immunoglobulin	X	X				X	X	X	X	X	X	X	X	

Study Period:	**Screening**	**Treatment**												**Notes**
		C1/D1 (W0)	**C1/D8 (W1)**	**C1/D15 (W2)**	**C1/D22 (W3)**	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	
Visit Number/Frequency:	**1**	**2**	**4**	**5**	**6**	**7**	**9**	**10**	**11**	**12**	**13**	**Every cycle**	**Every 3 cycles (Q12W)**	Each cycle consists of 4weeks (28 calendar days).
Window (days):	**-28 to 1**	**0**	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Infection Testing (HCV, HBV, HIV)	X	HBV/HCV monitoring as per Notes column ◄----------►												Participants with CLL/SLL, RT, FL, MCL, WM, cGVHD – HCV and HBV positive participants are excluded. If participant has history of HBV then monitoring is required Q12W. Participants with MZL – the following participants can be included: a) past or ongoing HCV infection. Treated participants must have completed their treatment at least 1 month prior to starting study intervention. Untreated or incompletely treated HCV participants may initiate anti-viral therapy for HCV if liver function remains stable for at least 3 months on study intervention. b) controlled HBV, as long as they meet the following criteria: i. Participants with chronic HBV infection, defined as HBsAg positive and/or detectable HBV DNA, must be given antiviral therapy for HBV for at least 4 weeks prior to the first dose of study intervention and HBV viral load must be less than 100 IU/mL prior to first dose of study treatment. Participants on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study intervention. Antiviral therapy after completion of study intervention should follow local guidelines.

Study Period:	**Screening**	**Treatment**												**Notes**
		C1/D1 (W0)	**C1/D8 (W1)**	**C1/D15 (W2)**	**C1/D22 (W3)**	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	
Visit Number/Frequency:	**1**	**2**	**4**	**5**	**6**	**7**	**9**	**10**	**11**	**12**	**13**	**Every cycle**	**Every 3 cycles (Q12W)**	Each cycle consists of 4weeks (28 calendar days).
Window (days):	**-28 to 1**	**0**	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
														ii. Participants with clinically resolved HBV infection, defined as HBsAg negative and anti-HBc positive, and who have an undetectable HBV viral load at screening should be checked Q6W for HBV viral load and treated for HBV if viral load is over 100 IU/mL. Antiviral therapy after completion of study intervention should follow local guidelines. All cohorts - testing not required unless mandated by local health authority HIV as per local regulations. Refer to Appendix 7 for country-specific testing requirements.
Pharmacokinetics/Pharmacodynamics/Biomarkers														Central laboratories.
Blood PK Sample		See Table 2												
Blood for TBNK (CLL/SLL participants only)		X	Q12W ◄----------►											C1D1 sample required. Sample collection should coincide with disease response assessments (±7 days), when blood samples are collected.
Blood for Genetic Analysis		X												Predose sample required. See Section 8.8
Blood for Genomic Mutational Analysis (CLL/SLL participants only)		X	Q12W ◄----------►											C1D1 sample required. Sample collection should coincide with disease response assessments (±7 days), when blood samples are collected.
Blood for ctDNA Analysis		X				X	X	X	Q12W ◄----------►					Predose samples required Post C4/D1 (W12) sample collection should be Q12W. ctDNA samples should coincide with disease response assessments when blood samples are

Study Period:	**Screening**	**Treatment**											**Notes**
		C1/D1 (W0)	**C1/D8 (W1)**	**C1/D15 (W2)**	**C1/D22 (W3)**	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	
Visit Number/Frequency:	**1**	**2**	**4**	**5**	**6**	**7**	**9**	**10**	**11**	**12**	**13**	**Every cycle**	**Every 3 cycles (Q12W)**	Each cycle consists of 4weeks (28 calendar days).
Window (days):	**-28 to 1**	**0**	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
														collected.
Blood for Serum Biomarker Analyses		See Table 2												

Abbreviations: AE=adverse event; CT=computer tomography; ctDNA=circulating tumor deoxyribonucleic acid; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; EORTC=European Organization for Research and Treatment of Cancer; EOT=end of treatment; ICR=independent central review; ID=identification; IWCLL=International Workshop on Chronic Lymphocytic Leukemia; MRD=minimal residual disease; PK=pharmacokinetics; Q4W=every 4 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; RNA=ribonucleic acid; SAE=serious AE; TBNK=T and B lymphocyte and natural killer cell profile; W=Week; WOCBP=women of child-bearing potential.

Table 2 Schedule of Assessments for Part 1: Pharmacokinetic and Biomarker Samples (Cycles 1 to 3)

Study Period	**Treatment Phase**															**Notes**
	C1 (W0/Day 1)					**C1 (W0/Day 2)**	**C2 (W4/Day 29)**					**C2 (W4/Day 30**	**C3 (W8)**			
Visit Number:	**2**					**3**	**7**					**8**	**9**			Each cycle consists of 4weeks (28 calendar days)
Time-frame (hours):	**Predose**	**Postdose**					**Predose**	**Postdose**					**Predose**	**Postdose**		
		2	**4**	**6**	**8**	**24**		**2**	**4**	**6**	**8**	**24**		**2**	**4**	**6**
Window (minutes):	**N/A**	**±10**	**±10**	**±10**	**±10**	**±1 hour**	**N/A**	**±10**	**±10**	**±10**	**±10**	**±1 hour**	**N/A**	**±10**	**±10**	**±10**	
Pharmacokinetics/Pharmacodynamics/Biomarkers																	
12-lead ECG	X	X	X	X	X	X	X	X	X	X			X		X		Triplicate 12-lead ECG will be measured and sent for central reading, within approximately 30 minutes prior to PK sample collection predose and +2 hours post-dose.
Blood PK Sample	X	X	X	X	X	X	X	X	X	X			X	X	X	X	Central laboratory.
Blood for Serum Biomarker Analyses	X	X	X	X	X	X	X	X	X	X			X	X	X	X	Central laboratory.

Abbreviations: C=cycle; ECG=electrocardiogram; N/A=not applicable; PK=pharmacokinetic.

1.3.2 Cohort Expansion (Part 2)

Table 3 Schedule of Assessments for Part 2: Screening and Treatment (Cohorts A to I)

Study Period:	**Screening**	**Treatment**									**Notes**
		C1/D1 (W0)	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	
Visit Number/Frequency:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Every cycle**	**Every 3 cycles (Q12W)**	Each cycle consists of 4weeks (28 calendar days).
Window (days):	**-28 to 1**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Administrative Procedures											
Informed Consent	X										Informed consent must be obtained prior to any protocol-specific procedures.
Informed Consent for Future Biomedical Research	X										
Inclusion/Exclusion Criteria	X										
Participant Identification Card	X	X									At Visit 2, site personnel should add the allocation number to the participant ID card.
Demography and Medical History	X										Data collection should follow local regulations where applicable.
Prior /Concomitant Medication	X	X	X	X	X	X	X	X	X	X	
MK-1026 Dispensing		X	X	X	X	X	X	X	X	X	MK-1026 tablets will be administered QD by mouth under fasted condition (either 1 hour prior to, or 2 hours after the meal). Participants should be instructed NOT to take their dose of MK-1026 on study visit days.
MK-1026 Return Compliance			X	X	X	X	X	X	X	X	
Disease Sample Collection											
Archival or Newly obtained tissue collection (Cohorts A to H)	X										Tissue collection should only be performed once all other eligibility criteria has been collected and reviewed <60 days relative to the date of submission to central laboratory. A lymph node sample is required. If a lymph node sample is considered medically unsafe to perform other appropriate tissue may be submitted (eg, bone marrow).

Study Period:	**Screening**	**Treatment**									**Notes**
		C1/D1 (W0)	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	
Visit Number/Frequency:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Every cycle**	**Every 3 cycles (Q12W)**	Each cycle consists of 4weeks (28 calendar days).
Window (days):	**-28 to 1**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Efficacy Assessments											
Treatment Response Assessments:	(See cohort requirements below) (±7 day window for scans)										Imaging and treatment response assessments are required every 12 weeks and should follow calendar days from C1D1. If dosing is delayed treatment response assessments should continue as scheduled. Unscheduled imaging can be performed as clinically indicated.
Cohorts A to C	X	◄----------Q12W----------►									Using IWCLL 2018 criteria (Appendix 10) assessed by ICR and investigator Assessments to include symptoms, biomarker/cytogenetics, staging, PE, blood sample, CT, bone marrow aspirate + biopsy at screening and in the event of CR, as defined in Section 8.2.1.1.
MRD (Cohorts A to C who achieve a CR only)		◄----------Q12W only when participant achieves CR----------►									MRD to be obtained Q12W from CR confirmation until progression. Local testing is acceptable.
Cohorts D to G	X	◄----------Q12W----------►									Using Lugano 2014 criteria assessed by ICR and investigator. Cheson 2007 criteria assessed by ICR (Appendix 10). Assessments to include disease burden and symptoms, staging, PET-CT, PE, bone marrow aspirate + biopsy at screening and in the event of CR as defined in Section 8.2.1.2. No further PET scans are required for lymphomas which are not FDG-avid at baseline, unless clinically indicated. For FDG-avid lymphomas, PET is required at baseline, weeks 12 and 24, to confirm CR or as clinically indicated.
Cohort H	X	◄----------Q12W----------►									IWWM 2014 criteria (Appendix 10) assessed by ICR and investigator. Assessments will include pathognomonic symptoms, IgM, CT, PE and bone marrow aspirate/trephine in the event of CR as defined in

Study Period:	**Screening**	**Treatment**									**Notes**
		C1/D1 (W0)	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	Each cycle consists of 4weeks (28 calendar days).
Visit Number/Frequency:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Every cycle**	**Every 3 cycles (Q12W)**	
Window (days):	**-28 to 1**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
											Section 8.2.1.3.
Cohort I	X	Q12W									cGVHD 2015 criteria (Appendix 10) assessed by investigator. Assessments to include GVHD core specific measures as defined in Section 8.2.1.4.
Cryoglobulins (WM participants only)	X	Q12W									To be performed at each response assessment visit and if clinically indicated.
Assessment of B Symptoms	X	Q12W									
EORTC QLQ-C30		X	X	X	X	X	X	X	Q4W for Cycles 8 (Wk28), 9 (Wk32), 10 (Wk36), 11 (Wk40), 12 (Wk44), & 13 (Wk48) Q12W for Cycles 16 (Wk60), 19 (Wk72), 22 (Wk84), 25 (Wk96), 28 (Wk108)	Q24W for remaining cycles (eg, Cycles 34 (Wk132), 40 (Wk156), 46 (Wk180), 52 (Wk 228) etc)	PROs should be performed at the scheduled study visit until treatment discontinuation. PROs are to be administered by trained study personnel and completed electronically by participants. PROs should be completed prior to all other study procedures and receiving results of any tests (including disease status). PROs should be administered in the following order: EORTC QLQ-C30 and EQ-5D-5L.
EQ-5D-5L		X	X	X	X	X	X	X			
Safety Assessments											
Full Physical Examination	X										For Cohorts A to H physical examination must include liver and/or spleen size. Other system-based examinations should be included if clinically indicated.
Directed Physical Examination		X	X	X	X	X	X	X	X	X	Review of new clinically significant abnormal findings. Neurological/skin examinations should be included if clinically indicated.

Study Period:	**Screening**	**Treatment**									**Notes**
		C1/D1 (W0)	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	Each cycle consists of 4weeks (28 calendar days).
Visit Number/Frequency:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Every cycle**	**Every 3 cycles (Q12W)**	
Window (days):	**-28 to 1**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	To be performed at each cycle.
ECOG PS	X	X	X	X	X	X	X	X	X	X	Screening assessment to be performed within 7 days of treatment allocation.
Vital Signs	X	X	X	X	X	X	X	X	X	X	Temperature, respiration rate, pulse, and blood pressure.
12-lead ECG	X	See Table 4									After Cycle 3, ECG is only required where clinically indicated. Triplicate 12-lead ECG will be measured and sent for central reading for Cohorts B and C only.
AE/SAE review		X	X	X	X	X	X	X	X	X	Record all AEs occurring within 30 days after last dose of trial treatment. After 30 days, record all SAEs occurring up to 90 days after last dose of trial treatment or 30 days following last dose if the subject initiates new anticancer therapy, whichever comes first. Any treatment related SAEs must be reported regardless of time they occur.
Laboratory Procedures											Local laboratories.
Hematology, Serum Chemistry	X	X	X	X	X	X	X	X	X	X	Screening samples must be taken within 7 days of allocation. See Appendix 2 for parameters.
Urinalysis	X										Post screening sample only required if clinically indicated.
Pregnancy Test (WOCBP only)	X	X	X	X	X	X	X	X	X	X	WOCBP require negative test prior to allocation. If more than 72 hours have elapsed prior to first dose of study intervention, another pregnancy test is required prior to starting study intervention. Pregnancy tests should be performed at every study visit as per local regulations.
B2 Microglobulin	X	X	X	X	X	X	X	X	X	X	
Serum Immunoglobulin (Cohorts A to H only)	X	X	X	X	X	X	X	X	X	X	

Study Period:	**Screening**	**Treatment**									**Notes**
		C1/D1 (W0)	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	
Visit Number/Frequency:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Every cycle**	**Every 3 cycles (Q12W)**	Each cycle consists of 4weeks (28 calendar days).
Window (days):	**-28 to 1**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Infection Testing (HCV, HBV, HIV)	X	Cohorts A to E, G, H, and I – HBV monitoring as per Notes column Cohort F only – HBV monitoring as per Notes column									Cohorts A to E, G, H, and I – HCV and HBV positive participants are excluded. If participant has history of HBV then monitoring is required Q12W. Cohort F – the following participants can be included: a) past or ongoing HCV infection. Treated participants must have completed their treatment at least 1 month prior to starting study intervention. Untreated or incompletely treated HCV participants may initiate anti-viral therapy for HCV if liver function remains stable for at least 3 months on study intervention. b) controlled HBV, as long as they meet the following criteria: i. Participants with chronic HBV infection, defined as HBsAg positive and/or detectable HBV DNA, must be given antiviral therapy for HBV for at least 4 weeks prior to the first dose of study intervention and HBV viral load must be less than 100 IU/mL prior to first dose of study treatment. Participants on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study intervention. Antiviral therapy after completion of study intervention should follow local guidelines. ii. Participants with clinically resolved HBV infection, defined as HBsAg negative and anti-HBc positive, and who have an undetectable HBV viral load at screening should be checked Q6W for HBV viral load and treated for HBV if viral load is over 100 IU/mL. Antiviral therapy after completion of study intervention should follow local guidelines. All cohorts - testing not required unless mandated

Study Period:	**Screening**	**Treatment**									**Notes**
		C1/D1 (W0)	**C2/D1 (W4)**	**C3/D1 (W8)**	**C4/D1 (W12)**	**C5/D1 (W16)**	**C6/D1 (W20)**	**C7/D1 (W24)**	**C8/D1 - C27/D1 (W28 – W104)**	**C28/D1+ (W108+)**	
Visit Number/Frequency:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Every cycle**	**Every 3 cycles (Q12W)**	Each cycle consists of 4weeks (28 calendar days).
Window (days):	**-28 to 1**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
											by local health authority. HIV as per local regulations. Refer to Appendix 7 for country-specific testing requirements.
Pharmacokinetics/Pharmacodynamics/Biomarkers											Central laboratories.
Blood PK Sample		See Table 4									
Blood for TBNK (Cohorts A to C)		X	Q12W ◄----------►								C1D1 sample required. Sample collection should coincide with disease response assessments (±7 days), when blood samples are collected.
Blood for Genetic Analysis (Cohorts A to H)		X									Predose sample required. See Section 8.8.
Blood for Genomic Mutational Analysis (Cohorts A to C)		X	Q12W ◄----------►								C1D1 sample required. Sample collection should coincide with disease response assessments (±7 days), when blood samples are collected.
Blood for ctDNA Analysis (Cohorts A to H)		X	X	X	X	Q12W ◄----------►					Predose samples required Post C4/D1 (W12) sample collection should be Q12W. ctDNA samples should coincide with disease response assessments when blood samples are collected.
Blood for Serum Biomarker Analyses		See Table 4									
Blood for RNA analysis (Cohort I only)		X	X			X					To be collected at predose on C1D1, C2D1 and C5D1.
Blood for immunophenotyping (Cohort I only)		X			X						To be collected at predose on C1D1 and anytime on C4D1.

Abbreviations: AE=adverse event; CT=computer tomography; ctDNA=circulating tumor deoxyribonucleic acid; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; EORTC=European Organization for Research and Treatment of Cancer; EOT=end of treatment; ICR=independent central review; ID=identification; IWCLL=International Workshop on Chronic Lymphocytic Leukemia; MRD=minimal residual disease; PK=pharmacokinetics; Q4W=every 4 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; RNA=ribonucleic acid; SAE=serious AE; TBNK=T and B lymphocyte and natural killer cell profile; W=Week; WOCBP=women of child-bearing potential.

Table 4 Schedule of Assessments: Pharmacokinetic and Biomarker Samples (Cycles 1 to 3)

Study Period	**Treatment**												**Notes**
	C1/D1 (W0)				**C2/D1 (W4)**				**C3/D1 (W8)**				
Visit Number:	**2**				**3**				**4**				
Time-frame (hours):	**Predose**	**Postdose**			**Predose**	**Postdose**			**Predose**	**Postdose**			Each cycle consists of 4weeks (28 calendar days).
		2	**4**	**6**		**2**	**4**	**6**		**2**	**4**	**6**	
Window (minutes):	**N/A**	**±10**	**±10**	**±10**	**N/A**	**±10**	**±10**	**±10**	**N/A**	**±10**	**±10**	**±10**	
Pharmacokinetics/Pharmacodynamics/Biomarkers													
12-lead ECG (Cohort B and C only)	X	X	X	X	X	X	X	X	X		X		Triplicate 12-lead ECG will be collected and sent for central reading, within approximately 30 minutes prior to PK sample collection predose and +2 hours post-dose.
Blood PK Sample	X	X	X	X	X	X	X	X	X	X	X	X	Central laboratory.
Blood for Serum Biomarker Analyses	X	X	X	X	X	X	X	X	X	X	X	X	Central laboratory.

