Official Protocol Title:	A Phase 1/2 Open-label Study to Evaluate the Safety and Efficacy of MK-1200 in Participants with Advanced Solid Tumors
NCT Number:	NCT06242691
Document Date:	13-Jun-2024

TITLE PAGE

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Protocol Title:

A Phase 1/2 Open-label Study to Evaluate the Safety and Efficacy of MK-1200 in Participants with Advanced Solid Tumors

Protocol Number: 002-04

Compound Number: MK-1200

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

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

NCT	NCT06242691
EU CT	2023-508684-68
EudraCT	Not applicable
JRCT	To be determined
WHO	Not applicable
UTN	U1111-1298-7820
IND	169109

Approval Date: 13 June 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	13-JUN-2024	To harmonize the changes made in Amendment 02 and Amendment 03, correct typographical errors, and to address agency feedback.
Amendment 03	02-APR-2024	To correct the DLT criteria to not classify certain hematologic Grade 3 AEs that are medically manageable and resolve readily as DLTs.
Amendment 02	02-APR-2024	To address health agency feedback regarding the dose finding methodology and several other changes.
Amendment 01	11-JAN-2024	To address feedback from the US FDA regarding the starting dose for Part 1 and several other changes.
Original Protocol	06-NOV-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendment:

To harmonize the changes made in Amendment 02 and Amendment 03, correct typographical errors, and to address agency feedback.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 4.4.1, Clinical Criteria for Early Study Termination	Added safety criteria that may lead to the stopping of the study.	To address health agency feedback.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.3, Schedule of Activities	Combined the Day 3 and Day 5 visits into a Day 4 visit.	For participant convenience and to ensure PK samples are collected at the necessary timepoints.
	Clarified that ECGs are collected in Cycles 1 and 2 only.	To clarify when these are collected.
	Updated the note about weight change.	To instruct sites that weight-based therapy must be readjusted for ≥10% change in body weight from baseline. Dose can be recalculated at the Investigator's discretion.
Section 4.1, Overall Design	Updated description of participants to clarify that they have received, or been intolerant to, SOC treatments rather than all treatments known to confer benefit.	To clarify eligibility criterion for prior treatment.
Section 4.3.1, Justification for MK-1200 Dose	Clarified the timing of when the 3.6 mg/kg dose level was determined as safe in SKB315-I-01.	To account for this study being ongoing with additional dose levels evaluated since this protocol was originally finalized.
Section 5.1.1, Part 1 Specific Inclusion Criteria	Updated Inclusion Criterion 14 to clarify that participants are to have received, or been intolerant to, SOC treatments rather than all treatments known to confer benefit.	See Section 4.1 rationale about prior treatment.
Section 5.2, Exclusion Criteria	Removed several exclusion criteria related to cardiac function.	To remove unnecessary exclusion criteria to increase inclusion for participants into the study.
Section 6.1.1, Treatment	Added a cross-reference to Section 8.1.8.1 for information on timing of MK-1200 infusions.	To ensure these important instructions for the MK-1200 infusion timing are not overlooked.
Section 6.4, Study Intervention Compliance	Removed a statement about confirmation by a second study site staff member.	To account for differences in site standard operating procedures globally.
Section 6.5.1, Rescue Medications and Supportive Care	Added information on the prophylactic use of G-CSF for participants who experience Grade 3 neutropenia.	To ensure participant safety.
Section 6.6, Dose Modification	Updated the information about weight change and dose recalculations.	Refer to Section 1.3 rationale regarding weight change.
Section 6.6.1, Guidelines for Dose Modification due to Adverse Events for MK-1200	Clarified in Table 6 that dose reductions should occur by one dose level, not 1 mg/kg.	To align with the dose levels included in the study.
	Added to Table 6 that G-CSF should be repeated for all subsequent cycles when participants experience Grade 3 neutropenia	Refer to Section 6.5.1 rationale.
	Removed from Table 6 the requirement for dose reduction after the first occurrence of Grade 4 anemia or Grade 3 thrombocytopenia.	These events are medically manageable and do not warrant dose reduction after the first occurrence.

Section Number and Name	Description of Change	Brief Rationale
Section 6.6.2, Definition of Dose-limiting Toxicity	Clarified that any Grade 3 diarrhea, nausea, or vomiting lasting <3 days, or any Grade 3 rash lasting <7 days, are not considered DLTs, regardless of whether appropriate standard care was administered or not.	Whether a participant receives or does not receive appropriate supportive care for these events should not change whether they are considered DLTs or not.
	Clarified that Grade 3 thrombocytopenia is not a DLT as long as it is in the absence of clinically significant bleeding.	Grade 3 thrombocytopenia with clinically significant bleeding should be considered a DLT.
Section 8.10.5, Vital Status	Removed eDMC meeting as an example of what would trigger a vital status request.	This study does not have an eDMC.
Section 10.1.1, Code of Conduct for Interventional Clinical Trials	Removed a statement about DMCs.	Refer to Section 8.10.5 rationale.
Section 10.7.3, Japan	Updated Figure 2 to show that only 3-6 participants will be enrolled at each dose level in Japan.	For clarity.
	Clarified that the dose levels will be determined based on the totality of data from Part 1 of this study.	To clarify how these doses will be selected.
	Added that participants are eligible in Japan are eligible for Part 2 Cohort C if they have failed standard of care, have no available standard of care, or are unqualified for standard of care.	To allow for these participants to enroll in the study.
	Removed the Japan-specific restriction on prophylactic use of G-CSF during the DLT evaluation period.	To maintain a consistent list of restrictions on concomitant therapy globally.

Amendment 02 and Amendment 03 were both released to a subset of countries participating in this global study. Amendment 04 harmonizes changes from the previous two amendments into one global version of the protocol. For completeness, the changes made in Amendment 02 and Amendment 03 are summarized below.

The following changes were made in Amendment 02:

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 2.2.1.3, Gastrointestinal Cancers Therapeutic Background	Added additional background information on gastric cancer.	To address health agency feedback to support the enrollment of these participants in this study.
Section 2.3, Benefit/Risk Assessment	Added that benefits/risks and alternative treatments should be discussed by the physician and participant.	To address health agency feedback and ensure participants are adequately informed of the benefits/risks of and alternatives to participating in this clinical study.

Section Number and Name	Description of Change	Brief Rationale
Section 4.1, Overall Design	CCI [redacted]	To address health agency feedback regarding the inclusion of these analyses.
Section 4.3.1, Justification for MK-1200 Dose	Changed the dose escalation to follow an mTPI-2 design.	To address health agency feedback regarding acceptable toxicity rates for dose finding.
Section 4.3.2, Dose Finding Using a Modified Toxicity Probability Interval 2 Design in Part 1	Changed the dose escalation to follow an mTPI-2 design.	See rationale for Section 4.3.1.
Section 4.4.1, Clinical Criteria for Early Study Termination	Added cross-references that outline criteria for discontinuing study intervention for individual participants and early closure of study sites.	To address health agency feedback regarding discontinuation criteria.
Section 9.6, Interim Analyses	CCI [redacted]	See rationale for Section 4.1.
Section 10.7.4, All European Economic Area Member States	Created a new appendix specific to all EEA member states, and added new required durations for continuing contraception after the last dose of study intervention specific for participants in the EEA.	To address health agency feedback regarding these durations.

The following changes were made in Amendment 03:

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.1, Synopsis – Intervention Groups and Duration	Added additional lower dose levels to Part 1.	To include lower doses that may be evaluated in Part 1.
Section 1.2, Schema	Added additional lower dose levels to Part 1.	See rationale for Section 1.1.
Section 4.3.1, Justification for MK-1200 Dose	Added additional lower dose levels to Part 1.	See rationale for Section 1.1.

Section Number and Name	Description of Change	Brief Rationale
Section 6.1 Study Intervention(s) Administered	Table 5 - Added additional lower dose levels to Part 1.	See rationale for Section 1.1.
Section 6.6.2, Definition of Dose-limiting Toxicity	Added Grade 3 neutropenia and thrombocytopenia that are manageable and resolve quickly to the list of exceptions for laboratory value DLTs.	To ensure that these events which are clinically manageable are not classified as DLTs.
	Corrected a typographical error in the list of exceptions for DLTs for AST and ALT values.	To ensure clarity and accurate interpretation of the intent of the protocol.
Section 8.1.1.1, General Informed Consent	Removed a paragraph about participants continuing to receive treatment beyond progression.	Participants are not eligible to receive treatment beyond progression.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1/2 Open-label Study to Evaluate the Safety and Efficacy of MK-1200 in Participants with Advanced Solid Tumors

Short Title: MK-1200 for Advanced Solid Tumors

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In individuals of any sex/gender ≥18 years of age with various advanced/metastatic solid tumors:

Primary Objective	**Primary Endpoint**
Objective: To evaluate the safety and tolerability of MK-1200 monotherapy (Part 1 and Part 2)	DLT (Part 1 only) AE Discontinuing study intervention due to an AE
Secondary Objectives	**Secondary Endpoints**
Objective: To evaluate the antitumor activity of MK-1200 monotherapy during randomized dose evaluation at 2 different doses as measured by ORR per RECIST 1.1 as assessed by BICR (Part 2 Cohort A)	Objective response: CR or PR
Objective: To evaluate the antitumor activity of MK-1200 monotherapy measured by ORR per RECIST 1.1 as assessed by the investigator (Part 1 and Part 2 Cohort B)	Objective response: CR or PR
Objective: To evaluate the PK of MK-1200 monotherapy (Part 1 and Part 2)	PK parameters such as AUC, C_{min}, and C_{max}

Objective: To evaluate the antitumor activity of MK-1200 monotherapy as assessed by BICR (as appropriate) and measured by DOR, PFS, and OS (Part 2 Cohort A)	DOR: For participants who show confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever comes first OS: The time from randomization to death due to any cause
Objective: To evaluate the antitumor activity of MK-1200 monotherapy as assessed by the investigator (as appropriate) and measured by DOR, PFS, and OS (Part 1 and Part 2 Cohort B)	DOR: For participants who show confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first PFS: The time from first dose to the first documented disease progression or death due to any cause, whichever comes first OS: The time from first dose to death due to any cause

Overall Design:

Study Phase	Phase 1/2
Primary Purpose	Treatment
Indication	Advanced solid tumor
Population	Participants with advanced solid tumors
Study Type	Interventional
Intervention Model	Single Group This is a multi site study and utilizes a parallel intervention model for Part 2 Cohort A only.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label

Blinding Roles	Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 26 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 304 participants will be enrolled in the study.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Part 1	MK-1200	200 mg/vial	CCI [redacted]	IV Infusion	Q2W	Test Product
Part 2 Cohort A (Arm 1) and Cohort B	MK-1200	200 mg/vial	(Dose 1) mg/kg	IV Infusion	Q2W	Test Product
Part 2 Cohort A (Arm 2)	MK-1200	200 mg/vial	(Dose 2) mg/kg	IV Infusion	Q2W	Test Product
All Arms	Antiemetic (eg, 5-HT3 Receptor)	Per Approved Product Label	Per Approved Product Label	Per Approved Product Label	Before MK-1200 Infusion	Rescue Medication

IV=intravenous; Q2W=every 2 weeks

Other current or former names or aliases for MK-1200 are as follows: SKB315.

Total Number of Intervention Groups/Arms	6
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final contact. After the screening phase, each participant will receive assigned study intervention until one of the reasons for discontinuation of study intervention (Section 7.1) is met or the participant withdraws from the study. After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy. All participants will be followed for overall survival until death, withdrawal of consent, or end of the study.

Study Governance Committees:

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

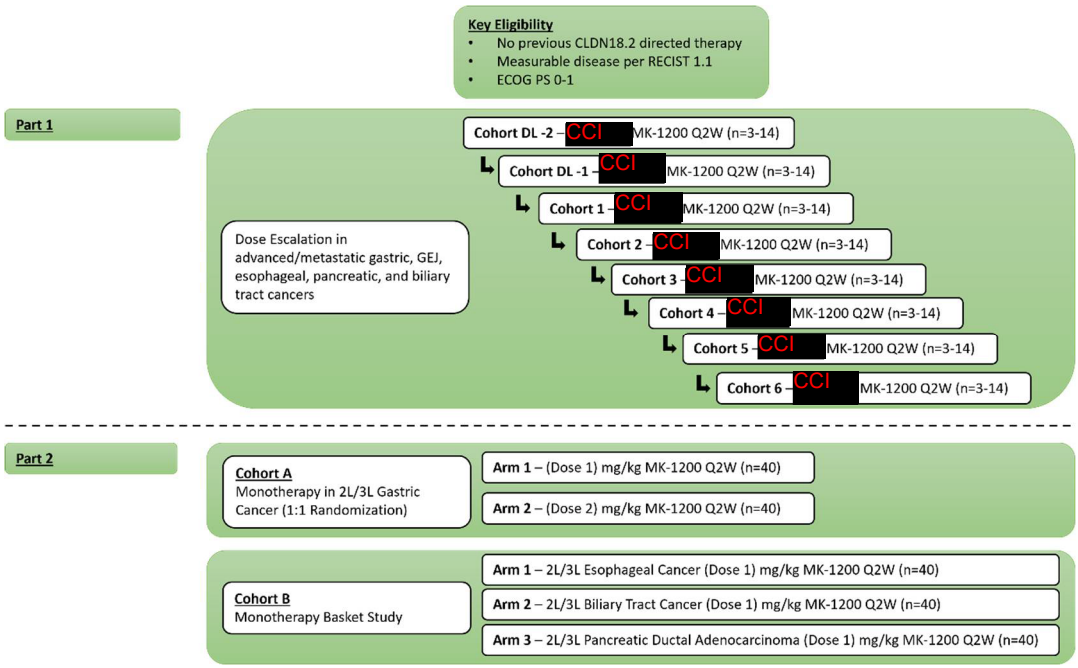
There are no governance committees in this study. Regulatory, ethical, and study oversight considerations are outlined in Appendix 1.