Abbreviations: C=cycle; ECG=electrocardiogram; N/A=not applicable; PK=pharmacokinetic.

1.3.3 Assessments for both Parts 1 and 2

Table 5 Schedule of Assessments: Follow-up (All Participants)

Study Period:	**Follow-up**				**Notes**
	End of Intervention	**Safety FU**	**FU**	**Survival FU**	Safety FU visits can be at clinic or telephone visit.
Visit Number:	**At treatment discontinuation**	**30 Days Post discontinuation**	**Every 12 weeks**	**Every 12 weeks**	
Window (days):		**±3**	**N/A**	**±14**	
Disease Sample Collection					
Optional newly obtained tissue collection (Cohorts A to H)	X				Participants may provide an additional biopsy at end of treatment.
Efficacy Assessments					
Treatment Response Assessments:	(See cohort requirements below) (±7-day window)				FU=For participants withdrawn from study intervention, without disease progression, disease response assessments are required Q12W.
Cohorts A to C	X		X		Using IWCLL 2018 criteria (Appendix 10) assessed by ICR and investigator Assessments to include PE, blood sample, CT, bone marrow/aspirate as defined in Section 8.2.1.1.
MRD (Cohorts A to C who achieve a CR only)	Only when participant achieves CR (Q12W post CR)				MRD to be obtained Q12W from CR confirmation until progression. Local testing is acceptable.
Cohorts D to G	X		X		Using Lugano 2014 criteria assessed by ICR and investigator and Cheson 2007 criteria assessed by ICR (Appendix 10). Assessments to include PET-CT/CT and PE as defined in Section 8.2.1.2.
Cohort H	X		X		IWWM 2014 criteria (Appendix 10) assessed by ICR and investigator. Assessments will include IgM, CT, PE and bone marrow aspirate/trephine sample as defined in Section 8.2.1.3.
Cohort I	X		X		cGVHD 2015 criteria (Appendix 10) assessed by investigator. Assessments to include signs and symptoms, symptom and global scale as defined in Section 8.2.1.4.
Cryoglobulins (WM participants only)	X		X		
Assessment of B Symptoms	X		X		
EORTC QLQ-C30	X	X			PROs are to be administered by trained study personnel and completed electronically by participants. PROs should be completed prior to all other study procedures and receiving results of any tests (including disease status). PROs should be administered in the following order: EORTC QLQ-C30 and
EQ-5D-5L	X	X			

Study Period:	**Follow-up**				**Notes**
	End of Intervention	**Safety FU**	**FU**	**Survival FU**	
Visit Number:	**At treatment discontinuation**	**30 Days Post discontinuation**	**Every 12 weeks**	**Every 12 weeks**	Safety FU visits can be at clinic or telephone visit.
Window (days):		**±3**	**N/A**	**±14**	
					EQ-5D-5L.
Survival FU				X	After investigator determined PD or the start of new anticancer treatment. In addition, upon sponsor request, participants may be contacted for survival status at any time during the course of the study.
Safety Assessments					
ECG	X				Triplicate 12-lead ECG will be required for Part 1 participants and Cohorts B and C of Part 2, and will be collected and sent for central reading.
Full Physical Examination	X				For Cohorts A to H include liver and/or spleen size. Other system-based examinations should be included if clinically indicated.
AE/SAE review	X	X			Record all AEs occurring within 30 days after last dose of trial treatment. After 30 days, record all SAEs occurring up to 90 days after last dose of trial treatment or 30 days following last dose if the subject initiates new anticancer therapy, whichever comes first. Any treatment related SAEs must be reported regardless of time they occur.
Concomitant Medication	X				
Pharmacokinetics/Pharmacodynamics/Biomarkers					
Blood for Genomic Mutational Analysis (CLL/SLL participants and those in Cohorts A to C)	X				
Blood for RNA analysis (Cohort I only)	X				
Blood for ctDNA Analysis (All participants – excluding cGVHD)	X		X		ctDNA samples should coincide with disease response assessments when blood samples are collected.

Abbreviations: AE=adverse event; cGVDH=chronic graft versus host disease; CT=computer tomography; ECG=electrocardiogram; EOI=end of intervention; EORTC=European Organization for Research and Treatment of Cancer; FU=follow-up; ICR=independent central review; ID=identification; IgM=immunoglobulin M; IWCLL=International Workshop on Chronic Lymphocytic Leukemia; IWWM=International Workshop on Waldentrom's Macroglobulinemia; MRD=minimal residual disease; PD=progressive disease; PET=positron emission tomography; RNA=ribonucleic acid; SAE=serious adverse event.

2 INTRODUCTION

This Phase 2 open-label, dose escalation and confirmation followed by a single group parallel study to evaluate the safety and efficacy of the BTK inhibitor MK-1026 (formerly ARQ 531) in participants with transplant-associated cGVHD and hematologic malignancies of CLL/SLL, Richter's transformation, MZL, MCL, FL, and WM.

BTK is a key regulator of the B-cell receptor signaling pathway that mediates signaling from the cell surface to the cytoplasm and into the nucleus. BTK is expressed in the cells of all hematopoietic lineages except for T and plasma cells, and regulates all aspects of B-cell development, including proliferation, maturation, differentiation, apoptosis, and cell migration. B cells (including host-reactive) also play a critical role in the pathogenesis of cGVHD. Activation of the B-cell BTK signaling pathway regulates B-cell survival providing rationale for use of a BTKi {05HPXL}.

2.1 Study Rationale

The purpose of this study is to evaluate the efficacy and safety of MK-1026, an orally available reversible non-covalent ATP competitive inhibitor of BTK, in participants at least 18 years of age who have hematologic malignancies or transplant-associated cGVHD. BTK is a critical signaling molecule in the B-cell receptor signaling pathway and functions via the activation of pathways mediating B-cell growth, adhesion, survival, and pathogenesis of cGVHD.

2.1.1 Rationale for MK-1026

ARQ 531-101 is an ongoing open-label, single arm, Phase 1/2 dose escalation study of MK-1026 (formerly ARQ 531) in selected participants with relapsed or refractory hematologic malignancies. The primary objectives of that study are to assess the safety and tolerability of MK-1026 and to determine the RP2D and dosing schedule. Secondary objectives are to establish PK and pharmacodynamic profiles of MK-1026 at the RP2D, and to evaluate preliminary evidence of antitumor activity. As of the 07-APR-2020 cutoff date, 80 participants have been enrolled and 73 have received treatment: 41 (56%) with CLL/SLL and 25 (34%) with B-cell NHL, 5 (7%) with tumor type unavailable at time of data cutoff date, and single participants with WM and other tumor types. Clinical responses including 17 PRs have been observed across multiple B-cell malignancies, mainly in the higher dose cohorts. These included participants with CLL (n = 9), Richter’s transformation (n = 3), DLBCL (n = 1) and FL (n = 1). One CLL participant had SD at a dose of 45 mg QD and achieved a PR after a dose increase to 65 mg QD. Ten additional participants experienced SD with tumor reduction of between 0 to 48%. Thirteen participants who are being treated with MK-1026 at ≥45 mg QD remain on the study, and 3 additional Richter’s transformation participants have proceeded to CAR-T therapy. Across all disease subsets, MK-1026 showed a low incidence of associated toxicities with 1 DLT of Grade 3 rash. These preliminary results demonstrate encouraging antitumor activity of MK-1026 in selected participants with multiple B-cell malignancies, and thus support the ongoing clinical investigation of MK-1026 in this Phase 2 study.

A more comprehensive review of nonclinical and clinical data is included in the IB.

The preliminary results from ARQ 531-101 suggest that MK-1026 is well-tolerated at 65 mg QD and has a manageable safety profile in multiple B-cell malignancies. The highest dose tested in the ARQ 531-101 study is 75 mg QD and no MTD was established. Robust anti-tumor activity has been observed at a dose of 65 mg QD in heavily pretreated participants; however, preliminary analysis of safety and PK data from ARQ 531-101 suggests that data at 75 mg is limited to conclude differences in AE profile between the 65 mg and 75 mg dose cohorts. Exploring doses higher may maximize the efficacy potential of MK-1026 due to higher PK exposures, while simultaneously establishing the safety profile for MK-1026. Therefore, this study (MK-1026-003) will explore higher doses of 80 mg QD, 100 mg QD, and 120 mg QD in the dose escalation and confirmation (Part 1) to establish the RP2D of MK-1026 in the cohort expansion (Part 2).

2.2 Background

This study includes participants with a variety of hematologic malignancies as defined in Cohorts A to I in Section 4.1. These hematologic malignancies were selected because each represents a significant unmet medical need, and there is preliminary evidence of activity with BTK inhibitors in these malignancies.

2.2.1 B-cell Malignancies

CLL is the most common type of leukemia in western countries. CLL is characterized by the clonal proliferation and accumulation of mature, typically CD5-positive B-cells within the blood, bone marrow, lymph nodes and spleen. Deletions of the short arm of chromosome 17 (17p) are found in 5% to 8% of treatment-naïve patients. These deletions almost always include the prominent tumor suppressor gene *TP53*, and these patients show marked resistance to chemotherapies.

MCL is a distinct subtype of NHL, accounting for 10% of lymphoma cases. Patients usually present with extensive disease, including widespread lymphadenopathy and bone marrow involvement. MCL is not curable, and relapse is common. Existing chemotherapeutic regimens can cause myelosuppression; therefore, there is an unmet medical need for effective therapies {05HPXT}.

MZLs consist of a diverse family of malignancies, which are derived from B-cells. MZL originates from memory B lymphocytes harbored in the marginal zone of secondary lymphoid follicles present in the spleen, mucosa-associated lymphoid tissues, and rarely lymph nodes. The development of MZL is associated with chronic BCR activation in most cases, which has implications for BTK inhibition {05HPJ4}.

FL is the second most common NHL, comprising 17% to 22% of cases. Most patients are initially treated with chemoimmunotherapy or rituximab; however, despite good initial responses, FL is incurable in most patients with poor outcomes including relapse and resistant disease. Data suggests that the tumor microenvironment may contribute to the

development and progression of FL, and the interaction of FL cells with immune cells in the tumor may influence the clinical course and response to therapy {05HPHH}. This Phase 2 study will enroll participants with histology grade 1, 2, and 3A FL.

Richter's transformation is a life-threatening complication of CLL and represents a unique biological entity with defined mutational events that are both present in the preceding CLL clone, or are acquired at time of transformation. The development of Richter's transformation is characterized by the onset of B symptoms, rapid growth of lymphadenopathy, extra-nodal disease, significant elevations of LDH, and associated multiorgan dysfunction from invasive or obstructive processes {05DVRD}. Most cases represent transformation to DLBCL and are historically chemorefractory. Current monotherapy approaches with novel agents have done little to impact upon outcomes.

WM is a rare form of B-cell lymphoma that is characterized by elevated serum levels of IgM and infiltration of the bone marrow and other organs by IgM-producing clonal lymphoplasmacytic cells. Rituximab monotherapy and rituximab in combination with alkylating agents, proteasome inhibitors, nucleoside analogues, and more recently ibrutinib are frequently used in these patients {05HPXZ}. In WM, tumor-cell survival is influenced through BTK-triggered activation of NF-κB.

2.2.2 Chronic GVHD

cGVHD is a serious and life-threatening complication of allogeneic hematopoietic stem cell transplantation affecting 30% to 70% of patients. It is a leading cause of late non-relapse mortality for transplant patients, also contributing to morbidity and a decrease in quality of life. Corticosteroids are the standard frontline treatment and are typically administered for a median of 2 to 3 years, leading to substantial morbidity. An effort to decrease corticosteroid doses has led to their use in combination with other immunosuppressants, such as cyclosporine, tacrolimus, and sirolimus, in frontline or second-line settings, despite a lack of clinical evidence supporting additional efficacy after combining these agents with corticosteroids. Patients who have persistent cGVHD after frontline therapy have a 2.5 times increased risk of non-relapse mortality. Both B and T cells play critical roles in the pathogenesis of cGVHD; a lower incidence of cGVHD after in vivo T-cell depletion confirms T-cell involvement and host-reactive B cells are also associated with the development of cGVHD. As result of clinical evidence submitted, the FDA approved ibrutinib for the treatment of adult patients with cGVHD following the failure of 1 or more lines of systemic therapy {05HPXL}.

2.2.3 Pharmaceutical and Therapeutic Background

This study includes the evaluation of MK-1026 as monotherapy.

2.2.3.1 Pharmacology

MK-1026 is a reversible non-covalent ATP competitive inhibitor of BTK that does not require the C481 residue of BTK for binding and inhibition of kinase activity. Although a

number of BTK inhibitors eg, ibrutinib are currently approved for the treatment of several lymphoproliferative malignancies, resistance to these therapies is known to develop {05F7QW}. One mechanism of resistance is the development of a mutations at the C481 residue of BTK. Since MK-1026 does not require this residue for binding and inhibition of activity, it can target both the wild-type and C481 mutant forms of BTK and therefore offers a potential treatment for ibrutinib resistant B cell malignancies in patients who harbor the BTK-C481 mutation. Studies to date have not revealed any safety pharmacology issues with MK-1026 treatment in vitro or in vivo. Refer to the IB for additional information.

2.2.3.2 Preclinical Studies

To date, MK-1026 has demonstrated a manageable safety profile, long PK half-life, and preliminary anti-tumor activity in both BTK-C481 mutant CLL and NHL patients. A comprehensive review of nonclinical data is included in the IB.

Nonclinical Pharmacology Studies

The pharmacological activity of MK-1026 has been studied in both in vitro and in vivo models. MK-1026 is a potent inhibitor of BTK and does not require C481 residue for binding to BTK. MK-1026 has displayed distinct kinase selectivity profile, showing specificity for additional kinases that are oncogenic drivers in B-cell malignancies. In vitro treatment of patient derived CLL cells with MK-1026 decreased BTK-mediated functions including BCR signaling, viability, migration, CD40 and CD86 expression, and NF-κB gene transcription. In vivo, MK-1026 was found to increase survival over ibrutinib in a murine Eμ-TCL1 engraftment model of CLL and a murine Eμ-MYC/TCL1 engraftment model resembling Richter's transformation. Additionally, MK-1026 inhibited CLL cell survival and suppressed BCR-mediated activation of C481S BTK and PLCγ2 mutations which facilitate clinical resistance to ibrutinib. In diffused large DLBCL tumor models, MK-1026 suppressed BCR signaling, downregulated the expression of c-MYC, BCL-6, anti-apoptotic MCL-1 proteins and showed potent anti-tumor activity in the mouse xenograft tumor models of ABC and GCB DLBCL subtypes.

Nonclinical Pharmacokinetic Characteristics and Metabolism of MK-1026

Overall, MK-1026 showed good absolute bioavailability in monkeys (72%) and moderate absolute bioavailability in rats (22%) and dogs (38%). Across all species for which IV PK data are available, MK-1026 showed low clearance (apparent systemic CL = 3.7 mL/hr/kg [rat], 130 mL/hr/kg [dog], 66 mL/hr/kg [monkey]), and moderate distribution (V_{ss} = 857 mL/kg [rat], 1600 mL/kg [dog], and 1140 mL/kg [monkey]). Increases in the MK-1026 dose generally resulted in dose proportional increases in exposure. Upon repeat dosing, MK-1026 generally had an accumulation ratio of less than 2. The half-life following IV administration varied across species with values of 2.9, 9.27, and 13.6 hours in rats, dogs, and monkeys, respectively. Following oral administration, the half-life was approximately 3.3 and 7.05 hours in rats and dogs, respectively, and ranged from 13.4 to 22.7 hours in monkeys. Further details are provided in the IB.

Preliminary in vitro metabolism studies with human expressed CYP450s demonstrated that MK-1026 is not significantly metabolized in vitro by any of the major drug metabolizing CYP450 enzymes, including CYP1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. In addition, MK-1026 was not significantly metabolized in vitro by S9 fractions from rat, dog, monkey, and human livers. These preliminary data suggest that the likelihood of other drugs affecting the exposure of MK-1026 in participants due to CYP450 drug-drug interactions is low. Additionally, MK-1026 was not shown to be a P-glycoprotein substrate but could potentially inhibit P-gp as well as the transport proteins BCRP and BSEP.

MK-1026 did not inhibit CYP1A2 or CYP3A4 (IC_{50} values >100 µM) suggesting MK-1026 could be safely administered with drugs which are CYP1A2 or 3A4 substrates. MK-1026 did show some inhibition of CYP 2C8, 2C9, 2C19, and 2D6 suggesting that caution should be taken when administering MK-1026 with drugs that are metabolized by these CYP450 enzymes. MK-1026 was highly bound to proteins in rat (99.8%), dog (99.9%), monkey (99.8%), and human (99.8%) plasma.

Overall, the PK and ADME properties of MK-1026 did not raise any safety concerns for the planned clinical study.

Nonclinical Toxicology and Safety Pharmacology

The toxicity profile of orally administered MK-1026 in both rats and monkeys was characterized principally by findings in the GI tract, hematopoietic system, and brain (rats only, >MTD only); some of which were secondary to reduced food consumption, weight loss, inflammation, and/or dehydration.