Study Accepts Healthy Participants:
No

A list of abbreviations is in Appendix 9.

1.2 Schema

Figure 1 Study Schema



2L=second line; 3L=third line; CLDN18.2=Claudin 18.2; DL=dose level; ECOG PS=Eastern Cooperative Oncology Group performance status; GEJ=gastroesophageal junction; Q2W=every 2 weeks; RECIST=Response Evaluation Criteria in Solid Tumors

See Appendix 7 for country-specific requirements.

1.3 Schedule of Activities

Table 1 Schedule of Activities

	FS	RS (Optional)	Treatment Phase (14-Day Cycle)															Posttreatment Phase			Notes
Cycle			**1**					**2-3**		**4**					**5-8**	**9+**		**Safety FU**	**Efficacy FU**	**Survival FU**	If RS is needed, the RS period starts after the FS period has elapsed. See Section 5.4 for more details on screen failures and rescreening. † Part 1 only.
Cycle Day			**1**	**2†**	**4†**	**8**	**11**	**1**	**8**	**1**	**2†**	**4†**	**8**	**11**	**1**	**1**	**EOT/DC[a]**	**30 days post last dose**	**Per the Imaging Schedule**	**Every 12 weeks**	
Scheduling Window (Days)					**±1**	**±1**	**±1**	**±3**	**±3**	**±3**		**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Maximum Duration (Days)	**28**	**28**																			
Administrative and General Procedures																					
Informed Consent	X																				
Informed Consent for FBR	X																				This is optional for the participant.
Participant Identification Card	X		X																		Add the intervention allocation/ randomization number at the time of intervention allocation/ randomization.
Inclusion/ Exclusion Criteria	X	X																			
Disease/Cancer History and Treatment	X	X																			Oncologic disease details and prior treatment. See Sections 8.1.4 and 8.1.5.1.
HER2 Testing	X	X																			For gastric/GEJ cancer (Part 2 Cohort A) and Siewert type 1 esophagogastric junction adenocarcinoma (Part 2 Cohort B) only. Only test if status is not previously known. See Sections 5.1.2 and 5.1.3 for more details.

	FS	RS (Optional)	Treatment Phase (14-Day Cycle)														Posttreatment Phase			Notes
Cycle			**1**					**2-3**		**4**				**5-8**	**9+**		**Safety FU**	**Efficacy FU**	**Survival FU**	If RS is needed, the RS period starts after the FS period has elapsed. See Section 5.4 for more details on screen failures and rescreening. † Part 1 only.
Cycle Day			**1**	**2†**	**4†**	**8**	**11**	**1**	**8**	**1**	**2†**	**4†**	**8**	**11**	**1**	**1**	**EOT/DC[a]**	**30 days post last dose**	**Per the Imaging Schedule**	**Every 12 weeks**	
Scheduling Window (Days)					**±1**	**±1**	**±1**	**±3**	**±3**	**±3**		**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Maximum Duration (Days)	**28**	**28**																			
Intervention Assignment by IRT			X																	All participants will be assigned to intervention by IRT, but participants will be randomized in Part 2 Cohort A only.
Medical/Surgical History and Demographics	X	X																		
Prior/ Concomitant Medication Review	X	X	←==========→													X	X			
New Anticancer Treatment Status																X	X	X		Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

	FS	RS (Optional)	Treatment Phase (14-Day Cycle)														Posttreatment Phase			Notes
Cycle			**1**					**2-3**		**4**				**5-8**	**9+**		**Safety FU**	**Efficacy FU**	**Survival FU**	If RS is needed, the RS period starts after the FS period has elapsed. See Section 5.4 for more details on screen failures and rescreening. † Part 1 only.
Cycle Day			**1**	**2†**	**4†**	**8**	**11**	**1**	**8**	**1**	**2†**	**4†**	**8**	**11**	**1**	**1**	**EOT/DC[a]**	**30 days post last dose**	**Per the Imaging Schedule**	**Every 12 weeks**	
Scheduling Window (Days)					**±1**	**±1**	**±1**	**±3**	**±3**	**±3**		**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Maximum Duration (Days)	**28**	**28**																			
Disease Status																	X	X	X		Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, PD, death, or end of study.
Vital Status			←==========→														X	←==========→			On Sponsor request, participants may be contacted for survival information at any time during the study.
Study Intervention																					
MK-1200			X					X		X					X	X					Refer to Section 6.5.1 for required premedication information and Section 6.6.1.1 for strongly recommended premedication information.

	FS	RS (Optional)	Treatment Phase (14-Day Cycle)														Posttreatment Phase			Notes
Cycle			**1**					**2-3**		**4**				**5-8**	**9+**		**Safety FU**	**Efficacy FU**	**Survival FU**	If RS is needed, the RS period starts after the FS period has elapsed. See Section 5.4 for more details on screen failures and rescreening. † Part 1 only.
Cycle Day			**1**	**2†**	**4†**	**8**	**11**	**1**	**8**	**1**	**2†**	**4†**	**8**	**11**	**1**	**1**	**EOT/DC[a]**	**30 days post last dose**	**Per the Imaging Schedule**	**Every 12 weeks**	
Scheduling Window (Days)					**±1**	**±1**	**±1**	**±3**	**±3**	**±3**		**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Maximum Duration (Days)	**28**	**28**																			
Efficacy Procedures																				Imaging timing should follow calendar days from intervention allocation/randomization and should not be adjusted for delays in study intervention. See Section 8.2.1 for more details.
Tumor Scan (Chest, Abdomen, Pelvis)	X	X	←==========→													X		X		Screening images are to be captured within 28 days prior to intervention allocation/randomization. The first on-study tumor scan should be performed at 6 weeks (42 days +7 days) from the date of intervention allocation/ randomization. Subsequently, perform every 6 weeks (±7 days) up to Week 54 (±7 days), and every 12 weeks (±14 days) thereafter, or more frequently as clinically indicated. An EOT/DC scan is not needed if a scan was performed less than 4 weeks before EOT/DC.

	FS	RS (Optional)	Treatment Phase (14-Day Cycle)														Posttreatment Phase			Notes
Cycle			**1**					**2-3**		**4**				**5-8**	**9+**		**Safety FU**	**Efficacy FU**	**Survival FU**	If RS is needed, the RS period starts after the FS period has elapsed. See Section 5.4 for more details on screen failures and rescreening. † Part 1 only.
Cycle Day			**1**	**2†**	**4†**	**8**	**11**	**1**	**8**	**1**	**2†**	**4†**	**8**	**11**	**1**	**1**	**EOT/DC[a]**	**30 days post last dose**	**Per the Imaging Schedule**	**Every 12 weeks**	
Scheduling Window (Days)					**±1**	**±1**	**±1**	**±3**	**±3**	**±3**		**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Maximum Duration (Days)	**28**	**28**																			
Brain Scan	X*	X*	←═══													→|		X		*Brain imaging is required at Screening only if there is a known history of brain metastases or brain metastases are suspected. Brain imaging is required on study only if clinically indicated or to confirm CR for those who had brain metastases at Screening.
Bone Scan	X*	X*	←═══													→|		X		*Bone scan is required at Screening only if there is a known history of bone metastases or bone metastases are suspected. Bone scan is required on study only if clinically indicated or to confirm CR for those who had bone metastases at Screening.
Safety Procedures																					
Full Physical Examination	X	X																			Perform within 7 days before intervention allocation/ randomization.
Directed Physical Examination			X	X		X		X	X	X			X		X	X	X	X			

	FS	RS (Optional)	Treatment Phase (14-Day Cycle)														Posttreatment Phase			Notes
Cycle			**1**					**2-3**		**4**				**5-8**	**9+**		**Safety FU**	**Efficacy FU**	**Survival FU**	If RS is needed, the RS period starts after the FS period has elapsed. See Section 5.4 for more details on screen failures and rescreening. † Part 1 only.
Cycle Day			**1**	**2†**	**4†**	**8**	**11**	**1**	**8**	**1**	**2†**	**4†**	**8**	**11**	**1**	**1**	**EOT/DC[a]**	**30 days post last dose**	**Per the Imaging Schedule**	**Every 12 weeks**	
Scheduling Window (Days)					**±1**	**±1**	**±1**	**±3**	**±3**	**±3**		**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Maximum Duration (Days)	**28**	**28**																			
Height	X	X																			
Weight	X	X	X					X		X					X	X	X	X			If ≥10% change in body weight from baseline (C1D1) occurs, weight-based therapy must be readjusted, and an AE of weight loss must be reported. The dose can be recalculated for changes in body weight <10% at the Investigator's discretion.
Vital Signs	X	X	X	X		X		X	X	X			X		X	X	X	X			Includes BP, heart rate, RR, SpO_2 (pulse oximetry), and body temperature. See Section 8.3.2 for more details.
ECG	X	X	X					X									X				On C1D1 and C2D1 only, perform pre-dose (up to 1 hour) and 30 min post-dose (±15 min). Perform prior to PK/ADA sample collection. See Section 8.3.3 for more details.
ECHO/MUGA	X	X															X				ECHO is preferred.
ECOG Performance Status	X*	X*	X					X		X					X	X	X	X			*Assess within 3 days before intervention allocation/ randomization.

	FS	RS (Optional)	Treatment Phase (14-Day Cycle)														Posttreatment Phase			Notes
Cycle			**1**					**2-3**		**4**				**5-8**	**9+**		**Safety FU**	**Efficacy FU**	**Survival FU**	If RS is needed, the RS period starts after the FS period has elapsed. See Section 5.4 for more details on screen failures and rescreening. † Part 1 only.
Cycle Day			**1**	**2†**	**4†**	**8**	**11**	**1**	**8**	**1**	**2†**	**4†**	**8**	**11**	**1**	**1**	**EOT/DC[a]**	**30 days post last dose**	**Per the Imaging Schedule**	**Every 12 weeks**	
Scheduling Window (Days)					**±1**	**±1**	**±1**	**±3**	**±3**	**±3**		**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Maximum Duration (Days)	**28**	**28**																			
AE/SAE Monitoring	X	X	←==========→													X	X				Any AEs noted before documented consent should be recorded as medical history. See Section 8.4.1 for more details.
Safety Labs																					
HIV Testing	X*																				*Required at Screening for participants with known history of HIV infection or if mandated by local health authority. See Sections 5.1 and Appendix 7 for more details. Retest as clinically indicated for applicable participants. See Section 8.1.13 for more details.
HBV and HCV Testing	X*																				*HBV testing is required at Screening for all participants with biliary tract cancer. Otherwise, only test for HBV and HCV if mandated by local health authority. See Appendix 7 for country-specific requirements.
Urinalysis	X	X	X					X		X					X	X	X	X			Screening sample to be performed within 7 days before first dose of study intervention.

	FS	RS (Optional)	Treatment Phase (14-Day Cycle)														Posttreatment Phase			Notes
Cycle			**1**					**2-3**		**4**				**5-8**	**9+**		**Safety FU**	**Efficacy FU**	**Survival FU**	If RS is needed, the RS period starts after the FS period has elapsed. See Section 5.4 for more details on screen failures and rescreening. † Part 1 only.
Cycle Day			**1**	**2†**	**4†**	**8**	**11**	**1**	**8**	**1**	**2†**	**4†**	**8**	**11**	**1**	**1**	**EOT/DC[a]**	**30 days post last dose**	**Per the Imaging Schedule**	**Every 12 weeks**	
Scheduling Window (Days)					**±1**	**±1**	**±1**	**±3**	**±3**	**±3**		**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Maximum Duration (Days)	**28**	**28**																			
Urine or Serum Pregnancy Test (POCBP Only)	X	X	X					X		X				X	X	X	X*			*During the Posttreatment Phase, monthly pregnancy testing should be conducted for the time required to eliminate systemic exposure after the last dose of study intervention. See Sections 5.1 and 8.3.6 for more details.
Hematology	X	X	X	X		X		X	X	X			X		X	X	X	X			Screening sample to be performed within 7 days before first dose of study intervention. Tests do not have to be repeated on C1D1 if Screening sample was within 72 hours before the first dose of study intervention and within acceptable limits.
Chemistry	X	X	X	X		X		X	X	X			X		X	X	X	X			Screening sample to be performed within 7 days before first dose of study intervention. Tests do not have to be repeated on C1D1 if Screening sample was within 72 hours before the first dose of study intervention and within acceptable limits.

	FS	RS (Optional)	Treatment Phase (14-Day Cycle)														Posttreatment Phase			Notes
Cycle			**1**					**2-3**		**4**				**5-8**	**9+**		**Safety FU**	**Efficacy FU**	**Survival FU**	If RS is needed, the RS period starts after the FS period has elapsed. See Section 5.4 for more details on screen failures and rescreening. † Part 1 only.
Cycle Day			**1**	**2†**	**4†**	**8**	**11**	**1**	**8**	**1**	**2†**	**4†**	**8**	**11**	**1**	**1**	**EOT/DC[a]**	**30 days post last dose**	**Per the Imaging Schedule**	**Every 12 weeks**	
Scheduling Window (Days)					**±1**	**±1**	**±1**	**±3**	**±3**	**±3**		**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Maximum Duration (Days)	**28**	**28**																			
Coagulation (PT/INR and aPTT/PTT)	X	X	←==========→*														X*	X*			Screening sample to be performed within 7 days before first dose of study intervention. *Retest as clinically indicated for participants taking anticoagulants.
Glycosylated Hemoglobin	X	X	←==========→														X	X			For diabetic participants only. Retest as clinically indicated.
Pharmacokinetics/Future Biomedical Research/Biomarkers																					
MK-1200 PK			X*	X	X	X	X	X		X*	X	X	X	X	X	X**	X	X			Collections on D1 of each indicated cycle include both pre-dose (up to 1 hour) and 30 min post-dose (±15 min) samples. *Refer to Table 2 for Part 1 intensive PK sampling schedule. **C14, C20 and every 12 cycles thereafter (C32, C44, etc.)
MK-1200 ADA			X					X		X					X	X**	X	X			Collect pre-dose (up to 1 hour). **C14, C20 and every 12 cycles thereafter (C32, C44, etc.)

	FS	RS (Optional)	Treatment Phase (14-Day Cycle)														Posttreatment Phase			Notes
Cycle			**1**					**2-3**		**4**				**5-8**	**9+**		**Safety FU**	**Efficacy FU**	**Survival FU**	If RS is needed, the RS period starts after the FS period has elapsed. See Section 5.4 for more details on screen failures and rescreening. † Part 1 only.
Cycle Day			**1**	**2†**	**4†**	**8**	**11**	**1**	**8**	**1**	**2†**	**4†**	**8**	**11**	**1**	**1**	**EOT/DC[a]**	**30 days post last dose**	**Per the Imaging Schedule**	**Every 12 weeks**	
Scheduling Window (Days)					**±1**	**±1**	**±1**	**±3**	**±3**	**±3**		**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	
Maximum Duration (Days)	**28**	**28**																			
Blood for Genetic Analysis			X																	Collect pre-dose.
Archival or Newly Obtained Tumor Tissue Collection	X																			

ADA=antidrug antibodies; AE=adverse event; aPTT=activated partial thromboplastin time; BP=blood pressure; C1, C2, etc.=Cycle 1, Cycle 2, etc.; C1D1, C2D2, etc.=Cycle 1 Day 1, Cycle 2 Day 2, etc.; CR=complete response; D1, D2, etc.=Day 1, Day 2, etc.; DC=treatment discontinuation; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FBR=future biomedical research; FS=full screening; FU=follow-up; GEJ=gastroesophageal junction; HBV=hepatitis B virus; HCV=hepatitis C virus; HER2=human epidermal growth factor receptor 2; HIV=human immunodeficiency virus; IRT=interactive response technology; min=minute(s); MUGA=multiple gated acquisition; PD=progressive disease; PK=pharmacokinetics; POCBP=participant of childbearing potential; PT/INR=prothrombin time/international normalized ratio; PTT=partial thromboplastin time; RR=respiratory rate; RS=rescreening; SAE=serious adverse event; SpO_2=oxygen saturation

[a] If the EOT/DC Visit occurs more than 30 days after the last dose of study intervention, the EOT/DC Visit procedures and any additional Safety FU procedures should be performed and combined into 1 visit.

Table 2 Intensive Pharmacokinetics Sampling Schedule for Part 1 Only

Cycle	**Cycles 1 and 4**								
Cycle Day	1					2	4	8	11
Sample Time from Dosing (±Window)	Pre-dose (up to -1 h)	+30 min (±15 min)	+2 h (±0.5 h)	+4 h (±0.5 h)	+8 h (±1 h)	+24 h (±2 h)	+72 h (±2 h)	+168 h (±24 h)	+240 h (±24 h)
MK-1200 PK	X	X	X	X	X	X	X	X	X
Note: For all other cycles, follow the collection schedule in Table 1.									

See Appendix 7 for country-specific requirements.

2 INTRODUCTION

This study will evaluate the safety and efficacy MK-1200, an investigational ADC targeted to Claudin 18.2, as monotherapy in participants with advanced solid tumors.

2.1 Study Rationale

Claudin 18.2 is a protein critical for formation of tight junctions in cells. The expression of Claudin 18.2 is typically restricted to differentiated gastric epithelial cells and gastric glands. However, during malignant transformation, Claudin 18.2 can be aberrantly and stably expressed in tumor tissue [Zhu, G., et al 2019] [Woll, S., et al 2014] [Moentenich, V., et al 2020] [Micke, P., et al 2014].

Clinical studies of investigational mAbs targeting Claudin 18.2 in combination with chemotherapy have demonstrated efficacy in patients with Claudin 18.2–positive gastric tumors [Sahin, U., et al 2021] [Shitara, K., et al 2023] [Shah, M. A., et al 2023]. Furthermore, ADCs may enhance the efficacy of chemotherapy while reducing off-target toxicity [Chau, C. H., et al 2019]. Therefore, MK-1200 as monotherapy and in combination with other agents may have broad therapeutic applications in oncology.

This study will include patients with advanced gastric, esophageal, biliary tract, or pancreatic cancer. Such patients may benefit from MK-1200 therapy, as these types of cancers are known to express Claudin 18.2 [Zhu, G., et al 2019] [Woll, S., et al 2014] [Moentenich, V., et al 2020] [Dottermusch, M., et al 2019] [Arnold, A., et al 2020] [Sahin, U., et al 2008] [Kubota, Y., et al 2023] [Rohde, C., et al 2019] [Baek, J. H., et al 2019] [Hong, J. Y., et al 2020] [Coati, I., et al 2019] [Kayikcioglu, E., et al 2023] [Zhang, Z., et al 2022] [Wang, X., et al 2022] [Kayikcioglu, E. and Yuceer, R. O. 2023] [Shinozaki, A., et al 2011] [Iwaya, M., et al 2021].

2.1.1 Scientific Rationale

In vitro data indicate that MK-1200 binds to human Claudin 18.2 with high affinity, is endocytosed by target-expressing cells, and effectively induces tumor cell apoptosis. The effect of MK-1200 is primarily attributed to intracellular release of a conjugated toxin payload (denoted “KL610023”), a topoisomerase inhibitor that blocks cell cycle progression and activates apoptotic cell signaling pathways. Tumor models in mice show that MK-1200 inhibits tumor growth in a dose-dependent manner, and the ADC is well-tolerated at each dose. These preclinical data provide further rationale for clinical development of MK-1200.

Refer to the IB for more information on preclinical studies with MK-1200.

2.2 Background

Refer to the IB for detailed background information on MK-1200.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 MK-1200

ADCs are immunoconjugates consisting of a cytotoxic drug called a payload attached to a mAb via a chemical linker. ADCs yield increased efficacy of chemotherapy through a delivery system with high selectivity, resulting in decreased toxicity. ADCs have been approved for numerous indications including lymphoma, breast cancer, urothelial cancer, NSCLC, gastric cancer, and leukemia, and are currently being evaluated in studies involving a wide variety of targets across different cancer indications [Chau, C. H., et al 2019].

MK-1200 is an ADC comprising 3 major components: a recombinant anti-Claudin 18.2 mAb, an acid-labile linker, and a chemically conjugated cytotoxin, KL610023. KL610023 is a topoisomerase inhibitor that blocks cell cycle progression and induces tumor cell apoptosis after intracellular release.

Refer to the MK-1200 IB for details about the nonclinical safety profile of MK-1200.

2.2.1.2 Claudin 18.2–targeted Therapies Background

Zolbetuximab was the first Claudin 18.2 targeted therapy to show promise as monotherapy for late-line gastric cancer and in combination with 1L chemotherapy, as reported in the Phase 2 FAST study [Sahin, U., et al 2021]. Zolbetuximab is a chimeric monoclonal IgG1

antibody that binds Claudin 18.2 to cause tumor cell death through ADCC and CDC. The Phase 3 SPOTLIGHT study enrolled 1L patients with metastatic gastric cancer who had high Claudin 18.2 expression (IHC H-score ≥150), showing median OS of 18.2 months for zolbetuximab plus mFOLFOX6 chemotherapy vs. 15.5 months with chemotherapy alone (HR=0.75; 95% CI: 0.60, 0.94; *p*=0.0053) [Shitara, K., et al 2023]. Likewise, the Phase 3 GLOW study in a similar patient population showed median OS of 14.4 months for zolbetuximab plus CAPOX chemotherapy vs. 12.2 months with CAPOX alone (HR=0.771; 95% CI: 0.615, 0.965; *p*=0.0118) [Shah, M. A., et al 2023]. Combination with zolbetuximab also improved PFS (10.61 vs. 8.67 months for SPOTLIGHT; 8.21 vs. 6.80 months for GLOW), but ORR was similar between arms in both studies (61% vs. 62% in SPOTLIGHT; 54% vs. 49% in GLOW).

2.2.1.3 Gastrointestinal Cancers Therapeutic Background

Gastric cancer is the sixth most common cancer, and seventh leading cause of cancer death worldwide [International Agency for Research on Cancer 2024]. For HER2-negative gastroesophageal adenocarcinoma, the combination of anti-PD-1/L1 therapies with chemotherapy (platinum and fluoropyrimidine) has become 1L SOC for patients with PD-L1+ HER2- tumors based on the results of the CHECKMATE 649 and KEYNOTE-859 studies [National Comprehensive Cancer Network 2023] [Lordick, F., et al 2022] [Janjigian, Y. Y., et al 2021] [Rha, S. Y., et al 2023]. In CHECKMATE-649, median OS in participants treated with nivolumab plus SOC chemotherapy was 13.8 months vs. 11.6 months in participants treated with SOC chemotherapy alone (HR=0.80; 99.3% CI: 0.68, 0.94; p=0.0002) [Janjigian, Y. Y., et al 2021]. In KEYNOTE-859, pembrolizumab plus SOC chemotherapy vs. chemotherapy alone showed ORR 51.3% vs. 42.0% (p=0.00009), median PFS 6.9 months vs. 5.6 months (HR=0.76; 95% CI: 0.67, 0.85; p<0.0001), and median OS 12.9 months vs. 11.5 months (HR=0.78; 95% CI: 0.70, 0.87; p<0.0001) [Rha, S. Y., et al 2023a]. Based on these results, the combination of immuno-oncology therapies and chemotherapy with platinum and fluoropyrimidine has become SOC in 1L gastroesophageal adenocarcinomas in patients with PD-L1+ HER2- tumors [National Comprehensive Cancer Network 2023] [Lordick, F., et al 2022] [Muro, K., et al 2019]. For 2L treatment of advanced HER2-negative gastroesophageal adenocarcinoma, the combination of paclitaxel and ramucirumab showed an ORR of 28% and a median OS of 9.6 months vs. 7.4 months for paclitaxel monotherapy (HR=0.807; 95% CI: 0.678, 0.962; *p*=0.017) in the Phase 3 RAINBOW study [Wilke, H., et al 2014]. FOLFIRI is another 2L option for patients who previously received taxanes (FLOT) [National Comprehensive Cancer Network 2023]. 3L options include trifluridine/tipiracil as compared with placebo in the TAGS study demonstrating median OS 5.7 months vs. 3.6 months with placebo (HR=0.69; 95% CI: 0.56, 0.85; *p*=0.00058) [Shitara, K., et al 2018]. Given the relatively recent approval of immuno-oncology therapies in the first line, there is limited 2L data for patients with metastatic gastroesophageal cancers who have progressed beyond immuno-oncology plus SOC chemotherapy combinations in the first line; this study will provide a good opportunity to evaluate this setting.

For esophageal cancer, treatment depends on histology (SCC vs. adenocarcinoma). For squamous cell esophageal cancer, 1L SOC includes chemotherapy with a platinum (cisplatin or oxaliplatin) and fluoropyrimidine, with recent addition of anti-PD-1 immunotherapy based

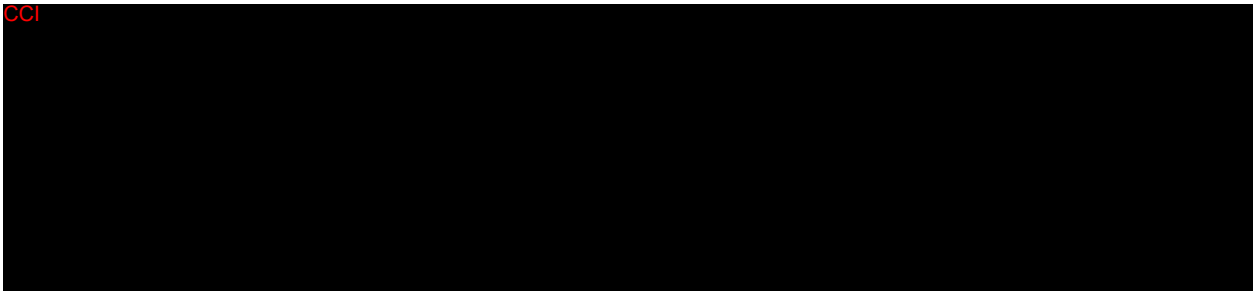
on the KEYNOTE-590 and CHECKMATE 648 studies [Sun, J. M., et al 2021] [Doki, Y., et al 2022]. Anti-PD-1 agents can also both be used in the second line setting for advanced squamous esophageal cancer based on the KEYNOTE-181, ATTRACTION-3, and RATIONALE-302 studies, with improvement in OS compared with single-agent paclitaxel or docetaxel [Kojima, T., et al 2020] [Kato, K., et al 2019] [Shen, L., et al 2022]. Pembrolizumab can also be used in the 3L setting based on the results of the KEYNOTE-180 study [Shah, M. A., et al 2018]. Treatment of esophageal adenocarcinoma is further discussed above for gastroesophageal adenocarcinoma.

For advanced biliary tract cancer, 1L SOC is chemotherapy with gemcitabine/cisplatin based on the ABC-02 study and BT22 study in Japan, and more recently combined with anti-PD-1/L1 immunotherapy in the TOPAZ-1 and KEYNOTE-966 studies [Valle, J., et al 2010] [Okusaka, T., et al 2010] [Oh, D. Y., et al 2022] [Kelley, R. K., et al 2023]. 2L chemotherapy offers a minimal 1-month improvement in OS over active symptom control (6.2 vs. 5.3 months, p=0.031), as shown for FOLFOX in the ABC-06 study [Lamarca, A., et al 2021]. Less toxic and more effective 2L treatment options for advanced biliary tract cancer are needed.

For pancreatic cancer, 1L SOC for fit patients is intensive chemotherapy with FOLFIRINOX or the emerging regimen NALIRIFOX vs. gemcitabine/nab-paclitaxel or S-1 in other clinical settings, including less fit patients and patients treated in Japan [Conroy, T., et al 2011] [Wainberg, Z. A., et al 2023] [Von Hoff, D. D., et al 2013] [Imaoka, H., et al 2016]. For 2L treatment, the combination of liposomal irinotecan and 5-FU/LV was superior to 5-FU/LV in the NAPOLI-1 study with OS 6.2 vs. 4.2 months (HR=0.75; 95% CI: 0.57, 0.99, p=0.039) [Wang-Gillam, A., et al 2019]. Older or less fit patients may benefit from single-agent chemotherapy as opposed to combinations [Lewis, A. and Nagrial, A. 2023]. Novel approaches to improve response duration and decrease toxicity are needed in both the 1L and 2L settings.