MK-1026 was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and was not phototoxic in an in vitro assay. Respiratory and CNS safety pharmacology studies showed there was no effect of MK-1026 on respiratory or neurological function in rats at single oral dose levels tested. The hERG IC50 of MK-1026 was determined to be greater than 30 µM. In a cardiovascular safety pharmacology study in telemeterized male monkeys, administration of ≥1.5 mg/kg was associated with effects on quantitative cardiovascular telemetry parameters. These changes included increased arterial pressure parameters (systolic, diastolic, and mean arterial pressure; and arterial pulse pressure), decreased heart rate (with secondary increase in QT interval), and decreased QTc interval. In the 14-day and 4-week toxicity studies in monkeys, there were no reported MK-1026 effects on ECGs in monkeys dosed up to 25 mg/kg. Most, if not all, findings in the toxicity and safety pharmacology studies conducted to date appear to be consistent with those expected with small molecule inhibitors of the receptor tyrosine kinase BTK, and further, are consistent with the mechanism of action and pharmacology of these class of inhibitors.

A comprehensive review of nonclinical data is included in the IB.

2.2.3.3 Ongoing Clinical Studies

ARQ 531-101 is an ongoing open-label, single arm, Phase 1/2 dose escalation study of MK-1026 in selected participants with relapsed or refractory hematologic malignancies. The results of this study are summarized in Section 2.1.1 and demonstrate that MK-1026 has a manageable safety profile and preliminary anti-tumor activity in both BTK-C481 mutant CLL and NHL patients.

A total of 80 participants have been enrolled and 73 treated with MK-1026. In this study, MTD was not reached; however, 1 participant experienced a DLT of Grade 3 rash. Thirty eight (52.1%) treated participants have discontinued the study treatment and 35 (47.9%) participants are continuing on treatment.

In this study, MTD was not reached, however, 1 DLT (Grade 3 rash erythematous) was observed at 65 mg QD. Based on safety, PK/PD and efficacy analysis, 65 mg QD was considered as RP2D. Additional eligible participants were enrolled and treated at RP2D in the Phase 1 expansion to further evaluate the safety at RP2D. The Phase 2 part of the study will evaluate the safety and efficacy at RP2D across 8 specified disease cohorts (Cohort A: BTK-C481S mutant CLL, Cohort B: covalent BTKi intolerant, Cohort C: Richter's transformation, Cohort D: FL, Cohort E: MCL, Cohort F: MZL, Cohort G: HGBCL and Cohort H: WM). In addition, a food effect cohort is included to assess the PK before and after food intake with MK-1026 at RP2D. The most common (≥5%) drug-related AEs included neutrophil count decreased (12.3%), nausea and dysgeusia (9.6% each), diarrhea (8.2%), fatigue (6.8%), abdominal pain, arthralgia, rash and hypertension (5.5% each). Drug-related severe (≥Grade 3) AEs occurred in 15 participants; neutrophil count decreased (9.6%), lipase increased, platelet count decreased and rash maculo-papular (2.7% each), febrile neutropenia, stomatitis, cellulitis, blood creatinine increased and rash erythematous (1.4% each). Drug-related AEs which led to treatment discontinuation occurred in 6 (8.2%) participants; drug hypersensitivity, blood creatinine increased, burning sensation, acute kidney injury, rash and rash maculo-papular.

There was one DLT that occurred in a single participant, Grade 3 rash erythematous (reported as a generalized skin rash from head to toe) which was reported as a SAE and drug-related. The participant was dosed with 65 mg QD MK-1026. The AE occurred on Day 10 and was assessed as serious due to hospitalization and being an important medical event by the investigator. Treatment with MK-1026 was temporarily interrupted. On Day 18, the event was resolved. The participant was re-challenged with MK-1026 on Day 22 at a reduced dose of 45 mg QD; however, the rash recurred the participants discontinued MK-1026 treatment the same day. As a result, dose modification recommendations are provided in Section 6.5.2. SUSARs occurred in 5 participants; rash generalized, febrile neutropenia, blood creatinine increased, lipase increased and rash maculo-papular. Refer to the current IB for further details.

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. Current experience with MK-1026 in the clinical setting is summarized in Section 2.2.3.3 and the IB.

The proposed study will enroll participants with hematological malignancies who have relapsed or are refractory to prior therapies. As described in Section 2.2.3, MK-1026 is a non-covalent ATP competitive inhibitor of BTK. Preclinical studies and clinical data (see Section 2.1.1) demonstrate encouraging antitumor activity of MK-1026, which warrants further investigation. Given the high risk of progression of disease and development of resistance to currently available BTKi' s in patients with hematological malignancies, there is an unmet medical need for more effective and tolerable treatment. MK-1026 has been shown to be well-tolerated across various B-cell malignancies.

Additional details regarding specific benefits and risks for participants participating in this clinical study are summarized in the IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Formal hypothesis testing will not be performed in this protocol.

This study will be performed in 2 parts: Dose Escalation and Confirmation (Part 1) and Cohort Expansion (Part 2) in male and female participants at least 18 years of age with various hematological malignancies (Cohorts as defined in Sections 1.2 and 4.1) who have either relapsed following or are refractory to available therapies.

Objectives	Endpoints
Primary	
• Part 1: To determine the safety and tolerability and to establish a recommended Phase 2 dose (RP2D) of MK-1026.	• Dose-limiting toxicity (DLT). • Adverse Event (AE). • Discontinuing study intervention due to an AE.
• Part 2: Cohorts A to C (chronic Lymphocytic Leukemia [CLL]/Small Lymphocytic Leukemia [SLL]): To evaluate the objective response rate (ORR) of MK-1026 per International Workshop on CLL (iwCLL) criteria 2018 as assessed by independent central review (ICR).	• Objective response (OR): complete response (CR), or complete response with incomplete bone marrow recovery (CRi), or partial response (PR).

Objectives	Endpoints
• Part 2: Cohorts D to G (Richter's Transformation [RT], Mantle cell Lymphoma [MCL], Marginal zone Lymphoma [MZL], Follicular Lymphoma [FL]): To evaluate the ORR of MK-1026 per the Lugano criteria 2014 as assessed by ICR.	• OR: CR or PR.
• Part 2: Cohort H (Waldenstrom's Macroglobulinemia [WM]): To evaluate the ORR of MK-1026 per International Workshop on WM (IWWM) 2014 as assessed by ICR.	• OR: CR, very good partial response (VGPR) or PR.
• Part 2: Cohort I (chronic Graft Versus Host Disease [cGVHD]): To evaluate the cGVHD response rate of MK-1026 per cGVHD Consensus Panel 2015 as assessed by investigator review.	• Objective cGVHD response: National Institute of Health (NIH)-defined CR or PR.
Secondary	
• Part 1: To characterize the pharmacokinetic (PK) profile of MK-1026.	• PK parameters including area under the curve (AUC), minimum concentration (C_{min}), and maximum concentration (C_{max}).
• Part 1: To evaluate the ORR and duration of response (DOR) of MK-1026 for CLL/SLL participants per iwCLL criteria 2018 as assessed by ICR.	• OR: CR, CRi, or PR. • DOR, defined as the time from the first documented evidence of at least PR that led to response until disease progression or death due to any cause, whichever occurs first.
• Part 1: To evaluate the ORR and DOR of MK-1026 for lymphoma participants per the Lugano criteria 2014 as assessed by ICR.	• OR: CR or PR. • DOR.
• Part 1: To evaluate the ORR and DOR of MK-1026 for WM participants per IWWM 2014 as assessed by ICR.	• OR: CR, VGPR, or PR. • DOR.
• Part 2: All Cohorts: To determine the safety and tolerability of MK-1026.	• AE. • Discontinuing study intervention due to

Objectives	Endpoints
	an AE.
• Part 2: All Cohorts: To characterize the PK profile of MK-1026.	• PK parameters including AUC, C_{min}, and C_{max}.
• Part 2: Cohorts A to C (CLL/SLL): To evaluate DOR of MK-1026 per iwCLL criteria 2018 as assessed by ICR.	• DOR.
• Part 2: Cohorts D to G: (RT, MCL, MZL, FL): To evaluate the DOR of MK-1026 per the Lugano criteria 2014 as assessed by ICR.	• DOR.
• Part 2: Cohort H (WM): To evaluate the DOR of MK-1026 per IWWM 2014 as assessed by ICR.	• DOR.
• Part 2: Cohort I (cGVHD): To evaluate the durability of response of MK-1026 per cGVHD Consensus Panel 2015 as assessed by investigator.	• Sustained response, defined as NIH-defined CR or PR that was sustained for at least 20 weeks.
Tertiary/Exploratory (Part 2 only)	
• Cohorts A to C (CLL/SLL): To evaluate response category of partial response with lymphocytosis (PRL) of MK-1026 per iwCLL criteria 2018 as assessed by ICR.	• PRL, defined as meeting all criteria for partial response except for lymphocytosis.
• Cohorts D to G (RT, MCL, MZL, FL): To evaluate the ORR of MK-1026 per the Cheson criteria (IWG 2007) as assessed by ICR.	• OR: CR or PR.
• Cohorts H (WM): To evaluate response category of minor response (MR) of MK-1026 per IWWM 2014 as assessed by ICR.	• MR, defined as 25 to 49% reduction in serum IgM levels.
• Cohorts A to C (CLL/SLL): To evaluate minimal residual disease (MRD) and progression-free survival (PFS) of MK-1026 per iwCLL criteria 2018 as assessed by ICR.	• MRD, defined as having undetectable MRD (MRD-neg) remission if they have blood or marrow with less than one CLL cell per 10,000 leukocytes ($<10^4$). • PFS, defined as the time from first dose to the first documented disease progression per cohort-specific criteria

Objectives	Endpoints
	as assessed by ICR, where indicated; or death due to any cause, whichever occurs first.
• Cohorts D to G (RT, MCL, MZL, FL): To evaluate the PFS of MK-1026 per the Lugano Classification 2014 as assessed by ICR.	• PFS.
• Cohort H (WM): To evaluate the PFS of MK-1026 per IWWM 2014 as assessed by ICR.	• PFS.
• All cohorts: To evaluate overall survival (OS) of MK-1026.	• OS, defined as the time from the first dose of study treatment to death due to any cause.
• All cohorts: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-1026.	• Germline genetic variation, genetic (deoxyribonucleic [DNA]) mutations from tumor, tumor and blood ribonucleic acid (RNA) variation, proteomics and immunohistochemistry (IHC), and other blood-derived biomarkers.
• All cohorts: To evaluate changes in health-related quality-of-life assessments from baseline using the Electronic European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (eEORTC QLQ-C30).	• Mean score change from baseline at a predefined timepoint evaluated by EORTC QLQ-C30. o Global Health Status/QoL (Items 29, 30). o Physical functioning (Items 1 through 5). o Fatigue (Items 10, 12, 18).
• All cohorts: To evaluate the use of health services for the purpose of treating participants in this study.	• Health Care Resource Utilization/Medical Care Resource Utilization form.
• All cohorts: To evaluate health status using the EuroQoL (EQ)-5D-5L VAS.	• Mean change from baseline per predefined time point of EQ-5D-5L VAS score.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2 open-label, nonrandomized, dose escalation and confirmation followed by a single group parallel assignment study to evaluate the safety and efficacy of MK-1026 in

approximately 465 participants with various hematological malignancies and cGVHD. The study will be divided into 2 parts; dose escalation and confirmation (Part 1) and cohort expansion (Part 2).

Part 1 consists of dose escalation and confirmation of MK-1026 in CLL/SLL, lymphoma, and WM participants, that aims to establish the RP2D of MK-1026, which will be assessed as a primary objective. The final RP2D for Part 2 (cohort expansion) will be determined using PK and PD endpoints, as well as all available safety data, including DLT rates and the cumulative incidence of late toxicities (ie, toxicities that occur after the DLT observation period) from participants in both parts of the study (including study ARQ 531-101). Following determination of a RP2D, this study will proceed with Part 2 (Section 4.1.1) in 9 expansion cohorts (Cohorts A to I). Participants include those with various hematological malignancies and cGVHD (as described in Section 4.1.1 and Section 4.1.2).

4.1.1 Dose Escalation and Confirmation (Part 1)

Approximately 15 participants (a minimum of 3 to a maximum of 10 participants per dose level) will be enrolled in Part 1. Participants with various hematological malignancies will be enrolled and no minimum number will be required per disease type. Participants will include:

- CLL/SLL,
    - who have are relapsed or refractory to prior therapy with a covalent irreversible BTKi, a BCL2i and a PI3Ki, or
    - who are relapsed or refractory following 1 line of therapy and are BTKi treatment naïve, or
    - with 17p deletion who are relapsed or refractory following at least 1 line of prior therapy
- Richter's transformation who are relapsed or refractory following at least 1 line of prior therapy
- MCL who are relapsed or refractory following at least 2 lines of prior therapies
- MZL (including splenic, nodal and extra nodal MZL) who are relapsed or refractory following at least 2 lines of prior therapies
- FL who are relapsed or refractory following at least 2 lines of prior therapies and are histology grade 1, 2, or 3A
- WM who are relapsed or refractory following at least 1 line of prior therapy, including a covalent irreversible BTKi

The primary endpoints of Part 1 of the study are to evaluate the DLTs, AEs, and AEs resulting in treatment discontinuation with the aim to establish a RP2D of MK-1026 for Part 2. In Part 1 of the study, a mTPI design {03TFYL} will be used to identify and confirm the RP2D of MK-1026. Three predetermined dose levels of MK-1026 will be evaluated:

- Dose level 1 (DL1): 80 mg
- Dose level 2 (DL2): 100 mg
- Dose level 3 (DL3): 120 mg

Dose escalation and de-escalation decisions will be based on the mTPI design and will depend on the number of participants enrolled and the number of DLTs observed at the current dose level as described in Section 4.3.2. The definition of DLTs is provided in Section 4.3.1. A minimum of 3 participants are required for each dose level, with the potential to treat up to a maximum of 10 participants depending on dose decisions. A minimum of 28 days of safety data will be reviewed for those participants treated at that dose level before dosing decisions are made. Data from Part 1 of this study and all phases (including study ARQ 531-101 at 65 mg and lower doses) will be used to determine the final RP2D for Part 2 (cohort expansion). In the event of DLTs requiring de-escalation at dose level 1 (80 mg), Part 1 of this study will be stopped and the dose for Part 2 will be evaluated using 65 mg PO QD.

4.1.2 Cohort Expansion (Part 2)

Approximately 450 participants (a minimum of 30 to a maximum of 100 participants) will be enrolled in Part 2. Participants will be allocated to 1 of the following cohorts:

A. CLL/SLL who are relapsed or refractory to prior therapy with a covalent, irreversible BTKi, a BCL2i, and a PI3Ki.

B. CLL/SLL who are relapsed or refractory following 1 line of prior therapy and are BTKi treatment naïve.

C. CLL with 17p deletion who are relapsed or refractory following at least 1 line of prior therapy.

   Note: Participants with the 17p deletion will be assigned to Cohort C preferentially.

D. Richter's transformation who are relapsed or refractory following at least 1 line of prior therapy.

E. MCL who are relapsed or refractory following at least 2 lines of prior therapies.

F. MZL (including splenic, nodal, and extra nodal MZL) who are relapsed or refractory following at least 2 lines of prior therapies.

G. FL who are relapsed or refractory following at least 2 line of prior therapies and are histology grade 1, 2, or 3A.

H. WM who are relapsed or refractory following at least 1 line of prior therapy including a covalent, irreversible BTKi.

I. cGVHD, who are relapsed or refractory following at least 1 line of prior systemic therapy and a covalent, irreversible BTKi.

Details for each cohort are provided in the Study Schema in Section 1.2.

All cohorts will receive MK-1026 monotherapy.

Potential for cohort expansion to 100 participants will be assessed for each cohort using IAs for efficacy. The IAs will occur after the initial 30 enrolled and treated participants have been followed up for approximately 24 weeks after study entry. For cohorts with slow enrollment, IAs will take place when the majority of participants have been followed up for 24 weeks from study entry. IAs will be performed by ICR (except for Cohort I) and recommendations for cohort expansion will be provided. Each expansion cohort will include a total of 100 participants, 30 from the initial cohort, and an additional 70 participants in the expansion. For cohorts in rare disease indications, eg, WM and Richter's transformation, a total of 50 participants may be considered instead of 100. Further details are provided in Section 9.0. Additional IAs may be conducted to enable future study planning at the Sponsor's discretion.

After signing the informed consent, suitable candidates will be screened to assess they meet all study eligibility criteria. Eligible participants will be assigned to 1 of 9 cohorts (Cohorts A to I), according to the hematologic malignancy/cGVHD and prior therapy received. The study will be conducted in conformance with GCP.

The primary endpoint of Part 2 of the study is OR (cGVHD response for Cohort I), defined as at least PR, assessed by specific response criteria for each hematologic malignancy/cGVHD as defined in Section 3. Secondary endpoints include safety, PK, and DOR.

For both Parts, treatment with MK-1026 monotherapy will continue until unacceptable toxicity, documented progression, or another discontinuation criterion is met (as defined in Section 7.1).

AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE version 5.0. Each participant will be monitored for AEs and SAEs for 30 day and 90 days, respectively, after discontinuation of study intervention.

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

4.2 Scientific Rationale for Study Design

This multicenter, non-randomized open-label, Phase 2 dose escalation and confirmation followed by a single-group parallel assignment study. This study is designed to firstly establish the RP2D and then as a proof-of-concept to assess the efficacy and safety of MK-1026 monotherapy across disease cohorts who have relapsed or are refractory to prior therapies in participants with various hematological malignancies and cGVHD. BTK inhibitors are approved for the treatment of several lymphoproliferative malignancies; however, resistance is known to develop. These hematologic malignancies were selected because each represents a significant unmet medical need and prior BTK inhibitors have shown efficacy in these malignancies.