2.2.2 Ongoing Clinical Studies

CCI



Refer to the MK-1200 IB for additional details about ongoing clinical studies.

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.

Risk/benefit and alternative treatments should be discussed between the treating physician and the participant, as guided by the informed consent document.

Given the unmet medical need that exists for patients with advanced malignancies, new agents are needed. Preclinical data suggest that MK-1200 may be broadly effective against advanced malignancies including those positive for Claudin 18.2.

CCI

In general, topoisomerase inhibitors (including irinotecan) are associated with diarrhea, nausea/vomiting, myelosuppression, and elevated liver enzymes [Cunningham, D., et al 1998]. The most common AEs associated with zolbetuximab Claudin 18.2 mAb treatment are nausea/vomiting and decreased appetite [Shitara, K., et al 2023] [Shah, M. A., et al 2023].

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In individuals of any sex/gender ≥18 years of age with various advanced/metastatic solid tumors:

Primary Objective	**Primary Endpoint**
Objective: To evaluate the safety and tolerability of MK-1200 monotherapy (Part 1 and Part 2)	DLT (Part 1 only) AE Discontinuing study intervention due to an AE
Secondary Objectives	**Secondary Endpoints**
Objective: To evaluate the antitumor activity of MK-1200 monotherapy during randomized dose evaluation at 2 different doses as measured by ORR per RECIST 1.1 as assessed by BICR (Part 2 Cohort A)	Objective response: CR or PR
Objective: To evaluate the antitumor activity of MK-1200 monotherapy measured by ORR per RECIST 1.1 as assessed by the investigator (Part 1 and Part 2 Cohort B)	Objective response: CR or PR
Objective: To evaluate the PK of MK-1200 monotherapy (Part 1 and Part 2)	PK parameters such as AUC, C_{min}, and C_{max}
Objective: To evaluate the antitumor activity of MK-1200 monotherapy as assessed by BICR (as appropriate) and measured by DOR, PFS, and OS (Part 2 Cohort A)	DOR: For participants who show confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever comes first OS: The time from randomization to death due to any cause

Objective: To evaluate the antitumor activity of MK-1200 monotherapy as assessed by the investigator (as appropriate) and measured by DOR, PFS, and OS (Part 1 and Part 2 Cohort B)	DOR: For participants who show confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first PFS: The time from first dose to the first documented disease progression or death due to any cause, whichever comes first OS: The time from first dose to death due to any cause
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
Objective: To evaluate the development of circulating anti-MK-1200 antibodies after administration of MK-1200 monotherapy (Part 1 and Part 2)	ADA levels
Objective: 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-1200 monotherapy (Part 1 and Part 2)	Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood, and/or tumor tissue
Objective: To evaluate the relationship between expression of Claudin 18.2 and clinical response to MK-1200 monotherapy (Part 1 and Part 2)	Claudin 18.2 expression

4 STUDY DESIGN

4.1 Overall Design

This is an open-label, multicenter, Phase 1/2 study to evaluate the safety and efficacy of MK-1200 monotherapy.

In Part 1, MK-1200 dose escalation and MTD will be assessed (Section 4.3.2) in participants with advanced/metastatic gastric/GEJ cancer, esophageal cancer, biliary tract cancer, and pancreatic ductal adenocarcinoma who have received, or been intolerant to, SOC treatments.

In Part 2, participants will be allocated/randomized into the following cohorts:

- Cohort A: 80 participants with 2L or 3L gastric/GEJ cancer randomized 1:1 to 2 different doses of MK-1200
  - Participants will be stratified according to which line of therapy MK-1200 is for them (2L or 3L)
  - 3L enrollment will be capped at 20 participants
- Cohort B: 120 participants with esophageal cancer (n=40), biliary tract cancer (n=40), and pancreatic ductal adenocarcinoma (n=40)

Additional cohorts for evaluation of combination treatments are forthcoming.

Intervention allocation/randomization will occur centrally using an IRT system.

In Part 2, Cohort A will be a randomized dose evaluation cohort for evaluation of MK-1200 safety and efficacy at 2 different doses (corresponding to 2 intervention arms). Participants will be randomly assigned to the 2 arms in a 1:1 ratio. Cohort B will include a basket of gastrointestinal cancers for additional evaluation of MK-1200 safety and efficacy across tumor types.

Participants will receive MK-1200 at the assigned dose until one of the criteria for discontinuation of study intervention (Section 7.1) is met or the participant withdraws from the study. There is no protocol-defined limit on the number of treatment cycles for MK-1200. The criteria for dose modification of MK-1200 and definition of DLTs are outlined in Section 6.6.1 and Section 6.6.2, respectively.

The first on-study tumor scan should be performed at 6 weeks (42 days +7 days) from the date of intervention allocation/randomization. Subsequent tumor scans should be performed every 6 weeks (±7 days) up to Week 54 (±7 days), and every 12 weeks (±14 days) thereafter, or more frequently as clinically indicated. Details for tumor imaging and assessments are provided in Section 8.2.1.

Participants who discontinue from treatment for reasons other than radiographic disease progression will have posttreatment follow-up imaging to assess disease status until any of the conditions for discontinuation of imaging are met (as discussed in Section 8.2.1.3).

Preliminary efficacy will be evaluated using ORR assessed by BICR (Part 2 Cohort A) or investigator (Part 1 and Part 2 Cohort B) as secondary endpoints. Additional efficacy endpoints include DOR, PFS, and OS. Nonbinding futility analyses will be performed for Part 2 as described in Section 9.6. After disease progression per RECIST 1.1 by investigator and/or initiation of a subsequent anticancer treatment, all participants will be followed for survival (by phone contact or clinic visit) until death, withdrawal of consent, loss to follow-up, or until the study is concluded or terminated early, whichever occurs first.

AEs and SAEs will be reported for participants for the time periods specified in Section 8.4.1 and will be graded for severity according to the guidelines outlined in the NCI CTCAE, Version 5.0.

The study design is summarized in Figure 1. See Appendix 7 for country-specific requirements.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 (Table 1 and Table 2) of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

A secondary objective for this study is to evaluate the antitumor activity of MK-1200 monotherapy as measured by ORR per RECIST 1.1 in participants with advanced solid tumors, as detailed in the Inclusion Criteria (Section 5.1).

Because findings from Part 2 Cohort A will help determine the dose for future studies in the MK-1200 program, ORR in this cohort will be assessed by BICR to eliminate variability associated with investigator assessment. In contrast, ORR in Part 1 and Part 2 Cohort B will be assessed by investigator because the purpose of this cohort is signal finding, which neither requires the precision of BICR nor justifies the logistical challenge of its implementation. However, confirmation of investigator assessments by BICR may be considered for Part 1 and Part 2 Cohort B if promising signals are found.

Other efficacy endpoints include DOR, PFS, and OS. CCI [redacted]

Efficacy endpoints are further described in Section 9.3.1.

4.2.1.2 Safety Endpoints

The primary objective of this study is to evaluate the safety and tolerability of MK-1200 monotherapy in participants with advanced solid tumors, as detailed in the Inclusion Criteria (Section 5.1). Reported verbatim terms of all AEs will be coded to a preferred term according to MedDRA.

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 5.0.

4.2.1.3 Pharmacokinetic Endpoints

A secondary objective of this study is to characterize the PK profile of MK-1200 monotherapy after administration. The serum concentrations of MK-1200 will serve as the primary readout for the PK, and these data will be used to derive PK parameters of MK-1200 monotherapy. Furthermore, the results of this analysis will be used in conjunction with the pharmacodynamics, safety, and exploratory endpoint data to help assess future dosing strategies for MK-1200.

4.2.1.4 Antidrug Antibodies

Formation of ADA can potentially confound drug exposures at therapeutic doses and prime for subsequent infusion-related toxicity. ADA response at the beginning of each cycle will be determined to understand drug metabolism, exposure, and safety. The incidence of ADA and neutralizing ADA will be evaluated and summarized over time by dose. Correlations between the presence/absence of positivity for ADA and PK and pharmacodynamic markers, activity, and safety of MK-1200 will be explored.

4.2.1.5 Planned Exploratory Biomarker Research

The mechanism of action of many antitumor agents is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer treatments. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapy with antineoplastic drugs. To identify novel biomarkers, biospecimens (eg, blood components, tumor material, etc) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include, but are not limited to the following:

Germline 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, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations.

Genetic (DNA) tumor analyses

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify important tumor-specific DNA changes (eg, mutations,

methylation status, microsatellite instability, etc). Key molecular changes of interest to oncology drug development may also include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (eg, colorectal cancer). Genome-wide approaches may be used for this effort. Note that to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Circulating tumor DNA may also be evaluated from biospecimens (eg, blood, urine, etc).

Tumor and/or blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that might correlate to clinical response to treatment with antitumor therapies. Specific gene sets (eg, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Expression of individual genes may also be evaluated. MicroRNA profiling may also be pursued as well as exosomal profiling. Circulating tumor RNA may also be evaluated from biospecimens (eg, blood, urine, etc).

Immunohistochemical (IHC) and/or proteomic analyses using tumor

Tumor samples from this study may undergo histopathological (eg, PD-L1 IHC), proteomic, and/or immunological analyses. These approaches could identify novel protein biomarkers that could aid in patient selection for antitumor therapy.

Other biomarkers

In addition to expression on the tumor tissue, tumor-derived proteins can be shed from tumor and released into the blood. Assays such as ELISA may be used to measure such proteins in serum and/or plasma. Correlation of expression with response to therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers.

Other molecular changes of interest may include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated. Furthermore, when applicable, cell populations may be also separated by either flow cytometry or mass cytometry-based sorting. These approaches may be used to quantify cell- and/or tissue-based analytes to further elucidate mechanism of action and/or assess disease-related parameters.

4.2.1.6 Future Biomedical Research

The Sponsor will conduct FBR 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 FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented

participants. The objective of collecting/retaining specimens for FBR 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 FBR research are presented in Appendix 6.

4.2.2 Rationale for Stratification (Part 2 Cohort A)

Stratification by line of therapy in Part 2 Cohort A is to account for differing prognoses of participants, as 2L participants have earlier-stage disease and unequivocally better prognoses than 3L participants [Wilke, H., et al 2014] [Shitara, K., et al 2018].

4.3 Justification for Dose

4.3.1 Justification for MK-1200 Dose

The safety and tolerability of escalating doses of MK-1200 is currently being evaluated in a Phase 1 clinical study (SKB315-I-01) run by MSD's strategic partner, Kelun-Biotech. SKB315-I-01 is evaluating the safety and tolerability of CCI [redacted]

CCI [redacted] The highest planned dose level of MK-1200 CCI [redacted] is below the human equivalent of the HNSTD in cynomolgus monkeys CCI [redacted]

As of CCI [redacted] and received MK-1200 doses of CCI [redacted] with no DLTs observed. Escalation proceeded using a BLRM with overdose control. CCI [redacted]

CCI [redacted]

Dose escalation will continue in Part 1 of this study using the mTPI-2 method (Section 4.3.2) using the dose levels summarized in Figure 1 until a preliminary MTD is determined.

4.3.2 Dose Finding Using a Modified Toxicity Probability Interval 2 Design in Part 1

Dose finding will follow the mTPI-2 design [Guo, W., et al 2017] with a target DLT rate of 27%. Dose-escalation and deescalation decisions are based on the mTPI design and depend on the number of participants enrolled and number of participants with at least 1 DLT observed at the current dose level.

A minimum of 3 participants are required at each dose. However, depending on the accrual rate, 3, 4, 5, or 6 participants may be enrolled within 7 to 14 days of the opening of a dose cohort. In order to allow for sentinel dosing, no two participants will be allowed to receive the first dose of study intervention on the same day. In Table 3, the columns indicate the numbers of participants treated at the current dose level, and the rows indicate the numbers of participants experiencing DLT. The entries of the table are the dose-finding decisions: E, S, D, and DU represent escalating the dose, staying at the same dose, deescalating the dose, and excluding the dose from the study due to unacceptable toxicity, respectively. A dose is deemed unacceptably toxic if, given the observed data, we have high confidence (posterior probability >95%) that the DLT rate is >27%. For example, if 0 of 3 participants at a given dose level develop a DLT, then the dose can escalate to the next level. If 1 or 2 participants of 3 develop a DLT, the dose will be deescalated to the next lower dose level, but may be reescalated at a later time if the lower dose is well-tolerated. If 3 of 3 participants develop a DLT, this indicates an unacceptable toxicity at this dose. The dose should be deescalated, if allowed per protocol, and the current dose will not be explored further.

In general, the number of additional participants to be enrolled to a dose is capped to minimize the exposure to a dose that may be unacceptably toxic (denoted as DU in Table 3). To determine how many more participants can be enrolled at the dose level, one can count steps in diagonal direction (down and to the right) from the current cell to the first cell marked DU. For example, if 1 of 3 participants have experienced a DLT at a given dose level, no more than an additional 2 participants should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 2 of the additional participants experience a DLT (ie, 3/5 participants with DLT in Table 3). The number of additional participants to be enrolled to a dose level will not exceed 3.

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

After 14 participants have been enrolled at any of the tested doses (including intermediate doses), dose finding will stop if the mTPI-2 table indicates “S” for staying at current dose. Otherwise, up to 14 new participants may be enrolled at a lower dose if “D” or “DU” is indicated, or at a higher dose if “E” is indicated.

The pool-adjacent-violators algorithm [Ji, Y., et al 2007] will be used to estimate the DLT rates across doses. The dose with an estimated DLT rate closest to 27% will be treated as a preliminary MTD. However, the totality of the data will be considered before deciding on the dose(s) to carry forward to dose expansion (eg, Part 2 or Phase 2) and the escalation schedule may be adjusted based on data emerging throughout the study.

Note that although 27% was the target toxicity rate used to generate the guidelines in Table 3, the observed rates of participants with DLTs at the MTD may be slightly above or below 27%.

Table 3 Dose-finding Rules per mTPI-2 Design

Number of Participants With At Least 1 DLT	**Number of Participants Evaluable for DLT at Current Dose**											
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
0	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	E	E	E	E	E	E	E	E	E	E
2	D	D	D	D	S	S	S	E	E	E	E	E
3	DU	DU	DU	D	D	D	D	S	S	S	S	E
4		DU	DU	DU	DU	D	D	D	D	D	S	S
5			DU	DU	DU	DU	DU	DU	D	D	D	D
6				DU	DU	DU	DU	DU	DU	DU	D	D
7					DU	DU	DU	DU	DU	DU	DU	DU
8						DU	DU	DU	DU	DU	DU	DU
9							DU	DU	DU	DU	DU	DU
10								DU	DU	DU	DU	DU
11									DU	DU	DU	DU
12										DU	DU	DU
13											DU	DU
14												DU

D=Deescalate to the next lower dose; DLT=dose-limiting toxicity; DU=The current dose is unacceptably toxic; E=Escalate to the next higher dose; mTPI=modified toxicity probability interval; S=Stay at the current dose.
Target toxicity rate = 27%
Flat noninformative prior Beta (1,1) is used as a prior and $\varepsilon1=\varepsilon2=0.05$.

4.3.3 Part 2 Dose Levels

Once an MTD is determined in Part 1, the totality of data collected in Part 1 will be used to determine the dose level to evaluate in Part 2 (the dose for Part 2 will not exceed the MTD from Part 1). The randomized dose evaluation in Part 2 Cohort A will use the Part 1 MTD and an additional lower dose as the two doses for evaluation.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

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 if the number of discontinuations for administrative reasons is too high.

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

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

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-1200.

Refer to Section 6.6 and Section 7.1 for criteria for study intervention discontinuation for individual participants, and Appendix 1.10 for criteria for early closure of a study site. In the event that >33% of trial participants in a given study intervention arm experience a Grade ≥4 drug-related AE, as determined by the investigator, enrollment into that arm will be paused and all available safety data will be reviewed to inform further decisions on study conduct.

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Has a confirmed advanced (unresectable and/or metastatic) solid tumor in one of the following parts:

<table>
<tr><th colspan="2">Part 1</th></tr>
<tr><td colspan="2">Gastric cancer (including GEJ cancer), esophageal cancer, biliary tract cancer or pancreatic ductal adenocarcinoma</td></tr>
<tr><th colspan="2">Part 2</th></tr>
<tr><th>Cohort</th><th>Tumor Type</th></tr>
<tr><td>A</td><td>Gastric cancer (including GEJ cancer)</td></tr>
<tr><td rowspan="3">B</td><td>Esophageal cancer</td></tr>
<tr><td>Biliary tract cancer</td></tr>
<tr><td>Pancreatic ductal adenocarcinoma</td></tr>
<tr><td colspan="2">Note: See cohort-specific criteria (Sections 5.1.1 through 5.1.5) for details and any additional criteria for diagnosis and prior therapies.</td></tr>
</table>

Demographics

2. Is an individual of any sex/gender, from 18 years of age inclusive at the time of providing the informed consent or assent, as applicable.

Male Participants

3. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The length of time required to continue contraception for the study intervention is: 98 days according to the IB.

- Refrains from donating sperm
  PLUS either:

- Abstains from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent
  OR

- Uses contraception as detailed below unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:
  - Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant PLUS partner use of an additional contraceptive method, as a condom may break or leak.
    Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use a penile/external condom during each episode of sexual activity in which the partner is at risk of drug exposure via ejaculate.
  - Contraceptive use by participants capable of producing sperm should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed according to IB.

Female Participants

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

- Is not a POCBP
  OR

- Is a POCBP and:
  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or is abstinent from penile-vaginal 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 the time needed to eliminate the study intervention after the last dose of study intervention. The participant agrees not to donate eggs (ova, oocytes) to others or freeze/store eggs during this period for the purpose of reproduction. The length of time required to continue contraception for the study intervention is: 188 days according to the IB.
  - The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed according to the IB.
  - Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.6.
  - Abstains from breastfeeding during the study intervention period and for at least 188 days after study intervention.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

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

Additional Categories

6. Measurable disease by RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions.
7. Archival tumor tissue sample or newly obtained biopsy of a tumor lesion not previously irradiated has been provided. Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

8. Participants who have AEs due to previous anticancer therapies must have recovered to ≤Grade 1 or baseline. Participants with endocrine-related AEs who are adequately treated with hormone replacement or participants who have ≤Grade 2 neuropathy are eligible.
9. HIV-infected participants must have well controlled HIV on ART, defined as:
    a. Participants on ART must have a CD4+ T-cell count ≥350 cells/mm^3 at the time of screening
    b. Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks before screening
    c. It is advised that participants must not have had any AIDS-defining opportunistic infections within the past 12 months
    d. Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before study entry (Day 1) and agree to continue ART throughout the study
    e. The combination ART regimen must not contain any antiretroviral medications that interact with CYP3A4 inhibitors/inducers/substrates (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)
    f. *Note:* HIV screening tests are <u>not</u> required unless there is a known history of HIV infection or if mandated by local health authority

10. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to allocation.

    Note: Participants should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention.

    Hepatitis B screening tests are required for participants with biliary tract cancer. For all other participants, this testing is not required unless:

    - Known history of HBV infection
    - As mandated by local health authority

11. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.

    Note: Participants must have completed curative antiviral therapy at least 4 weeks prior to allocation.

    Hepatitis C screening tests are not required unless:

    - Known history of HCV infection
    - As mandated by local health authority

12. An ECOG performance status of 0 to 1 assessed within 3 days before intervention allocation/randomization.

13. Adequate organ function as defined in the following table (Table 4). Specimens must be collected within 7 days before the start of study intervention.

Table 4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100,000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L [a]
Renal	
Measured or calculated creatinine clearance [b]	≥50 mL/min
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	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl=creatinine clearance; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Cockcroft-Gault CrCl formula = [[140 – age (yr)] × weight(kg)] / [72 × serum Cr (mg/dL) × 0.85 for females]. As an alternative, CrCl can be determined from a 24-hour urine collection

5.1.1 Part 1 Specific Inclusion Criteria

14. Have a histologically or cytologically confirmed diagnosis of one of the following tumor types and has received, or been intolerant to, all available SOC treatments:
    a. Gastric or GEJ adenocarcinoma that is metastatic
    b. Adenocarcinoma or SCC of the esophagus or Siewert type 1 adenocarcinoma of the EGJ (defined as adenocarcinomas of the lower esophagus with the center located within 1 cm to 5 cm above the anatomic EGJ) that is unresectable and/or metastatic
    c. CCA (intrahepatic or extrahepatic) or gall bladder cancer (collectively called biliary tract cancer) that is unresectable and/or metastatic
    d. Pancreatic ductal adenocarcinoma that is metastatic. Histology other than adenocarcinoma, including mixed histologies, is not allowed.

See Appendix 7 for country-specific requirements.

5.1.2 Part 2 - Gastric Cancer (Cohort A) Specific Inclusion Criteria

15. Have histologically or cytologically confirmed gastric or GEJ adenocarcinoma that is metastatic. Participants with SCC or undifferentiated histology are not eligible.
16. Have HER2-negative cancer. HER2-negative is defined as: IHC (0 or 1+) or FISH-negative (HER2:CEP17 ratio <2 with an average HER2 copy number <4.0 signals/cell). FISH can be replaced with locally available ISH methods acceptable as per institutional guidelines.
17. Have received and progressed on or after 1 or 2 prior lines of therapy for their metastatic gastric cancer. This cohort will include only 2L and 3L participants, and 3L enrollment will be capped at 20 participants.

    Note: Treatment with neoadjuvant/adjuvant treatment, given as chemotherapy or chemoradiotherapy, using SOC agents or definitive chemoradiation, will count as a line of therapy if disease progression occurs during treatment or within 6 months of cessation of treatment.

    Note: To be considered 2L, the participant needs to have documentation of disease progression on 1L treatment. The disease progression can be confirmed by CT or by clinical evidence (such as cytology report from newly developed ascites and pleural effusion). To be considered 3L, the participant needs similar documentation of disease progression on 2L treatment.

    Note: All systemic cytotoxic chemotherapy, including ADCs with a cytotoxic payload, biologics, tyrosine kinase inhibitors, immunotherapies, and investigational agents are considered prior lines of therapy.

    Note: Definitive surgical intervention with curative intent and radiation therapy or systemically administered radiopharmaceutical therapy are **NOT** considered prior lines of therapy.

    Note: Switching to a different treatment regimen is considered a new line of therapy **UNLESS** the switch was due to toxicity and is to a regimen with the same mechanism of action (eg, cisplatin to carboplatin). Treatment interruptions do not count as a new line of therapy.

    Note: Maintenance regimens administered with the purpose of maintaining response after treatment are not considered lines of therapy.

5.1.3 Part 2 - Esophageal Cancer (Cohort B) Specific Inclusion Criteria

18. Have histologically or cytologically confirmed adenocarcinoma or SCC of the esophagus or Siewert type 1 adenocarcinoma of the EGJ (defined as adenocarcinomas of the lower esophagus with the center located within 1 cm to 5 cm above the anatomic EGJ) that is unresectable and/or metastatic.
19. *For participants with Siewert type 1 adenocarcinoma of the EGJ:* Have HER2-negative cancer. HER2-negative is defined as: IHC (0 or 1+) or FISH-negative (HER2:CEP17 ratio <2 with an average HER2 copy number <4.0 signals/cell). FISH can be replaced with locally available ISH methods acceptable as per institutional guidelines.

20. Have received and progressed on or after 1 or 2 prior lines of therapy for their esophageal cancer. This cohort will include only 2L and 3L participants.

    Note: Treatment with neoadjuvant/adjuvant treatment, given as chemotherapy or chemoradiotherapy, using SOC agents or definitive chemoradiation, will count as a line of therapy if disease progression occurs during treatment or within 6 months of cessation of treatment.

    Note: To be considered 2L, the participant needs to have documentation of disease progression on 1L treatment. The disease progression can be confirmed by CT or by clinical evidence (such as cytology report from newly developed ascites and pleural effusion). To be considered 3L, the participant needs similar documentation of disease progression on 2L treatment.

    Note: All systemic cytotoxic chemotherapy, including ADCs with a cytotoxic payload, biologics, tyrosine kinase inhibitors, immunotherapies, and investigational agents are considered prior lines of therapy.

    Note: Definitive surgical intervention with curative intent and radiation therapy or systemically administered radiopharmaceutical therapy are **NOT** considered prior lines of therapy.

    Note: Switching to a different treatment regimen is considered a new line of therapy **UNLESS** the switch was due to toxicity and is to a regimen with the same mechanism of action (eg, cisplatin to carboplatin). Treatment interruptions do not count as a new line of therapy.

    Note: Maintenance regimens administered with the purpose of maintaining response after treatment are not considered lines of therapy.

5.1.4 Part 2 - Biliary Tract Cancer (Cohort B) Specific Inclusion Criteria

21. Have histologically or cytologically confirmed CCA (intrahepatic or extrahepatic) or gall bladder cancer (collectively called biliary tract cancer) that is unresectable and/or metastatic.

    Note: Ampullary cancer is not allowed. Small cell cancer, lymphoma, sarcoma, neuroendocrine tumors, mixed tumor histology, and/or mucinous cystic neoplasms are not allowed.

22. Have received and progressed on or after 1 or 2 prior lines of therapy for their biliary tract cancer (that contains gemcitabine or fluoropyrimidine). This cohort will include only 2L and 3L participants.

    Note: Prior adjuvant systemic cytotoxic chemotherapy used in the initial treatment is not considered a prior line of therapy unless such treatments were completed within 6 months before the current tumor recurrence.

    Note: To be considered 2L, the participant needs to have documentation of disease progression on 1L treatment. The disease progression can be confirmed by CT or by clinical evidence (such as cytology report from newly developed ascites and pleural effusion). To be considered 3L, the participant needs similar documentation of disease progression on 2L treatment.

Note: All systemic cytotoxic chemotherapy, including ADCs with a cytotoxic payload, are considered prior lines of therapy.

Note: Definitive surgery with curative intent and radiation therapy or systemically administered radiopharmaceutical therapy are **NOT** considered prior lines of therapy.

Note: Switching to a different treatment regimen is considered a new line of therapy **UNLESS** the switch was due to toxicity and is to a regimen with the same mechanism of action (eg, cisplatin to carboplatin). Treatment interruptions do not count as a new line of therapy.

Note: Maintenance regimens administered with the purpose of maintaining response after treatment are not considered lines of therapy.

Note: TACE or other locoregional therapies are allowed but are not counted as prior lines of therapy.

5.1.5 Part 2 - Pancreatic Ductal Adenocarcinoma (Cohort B) Specific Inclusion Criteria

23. Have histologically or cytologically confirmed pancreatic ductal adenocarcinoma that is metastatic. Histology other than adenocarcinoma, including mixed histologies, is not allowed.
24. Have received and progressed on or after 1 or 2 prior lines of therapy for their pancreatic cancer (platinum-containing regimen or gemcitabine-containing regimen). This cohort will include only 2L and 3L participants.

    Note: Participants with known deleterious BRCA mutation (germline) should have received a platinum-containing regimen (with or without maintenance PARP inhibitors) to be eligible.

    Note: Maintenance regimens administered with the purpose of maintaining response after treatment will not be considered as separate lines of therapy. For example, PARP inhibitor maintenance therapy after initial chemotherapy will be counted as 1 line of systemic therapy (such as FOLFIRINOX followed by olaparib for BRCA-mutated pancreatic cancer). Participants who have not received PARP maintenance after initial platinum-based chemotherapy for known BRCA-mutated pancreatic cancer but initiate PARP therapy alone after 1L chemotherapy will be counted as a separate line of therapy, provided PARP therapy was given after documented disease progression after initial chemotherapy.