MK-1026 is a non-covalent irreversible inhibitor of BTK, a critical signaling molecule in the B-cell receptor signaling pathway mediating B-cell growth, adhesion, survival, and pathogenesis of cGVHD. Prior BTK inhibitors such as ibrutinib and acalabrutinib have shown dramatic clinical efficacy and a very tolerable safety profile that have led to multiple accelerated approvals either as monotherapy or combination therapy for the first-line treatment of CLL/SLL. In the CLL/SLL indication, resistance mutations occur in approximately 20% of patients following 4 years of treatment with covalent, irreversible inhibitors (eg, ibrutinib). Initial data with MK-1026 has shown higher response rates in Richters transformation, which is known to be a very aggressive disease transformation from CLL that is without any effective therapies. MK-1026 has the ability to inhibit both the wild-type BTK as well as the BTK mutant population.

Part 1 of the study will test doses up to 120 mg to achieve MK-1026 exposures that maximize efficacy and ensure adequate safety evaluation at each planned dose. A minimum of 3 participants, with the potential to treat up to a maximum of 10 participants depending on dose decisions, are required for each dose level.

The starting sample size for Part 2 of 30 participants per cohort is estimated based on the primary endpoint and the required target ORR to produce a confidence interval for the true ORR. A cohort which achieves its target ORR may be expanded to a total of 100 participants. In expanded cohorts that achieve target ORR (exceeding historical ORR/current therapies), the sample size could support the regulatory approval of MK-1026 monotherapy in participants of these expanded cohorts.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Endpoint definitions are provided in Section 9.4.1.

Primary Efficacy Endpoints

Part 2

The primary efficacy objective of Part 2 of the study is to evaluate the ORR (for Cohorts A to H) and cGVHD response rate for Cohort I of MK-1026. Treatment effect measured by ORR can represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, number of CRs, durability of response, disease setting, location of the tumors, available therapy, and risk-benefit relationship. Treatment effect measured by ORR can be a surrogate endpoint to support accelerated approval according to FDA guidance (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry, Dec 2018).

Each hematological malignancy and GVHD has specific response criteria developed by experts that will be applied in the assessment of ORR (for Cohorts A to H) and cGVHD response rate (for Cohort I) as summarized in Section 3.

Secondary Efficacy Endpoints

Part 1

The secondary efficacy objectives of Part 1 of this study are to characterize the PK profile of MK-1026, and to evaluate ORR and DOR in participants with CLL/SLL, lymphoma, and WM. Treatment effect measured by ORR can be a surrogate endpoint to support accelerated approval according to FDA guidance. Improved DOR can result in a meaningful delay in disease progression as opposed to a temporary response without lasting benefit.

Part 2

The secondary efficacy objective of Part 2 of this study is the evaluation of DOR of MK-1026 in each cohort. Improved DOR can result in a meaningful delay in disease progression as opposed to a temporary response without lasting benefit.

Exploratory Efficacy Endpoints (Part 2 only)

Exploratory efficacy objectives for this study include evaluation of PRL (Cohorts A to C only), ORR (Cohorts D to G only), MR (Cohort H only), MRD (Cohorts A to C only), PFS, and OS of MK-1026 in each of the cohorts. OS represents a precise and reliable measure of time to event endpoint. PFS is a surrogate endpoint that reflects tumor growth and includes deaths and therefore correlates to OS. MRD is a surrogate endpoint for CLL and correlates with improved OS and PFS. PRL represents a reduction in lymph nodes, splenomegaly and other markers of response with no sign of progression other than lymphocytosis, and has been used in other BTKi studies,

4.2.1.2 Safety Endpoints

In support of the primary objectives (Part 1) of safety, tolerability, and establishment of RP2D of MK-1026 for Part 2, and secondary objectives (Part 2) to evaluate the safety and tolerability profile of the RP2D of MK-1026 monotherapy, the safety and tolerability endpoints will be assessed by clinical evaluation of AEs and inspection of other study parameters including vital signs, physical examination, and laboratory safety tests at time points specified in the SoA. AEs are graded and recorded according to Section 8.4 and Appendix 3.

4.2.1.3 Patient-reported Outcomes

In support of the exploratory objective to evaluate changes in patient-reported outcomes from baseline, the EORTC QLQ-C30 and EQ-5D-5L questionnaires will be used. These patient-reported assessments are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3.1 EORTC QLQ-C30

EORTC QLQ-C30 is the most widely used cancer-specific, health-related, QoL instrument. It contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact). It is scored on a 4-point scale (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much). The EORTC QLQ-C30 instrument also contains 2 global scales that use 7-point scale scoring with anchors (1 = very poor and 7 = excellent). The EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing QoL in oncology studies. It has been translated and validated into over 100 languages and is used in more than 3,000 studies worldwide.

4.2.1.3.2 EuroQoL EQ-5D

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses. The 5 health state dimensions in the EQ-5D-5L include the following: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1

(no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability.

4.2.1.4 Pharmacokinetic Endpoints

In support of the secondary objective to characterize the PK profile of MK-1026 monotherapy, the PK endpoints will include AUC, C_{min}, and C_{max}.

4.2.1.5 Pharmacodynamic Endpoints

In support of the exploratory objective to identify molecular biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-1026, germline genetic variation, genetic variation, proteomics and IHC, and other blood-derived biomarkers will be evaluated.

4.2.1.6 Planned Exploratory Biomarker Research

Molecularly targeted therapies represent an important class of anti-tumor agents. The efficacy of these novel therapies relies heavily on abundance and maintenance of the target molecule. Several clinical examples exist of patients who have failed this class of compounds due to emergence of mutations within the target protein that render the drug no longer effective {046QNR; 0402V5; 05F7QR}. Monitoring of these resistance mechanisms is critical in the evaluation of drug efficacy. Collection of biospecimens (eg, blood components, tumor material) may be conducted in order to not only evaluate the emergence of any resistance mechanisms, but also to evaluate any correlates of response to single-agent or combination therapy. These assessments 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 in order to interpret tumor-specific DNA mutations.

Genetic (DNA) analyses from tumor/tumor cells

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (i.e. mutations, methylation status, microsatellite instability). 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 in order to understand tumor-

specific mutations, it is necessary to compare the tumor genome with the germline genome. Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

In addition to next-generation sequencing approaches, cytogenetic analysis of tumor tissue or leukemic B cells may be utilized to understand important genomic changes (translocations, deletions, and rearrangements) and their correlation to treatment. Cytogenetic testing is commonly used in treatment decisions for B cell malignancies.

Tumor and blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue, leukemic B cells and in blood may be performed to define gene expression or genomic translocations, rearrangements, and deletions that correlate to clinical response to treatment. These types of genomic alterations have been shown in some studies of B cell malignancies to correlate to overall survival and have been further evaluated in the context of disease prognosis. Understanding of these genomic alterations and gene expression patterns will help to evaluate their prognostic utility in the context of this treatment, as well as determine novel prognostic markers that could emerge in this study.

Other blood-derived biomarkers

In addition to genomic based markers, circulating chemokines and cytokines can help elucidate the pharmacodynamic response and its relation to drug pharmacokinetics. Assays such as ELISA measure such proteins in serum and may be utilized to understand the pharmacodynamic response to drug.

Immunophenotyping by flow cytometry may also be utilized to understand important pharmacodynamic changes to patients' immune system during treatment.

4.2.1.7 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

4.2.1.8 Health Economics Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data will be collected regarding all-cause hospitalization and emergency room visits.

4.3 Justification for Dose

Preliminary results from the ongoing study, ARQ 531-101, suggest that MK-1026 is well tolerated at 65 mg QD and has a manageable safety profile in multiple B-cell malignancies. The highest dose tested in the ARQ 531-101 study is 75 mg QD. Robust anti-tumor activity has been observed at a dose of 65 mg QD in heavily pretreated participants with an ORR of with an ORR of 43.5% (10/23 participants) in relapsed or refractory CLL/SLL. However, preliminary analysis of safety and PK data from ARQ-531-101 suggests that data at 75 mg is limited to conclude differences in AE profile between the 65 mg and 75 mg dose cohorts. Exploring doses higher than 65 mg QD is expected to maximize the efficacy potential of MK-1026 due to higher PK exposures, while simultaneously establishing the safety profile for MK-1026. Based on the preliminary results from ARQ-531-101, higher doses of 80 mg QD, 100 mg QD, and 120 mg QD will be explored in dose escalation to establish the RP2D of MK-1026 in participants with B-cell malignancies.

4.3.1 Dose Limiting Toxicity Definition

DLTs will be defined from toxicities observed during the first cycle of the dose escalation phase. The occurrence of any of the following toxicities will be considered a DLT unless the investigator assessment determines the toxicity to be clearly related to the underlying disease:

- Grade ≥3 nonhematologic toxicity with exception of Grade 3 nausea, vomiting, diarrhea, rash, fatigue, and uncontrolled hypertension which will not be considered a DLT unless lasting more than 7 days despite optimal supportive care (not laboratory)
- Grade 4 hematologic toxicity lasting >7 days with the exception of Grade 3 lymphocytosis, which is considered to be an expected outcome of BTK inhibition, OR
    - Grade 4 platelet count decreased of any duration
    - Grade 3 platelet count decreased if associated with bleeding
- Any Grade 3 or Grade 4 nonhematologic laboratory abnormality, if:
    - Values result in DILI, or
    - Medical intervention is required, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week

Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc (see Section 8.4.1).

- Missing >25% of MK-1026 doses as a result of drug-related AE(s) during the first cycle

- Grade 5 toxicity

4.3.2 Dose Finding Using a Modified Toxicity Probability Interval Design

Dose finding will follow the mTPI design {03TFYL} with a target DLT rate of 30%. Dose escalation and de-escalation 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 to a maximum of 10 participants are required per dose level to ensure DLT evaluations are performed as described in Table 6. However, depending on the accrual rate, 3, 4, 5, or 6 participants may be enrolled within 21 days of the opening of a dose cohort. In the event less than 3 participants enrolled within 21 days of the opening enrollment, enrollment will continue until minimum of 3 participants reached. In the event that less than 3 participants are enrolled within 21 days of the opening enrollment, enrollment will continue until a minimum of 3 participants is reached. Regardless of how many participants are enrolled at each dose level, all must complete the DLT period (minimum of 28 days) prior to opening the next dose cohort.

In Table 6, 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, de-escalating the dose, and excluding the dose from the study due to unacceptable toxicity, respectively. For example, if 0 out of 3 participants at a given dose level develop a DLT, then the dose can escalate to the next level. If 2 participants out of 3 develop a DLT, the dose will be de-escalated to the next lower dose level. If 3 out of 3 participants develop a DLT, this indicates an unacceptable toxicity at this dose. The dose should be de-escalated, and the current dose will not be explored further. If 1 out 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. There is no intraparticipant dose escalation for individual participants enrolled in Part 1 of the study.

When adding participants to a dose level in a “stay” decision, the maximum number of participants that can be added is capped in order to minimize exposure to a potentially toxic dose (denoted as DU in Table 6). To determine how many more participants can be enrolled, steps can be counted in the diagonal direction (down and to the right) from the current cell to the one marked DU. For example, if 1/3 participants have experienced a DLT at a given dose level, a maximum of 3 additional participants can be enrolled at this dose level until additional DLT information is available. The dose level is considered unacceptably toxic if all 3 additional participants experience a DLT (ie, 4/6 participants with DLT in Table 6). The same principles apply whether 3, 4, 5, or 6 participants are enrolled at that dose level.

A D or DU decision at the lowest dose level will stop Part 1 of 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 which was not previously defined or studied if evaluation of toxicity at such a dose is desired. If this is the case, 3 to 6 new participants may be enrolled at the new intermediate dose, and the rules should be used for 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 {03FL3C} will be used to estimate the DLT rates across doses. The dose with an estimated DLT rate closest to 30% will be treated as a RP2D. However, the totality of the data will be considered before deciding on the final RP2D dose to carry forward to Part 2 Cohort expansion phase, and the escalation schedule may be adjusted based on PD, PK, and safety data emerging throughout the study.

Note that although 30% was the target toxicity rate used to generate the guidelines in Table 6, the observed rates of participants with DLTs at the MTD may be slightly above or below 30%.

Table 6 Dose-finding Rules per mTPI Design

	Number of Participants Evaluable for DLT at Current Dose							
Number of participants with at least 1 DLT	3	4	5	6	7	8	9	10
0	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E
2	D	S	S	S	S	S	S	S
3	DU	DU	D	S	S	S	S	S
4		DU	DU	DU	D	D	S	S
5			DU	DU	DU	DU	DU	D
6				DU	DU	DU	DU	DU
7					DU	DU	DU	DU
8						DU	DU	DU
9							DU	DU
10								DU
Abbreviations: D=De-escalate to the next lower dose; DLT-dose limiting toxicity; DU=The current dose is								

	Number of Participants Evaluable for DLT at Current Dose							
Number of participants with at least 1 DLT	3	4	5	6	7	8	9	10
unacceptably toxic; E=escalate to the next higher dose; mTPI=modified toxicity probability interval; S=Stay at the current dose. Target toxicity rate=30% Noninformative Beta (1,1) prior is used with ε1=ε2=0.03{03TFYL; 03FL3C; 04WC92}.								

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

Early study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study participants arising from clinical or preclinical studies with the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study. Recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Adult participants with various hematological malignancies/cGVHD will be enrolled in Cohorts A to I (see Section 4.1).

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

The following cohort-specific criteria must be met:

1. Part 1 and Part 2 (Cohorts A to C): confirmed diagnosis of CLL/SLL;

    a) Previous treatment to include;
        i. Cohort A: CLL/SLL participants who are relapsed or refractory to prior therapy with a covalent, irreversible BTKi, BCL2i and PI3Ki.
        ii. Cohort B: CLL/SLL participants who are relapsed or refractory following 1 line of prior therapy and are BTKi treatment naïve.
        iii. Cohort C: CLL/SLL participants with 17p deletion who are relapsed or refractory following at least 1 line of prior therapy.
    b) Active disease for CLL/SLL should be clearly documented to initiate therapy. At least 1 of the following criteria should be met:
        i. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia. Cutoff levels of Hb <10 g/dL or platelet counts <100 x 10^9/L are generally regarded as indication for treatment. However, in some patients, platelet counts <100 x 10^9/L may remain stable over a long period; this situation does not automatically require therapeutic intervention.
        ii. Massive (ie, >+6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
        iii. Massive nodes (ie, ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
        iv. Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or LDT, 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months; participants with initial blood lymphocyte counts ≥30 x 10^9/L may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (eg, infections, steroid administration) should be excluded.
        v. Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.
        vi. Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine).
        vii. Disease-related symptoms as defined by any of the following:
            – Unintentional weight loss ≥10% within the previous 6 months.
            – Significant fatigue (ie, ECOG performance score 2 or worse; cannot work or unable to perform usual activities).
            – Fever of 100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
            – Night sweats for ≥1 month without evidence of infection.

c) Provide an evaluable core or excisional lymph node biopsy for biomarker analysis from an archival (≤60 days relative to the date of sample submission to the central laboratory) or newly obtained biopsy at Screening. If a lymph node sample is considered medically unsafe to perform other appropriate tissue may be submitted (eg, bone marrow). This sample is optional for participants enrolling in Part 1 of the study.

2. Part 1 and Part 2 (Cohorts D to G):

   a) Confirmed diagnosis of and previous treatment to include;
      i. Cohort D: participants with Richter's transformation who are relapsed or refractory following at least 1 line of prior therapy.
      ii. Cohort E: participants with MCL who are relapsed or are refractory following at least 2 lines of prior therapy.
      iii. Cohort F: participants with MZL (including splenic, nodal, and extra nodal MZL) who are relapsed or refractory following at least 2 lines of prior therapy.
      iv. Cohort G: participants with FL who are relapsed or refractory following at least 2 lines of prior therapy and are histology Grade 1, 2, or 3A.
   b) Have measurable disease defined as at least 1 lesion that can be accurately measured in at least 2 dimensions with spiral CT scan. A minimum measurement must be >15 mm in the longest diameter or >10 mm in the short axis.
   c) Provide an evaluable core or excisional lymph node biopsy for biomarker analysis from an archival (≤60 days) or newly obtained biopsy at Screening. If a lymph node sample is considered medically unsafe to perform other appropriate tissue may be submitted (eg, bone marrow).

3. Part 1 and Part 2 (Cohort H): confirmed diagnosis of WM; participants who are relapsed or refractory following at least 1 line of prior therapy and a covalent, irreversible BTKi.

   a) Active disease is defined as 1 of the following:
      i. Systemic symptoms – Fever, drenching night sweats, fatigue, weight loss, and/or severe neuropathy.
      ii. Physical findings – Symptomatic or bulky (≥5 cm) lymphadenopathy, symptomatic hepatomegaly, and/or symptomatic splenomegaly.
      iii. Laboratory abnormalities – Hemoglobin ≤10 g/dL or platelet count <100,000/microL.
      iv. Coexisting disease – Immunoglobulin light chain amyloidosis with organ dysfunction, symptomatic cryoglobulinemia, cold agglutinin anemia, immune hemolytic anemia and/or thrombocytopenia, or nephropathy due to WM.
   b) Have measurable disease, satisfying any of the following: at least 1 lesion that can be accurately measured in at least 2 dimensions with spiral CT scan (minimum measurement must be >15 mm in the longest diameter or >10 mm in the short axis); IgM ≥4500 g/dL; or bone marrow infiltration of 70%.

c) Provide an evaluable core or excisional lymph node biopsy for biomarker analysis from an archival (≤60 days) or newly obtained biopsy at Screening. If a lymph node sample is considered medically unsafe to perform other appropriate tissue may be submitted (eg, bone marrow).