    Note: Prior adjuvant and neoadjuvant systemic cytotoxic chemotherapy used in the initial treatment is not considered a prior line of therapy unless such treatments were completed within 6 months before the current tumor recurrence.

    Note: To be considered 2L, the participant needs to have documentation of disease progression on 1L treatment. The disease progression can be confirmed by CT or by clinical evidence (such as cytology report from newly developed ascites and pleural effusion). To be considered 3L, the participant needs similar documentation of disease progression on 2L treatment.

    Note: All systemic cytotoxic chemotherapy, including ADCs with a cytotoxic payload, are considered prior lines of therapy.

Note: Definitive surgical intervention with curative intent and radiation therapy or systemically administered radiopharmaceutical therapy are **NOT** considered prior lines of therapy.

Note: Switching to a different treatment regimen is considered a new line of therapy **UNLESS** the switch was due to toxicity and is to a regimen with the same mechanism of action (eg, cisplatin to carboplatin). Treatment interruptions do not count as a new line of therapy.

Note: Locoregional therapies are not counted as lines of therapy.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Active severe digestive disease, including but not limited to complete or incomplete gastric outlet obstruction, persistent/recurrent vomiting, severe gastrointestinal hemorrhage, gastric or duodenal ulcers, acute gastrointestinal perforation, acute necrotizing pancreatitis, ulcerative enteritis, congenital megacolon, or Crohn's disease.
2. History of acute myocardial infarction; unstable angina; stroke or transient ischemic attack within 6 months prior to the first dose of study intervention; or Grade ≥2 congestive cardiac failure according to NYHA.
3. Congenital long QT syndrome.
4. Ventricular tachyarrhythmia or history of ventricular tachyarrhythmia.
5. Diabetes or hypertension that cannot be controlled by medication.
6. HIV-infected participants with a history of Kaposi’s sarcoma and/or Multicentric Castleman’s Disease.

Prior/Concomitant Therapy

7. *Part 2 Cohort A only:* Received prior therapy with topoisomerase 1 inhibitor (eg, irinotecan).
8. Received prior therapy with an anti-Claudin 18.2 agent.
9. Received strong cytochrome P450 (CYP3A4) inhibitors, inducers, or substrates within 2 weeks prior to the first dose of study intervention or within 5 half-lives of drug elimination, whichever is longer.
10. Received prior systemic anticancer therapy including investigational agents within 4 weeks or 5 half-lives, whichever is shorter, before intervention allocation/randomization.

11. Received prior radiotherapy within 2 weeks of start of study intervention, or has radiation-related toxicities, requiring corticosteroids.
    Note: Two weeks or fewer of palliative radiotherapy for non-CNS disease is permitted. The last palliative radiotherapy treatment must have been performed at least 7 days before the first dose of study intervention.

Prior/Concurrent Clinical Study Experience

12. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.

Diagnostic Assessments

13. QTc interval >470 msec (for female participants) or >450 msec (for male participants) at screening per Fridericia formula.
14. Clinically significant bradycardia (<50 bpm).
15. Known additional malignancy that is progressing or has required active treatment within the past 2 years.
    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded. Participants with low-risk early-stage prostate cancer (T1-T2a, Gleason score ≤6, and PSA <10 ng/mL) either treated with definitive intent or untreated in active surveillance with stable disease are not excluded.
16. Known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of progression) for at least 4 weeks as confirmed by repeat imaging performed during the study screening, are clinically stable and have not required steroid treatment for at least 14 days before the first dose of study intervention.
17. Active infection, requiring systemic therapy.
18. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
19. Known psychiatric or substance abuse disorder that would interfere with the participant’s ability to cooperate with the requirements of the study.
20. A known severe hypersensitivity reaction to MK-1200 and/or any of its excipients.

Other Exclusions

21. Participants who have not adequately recovered from major surgery or have ongoing surgical complications.

See Appendix 7 for country-specific requirements.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

Foods or alternative supplements that affect CYP3A4 activity should be avoided while receiving study intervention (Section 6.5).

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 rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

If a Full Screening assessment is performed within 28 days before Cycle 1 Day 1, then it does not need to be repeated during Rescreening unless specified otherwise in Section 1.3 (Table 1).

5.5 Participant Replacement Strategy

For safety monitoring in Part 1, all enrolled participants are required to meet safety evaluation criteria during Cycle 1 assessment. Replacement of a nonevaluable participant will occur if the participant is:

- Allocated, but not treated with study intervention
- Discontinued from study without completing required safety evaluations (excluding treatment-related AE discontinuation)
- Did not receive a complete dose of MK-1200 during infusion on Cycle 1 Day 1

Nonevaluable participants in Part 1 will not count toward total participant numbers for overall DLT assessment. If a DLT occurs during the DLT evaluation period, but participant shows clinical benefit, treatment may continue after Sponsor consultation and approval.

If a participant in the randomized dose evaluation cohort in Part 2 (Cohort A) withdraws from the study, a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. Participants in all other cohorts in Part 2 will not be replaced.

The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number. The study site should contact the Sponsor for the replacement participant's treatment/randomization number.

See Appendix 7 for country-specific requirements.

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 (ie, MK-1200) will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 5.

Country-specific requirements are noted in Appendix 7.

Table 5 Study Interventions

Arm Name	Arm Type	Intervention Name	Interven-tion Type	Dose Formula-tion	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Part 1	Experimental	MK-1200	Biological/ Vaccine	Solution	200 mg/vial	CCI	IV Infusion	Q2W	Test Product	IMP	Central by Sponsor
Part 2 Cohort A (Arm 1) and Cohort B	Experimental	MK-1200	Biological/ Vaccine	Solution	200 mg/vial	(Dose 1) mg/kg	IV Infusion	Q2W	Test Product	IMP	Central by Sponsor
Part 2 Cohort A (Arm 2)	Experimental	MK-1200	Biological/ Vaccine	Solution	200 mg/vial	(Dose 2) mg/kg	IV Infusion	Q2W	Test Product	IMP	Central by Sponsor
All Arms	Experimental	Antiemetic (eg, 5-HT3 Receptor)	Drug	Unassigned	Per Approved Product Label	Per Approved Product Label	Per Approved Product Label	Before MK-1200 Infusion	Rescue Medication	NIMP/ AxMP	Local

EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q2W=every 2 weeks

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

Prophylactic antiemetic is required for MK-1200. See Section 6.5.1.

MK-1200 will be provided centrally by the Sponsor, and required premedication will be provided locally (Table 5).

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

6.1.1 Treatment

The treatment of MK-1200 has no maximum number of cycles. Note: The number of treatments is calculated starting with the first dose. Treatment of MK-1200 will be initiated on Day 1 (+3 days) of Cycle 1 and should continue as described in the SoA (Table 1) until any of the criteria for discontinuation of study intervention (Section 7.1) are met. Refer to Section 8.1.8.1 for detailed information on the timing of MK-1200 infusions.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of MK-1200 is provided in the appropriate Pharmacy Manual.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation/randomization will occur centrally using an IRT system. In Part 2 Cohort A (randomized dose evaluation cohort), participants will be randomized 1:1 into 2 intervention arms, each corresponding to 1 of 2 doses of MK-1200. Participants in Part 1 and Part 2 Cohort B will be allocated by nonrandom assignment according to their tumor type.

6.3.2 Stratification

Intervention randomization in Part 2 Cohort A (randomized dose evaluation cohort) will be stratified according to which line of therapy MK-1200 is for the participant (2L or 3L).

6.3.3 Blinding

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

Imaging data for Part 2 Cohort A will be centrally reviewed by independent radiologist(s) without knowledge of participant dose assignment.

6.4 Study Intervention Compliance

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

Resumptions of protocol-specified treatment after interruptions that exceed or are expected to exceed 14 days from the originally scheduled dose (or 28 days from the last administered dose) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Participants will receive MK-1200 directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

6.5 Concomitant Therapy

If there is a clinical indication for any medications or vaccinations prohibited, the investigator must discuss any questions regarding this with the Sponsor's 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 and the Sponsor.

The following medications and vaccinations are prohibited during the study:

- Strong inhibitors, inducers, or substrates of CYP3A4 (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study, study intervention must be discontinued:

- Systemic antineoplastic chemotherapy, immunotherapy, or biological therapy not specified in this protocol
- Investigational agents other than those specified in this protocol
- Radiation therapy
  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion. Sponsor consultation is also required. If a participant received radiation therapy to a target lesion, they will no longer be evaluable per RECIST.
- Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.
  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the eCRF including all prescriptions, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

See Appendix 7 for country-specific requirements.

6.5.1 Rescue Medications and Supportive Care

Medications required to treat AEs or concurrent illnesses other than those prohibited in Section 6.5 are allowed during the study.

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Suggested supportive care measures for the management of AEs associated with study intervention are outlined along with the dose modification guidelines in Section 6.6.

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

Prophylactic dosing for nausea and vomiting is required prior to initial and subsequent study drug therapy. One or more of the following combinations may be selected based on previous response of participants to antiemetic medications and individual factors: 5-HT3 receptor antagonists, dexamethasone, NK-1 receptor antagonists, etc. Prophylactic dosing regimens may be adjusted if accompanied by other risk factors or in participants who have failed prophylaxis.

Prior to treatment with MK-1200, it is recommended that participants receive prophylactic treatment to mitigate the onset and severity of stomatitis/oral mucositis in accordance with published ASCO and MASCC/ISOO guidelines [Brown, T. J. and Gupta, A. 2020] [Elad, S., et al 2020]. Refer to Section 6.6.1 for information regarding recommended premedication to prevent hypersensitivity and/or infusion reactions.

For participants who have experienced a Grade 3 neutropenia, prophylactic use of G-CSF is indicated for subsequent cycles and described in [Table 6].

6.6 Dose Modification

If the participant experiences a ≥10% weight change, the dose of MK-1200 must be recalculated. The dose can be recalculated for changes in body weight <10% at the Investigator's discretion.

Dose reduction/interruption/discontinuation decisions should be made based on the CTCAE, Version 5.0 grade of the toxicity and the guidelines provided below. Dose modifications should be implemented according to guidelines in Section 6.6.1 regardless of investigator/Sponsor causality assessment and attribution to study intervention, unless clearly related to disease progression or intercurrent illness. Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

6.6.1 Guidelines for Dose Modification due to Adverse Events for MK-1200

Recommended dose modification guidelines for MK-1200 are provided in Table 6. A maximum of 2 dose reductions are allowed. Once the MK-1200 dose has been reduced due to a treatment-related AE as per the recommendations in Table 6, all subsequent doses should

be administered at the lower dose level unless further dose reduction is required (ie, reescalation is not permitted). If toxicity continues after all permitted dose reductions, then MK-1200 should be permanently discontinued.

A dosing delay due to treatment-related AEs that exceeds or is expected to exceed 14 days from the originally scheduled dose (or 28 days from the last administered dose) of study intervention should be discussed and approved by the Sponsor.

MK-1200 may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. Study intervention is to be restarted within 28 days from the last dose received, unless otherwise discussed with the Sponsor. The reason for study intervention interruptions described above should be documented in the participant's study record.

Table 6 MK-1200 Dose Modification and Treatment Discontinuation Guidelines for Drug-related Adverse Events

Event(s)	Toxicity Grade (CTCAE v5.0) / Result	Dose Delay or Modification
Hematologic Toxicities		
Anemia	Grade 3	• First occurrence: Delay until ≤Grade 2. • Recurrent Grade 3, reduce dose by one dose level. • Consider transfusion, as appropriate.
	Grade 4	• First occurrence: Delay until ≤Grade 2. • Recurrent Grade 4, reduce dose by one dose level or permanently discontinue. • Consider transfusion, as appropriate.
Neutropenia	≤Grade 1	• Maintain current dose and schedule.
	Grade 2	• Maintain current dose and schedule or delay until resolved to ≤Grade 1 at the investigator's discretion.
	Grade 3	• First occurrence: Delay until resolved to ≤Grade 2 or delay until resolved to ≤Grade 1 at the investigator's discretion. • Administer growth factors (eg, G-CSF) and repeat for all subsequent cycles per the ASCO guidelines and/or institutional standards. • Recurrent Grade 3, reduce dose by one dose level.
	Grade 4	• Permanently discontinue.
	Grade 3 febrile neutropenia	• First occurrence: Delay until resolved to <Grade 2 and reduce dose by one dose level. • Administer growth factors (eg, G-CSF) and repeat for all subsequent cycles per the ASCO guidelines and/or institutional standards. • Recurrent Grade 3 febrile neutropenia, reduce dose by one dose level.
	Grade 4 febrile neutropenia	• Permanently discontinue.