4. Part 2, Cohort I: cGVHD; participants who are relapsed or refractory following at least 1 line of prior systemic therapy and a covalent, irreversible BTKi. Both criteria below must be met:

    a) participants must have steroid-dependent or refractory cGVHD after HSCT;
        i. Steroid dependent disease is defined as cGVHD requiring prednisone ≤0.25 mg/kg per day for ≥12 weeks.
        ii. Refractory disease is defined as progressive cGVHD, despite treatment with prednisone ≥0.5 mg/kg per day for ≥4 weeks.
    b) Subjects must have active cGVHD with either ≥25% body surface area erythematous rash or a NIH mouth score 4.

5. Have an ECOG performance status of 0 to 2 within 7 days prior to allocation.

6. Have a life expectancy of at least 3 months, based on the investigator assessment.

7. Have the ability to swallow and retain oral medication.

8. Cohort F only (MZL):

    a) Participants with past or ongoing HCV infection are eligible for the study. Treated participants must have completed their treatment at least 1 month prior to starting study intervention. Untreated or incompletely treated HCV participants may initiate anti-viral therapy for HCV if liver function remains stable for at least 3 months on study intervention.
    b) Participants with controlled HBV are eligible for the study, as long as they meet the following criteria:
        i. Participants with chronic HBV infection, defined as HBsAg positive and/or detectable HBV DNA, must be given antiviral therapy for HBV for at least 4 weeks prior to the first dose of study intervention and HBV viral load must be less than 100 IU/mL prior to first dose of study treatment. Participants on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study intervention. Antiviral therapy after completion of study intervention should follow local guidelines.
        ii. Participants with clinically resolved HBV infection, defined as HBsAg negative and anti-HBc positive, and who have an undetectable HBV viral load at screening should be checked Q6W for HBV viral load and treated for HBV if viral load is over 100 IU/mL. Antiviral therapy after completion of study intervention should follow local guidelines.

9. Have adequate organ function as defined in Table 7. Specimens must be collected within 7 days prior to the start of study intervention.

Table 7 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥750/µL
Platelets	≥50 000/µL [a]
Hemoglobin	≥8.0 g/dL [b]
Renal	
Creatinine OR Measured or calculated [c] CrCl (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
INR or PT aPTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

Abbreviations: AIHA= autoimmune hemolytic anemia; ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl=Creatinine clearance; GFR=glomerular filtration rate; INR=International normalized ratio; pRBC=packed red blood cell; PT=prothrombin time; ULN=upper limit of normal.

[a] No platelet requirement in participants with significant bone marrow involvement.

[b] Criteria must be stable for 1 week, with the exception of AIHA for CLL/SLL.

[c] CrCl should be calculated per institutional standard.

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

Demographics

10. Is male or female, from 18 years of age inclusive, at the time of signing the informed consent.

Male Participants

11. Male participants are eligible to participate if they agree to the following during the intervention period and for 12 days after the last dose of study intervention:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

- Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

- Male participants must also agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.
- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

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

- Is not a WOCBP
  OR
- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, 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 30 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.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum 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 located in Appendix 2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

13. For women of child-bearing potential and male participants with a non-pregnant female partner of child-bearing potential, willing to use highly effective birth control for the duration of the study and for 30 days following the last dose of study drug (Appendix 5).

Informed Consent

14. Signed written informed consent granted prior to initiation of any study-specific procedures (or legally acceptable representative if applicable), including permitted by the participant future biomedical research. The participant may participate in the main study without participating in future biomedical research.

5.2 Exclusion Criteria

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

Medical Conditions

1. Part 1 and Part 2 (Cohort G): participants with histologic Grade 3B FL.

2. Part 1 and Part 2 (Cohorts A to E, G, H, and I): active HBV/HCV infection. See inclusion criteria 8 for Cohort F (MZL) participants.

3. Has a history of malignancy ≤3 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. For participants in Part 2, Cohort I (cGVHD), prior malignancies requiring treatment with a stem cell transplant will not be excluded.

4. Has known active CNS disease.

5. Has an active infection requiring systemic therapy.

6. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority. Refer to Appendix 7 for country-specific testing requirements.

7. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

8. Has QTc prolongation (defined as a QTcF >450 msecs) or other significant ECG abnormalities including 2nd degree AV block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min).

Prior/Concomitant Therapy

9. Has received prior systemic anti-cancer therapy within 4 weeks prior to allocation.
   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.
   Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study intervention.

10. Is currently being treated with the following drugs:

    a. CYP 2C9 substrates with a narrow therapeutic index (such as warfarin, phenytoin)
    b. CYP 2C8 substrates with a narrow therapeutic index (such as paclitaxel)
    c. CYP 2C19 substrates with a narrow therapeutic index (such as S-mephenytoin)
    d. CYP 2D6 substrates with a narrow therapeutic index (such as thioridazine, pimozide)
    e. P-gp substrates with a narrow therapeutic index (such as digoxin)

    Note: A washout period of at least 5 times the half-life after the last dose of any of the above treatments is required for a subject to be eligible for study enrollment.

Prior/Concurrent Clinical Study Experience

11. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.

    Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

12. Prior exposure to non-covalent, reversible BTK inhibitors.

Diagnostic Assessments

13. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

14. Has any clinically significant gastrointestinal abnormalities that might alter absorption.

5.3 Lifestyle Considerations

No specific lifestyle restrictions are required.

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.

Participants who fail screening may be re-screened for eligibility following consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

5.5.1 Replacement of Participants in Part 1

In order to adequately evaluate the safety of the doses administered in Part 1 of this study, all participants selected must meet the criteria for evaluability in the first cycle. Participants are considered non-evaluable for DLT assessment and will be replaced if:

- They are enrolled but not treated.
- They discontinue from the study prior to completing all the safety evaluations for a reason other than treatment-related AEs (eg, disease progression).
- In the first cycle, they received less than 75% of the total MK-1026 dose and did not experience a DLT.

A minimum of 3 participants per dose level is required. Once this is satisfied, replacement participants are not required. Non-evaluable participants will not be counted toward the total number of participants for DLT evaluation in Part 1.

If a participant experiences a DLT in Part 1, the investigator and sponsor will discuss the case. If the investigator feels the participant is deriving clinical benefit from the study intervention and is deemed clinically stable, the participant may be allowed to continue if agreed by the Sponsor. Participants must meet the following criteria for clinical stability:

- Participants must have adequate organ function as indicated by the laboratory values in Table 7;
- Participants must have no evidence of disease progression; and
- Participants must have an ECOG performance status of 0 or 1.

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 provided by the Sponsor 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 prior to 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 interventions to be used in this study are outlined in Table 8. Participants will be instructed not to take their dose of MK-1026 before their clinic visit on study visit days. MK-1026 should be taken after the clinic visit.

Table 8 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/ NIMP	Sourcing
All cohorts	Experimental	MK-1026	Drug	Tablet	5 mg and 20 mg	80 mg (DL 1)	Oral	Daily	Experimental	IMP	Central
All cohorts	Experimental	MK-1026	Drug	Tablet	5 mg and 20 mg	100 mg (DL 2)	Oral	Daily	Experimental	IMP	Central
All cohorts	Experimental	MK-1026	Drug	Tablet	5 mg and 20 mg	120 mg (DL 3)	Oral	Daily	Experimental	IMP	Central
All cohorts	Experimental	MK-1026	Drug	Tablet	5 mg and 20 mg	65 mg *	Oral	Daily	Experimental	IMP	Central

Abbreviations: DL=dose level; EEA=European Economic Area; IMP=Investigational Medicinal Product.
The classification of IMP 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 may exist. In these circumstances, local legislation is followed.

[a] in the event of sufficient DLTs observed at 80 mg, the 65 mg dose will be used in Part 2.

All supplies indicated in Table 8 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study interventions.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

MK-1026 tablets will be administered QD by mouth under fasting conditions (either 1 hour prior to, or 2 hours after the meal).

For administrative reasons, the treatment period is divided into 4-week cycles (28 days).

6.2.2 Missed or Vomited Doses

A missed or vomited dose should not be replaced. The participant should be instructed to take the next schedule dose. If the participant vomits the first dose of MK-1026, the participant may be re-challenged at the discretion of the investigator.

6.2.3 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

6.3.1.1 Dose Escalation and Confirmation Phase (Part 1)

Participants enrolled in Part 1 of the study will be assigned to the active dose level and will remain unless meeting a dose modification requirement as defined in Section 6.5.2.

6.3.1.2 Cohort Expansion Phase (Part 2)

Participants enrolled in Part 2 of the study, will be assigned to receive study intervention according to their cohort allocation (see Section 4.1).

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

Interruptions from the protocol-specified treatment require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of MK-1026 tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications or vaccinations

specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination 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.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Prohibited Treatment

The following treatments are not allowed during the study:

- Immunosuppressive therapies including continuous high dose corticosteroids (>30 mg prednisone equivalent per day)
- Any concurrent anticancer therapy including, but not limited to, chemotherapy, radiotherapy (except palliative radiotherapy for local pain control), hormonal therapy, immunotherapy, or locoregional therapy.
- Other investigational agents.
- MK-1026 is not significantly metabolized by any of the major drug metabolizing CYP450 enzymes including CYP2C8, 2C9, 2C19, 3A4, 2D6, or 1A2, so the exposure of MK-1026 should be unaffected by other drugs based on CYP450 drug-drug interaction. However, based on in-vitro data, MK-1026 has the potential to inhibit CYP2C8, 2C9, 2C19, and 2D6. MK-1026 is not a substrate of P-gp but has been shown to inhibit P-gp in-vitro. Concomitant medications with the following characteristics are prohibited during the study:

  – CYP 2C9 substrates with a narrow therapeutic index (such as warfarin, phenytoin)
  – CYP 2C8 substrates with a narrow therapeutic index (such as paclitaxel)
  – CYP 2C19 substrates with a narrow therapeutic index (such as S-mephenytoin)
  – CYP 2D6 substrates with a narrow therapeutic index (such as thioridazine, pimozide)
  – P-gp substrates with a narrow therapeutic index (such as digoxin)

A list of example in vivo substrates for specific CYP enzymes and P-gps is provided in Appendix 8.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.5.2 Dose Modification (Escalation/Titration/Other)

Dose modifications are applicable to participants in Part 1 and 2. At the occurrence of an AE, unless unequivocally due to the underlying malignancy or an extraneous cause, dose interruptions and/or reductions in MK-1026 administration are allowed. If dose reduction is indicated, the participants should be assigned to the previous (lower) dose. In the event of a dose modification, the dose change(s) must be captured in the EDC system.

A maximum of 2 dose reductions will be allowed before a participant is discontinued from study treatment.

Dose delays/reductions/modifications are specified in the event of non-hematological and non-skin toxicity (Table 10), hematological toxicity (Table 11), and for drug-related skin toxicities (Table 12). Further recommendations on the management of drug-related skin toxicities are provided in (Figure 3) for Grade 2/3 events and (Figure 4) for Grade 4 events.

Table 9 Dose Modifications for MK-1026

Dose Modification	**Dose of MK-1026**			
Dose level (assigned)	**65 mg QD (3×20 mg capsules plus 1×5 mg capsule)**	**80 mg QD (4×20 mg capsules)**	**100 mg QD (5×20 mg capsules)**	**120 mg QD (6×20 mg capsules)**
Dose modification 1	45 mg QD (2×20 mg capsules plus 1×5 mg capsule)	65 mg QD (3×20 mg capsules plus 1×5 mg capsule)	80 mg QD (4×20 mg capsules)	100 mg QD (5×20 mg capsules)
Dose modification 2	30 mg QD (1×20 mg capsules plus 2×5 mg capsule)	45 mg QD (2×20 mg capsules plus 1×5 mg capsule)	65 mg QD (3×20 mg capsules plus 1×5 mg capsule)	80 mg QD (4×20 mg capsules)

A single event of Grade 3 generalized skin rash was identified as a DLT in a participant treated with MK-1026. The event was considered serious due to hospitalization and an important medical event by the investigator, and resulted in the discontinuation of MK-1026 treatment. Refer to the current IB for further details. Dose modifications for drug-related skin toxicities are described in Table 12.

Table 10 Dose Delays/Reductions for Non-Hematological and Non-skin Toxicity

Event Grade	Action
Alopecia	Continue current dose level
Grade 1 or 2	Continue current dose level, however, at the discretion of the investigator, dose interruption/modification may be implemented
Grade 3 (except Grade 3 nausea, vomiting, diarrhea, or controlled hypertension)	Withhold MK-1026 until recovery to Grade 1 or baseline. • If recovery occurs within 21 days, restart MK-1026 at the same dose and schedule, unless a dose reduction is required (see Table 11). • If recovery occurs after more than 21 days on drug hold, permanently discontinue MK-1026. If, in the opinion of the investigator and with the agreement of the Medical Monitor, dose re-escalation to a higher level is in the best interest of a participant, the dose may be re-escalated after the participant is fully recovered.
Grade 4 (except Grade 4 nausea, vomiting, or diarrhea)	Permanently discontinue MK-1026.
Grade 3 or 4 nausea, vomiting, or diarrhea	Withhold MK-1026 until recovery to Grade 1 or baseline. • If recovery occurs within 24 hours, restart MK-1026 at the current dose. • If recovery occurs after 24 hours and within 21 days, restart MK-1026 at a reduced dose (see Table 11). • If recovery occurs after more than 21 days on drug hold, permanently discontinue MK-1026. For occurrence of nausea and vomiting, use prophylactic anti-emetics. If, in the opinion of the investigator and with the agreement of the Medical Monitor, dose re-escalation to a higher level is in the best interest of a participant, the dose may be re-escalated after the participant is fully recovered.

Table 11 Dose Delays/Reductions for Hematological Toxicity [a]

Event	Action
Anemia (Hgb ≥8 g/dL) **Thrombocytopenia** (Platelets ≥50×10^9/L)	Continue current dose level, however, at the discretion of the investigator, dose interruption/modification may be implemented
Anemia (Hgb <8 and ≥6 g/dL) **Thrombocytopenia** (Platelets <50 to ≥25×10^9/L)	Withhold MK-1026 and monitor hematology and/or chemistry at least once a week until relevant lab value(s) recover to the values outlined below: • If the relevant laboratory value recovers within 7 days to ≥8 g/dL for Hgb, ≥50×10^9/L for platelets, resume MK-1026 treatment at the same dose. • If the relevant laboratory value takes more than 7 days but within 21 days to recover with or without therapy to the level described above, restart MK-1026 administration at the next lower dose (see Table 11). • If recovery occurs after more than 21 days on drug hold, permanently discontinue MK-1026. If a second hold is required for the same event, administer MK-1026 at the next lower dose (see Table 11). If, in the opinion of the investigator and with the agreement of the Medical Monitor, dose re-escalation to a higher level is in the best interest of a participant, the dose may be re-escalated after the participant is fully recovered.
Anemia (Hgb <6 g/dL) **Thrombocytopenia** (Platelets <25×10^9/L) **Neutropenia** (ANC <0.5×10^9/L)	Withhold MK-1026 and monitor hematology and/or chemistry at least once a week until relevant laboratory value(s) recover to the values outlined below: • If the relevant lab value recovers within 21 days to ≥8g/dL for Hgb, ≥50×10^9/L for platelets, or ≥0.5×10^9/L for ANC with or without the use of GCSF support resume MK-1026 treatment at the next lower dose (see Table 11). • If recovery occurs after more than 21 days on drug hold, permanently discontinue MK-1026. If, in the opinion of the investigator and with the agreement of the Medical Monitor, dose re-escalation to a higher level is in the best interest of a participant, the dose may be re-escalated after the participant is fully recovered.

ANC=absolute neutrophil count; GCSF=granulocyte colony-stimulating factor; Hgb=hemoglobin

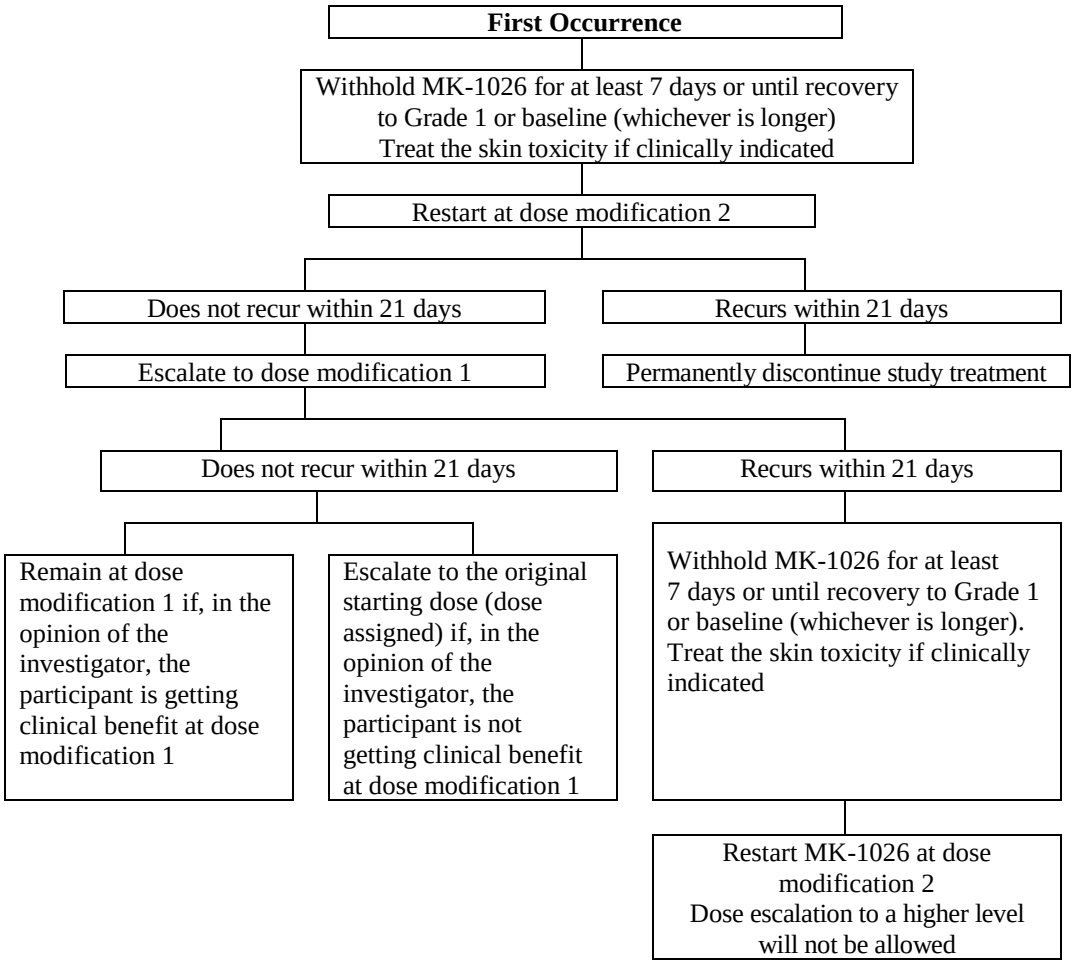
[a] Applicable to participants who had new toxicities or participants with cytopenia at baseline that worsen.

Table 12 Dose Modification for Drug Related Skin Toxicities

Event	Action
Grade 1 **Grade 2**	Continue current dose level, however, at the discretion of the investigator, dose interruption / modification may be implemented.
Grade 3	• First occurrence: withhold MK-1026 for at least 7 days or until recovery to Grade 1 or baseline (whichever is longer); meanwhile treat the skin toxicity if clinically indicated; then restart MK-1026 at dose modification 2. If the event does not recur within 21 days after restarting MK-1026, the dose may be escalated to dose modification 1. If the event does not recur within 21 days after starting treatment at dose modification 1, the participant may remain at this dose if, in the opinion of the investigator, the participant is getting clinical benefit at this dose level, OR increase the participant's dose to the original starting dose (dose assigned), if in the opinion of the investigator, the participant is not getting clinical benefit. • Second occurrence: if a participant experiences a second occurrence of the event while at dose modification 2, this participant should be permanently discontinued. If a participant experiences a second occurrence while at dose modification 1, withhold MK-1026 for at least 7 days or until recovery to Grade 1 or baseline (whichever is longer); meanwhile treat the skin toxicity if clinically indicated; then restart MK-1026 at dose modification 2. Dose escalation to a higher dose will not be allowed. If a participant experiences a second occurrence while at the original starting dose (dose assigned), withhold MK-1026 for at least 7 days or until recovery to Grade 1 or baseline (whichever is longer); meanwhile treat the skin toxicity if clinically indicated; then restart MK-1026 at dose modification 2. If the event does not recur within 21 days after starting treatment at dose modification 2, the participant's treatment dose may be escalated to dose modification 1. Dose escalation to the original starting dose (dose assigned) will not be allowed. • Third occurrence: permanently discontinue study treatment. Please see Flowcharts for First Occurrence and Second Occurrence in Figure 3.
Grade 4	• First occurrence: withhold MK-1026 for at least 7 days or until recovery to Grade 1 or baseline (whichever is longer); meanwhile treat the skin toxicity; then restart MK-1026 at dose modification 2. If the event does not recur within 21 days after restarting MK-1026 at dose modification 2, the participant's intervention dose may be escalated to dose modification 1. Dose escalation to the original starting dose (dose assigned) will not be allowed. • Second occurrence: if a participant experiences a second occurrence while at dose modification 2, this participant should be permanently discontinued. If a participant experiences a second occurrence while at dose modification 1, withhold MK-1026 for at least 7 days or until recovery to Grade 1 or baseline (whichever is longer); meanwhile treat the skin toxicity; then restart MK-1026 at dose modification 2. Dose escalation to a higher dose will not be allowed. • Third occurrence: permanently discontinue study treatment. Please see Flowcharts for First Occurrence and Second Occurrence in Figure 4.

Figure 3 Dose Modification for Grade 2/3 Drug Related Skin Toxicities

First Occurrence



Second Occurrence

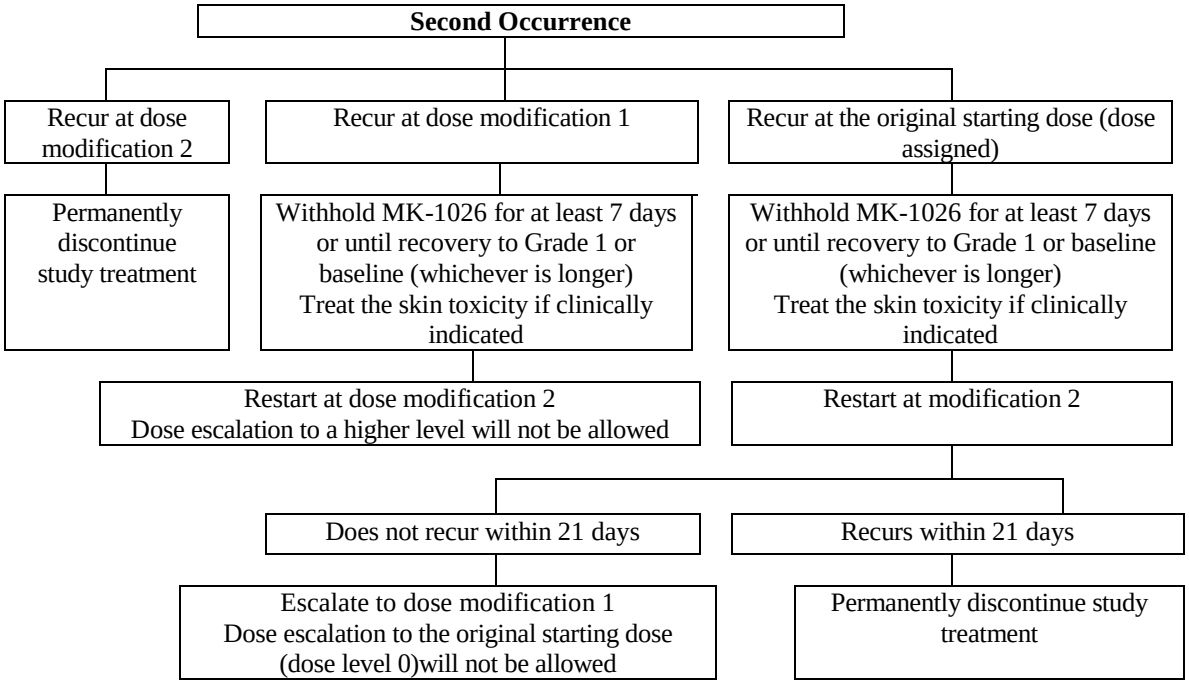
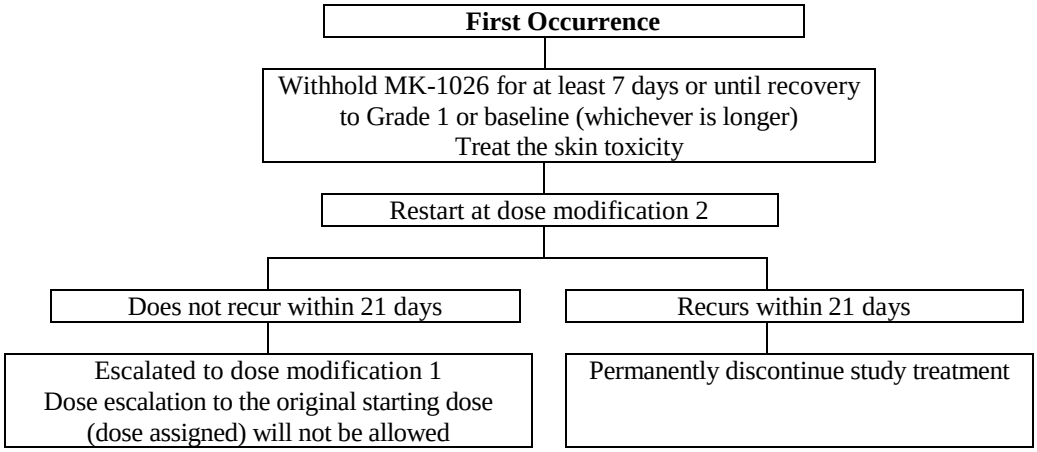
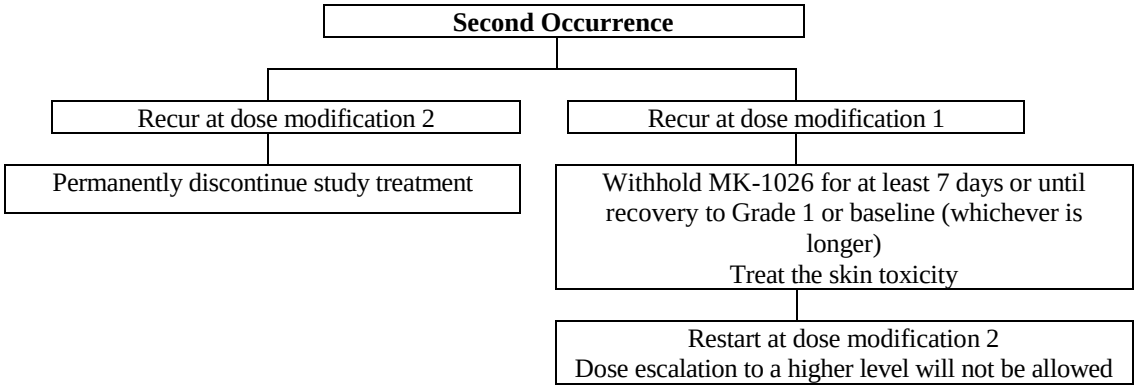


Figure 4 Dose Modification for Grade 4 Drug-related Skin Toxicities

First Occurrence



Second Occurrence



6.6 Intervention After the End of the Study

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

6.7 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 prior to completion of the protocol-specified treatment period/vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

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. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.11.3.

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.
- Discontinuation of study intervention recommended according to the dose delays/reductions/modifications instructions specified in Section 6.5.2.
- Has confirmed disease progression.
- Has a new secondary malignancy diagnosed and/or requires further anticancer therapy.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

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 future biomedical research, 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 utilized 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 is outlined in the Laboratory Manual.

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 consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. 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 consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written 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 dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The 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 future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant.

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 written informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare 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.

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

As part of medical history collection, known mutational status will be recorded.

For participants with WM, the presence of amyloid deposits will be recorded as part of medical history, if available.

Details regarding prognostic markers, current, and prior disease status will be obtained.

8.1.5 Prognostic Profile of CLL (Cohorts A to C only)

If available at Screening or performed during the study, test results should be provided to establish the prognostic profile of CLL participants from Part 1 and Part 2 (Cohorts A to C only):

- Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add (12) in peripheral blood lymphocytes
- Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)
- IGHV mutational status
- BTK mutation status on C481 residue

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.

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 prior to intervention dosing. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used 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 provided in Section 8.11.1.

8.1.8 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. The assigned screening number will become the participants' treatment number. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.9 Study Intervention Administration

The investigational drug MK-1026 is supplied as tablets for oral administration. MK-1026 tablets will be supplied in multiple strengths of 5 mg and 20 mg. The first dose of study intervention will be administered at the study site at Visit 2. Subsequent dosing will be performed once daily by the participant (ie, unsupervised at his/her home) at approximately

the same time each day. Participants will be instructed to take the assigned dose of MK-1026 unless the dose has been reduced due to management of an AE as specified in Section 6.5.2. Treatment will be continued until unacceptable toxicity, documented disease progression, or another discontinuation criterion is met.

For administrative reasons, the treatment period is divided into 4-week cycles (28 days).

A missed or vomited dose should not be replaced as summarized in Section 6.2.2.

The investigator/designee will be asked to check MK-1026 returned supplies for administration compliance.

8.1.9.1 Timing of Dose Administration

MK-1026 is administered orally under fasted conditions (1 hour prior to or 2 hours after the meal) daily. All doses will be administered at the participants home, with the exception of the first day of drug administration at the study clinic and on study visit days. On study visit days, the investigator/designee will instruct the participant not to take their dose of MK-1026 until after their assessments have been performed.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to 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 EOT 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 future biomedical research. 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@merck.com). Subsequently, the participant's consent for future biomedical research 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 prior to 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.

In the event that 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/Immunogenicity Assessments

Imaging and treatment response assessments are required every 12 weeks and should follow calendar days from C1D1. If dosing is delayed, treatment response assessments should continue as scheduled. For further details refer to the SoA in Section 1.3.

8.2.1 Assessment Criteria

8.2.1.1 CLL/SLL (Part 1 and Part 2: Cohorts A to C)

IWCLL Criteria

Participants with CLL/SLL will be assessed using response criteria defined in the 2018 IWCLL consensus (see Appendix 10). Assessment of response should include physical examination and evaluation of the blood and bone marrow as summarized below:

A thorough history, inclusive of constitutional symptoms

- Prognostic biomarkers and cytogenetics (screening only).
    - IGHV mutational status, serum b2-microglobulin, metaphase karyotyping, FISH for del(17p) and/orTP53mutations which indicate high-risk CLL.
- Staging using Rai and Binet (screening only).
- Physical examination including palpable cervical, axillary, and inguinal lymphadenopathy, and hepatomegaly or splenomegaly.
- CBC and differential count.
- CT of neck, chest, abdomen, and pelvis as defined in Table 4 of the iwCLL guidelines (see Appendix 10).
- Marrow aspirate and biopsy: at screening and in the event of a CR, as defined in Table 4 of the iwCLL guidelines (see Appendix 10), or for cytopenias of uncertain cause.

- MRD in the event of a CR - Using a suitably sensitive technique such as 6-color flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using an assay comparable to ClonoSEQ.

Response definitions are summarized in 2018 iwCLL publication in Appendix 10.

8.2.1.2 Lymphoma (Cohorts D to G)

Lugano Criteria (Primary)

Participants with RT, MCL, MZL, or FL will be assessed using the 2014 Lugano Classification (see Appendix 10). Assessment of response should include:

- A thorough history of disease burden and constitutional symptoms.
- Lymphoma staging (screening only).
- PET-CT of neck, chest, abdomen, and pelvis.
- Marrow aspirate and biopsy (screening only).
- Once a CR is confirmed, it is recommended that a bone marrow biopsy be performed to confirm presence/absence of residual disease.

Response definitions are summarized in 2014 Lugano publication in Appendix 10.

8.2.1.3 WM (Cohort H)

Participants with WM will be assessed using the 2014 IWWM Classification. Assessment of response should include:

- A thorough history, inclusive of pathognomonic as well as constitutional symptoms
- The presence of amyloid deposits
- IgM immunofixation and serum level
- CBC with differential
- CT for assessment of extramedullary disease (ie, lymphadenopathy/splenomegaly) if recorded at screening
- New signs/symptoms on physical examination
- Bone marrow aspirate or trephine biopsy in the event of CR
- Kappa light chains, Lambda light chains, and Kappa/Lambda ratio (or Free light chain ratio)
- Serum viscosity when clinically indicated
- Report the use of any extracorporeal therapies that might impact immunoglobulin assays, eg plasmapheresis

In addition to the above, cryoglobulins will be tested at each response assessment visit and if clinically indicated.

Response definitions are summarized in 2014 IWWM publication in Appendix 10.

8.2.1.4 cGVHD (Cohort I)

Chronic GVHD specific core measures, as listed below:

Organ-specific measures: Signs and symptoms potentially attributable to chronic GVHD:

- Skin and skin appendages:
  - NIH Skin Score (0 to 3 score) summarizes BSA involvement into 4 categories: no skin involvement; ≤18% without sclerosis; 19 to 50% or any moveable sclerosis; and >50% or any non-movable sclerosis, impaired mobility, or ulcers. BSA assessment should include superficial skin eruptions, moveable sclerosis and non-movable sclerosis.
  - Sclerotic changes should record the percentage of BSA involved with deep sclerosis/fasciitis and using an exploratory 0 to 10 semi-quantitative scale for capturing clinician perceived severity of sclerosis using the descriptor "skin and/or joint tightening."
- Musculoskeletal connective tissue: NIH Joint Score and the photographic range of motion (P-ROM) scales are recommended measures.
- Eyes: NIH Eye Score (0 to 3 based on symptoms, need for eye drops, and use of therapeutic procedures or devices) is recommended.
- Mouth: NIH-modified OMRS to include a) mucosal erythema (color intensity and percent of oral surface area); b) lichen-like changes (percent of oral surface area); and c) ulcerations (percent of oral surface area). Participants should report their mouth sensitivity (irritation resulting from normally tolerated spices, foods, liquids, or flavors), rated according to a 0 to 10 scale for peak severity during the past week.
- GI tract: GI symptoms during the preceding week are graded through interview by the examining clinician according to 0 to 3 severity scales for the upper and lower GI tract and esophagus.
- Lung: Record %FEV1, FEV1 (L), FVC, and parallel documentation of DLCO corrected for hemoglobin, TLC, and RV.
- Genitals: Women should be asked specific questions relating to vulvar and vaginal symptoms, such as burning, pain, discomfort, or dyspareunia. Both female and male genital symptoms should be captured using the "Worst genital discomfort" on a scale from 0 to 10.

Response definitions are defined in the 2015 cGVHD publication in Appendix 10.