Event(s)	Toxicity Grade (CTCAE v5.0) / Result	Dose Delay or Modification
Thrombocytopenia	Grade 1 or 2	• Maintain current dose and schedule.
	Grade 3	• Delay until resolved to ≤Grade 2. • Recurrent Grade 3, reduce dose by one dose level. • Consider transfusion, as appropriate.
	Grade 4	• Permanently discontinue.
Thrombocytopenia	Spontaneous hemorrhage in vital organs	• Permanently discontinue.
Nonhematologic Toxicities		
Diarrhea	Grade 1	• Maintain current dose and schedule. • Evaluate for infectious or other causes of diarrhea and treat, as appropriate. Provide antidiarrheal support.
	Grade 2 or 3	• First occurrence: Delay until resolved to <Grade 2. • Evaluate for infectious or other causes of diarrhea and treat, as appropriate. Provide antidiarrheal support. • Recurrent Grade 3, reduce dose by one dose level.
	Grade 4	• Permanently discontinue.
Neurological Toxicities (including peripheral neuropathy)	Grade 1	• Maintain current dose and schedule
	Grade 2 or 3	• Delay until resolved to <Grade 2. • Recurrent Grade 3, reduce dose by one dose level.
	Grade 4	• Permanently discontinue.
Nonhematologic Toxicity Not Otherwise Specified	≤Grade 2	• Maintain current dose and schedule.
	Grade 3	• First occurrence: Delay until ≤Grade 2. • Recurrent Grade 3, reduce dose by one dose level.
	Grade 4	• Permanently discontinue.
Oral mucositis	Grade 1 or 2	• Provide supportive treatment (eg, non-alcohol or peroxide mouthwash and topical treatments) per local guidelines or institutional standards as soon as participant complains of a sore mouth.
	Grade 3	• First occurrence: Delay until ≤Grade 2. • Provide supportive treatment (eg, non-alcohol or peroxide mouthwash and topical treatments) per local guidelines or institutional standards. • Recurrent Grade 3, reduce dose by one dose level.
	Grade 4	• Permanently discontinue.
Rash	Grade 3	• First occurrence: Delay until ≤Grade 2. • Recurrent Grade 3, reduce dose by one dose level.
	Grade 4	• Permanently discontinue.
QTcF Prolongation	≥500 msec	• Withhold treatment until QTcF is <480 msec or returns to baseline. • Monitor potassium, calcium, and magnesium, and replenish as appropriate.
ASCO=American Society of Clinical Oncology; CTCAE=Common Terminology Criteria for Adverse Events; G-CSF=granulocyte colony-stimulating factor; QTcF=corrected QT interval by Fridericia. Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov		

If toxicity does not resolve to Grade 0 to 1 within 12 weeks after last intervention, MK-1200 should be discontinued after consultation with the Sponsor.

With investigator and Sponsor agreement, participants with a laboratory AE still at Grade 2 after 12 weeks may continue intervention in the study only if asymptomatic and controlled.

6.6.1.1 Management of Infusion Reactions for MK-1200

ADCs such as MK-1200 may cause severe or fatal infusion-related reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Premedication to prevent hypersensitivity and/or infusion reactions is strongly recommended prior to each dose of MK-1200. Participants should be premedicated 1.5 hours (±30 min) prior to infusion of MK-1200. For the first 4 administrations, participants should be premedicated with diphenhydramine (50 mg po [or equivalent dose of antihistamine]), H2 receptor antagonist (per local or institutional guidelines), acetaminophen (500 to 1000 mg po [or equivalent dose of analgesic]), and a corticosteroid (dexamethasone 10 mg IV [or equivalent]). After the fourth infusion, in the absence of prior infusion-related or hypersensitivity AEs, participants should be premedicated with diphenhydramine (50 mg po [or equivalent dose of antihistamine]) and acetaminophen (500 to 1000 mg po [or equivalent dose of analgesic]) with the addition of a corticosteroid at the discretion of the Investigator. Refer to Section 6.5.1 for information regarding required antiemetic premedication.

Dose modification and toxicity management of infusion reactions following MK-1200 administration are provided in Table 7.

Table 7 Infusion Reaction Dose Modification and Treatment Guidelines for MK-1200

NCI CTCAE v5.0 Grade	**Treatment**	**Premedication and Infusion Timing at Subsequent Dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	Participants are strongly recommended to be premedicated 1.5 hours (±30 min) prior to infusion of study intervention with:

NCI CTCAE v5.0 Grade	Treatment	Premedication and Infusion Timing at Subsequent Dosing
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Stop infusion. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.	• Diphenhydramine 50 mg po (or equivalent dose of antihistamine) • H2 receptor antagonist (per local or institutional guidelines) • Acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic) • Dexamethasone 10 mg IV (or equivalent). The duration of the MK-1200 infusion should be 90 (±15) minutes and infusion-related AEs will be monitored for all subsequent dosing. The infusion duration may be adjusted to be longer than 105 minutes at the discretion of the investigator, but the infusion of MK-1200 needs to be completed within the timeframe specified in the Pharmacy Manual.
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: • Epinephrine (used immediately in the case of anaphylaxis) • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Participant is permanently discontinued from further study intervention.	No subsequent dosing

AE= adverse event; CTCAE=Common Terminology Criteria for Adverse Events, Version 5.0; h=hour(s); IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs; po=oral(ly).
Note: Emergency rescue medications (including epinephrine) and appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov

6.6.2 Definition of Dose-limiting Toxicity

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

The DLT window of observation will be 28 days after the first dose of study intervention.

The occurrence of any of the following toxicities within 28 days after the first dose of study intervention will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study intervention administration.

- Grade 4 nonhematologic toxicity (not laboratory).
- Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions:
  - Grade 3 fatigue lasting ≤3 days;
  - Grade 3 diarrhea, nausea, or vomiting lasting <3 days. Any Grade 3 diarrhea, nausea, or vomiting lasting ≥3 days would be considered a DLT;
  - Grade 3 rash lasting <7 days. Any Grade 3 rash lasting ≥7 days or requiring treatment with systemic corticosteroids would be considered a DLT.
- Any Grade 3 or Grade 4 laboratory value (hematologic or nonhematologic), except for the following:
  - Grade 3+ electrolyte abnormalities that last <72 hours, are not clinically complicated, and resolve spontaneously or with conventional medical interventions.
  - Grade 3+ amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis.
  - Grade 3-4 anemia or Grade 3 neutropenia or thrombocytopenia (in the absence of clinically significant bleeding) responsive to medical management and that resolves to Grade ≤1 within 7 days.
  - For participants without hepatic metastases: AST or ALT >5x ULN that resolves to Grade ≤1 or baseline within 7 days.
  - For participants with hepatic metastases: AST or ALT >8x ULN that resolves to Grade ≤1 or baseline within 7 days.
- Febrile neutropenia Grade 3 or Grade 4:
  - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than 1 hour.
  - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Prolonged delay (>2 weeks) in initiating Cycle 2 due to intervention-related toxicity.
- Any intervention-related toxicity that causes the participant to discontinue intervention during Cycle 1.

- Missing >25% of MK-1200 doses as a result of drug-related AEs during the first cycle.
- Grade 5 toxicity.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.10.4 unless the participant has withdrawn from the study (Section 7.2).

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods as noted in Section 6.4 require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, place the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant requires any prohibited medications or vaccinations during the study (Section 6.5).
- Radiographic disease progression outlined in Section 8.2.1.4
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
  Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (excluding carcinoma in situ of the bladder) who have undergone potentially curative resection do not have to discontinue study intervention.

- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.
- Side effects and/or concomitant medications required for treatment of HIV and/or its complications that are incompatible with continued study treatment (exceptions are permissible but should be discussed with the Sponsor).

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

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 (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- 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 providing documented informed consent or assent, when applicable, may be used for screening or baseline purposes provided the procedures meet 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 or assent, when applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed the volume mentioned in the Laboratory Manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

See Appendix 7 for country-specific study assessments and procedures.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use.

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

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

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

8.1.1.1 General Informed Consent

Specifics about the study and the study population are to be included in the ICF.

The participant (or their legally acceptable representative) should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

If rescreening is performed, follow local regulatory requirement(s) to obtain documented informed consent.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after

the participant provides documented informed consent or assent (as applicable). At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

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

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 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 28 days before first dose of study intervention. However, treatment for a cancer other than the one under study will be recorded as a concomitant medication regardless of the time since enrollment. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

In addition to systemic/local treatment and vaccines, the investigator or qualified designee will review and record all other treatments for the cancer under study, including radiation and surgeries. Additional information collected on these treatments will include, but is not limited to, dates of administration, reason for therapy, reason for discontinuation, and response.

8.1.5.2 Concomitant Medications

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

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

Safety Follow-up Visit should occur before the first dose of the new therapy. Refer to Section 6.5 for exceptions (such as for permitted concomitant radiation therapy).

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation/randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.10.1. Pre-trial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.7 Assignment of Treatment/Randomization Number

8.1.7.1 Part 2 Cohort A

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

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

8.1.7.2 Part 1 and Part 2 Cohort B

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

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

8.1.8 Study Intervention Administration

Study intervention will be administered by the investigator and/or an appropriately qualified designee according to the specifications within the Pharmacy Manual.

Study intervention should begin within 3 days after intervention allocation/randomization and as close as possible to the date on which the participant is randomized.

8.1.8.1 Timing of Dose Administration

MK-1200 should be prepared following the instructions in the Pharmacy Manual.

MK-1200 will be administered by IV infusion on Day 1 of each 14-day cycle (see the SoA, Section 1.3). The duration of the MK-1200 infusions should be 90 minutes (±15 minutes). Infusion-related AEs will be monitored. The infusion duration may be adjusted to be longer than 105 minutes at the discretion of investigator, but the infusion of MK-1200 needs to be completed within the timeframe specified in the Pharmacy Manual. After at least 4 administrations and in the absence of either infusion-related AEs or anaphylactic reactions, the infusion of MK-1200 may be shortened at the discretion of investigator but cannot be shorter than 60 minutes.

Refer to Section 6.5.1 and Section 6.6.1.1 for premedication guidelines. Participants are to be closely monitored during infusions for the development of hypersensitivity reactions and/or infusion reactions. Emergency rescue medications (including epinephrine) and appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA (Section 1.3) and Section 8.10.4.

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

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 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.

8.1.12 Tumor Tissue for Biomarker Status

During the Screening Period, tumor tissue is required for each participant. The most recent tissue sample is preferred. Only tissue samples that have not been previously irradiated should be submitted. Formalin-fixed, paraffin embedded tissue blocks are strongly preferred to slides. Details about collection and submission of tumor tissue samples are provided in the Laboratory Manual. See Appendix 7 for country-specific requirements.

The central laboratory will use the tissue sample to ascertain Claudin 18.2 expression via IHC.

8.1.13 Participants with Treated HIV

Participants with treated HIV should continue ongoing management of HIV during the study, including monitoring of HIV viral load, CD4+ T-cell count, and additional supportive care measures.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

Throughout this section, the term ‘scan’ refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. The process for scan collection, submission, and/or retention can be found in the SIM. Tumor scans by CT are strongly preferred. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same scan 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 scans.

Note: For the purposes of assessing tumor scans, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

If brain scans are performed, magnetic resonance imaging is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Bone scans may be performed to evaluate bone metastases. Any supplemental scans performed to support a positive or negative bone scan, such as plain X-rays acquired for correlation, should also be submitted and/or retained as specified in the SIM.

Other imaging modalities that may be collected, submitted and/or retained, and included in the response assessment include PET-CT. Other types of medical imaging (such as ultrasound) should not be submitted and will not be included in response assessment.

At screening, participant eligibility will require radiographic documentation of at least one lesion that meets the requirements for selection as a target lesion, as defined by RECIST 1.1, prior to participant intervention allocation/randomization.

All scheduled scans for participants will be submitted to the iCRO. In addition, a scan 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 disease progression, or if it is used to support a response assessment. All scans acquired within the protocol-specified window of time around a scheduled scan visit are to be classified as pertaining to that visit.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days prior to the date of intervention allocation/randomization. Any scans obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The site must review screening scans to confirm the participant has measurable disease per RECIST 1.1.

If there is a known history of brain metastases or brain metastases are suspected, a brain scan is required at screening.

Bone scans are required at screening for participants with a history of bone metastases and/or for those participants with indicative clinical signs/symptoms such as bone pain or elevated alkaline phosphatase levels.

Bone scan refers to imaging methods used to assess bone metastasis. The specific methods permitted for this study are described in the SIM.

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 6 weeks (42 days +7 days) from the date of intervention allocation/randomization. Subsequent tumor scans should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After 54 weeks (378

days ±7 days), participants will have scans performed every 12 weeks (84 days ±14 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

Scans are to be performed until disease progression is identified by the investigator or until any of the conditions in Section 8.2.1.3 are met.

Objective response should be confirmed by a repeat scan performed at least 4 weeks after the first indication of a response is observed. Participants will then return to the regular scan schedule, starting with the next scheduled time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

On-study brain or bone scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain or bone lesions existed at baseline).

8.2.1.3 End-of-treatment and Follow-up Tumor Scans

If participants discontinue study intervention, tumor scans should be performed at the time of discontinuation (±4-week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of intervention allocation/randomization. Refer to Section 8.2.1.2.

Scans are to be continued until one of the following conditions are met:

- disease progression as defined by RECIST 1.1
- the start of a new anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

8.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention).

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 Laboratory Manual.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

8.3.1.1 Full Physical Examination

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

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 examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

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

8.3.2 Vital Signs

- Temperature, pulse oximetry (SpO_2), heart rate, RR, and BP will be assessed by institutional standard.
- BP and pulse measurements will be assessed per institutional standards with a completely automated device. Manual techniques will be used only if an automated device is not available.

- BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

8.3.3 Electrocardiograms

Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures pulse rate, QRS, QT, and QTc intervals. Electronic records should be added (if possible) and archived. Refer to Appendix 10.3.2 for evaluation and potentially significant findings.

8.3.4 Echocardiogram or Multigated Acquisition Scan

A MUGA scan (using technetium-based tracer) or an ECHO will be performed to assess LVEF as designated in the SoA (Section 1.3). MUGA or ECHO scans should be performed locally in accordance with the institution's standard practice. Whichever modality is used for an individual participant at baseline should be used for any subsequent LVEF assessments for that participant. Investigator assessment will be based upon institutional reports.

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 (Section 1.3).
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. 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 Laboratory Manual. Refer to the Study Flow Chart (Section 1.3) for the timing of laboratory assessments.

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

8.3.6 Pregnancy Testing

Pregnancy testing requirements for study inclusion are described in Section 5.1.

Postmenopausal women who have not had menses for >12 months must have 2 FSH tests.

Pregnancy testing (urine or serum) should be conducted every 2 weeks.

- Home pregnancy tests are acceptable when a scheduled visit does not occur within the month (per local regulation); however, study-site personnel must conduct a monthly contact with the participant to determine the results of the pregnancy test.
- For treatment delays ≥28 days, perform pregnancy testing prior to dosing.