8.2.2 Treatment Response Assessments

8.2.2.1 Cohorts A to H

In addition to survival, efficacy will be assessed based on imaging evaluation of changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. Images will be collected by a central facility (iCRO) for ICR. Disease response assessments may use CT/MRI and/or PET imaging, laboratory studies, and physical examination. The details of image collection (including anatomic coverage, preferred modalities, and specifics of imaging technique) and transmission to the iCRO can be found in the SIM. The same imaging technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on imaging. Note: for the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility. Other imaging modalities that may be collected, submitted to the iCRO, and included in response assessment include bone scans and dedicated brain imaging. Other types of medical imaging (such as ultrasound) should not be submitted to the iCRO, and will not be included in response assessment.

All scheduled imaging for all study participants will be submitted to the iCRO. In addition, imaging that is obtained at an unscheduled time point for any reason (including suspicion of progression or other clinical reason) should also be submitted to the iCRO if it shows progression, or if it is used to support a response assessment. All imaging acquired within the protocol-specified window of time around a scheduled imaging visit can be classified as pertaining to that visit. Participant eligibility will be determined using local assessment (investigator assessment)

Initial tumor imaging at Screening must be performed within 28 days prior to the date of allocation. Any imaging obtained after Cycle 1 Day 1 of treatment cannot be included in the screening assessment. The site study team must review screening images to confirm the participant has measurable disease. For cohort H the iCRO will determine whether extramedullary disease is present, and inform the site, so that the participant can be scheduled for follow-up imaging if needed.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of allocation and can be assessed by the iCRO.

The first on-study imaging assessment should be performed at 12 weeks from the date of allocation. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently if clinically indicated, regardless of dose interruption or delays. For cohort H, no subsequent imaging is required if no extramedullary disease present at screening unless clinically indicated.

Treatment effect measured by ORR can represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, number of CRs, durability of response, disease setting, location of the tumors, available therapy, and risk-benefit relationship.

Disease response assessments and imaging should continue to be performed until documented disease progression by local investigator, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

ORR (Cohorts A to H) will be evaluated in each of the following cohorts:

- Cohorts A to C (CLL/SLL): per iwCLL criteria 2018 (Appendix 10) as assessed by ICR.
- Cohorts D to G (RT, MCL, MZL, FL): per the Lugano Classification 2014 (Appendix 10) as assessed by ICR.
- Cohort H (WM): per IWWM 2014 (Appendix 10) as assessed by ICR.

8.2.2.2 Cohort I

Cohort I (cGVHD) response rate will be evaluated per cGVHD Consensus Panel 2015 (Appendix 10) as assessed by the investigator.

8.2.2.3 Disease Progression Assessment

8.2.2.3.1 Imaging

If an investigator concludes the participant's disease has progressed, study treatment will be discontinued. The participant will enter post-treatment follow-up; ie, 30-day Safety Follow-up and Survival Follow-up. For participants who discontinue study intervention, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study intervention due to documented disease progression, this is the final required tumor imaging.

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment calculated from the date of allocation (see Section 8.2.2.1) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

Initial scans showing site-assessed disease progression should be submitted to the central imaging vendor. It is at the discretion of the investigator to stop study treatment or to keep a clinically stable participant on study treatment until repeat imaging performed 4 to 6 weeks later confirms progression. Participants that are deemed clinically unstable should not have repeat imaging for confirmation. Clinical stability may be defined as:

a) Absence of symptoms and signs indicating clinically significant progression of disease (including worsening of laboratory values).

b) No decline in ECOG performance status.

c) Absence of rapid progression of disease or progressive tumor at critical anatomical sites requiring urgent medical intervention (eg, cord compression).

If progression is confirmed, then the participant will be discontinued from study treatment. If progression is not confirmed, then the participant should resume/continue study treatment provided:

- The sponsor is consulted and provides approval to continue treatment.
- No other anti-tumor therapy (eg, chemotherapy, radiation, etc.) has been administered.

Participants should have their next scan according to the every 12-week schedule from the first dose of study treatment. When feasible, participants should not be discontinued until progression is confirmed. Treatment with MK-1026 must stop at any time a lymphoma disease response assessment is confirmed as PD.

8.2.2.3.2 Non-imaging

In disease indications where progression can be based on non-imaging parameters, it is at the discretion of the investigator to stop study treatment or to keep a clinically stable participant on study treatment until repeat assessment performed 4 to 6 weeks later confirms progression. For WM (Cohort H) a repeat assessment is preferred, after a result suggests progression, due to the potential impact to disease measures attributable to treatment initiation, or due to alternate etiologies. Participants that are deemed clinically unstable should not have repeat assessment for confirmation.

If progression is confirmed, then the participant will be discontinued from study treatment. If progression is not confirmed, then the participant should resume/continue study treatment provided:

- The sponsor is consulted and provides approval to continue treatment.
- No other anti-tumor therapy (eg, chemotherapy, radiation, etc.) has been administered.

8.2.3 Lymphoma B Symptoms

These symptoms include the following:

- Unintentional weight loss ≥10% within the previous 6 months.
- Significant fatigue (ie, ECOG performance score 2 or worse; cannot work or unable to perform usual activities).
- Fevers of 100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
- Night sweats for ≥1 month without evidence of infection.

8.2.4 Quality of Life Assessments

PROs will be assessed using the EORTC QLQ-C30 and the EQ-5D-5L.

8.2.4.1 Patient-reported Outcomes

The EORTC QLQ-C30 and EuroQoL EQ-5D-5L questionnaires will be administered by trained site personnel and completed electronically by participants themselves in the following order: EORTC QLQ-C30 first, then EuroQoL EQ-5D-5L. If the EOT visit occurs <30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, PROs do not need to be repeated.

The questionnaires should be completed prior to all other study procedures and receiving results of any tests (including disease status). If the participant does not complete the ePROs at a scheduled time point, the MISS MODE form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected 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 the Procedures Manual.

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height will be measured and recorded at screening only and weight will be measured and recorded according to the SoA in Section 1.3.1 (Table 1).

For Cohorts A to E physical examination must include liver and/or spleen size.

Other system-based examinations should be included if clinically indicated.

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

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical exam as defined in Section 1.3, the investigator or qualified designee will perform a directed physical exam as clinically indicated. New clinically significant abnormal findings should be recorded as AEs.

Other system-based examinations should be included if clinically indicated.

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

8.3.2 Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature (method must be kept consistent throughout study), systolic and diastolic blood pressure, pulse, and respiratory rate, as defined in Section 1.3.

8.3.3 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG performance status (see Appendix 9).

The investigator or qualified designee will assess ECOG status (see Appendix 9) as specified in the SoA (Section 1.3).

8.3.4 Electrocardiograms

12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR-interval, QRS, QT, and QTc intervals.

For all participants in Part 1 and Cohorts B and C participants in Part 2, triplicate ECGs are required which will be sent to a central ECG laboratory for overreading and for additional concentration-QT analysis.

8.3.5 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 90 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.

HIV screening will follow local regulations (see Appendix 7).

HBV Monitoring

Tests should be aligned with study intervention visits.

Cohorts A to E, G, H, and I: If participant has history of HBV then monitoring is required Q12W.

Cohort F:

- For participants HBsAg negative, anti-HBc positive, and HBV viral load is undetectable at screening and not taking HBV antiviral therapy, repeat HBV viral load and HBsAg tests approximately Q12W. For HBV viral load over 100 IU/mL, start HBV treatment.

- For participants on HBV antiviral therapy at screening, treatment should continue until the end of study intervention or as per local standard of care. Repeat HBV viral load and HBsAg tests should be performed approximately Q8W.

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 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.

AEs will not be collected for participants during the prescreening period (for determination of archival tissue status) as long as that participant has not undergone any protocol-specified procedure or intervention. If the participant requires a blood draw, fresh tumor biopsy, etc., the participant is first required to provide consent to the main study, and AEs will be captured according to guidelines for standard AE reporting.

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 consent form is signed but before intervention allocation/randomization 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 following cessation of study intervention must be reported by the investigator.

All AEs meeting serious criteria, from the time of intervention allocation through 90 days following cessation of study intervention or 30 days following 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 following cessation of study intervention, or 30 days following 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 of the time period 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 he/she 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 **Error! Reference source not found.**.

Table 13 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	Not required	Within 5 calendar days of learning of event

		reporting		

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 allocated 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 towards 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 SAE) 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), including the pregnancy of a male participant’s female partner, that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of 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 monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under 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:

- An overdose of Sponsor's product, as defined in Section 8.5.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon 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).

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for MK-1026. No specific information is available on the treatment of overdose of MK-1026. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

8.6.1 MK-1026

To evaluate MK-1026 exposures, sample collections for analysis of PK are currently planned as shown in Section 1.3. Blood samples will be obtained to measure plasma PK of MK-1026.

8.6.2 Blood Collection for Plasma MK-1026

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

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be provided in Procedure 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:

- Archival or newly obtained tissue collection (Cohorts A to H). Tissue collection should only be performed once all other eligibility criteria has been collected and reviewed. A lymph node sample is required; however, if obtaining a lymph node sample is considered medically unsafe to perform other appropriate tissue may be submitted.
- Blood for TBNK (Cohorts A to C).
- Blood for Genetic Analysis (Cohorts A-H).
- Blood for Genomic Mutational Analysis (Cohorts A to C).
- Blood for ctDNA Analysis (Cohorts A to H).
- Blood for Serum Biomarker Analyses (All Cohorts).
- Blood for RNA analysis (Cohort I only).
- Blood for immunophenotyping (Cohort I only).

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the Procedures 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 future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the Procedures Manual.

8.9 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover DNA for future research
- Leftover plasma from Blood for ctDNA Analysis
- Leftover serum from Blood for Serum Biomarker Analysis
- Leftover RNA from Blood for RNA Analysis
- Leftover main study tumor

8.10 Health Economics Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

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 28 days prior to intervention allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to 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 28 days prior to the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 7 days prior to the first dose of study intervention. An exception is hepatitis testing which may be done up to 28 days prior to the first dose of study intervention.

- Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.

- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to 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).

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

8.11.2 Treatment Period Visit

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section **Error! Reference source not found.**. Unless otherwise specified, assessments/procedures are to be performed prior to the first dose of study intervention for each cycle, and the window for each visit as defined in the SoA.

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study intervention for reasons other than progressive disease will move into Follow-up (Section 1.3 Table 5).

8.11.4 End of Treatment

Participants will be required to return to clinic as soon as possible after the last dose of study intervention for the EOT visit. A further safety follow-up visit will be performed 30 days after the last dose of study intervention. Survival follow-up will be performed every 12 weeks from last dose of MK-1026 for participants who discontinue from treatment after <24 months. If a participant is removed from the study treatment due to AEs, the participant will be followed until the AEs, occurring during the study or within 30 days after the last dose of MK-1026, have resolved to baseline, NCI CTCAE Grade 1, are stabilized, or deemed irreversible. Any SAE will be followed for 90 days after the last dose of MK-1026. If a

participant receives other anticancer therapy within the 90-day safety follow-up period, the follow-up for AEs will cease beginning on the first day of the new therapy.

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 prior to 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

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	Phase 2 Study to evaluate the efficacy and safety of MK-1026 in participants with hematologic malignancies. Part 1 (dose escalation and confirmation) applies an mTPI design to identify a RP2D, followed by Part 2 (cohort expansion) with 9 cohorts of various hematological malignancies.
Treatment Assignment	Approximately 465 participants will be assigned to MK-1026. This is an open label study.
Analysis Populations	Efficacy: All Participants as Treated (APaT) Safety: All Participants as Treated (APaT) and Dose-limiting toxicity-evaluable (DLTe)
Primary Endpoint(s)	Part 1 • DLT • AE • Discontinuing study treatment due to an AE Part 2 Cohorts A to C (CLL/SLL) • ORR (CR, CRi or PR) per iwCLL criteria 2018 (Appendix 10) as assessed by ICR Cohorts D to G (RT, MCL, MZL, FL) • ORR (CR or PR) per Lugano criteria 2014 (Appendix 10) as assessed by ICR

	Cohort H (WM) • ORR (CR, VGPR or PR) per IWWM criteria 2014 (Appendix 10) as assessed by ICR Cohort I (cGVHD) • Objective cGVHD response rate (NIH-defined CR or PR) per cGVHD Consensus Panel 2015 (Appendix 10) as assessed by investigator
Secondary Endpoints	Part 1 • PK parameters • ORR as assessed by ICR (per disease-specific criteria, see Section 3) • DOR as assessed by ICR (per disease-specific criteria, see Section 3) Part 2 All Cohorts • AE • Discontinuing study treatment due to an AE • PK parameters Cohorts A to C (CLL/SLL) • DOR per iwCLL criteria 2018 as assessed by ICR Cohorts D to G (RT, MCL, MZL, FL) • DOR per Lugano criteria 2014 as assessed by ICR Cohort H (WM): • DOR per IWWM 2014 as assessed by ICR Cohort I (cGVHD): • Sustained response rate per cGVHD Consensus Panel 2015 as assessed by investigator
Statistical Methods for Key Efficacy Analyses	ORR (Part 1 and Cohorts A to H in Part 2), cGVHD response rate and sustained response rate (Part 2: Cohort I), will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval) together with its 95% confidence interval. Time to event analyses (DOR, PFS and OS) will be based on Kaplan-Meier estimation and corresponding 95% CIs.
Statistical Methods for Key Safety Analyses	Summary statistics (counts, percentages, means, standard deviations, etc.) will be provided for the safety endpoints as appropriate. The pool-adjacent-violators-algorithm {03TFYL} will be used to estimate the DLT rates across doses. The estimate of the DLT rate among participants

	treated at RP2D of MK-1026 and the 90% Bayesian credible intervals for the estimate will be provided.
Interim Analyses	Multiple interim analyses are planned in this study. Details are provided in Section 9.7.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	Part 1 will enroll approximately 15 participants for dose escalation and confirmation. For Part 2, a minimum of 30 participants and a maximum of up to approximately 100 participants per cohort will be enrolled in this trial. A target sample size of approximately 465 participants will be used for study planning purposes. Section 9.9 provides the precision of possible ORR estimates.

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

There are no hypotheses to be tested in this study. Objectives of the study are outlined in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated as listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy/Pharmacokinetics Endpoints

Primary

- **Objective Response Rate**

  The ORR is defined as the percentage of participants who achieve at least a PR, per cohort-specific criteria (see Section 8.2).

- **Objective cGVHD Response Rate**

  The objective cGVHD response rate is defined as the percentage of participants in Cohort I who achieve an NIH-defined CR or PR per cGVHD Consensus Panel 2015 (see Section 8.2).

Secondary

- **Duration of Response**

  For participants who demonstrate at least a PR, per cohort-specific criteria, duration of response is defined as the time from the first documented evidence of at least a PR that led to response until disease progression or death due to any cause, whichever occurs first.

- **Sustained Response Rate**

  Sustained response rate is defined as the percentage of participants in Cohort I who achieved a NIH-defined CR or PR that was sustained for at least 20 weeks.

- **Pharmacokinetic endpoints**

  PK endpoints will include MK-1026 AUC, C_{max} and C_{min} parameters.

Exploratory

- **Progression-free Survival**

  PFS is defined as the time from first dose to the first documented disease progression per cohort-specific criteria (see Section 8.2) as assessed by ICR, where indicated; or death due to any cause, whichever occurs first.

- **Overall Survival**

  OS is defined as the time from the first dose of study treatment to death due to any cause. Participants without documented death will be censored at the date the participant was last known to be alive.

- **Minimal Residual Disease Rate**

MRD rate is defined as the percentage of participants in Cohorts A to C (CLL/SLL) having undetectable MRD (MRD-neg) remission if they have blood or marrow with less than one CLL cell per 10,000 leukocytes ($<10^{-4}$).

- **Partial Response with Lymphocytosis Rate**

  PRL rate is defined as the percentage of participants in Cohorts A to C (CLL/SLL) who met all criteria for partial response except for lymphocytosis.

- **Minor Response Rate**

  MR rate is defined as the percentage of participants in Cohort H (WM) who achieved 25 to 49% reduction in serum IgM levels.

9.4.2 Safety Endpoints

The safety endpoint is the number/proportion of participants with DLTs, AEs, and who discontinue study treatment due to AEs. 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 Sections 8.3 and 8.4.

9.4.3 PRO Endpoints

The pre-defined PRO endpoints in this study are mean change from baseline in EORTC QLQ-C30 global health/QoL scale (Items 29 and 30), mean change from baseline in EORTC QLQ-C30 physical functioning domain score (Items 1 through 5), mean change from baseline in EORTC QLQ-C30 fatigue domain score (Items 10,12,18), and mean score change from baseline in EQ-5D VAS score.

Based on prior literature {040VGM; 03Q3WF; 03Q4R5}, a $\geq$10 points worsening from baseline for each scale represents a clinically relevant deterioration.

Exploratory PRO endpoints as described in Section 8.2.4 will be evaluated. Details will be provided in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

Efficacy Analyses will be conducted in the APaT population, which consists of all allocated participants who received at least one dose of study treatment.

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all allocated participants who received at least one dose of study treatment.

In Part 1, the DLT evaluable population includes APaT participants that meet the criteria for DLT evaluability. See Section 4.3.1 and 5.5.1 for details.

At least one laboratory, vital sign, or ECG measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 PRO Analysis Populations

The PRO analyses are based on the PRO FAS population, defined for each PRO endpoint respectively as participants who have at least one PRO assessment available and have received at least one dose of study medication

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

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

Efficacy analyses will be performed separately by study part (Part 1 and Part 2). For Part 1, analyses will be conducted by dose level evaluated, pooled across all disease types; exploratory analyses by disease type may be conducted if numbers permit. For Part 2, all analyses will be conducted by cohort (Cohorts A to I). Additional analyses may be performed pooling Part 1 participants treated at the RP2D with corresponding Part 2 participants, according to disease type.

For Part 1, the efficacy endpoints (ORR and DOR, conducted by ICR) are secondary; supportive analyses by investigator assessment will be conducted.

For Part 2, the primary efficacy endpoint is ORR for Cohorts A to H and objective cGVHD response rate for Cohort I, based on cohort-specific criteria (see Section 8.2). The primary assessment will be conducted by ICR for Cohorts A to H and by investigator assessment for Cohort I. Supportive analyses will be performed based on investigator assessment for Cohorts A to H. The point estimate and exact 95% Clopper-Pearson CI for response rates will be provided.

The secondary efficacy endpoint of DOR (except for Cohort I) will be summarized separately by cohort. If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who achieve at least PR will be included in this analysis. Censoring rules for DOR are summarized in Table 14; additional details on cohort-specific censoring, where needed, will appear in the sSAP. For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responding participants who are alive, have not progressed, have not initiated new anti-cancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a participant meets multiple criteria

for censoring, the censoring criterion that occurs earliest will be applied. The secondary efficacy endpoint of sustained response rate for Cohort I will be summarized by point estimate and exact 95% Clopper-Pearson CI.

For Cohorts A to C, estimating the PRL rate will be conducted as an exploratory analysis. For Cohorts D to G, assessment of efficacy (ORR, DOR and PFS) by Cheson 2007 criteria (Appendix 10) may be conducted and will be considered exploratory. For Cohort H, an exploratory analysis of minor response rate per IWWM 2014 will be conducted. Details on analyses for exploratory endpoints will be provided in the sSAP.

Table 14 Censoring Rules for DOR

Situation	**Date of Progression or Censoring**	**Outcome**
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anti-cancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed disease assessments and before new anti-cancer therapy, if any	PD or death	End of response (Event)
Note: A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

For PFS and OS, the non-parametric Kaplan-Meier method will be used to estimate the PFS and OS curve. If data warrant, Kaplan-Meier quartile estimates along with the 95% CI will be provided. Censoring rules for PFS will be provided in sSAP.

9.6.1.1 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 15.

Table 15 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method (Estimation)	Analysis Population	Missing Data Approach
Primary Analyses			
ORR per cohort-specific criteria[a] by ICR[b]	Summary statistics with 95% CI using Exact method based on binomial distribution	APaT	Participants with missing data are considered nonresponders
Objective cGVHD response rate by investigator (Cohort I)	Summary statistics with 95% CI using Exact method based on binomial distribution	APaT	Participants with missing data are considered nonresponders
Key Secondary Analyses			
DOR per cohort-specific criteria [a] by ICR [b]	Summary statistics using Kaplan-Meier method	Responders in APaT population	See Table 14 for censoring rules
Sustained response rate by investigator (Cohort I)	Summary statistics with 95% CI using Exact method based on binomial distribution	APaT	Participants with missing data are considered nonresponders

Abbreviations: APaT=all participants as treated; DOR=duration of response; ICR=independent central review; ORR=objective response rate.

[a] See Section 8.2

[b] Supportive analyses based on investigator assessment will also be conducted

The strategy to address multiplicity issues with regard to multiple endpoints and interim analyses is described in Section 9.7 (Interim Analyses) and Section 9.8 (Multiplicity).

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory tests, vital signs, ECG measurements, and physical examinations. Safety analyses will be conducted pooled by MK-1026 cohorts; other individual cohorts may be presented separately.

AEs will be summarized by counts and frequencies for each dose level and/or cohort. In addition, the broad AE categories consisting of the percentage of participants with any AE, a drug related AE, a SAE, an AE which is both drug-related and serious, and who discontinued due to an AE will be summarized in the same manner. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

For Part 1 (Dose escalation and confirmation), dose-limiting toxicities will be listed and summarized by dose level. The pool adjacent violators-algorithm {03TFYL}, 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 90% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

9.6.3 Statistical Methods for Patient-Reported Outcome Analyses

Details of PRO analyses will be described in the sSAP.

9.7 Interim Analyses

For Part 1 (dose escalation and confirmation), data will be examined on a continuous basis to allow for dose-finding decisions. For Part 2 (cohort expansion), there is one IA per cohort planned for consideration of potential cohort expansion to 100 participants. IAs will be performed by ICR, and each IA will take place after the last of the initial enrolled and treated 30 participants have been followed up for approximately 24 weeks after study entry for each cohort. In the event of slow enrollment, IAs may take place when the majority of participants have been followed up for 24 weeks from study entry. Additional IAs may be conducted to enable future study planning at the Sponsor's discretion.

An interim futility check will be performed for each of the cohorts. For CLL/SLL cohorts (Part 2: Cohorts A to C), if there are 5 or less responders among approximately the first 30 evaluable participants, the cohort may be stopped early for futility. This futility bar is corresponding to 80% chance to observe at least 6 responders among 30 participants if the true response rate is 25%. For other cohorts (Part 2: Cohorts D to I), if there are 2 or less responders among approximately the first 30 evaluable participants, the cohort may be stopped early for futility. This futility bar is corresponding to 85% chance to observe at least 3 responders among 30 participants if the true response rate is 15%. The data will be analyzed on a continuous basis and enrollment will not be paused when interim analyses are performed.

Sufficiently positive results may result in cohort expansion to have approximately 100 participants in total; for cohorts in rare disease indications, eg, WM and Richter's transformation, a target of 50 total participants may be considered for enrollment rather than 100. If a sufficiently large, clinically meaningful, and durable response observed, the specific cohort may be stopped early for efficacy. The totality of the data will be evaluated before making a decision to discontinue / expand the cohort. Cohort expansion decisions will also be based on the regular safety review by the Sponsor. At each IA, ORR (objective cGVHD response rate for Cohort I) will be summarized along with corresponding DOR (sustained response rate for Cohort I).

The final analysis for primary endpoint within each cohort is to be performed approximately 24 weeks after the last participant is enrolled. Participants will continue to be followed after the final analysis until the overall study ends.

Further details regarding the timing and conduct of the IAs will be further clarified in the sSAP. Modification of the analysis plan will be documented, with major changes resulting in an amendment to the sSAP. The timing of additional IAs will be documented in the sSAP. The sSAP will also be updated as the trial evolves.

9.8 Multiplicity

There will be no multiplicity control in this study.

9.9 Sample Size and Power Calculations

Part 1 (Dose Escalation and Confirmation) Sample Size:

Each dose level assessed will have a minimum of 3 participants. Based on the occurrence of DLTs, up to 10 participants may enroll per dose level. The overall sample size of Part 1 is expected to be approximately 15. The actual sample size is dependent on the number of dose levels tested and emerging safety data. The minimum number of participants is 3 and the maximum possible number of participants, although unlikely, is 28 (since only 1 dose level can reach 10 participants).

Part 2 (Cohort Expansion) Sample Size:

For each cohort, a minimum of 30 participants and a maximum of up to approximately 100 participants will be enrolled in this study over a period of approximately 78 months. A target sample size of approximately 450 participants will be used for study planning purposes, noting that some cohorts could expand to 100 participants.

Since this is an estimation study with no formal statistical hypotheses, no power calculations have been incorporated into this study. The sample size calculation was based on the level of precision of the estimated ORR. Table 16 shows the two-sided 95% confidence interval for ORR with 30, 50 or 100 participants for a range of different observed response rates anticipated in this study based on the method of Clopper and Pearson (1934) {03RMKM}.

Table 16 Two-sided 95% Confidence Intervals for ORR with 30 to100 Participants

ORR Estimates	**Number of Observed Responders (95% CI of ORR)**		
	N=30	**N=50**	**N=100**
20%	6 (7.7%, 38.6%)	10 (10.0%, 33.7%)	20 (12.7%, 29.2%)
40%	12 (22.7%, 59.4%)	20 (26.4%, 54.8%)	40 (30.3%, 50.3%)
60%	18 (40.6%, 77.3%)	30 (45.2%, 73.6%)	60 (49.7%, 69.7%)

CI=Confidence Interval; ORR=Objective Response Rate

9.10 Subgroup Analyses

The point estimate of the ORR (with an exact 2-sided 95% confidence interval) will be provided within each disease cohort. For subgroups such as age (<65 vs ≥65 years), sex (female vs male), race (white vs all others), region (US, EU, ROW) and ECOG performance

status (0, 1, 2). Confidence intervals will be provided if the subgroup sample size is adequate. Additional cohort-specific subgroup analyses based on mutational status, eg, BTK-C481 in CLL/SLL and lymphoma cohorts, will be described in the sSAP.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of Exposure for a subject is defined as the number of cycles in which the subject receives the study medication infusion. Summary statistics will be provided on the Extent of Exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (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. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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.

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 pre-specified 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, commonly 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 prior to 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 International Committee of Medical Journal Editors 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 trial 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, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 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 signed ICF, 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 17 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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.

Pregnancy testing:

- Pregnancy testing requirements for study inclusion are described in Section 5.1.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.
- 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 subject's participation in the study.

Table 17 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential [a]: **Neutrophils** **Lymphocytes** Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen or urea[b]	Potassium	Aspartate Aminotransferase /Serum Glutamic-Oxaloacetic Transaminase	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Carbon dioxide (CO_2 or Bicarbonate)[c]	Chloride	Magnesium Phosphorous
	Creatinine or creatinine clearance[d]	Sodium	Alanine Aminotransferase /Serum Glutamic-Pyruvic Transaminase	Total Protein Lipase * Uric acid * *required for all Part 1 participants and only if clinically indicated for Part 2 participants
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Lactate dehydrogenase
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by			

	dipstick Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) as required by local health authority or institutional regulations. Refer to Appendix 7 for country-specific information. Coagulation factors (PT or INR, and aPTT/PTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy. Thyroid-stimulating hormone (TSH), free thyroxine (FT4), triiodothyronine (T3)

Abbreviations: aPTT=activated partial thromboplastin time; FT4=free thyroxine; HIV=human immunodeficiency virus; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; T3=triiodothyronine; TSH=thyroid stimulating hormone; WBC=white blood cell.

NOTES:

a. Absolute number is required and % differential is requested if available
b. BUN is preferred; if not available, urea may be tested.
c. Performed only if considered the local standard of care.
d. GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

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

10.3.1 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 pre-existing 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 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 pre-existing condition that has not worsened is not an SAE.) A pre-existing 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 room 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 in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

Is a new cancer (that is not a condition of the study)

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.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

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 investigational medicinal product)?
- **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 re-exposed 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, or (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 RE-EXPOSURE 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 his/her 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.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- 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 his/her 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 e-mail 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: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

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, Mullerian 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 two 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 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*

Progestogen-only subdermal contraceptive implant[b,c] IUS[c] Non-hormonal 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 can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
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] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation 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

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

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

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 are 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 which 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

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing 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

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. 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@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, 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 prior to 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.

In the event that 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 withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main 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 utilized 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

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

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

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

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@merck.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

Germany-specific Requirements

Section 5.2

Exclusion Criterion 6: HIV testing is required for study entry and needs to be performed in order to evaluate eligibility. This testing can be performed at any time during the Screening Period. Perform locally if required.

Exclusion Criterion 16: Has a known severe hypersensitivity (≥ Grade 3) to MK-1026, its active substance and/or any of its excipients. Refer to the MK-1026 IB for a list of excipients.

10.8 Appendix 8: Examples of General In Vivo Substrates for Specific CYP Enzymes and P-glycoproteins

CYP	Substrates	
2C8	amodiaquine	repaglinide
	cerivastatin	sorafenib
	paclitaxel	torsemide
2C9 (NSAIDS)	diclofenac	S-naproxen→Nor
	ibuprofen	piroxicam
	lornoxicam	suprofen
	meloxicam	
2C9 (Sulfonylureas)	glyburide	nateglinide
	glibenclamide	phenytoin-4-OH2
	glipizide	rosiglitazone
	glimepiride	tamoxifen
	tolbutamide	torsemide
	celecoxib	valproic acid
	fluoxetine	S-warfarin
	fluvastatin	zakirlukast
	glyburide	amitriptyline
2C9 (Oral Hypoglycemic Agents)	tolbutamide	
	glipizide	
2C9 (Angiotensin II Blockers)	losartan	
	irbesartan	
2C19 (PPIs)	esomeprazole	omeprazole2
	lansoprazole	pantoprazole
2C19 (Antiepileptics)	diazepam→Nor	indomethacin
	phenytoin(O)	labetalol
	S-mephenytoin	R-mephobarbital
	phenobarbitone	moclobemide
	amitriptyline	nelfinavir
	carisoprodol	nilutamide
	citalopram	primidone
	chloramphenicol	progesterone
	clomipramine	proguanil
	clopidogrel	propranolol
	cyclophosphamide	teniposide
	hexobarbital	R-warfarin→8-OH
	imipramine N-DeME	voriconazole
2D6 (Antidepressants)	amitriptyline	desipramine
	clomipramine	fluoxetine
2D6 (Beta Blockers)	carvedilol	propafenone
	S-metoprolol	timolol

Source: Cytochrome P450 Drug Interaction Table www.drug-interactions.com
Note: This is not an exhaustive list, adapted from {05HQF8}

10.9 Appendix 9: Eastern Cooperative Oncology Group

Grade	Performance Status
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Adapted from {04JT28}

10.10 Appendix 10: Disease Response Criteria

10.10.1 IWCLL Criteria (Cohorts A to C)

{05HPQL}

10.10.2 Lugano Classification (Cohorts D to G)

{045PKM}

10.10.3 IWWM Criteria (Cohort H)

{05HPRG}

10.10.4 cGVHD Criteria (Cohort I)

{05HPW9}

10.10.5 Cheson Criteria (Cohorts D to G)

{03MDJL}

10.11 Appendix 14: Abbreviations

Abbreviation	Expanded Term
ABC	Activated B-cell
ADL	Activities of daily living
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
ALT	Amino alanine transferase
APaT	All-Participants-as-Treated
AR	Adverse reaction
AST	Amino aspartate transaminase
ATP	Adenosine triphosphate
AUC	Area under the curve
AV	Atrial ventricular
BCL2i	B-cell lymphoma 2 inhibitor
BCR	B-cell receptor
BCRP	Breast cancer resistance protein
BSA	Body surface area
BSEP	Bile salt export pump
BTK	Bruton's tyrosine kinase
BTKi	BTK inhibitor
CAR	Chimeric antigen receptor
CBC	Complete blood cell
cGVHD	Chronic graft-versus-host disease
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
Cmax	Maximum concentration
Cmin	Minimum concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRF	Case Report Form
CRi	Complete response with incomplete bone marrow recovery
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
CYP	Cytochrome P450
D	De-escalate to the next lower dose;
DU	The current dose is unacceptably toxic
DILI	Drug-induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLCO	Diffusing capacity for carbon monoxide
DLT(e)	Dose limiting toxicity (evaluable)
DNA	Deoxyribonucleic acid
DOR	Duration of response
E	Escalate to the next higher dose
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

Abbreviation	Expanded Term
EDC	Electronic data collection
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ePROs	Electronic patient-reported outcomes
eEQ-5D	Electronic EQ-5D
EQ-5D	EuroQoL-5D
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FEV1	Forced expiratory volume in 1 second
FAS	Full Analysis Set
FISH	Fluoro insitu hydrization
FL	Follicular lymphoma
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCB	Germinal center B-cell
GCP	Good Clinical Practice
GI	Gastrointestinal
GVHD	Graft-versus-host Disease
Hb	hemagloblin
HBc	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hERG	Human ether-à-go-go-related gene
HGBCL	High-grade B-cell lymphoma
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplantation
HRT	Hormone replacement therapy
IA(s)	Interim Analysis(es)
IB	Investigator’s Brochure
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICR	Independent Central Review
iCRO	Imaging CRO
IEC	Independent Ethics Committee
IGHV	Immunoglobulin heavy chain variable region gene
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IND	Investigational new drug
IRB	Institutional review board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IWWM	International Workshop on Waldenström’s macroglobulinemia
LAM	Lactational amenorrhoea method
L	Liter(s)
LDH	Lactate dehydrogenase

Abbreviation	Expanded Term
LDT	Lymphocyte doubling time
MCL	Mantle cell lymphoma
MR	Minor response
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTD	Maximum tolerated dose
mTPI	Modified Toxicity Probability Interval
MZL	Marginal zone lymphoma
n	number
NCI	National cancer institute
NDA	New drug application
NF-κB	Nuclear factor kappa-light chain-enhancer of activated B cells
NHL	Non-Hodgkin's Lypmhoma
NIH	National Institute for Health
OMRS	Oral mucosa rating scale
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase Chain Reaction
PD	Disease progression
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PI3Ki	Phosphoinositide 3-kinase inhibitor
PK	Pharmacokinetic(s)
PO	Orally
PR	Partial response
PRL	Partial response with lymphocytosis
PRO	Patient-reported outcome
Q6W	Every 6 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
QD	Once daily
QLQ	Quality of life questionnaire
QOL	Quality of life
QT	QT interval
QTc	QT interval corrected
rrCLL	Relapsed or refractory CLL
rrDLBCL	Relapsed or refractory DLBCL
RNA	Ribonucleic acid
ROW	Rest of world
RP2D	Recommended Phase 2 dose
RT	Richter's Transformation
RV	Residual volume
S	Stay at the current dose.
SAE	serious adverse event
SD	Stable disease
SIM	Site Imaging Manual
SLL	Small lymphocytic lymphoma
SoA	Schedule of activities
sSAP	Supplemental Statistical Analysis Plan

Abbreviation	Expanded Term
SUSAR	Suspected unexpected serious adverse reaction
TBNK	T and B lymphocyte and natural killer cell profile
TLC	Total lung capacity
US	United states
VAS	Visual analog scale
VGFR	Vascular endothelial growth factor
WM	Waldenstrom's macroglobulinemia
WOCBP	Woman/women of childbearing potential

11 REFERENCES