Monthly pregnancy testing (urine or serum) should be conducted for the time required to eliminate systemic exposure after the last dose of study intervention and should correspond with the time frame for the participant's contraception, as noted in Section 5.1. The length of time required to continue pregnancy testing for MK-1200 is 188 days.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.7 Performance Assessments

8.3.7.1 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc) with Grades 0 to 5.

The investigator or qualified designee will assess ECOG status (see Appendix 8) at screening, before the administration of each dose of study intervention and during the follow-up period as specified in the SoA (Section 1.3).

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.

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

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

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

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

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

- All AEs from the time of intervention allocation/randomization through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.6, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 8.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 8 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting 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	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) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
New Cancer (that is not the cancer under study)	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless SAE)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event (unless SAE)

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. 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). The investigator will also make every attempt to follow nonserious AEs that occur in allocated/randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The

Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

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

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

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

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

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

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for MK-1200 by ≥20% of the indicated dose. No specific information is available on the treatment of overdose of MK-1200. 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

To further evaluate MK-1200 immunogenicity and exposure in this indication and to evaluate exposure of the proposed dosing regimen, sample collections for analysis of PK and ADA are currently planned as shown in Section 1.3. Blood samples collected may be stored and further analysis may be performed, if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued, and sites will be notified accordingly.

8.6.1 Blood Collection for PK

Sample collection, storage, and shipment instructions for serum samples will be provided in the Laboratory Manual. PK samples should be drawn according to the PK collection schedule for all participants. Every effort should be taken to collect samples at 30 days after end of study intervention.

8.6.2 Blood Collection for Antidrug Antibodies

Sample collection, storage, and shipment instructions for serum samples will be provided in the Laboratory Manual. Anti-MK-1200 samples should be drawn according to the ADA collection schedule for all participants (Section 1.3). Every effort should be taken to collect samples at 30 days after end of study intervention for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

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 in this study as specified in the SoA:

- Blood for genetic analysis
- Tumor tissue biopsies

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the laboratory manual.

8.8.1 Planned Genetic Analysis Sample Collection

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

The planned genetic analysis sample should be obtained pre-dose on Day 1 but may be collected at the next scheduled visit, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

All sample collections for study-specific assessments shown in the SoA are described within the main Informed Consent.

If the participant has provided documented informed consent for FBR, leftover samples will be used for FBR. The following specimens will be included for FBR:

- Leftover blood and tumor tissue (see Section 8.8)

8.10 Visit Requirements

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

8.10.1 Screening

Approximately 28 days before intervention allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures are to be completed within 28 days before the first dose of study intervention unless specified otherwise in the SoA (Section 1.3).

A test performed, as part of routine clinical management prior to the participant signing consent, is not to be repeated if performed within the specified time frame and the results are acceptable.

Screening procedures may be repeated after consultation with the Sponsor. If a study assessment needs to be repeated, the investigator may perform a retest of screening procedures to assess the eligibility of a participant as noted in Sections 5.1 and 5.2. Participants who are retested will retain their original screening number.

8.10.2 Treatment Period

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

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

When a participant discontinues study intervention during the treatment period, procedures for discontinuation will be performed.

The EOT/DC Visit should occur at the time study intervention is discontinued for any reason. If the EOT/DC Visit occurs more than 30 days after the last dose of study intervention, the EOT/DC Visit procedures and any additional safety follow-up procedures should be performed and combined into 1 visit. Visit requirements are outlined in the SoA (Section 1.3). Additional details regarding participant withdrawal and discontinuation are described in Section 7.

8.10.4 Posttreatment Visit

Posttreatment visit requirements are outlined in the SoA (Section 1.3).

8.10.4.1 Safety Follow-up Visit

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

8.10.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin Efficacy

Follow-up and should be assessed using the same schedule calculated from the date of intervention allocation/randomization (see Section 8.2.1.2) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, or end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

8.10.4.3 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).
- For participants who complete or discontinue assessments in Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.10.5 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. For example, updated vital status may be requested before but not limited to, an interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their vital status.

9 KEY STATISTICAL CONSIDERATIONS

This section details the principal statistical analysis strategy and procedures of the primary and secondary analyses for the study.

9.1 Responsibility for Analyses/In-house Blinding

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

This study is being conducted as an open-label study, i.e., participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

9.2 Hypotheses/Estimation

Objectives of the study are stated in Section 3 of the protocol.

9.3 Analysis Endpoints

Efficacy, PK and safety endpoints that will be evaluated are listed below.

9.3.1 Efficacy/Pharmacokinetics Endpoints

Efficacy endpoints include objective response rate (ORR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

For Part 2 Cohort A, ORR is defined as the proportion of participants who have achieved confirmed complete response (CR) or partial response (PR) per RECIST 1.1 by BICR.

For Part 1 and Part 2 Cohort B, ORR is defined as the proportion of participants who have achieved confirmed complete response (CR) or partial response (PR) per RECIST 1.1 by investigator.

For Part 2 Cohort A, for participants who demonstrate confirmed CR or PR, DOR is defined as the time from the first documented evidence of CR or PR per RECIST 1.1 by BICR until disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

For Part 1 and Part 2 Cohort B, for participants who demonstrate confirmed CR or PR, DOR is defined as the time from the first documented evidence of CR or PR per RECIST 1.1 by investigator assessment until disease progression per RECIST 1.1 by investigator assessment or death due to any cause, whichever occurs first.

For Part 2 Cohort A, PFS is defined as the time from randomization to the first documented disease progression by BICR or death due to any cause, whichever occurs first.

For Part 1 and Part 2 Cohort B, PFS is defined as the time from the first dose of study treatment to the first documented disease progression by investigator or death due to any cause, whichever occurs first.

For Part 2 Cohort A, OS is defined as the time from randomization to death due to any cause.

For Part 1 and Part 2 Cohort B, OS is defined as the time from the first dose of study treatment to death due to any cause.

PK endpoints include serum concentrations of MK-1200, as well as derived PK parameters.

ADA endpoints include ADA test results and titer values for MK-1200.

CCI [redacted]

9.3.2 Safety Endpoints

The primary safety endpoints for Part 1 include DLT, the number/proportion of participants with AEs, and who discontinue study treatment due to AEs. The primary safety endpoints for Part 2 include the number/proportion of participants with 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.

9.4 Analysis Populations

9.4.1 Efficacy/Pharmacokinetic Analysis Populations

The FAS population will be used for the analyses of efficacy data in this study other than DOR. It consists of all participants randomized (Part 2 Cohort A)/allocated (Part 1 and Part 2 Cohort B) who received at least 1 dose of study intervention. Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using the FAS population. The DOR analysis will be based on the population of responders (participants who achieved CR or PR).

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

9.4.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all participants randomized (Part 2 Cohort A)/allocated (Part 1 and Part 2 Cohort B) who received at least 1 dose of study intervention.

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

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

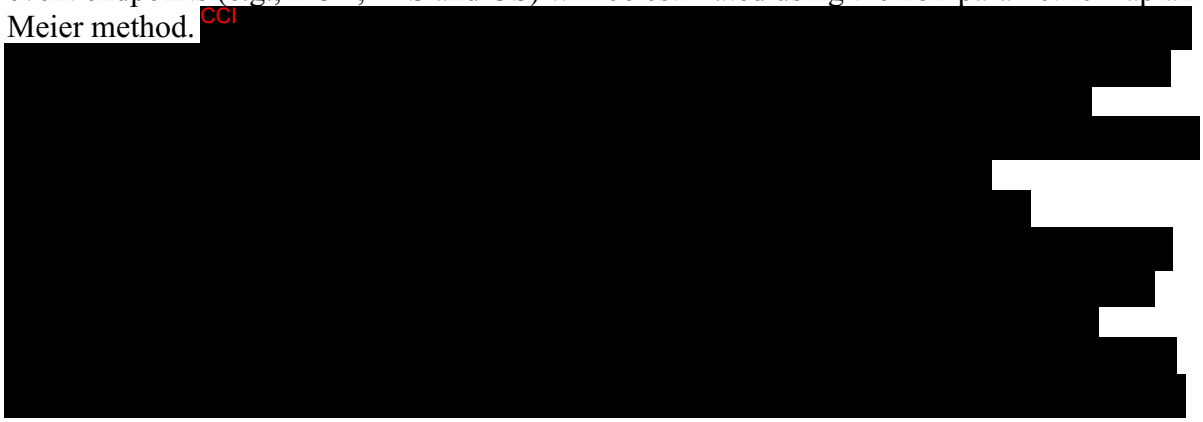
9.5 Statistical Methods

9.5.1 Statistical Methods for Efficacy/Pharmacokinetic Analyses

For each of the dose levels in Part 1, the point estimate of ORR, defined as the proportion of participants who have achieved confirmed complete response (CR) or partial response (PR) per RECIST 1.1 by investigator, will be provided together with 95% CI using exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934]. The survival curves of time-to-event endpoints (e.g., DOR, PFS and OS) will be estimated using the non-parametric Kaplan-Meier method [Kaplan, E. L. and Meier, P. 1958].

For each of the two dose levels in Part 2 Cohort A, the point estimate of ORR, defined as the proportion of participants who have achieved confirmed complete response (CR) or partial response (PR) per RECIST 1.1 by BICR, will be provided together with 95% CI using exact binomial method proposed by Clopper and Pearson. The survival curves of time-to-event endpoints (e.g., DOR, PFS and OS) will be estimated using the non-parametric Kaplan-Meier method. ORR by investigator will also be summarized as supportive analyses.

For each cancer cohort in Part 2 Cohort B, the point estimate of ORR, defined as the proportion of participants who have achieved confirmed complete response (CR) or partial response (PR) per RECIST 1.1 by investigator, will be provided together with 95% CI using exact binomial method proposed by Clopper and Pearson. The survival curves of time-to-event endpoints (e.g., DOR, PFS and OS) will be estimated using the non-parametric Kaplan-Meier method. CCI



CCI [redacted]

PK parameters of study interventions will be summarized by planned visit and time for each dose separately.

9.5.2 Statistical Methods for Safety Analyses

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

The overall safety evaluation will include a summary of the number and percentage of participants with at least one AE, drug-related AE, serious AE, serious drug-related AE, Grade 3-5 AE, drug-related Grade 3-5 AE, discontinuation from study intervention due to an AE, interruption of study intervention due to an AE, an AE resulting in dose reduction, and an AE resulting in death. The number and percentage of participants with specific AEs will also be provided.

The number and percentage of participants with laboratory toxicity grade increased from baseline will be summarized by the post-baseline maximum toxicity grade per CTCAE V5.0 for each gradable laboratory test**.**

For Part 1, DLTs will be listed and summarized by dose level. The pool-adjacent-violators algorithm [Ji, Y., et al 2007], which forces the DLT rate estimates to be nondecreasing with increasing dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The estimate of the DLT rate among participants treated at the preliminary RP2D and the 90% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

CCI [redacted]

CCI

[redacted]

9.7 Multiplicity

No multiplicity adjustment is planned as there are no statistical hypotheses in this study.

9.8 Sample Size and Power Calculations

For Part 1 of this study, with approximately 3 to 6 participants but no more than 14 at each dose level per arm, the sample size for Part 1 is expected to be approximately 44. The actual sample size depends on the safety profiles and number of doses studied. For example, suppose Arm 1 enrolls N=3 for DL1-DL5 and N=14 for DL6; the sample size will be 29. Alternatively, suppose participants experience DLTs at the lower dose levels such that each arm enrolls N=6 for DL1-DL5 and N=14 for DL6, the sample size in each arm will be 44.

Part 2 of this study is for estimation purpose. Table 9 shows the 2-sided 90% and 95% CIs for the ORR with 40 participants for different observed ORRs based on the method of Clopper and Pearson. With 14 observed responders, the estimated ORR and its corresponding 95% CI and 90% CI are 35% (21%, 52%) and 35% (23%, 49%).

Table 9 Confidence Intervals for Different Observed ORR

Total Sample Size per Arm	Observed # of Responders	Observed ORR	95% CI	90% CI
40	4	10%	(3%, 24%)	(3%, 21%)
	6	15%	(6%, 30%)	(7%, 27%)
	8	20%	(9%, 36%)	(10%, 33%)
	10	25%	(13%, 41%)	(14%, 39%)
	12	30%	(17%, 47%)	(18%, 44%)
	14	35%	(21%, 52%)	(23%, 49%)
	16	40%	(25%, 57%)	(27%, 54%)
	18	45%	(29%, 62%)	(31%, 59%)
	20	50%	(34%, 66%)	(36%, 64%)

Abbreviations: CI = confidence interval; ORR = objective response rate.

For safety, Table 10 shows the 2-sided 95% CIs for the observed proportion of participants who experienced the AE of interest for different observed AE rates with 40 participants based on the method of Clopper and Pearson.

Table 10 Confidence Intervals for Different Observed Proportion of Participants who Experienced the AE of Interest

Total Sample Size per Arm	Observed proportion of participants who experienced the AE of interest	95% CI
40	5%	(1%, 17%)
	10%	(3%, 24%)
	15%	(6%, 30%)
	20%	(9%, 36%)

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, 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 MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and 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. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the 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 and ICH Guidelines. 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. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. 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.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed.

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.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

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 medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

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

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

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, 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, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 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 Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

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

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

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 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.

Table 11 Protocol-required Clinical Laboratory Assessments

Assessments Conducted at Screening Only	
Other	HER2: Only for participants with gastric/GEJ cancer (Part 2 Cohort A) or Siewert type 1 esophagogastric junction adenocarcinoma (Part 2 Cohort B) only. See Sections 5.1.2 and 5.1.3 for more details. HBV: Only for participants with biliary tract cancer or if mandated by local health authority (see Appendix 7 for country-specific requirements). The following tests may be conducted. • Anti-HBs • HBsAg • Anti-HBc (total and IgM) • HBeAg (per local guidance) • Anti-HBe (per local guidance) • HBV viral load (per local guidance) HCV: Only if mandated by local health authority (see Appendix 7 for country-specific requirements). The following tests may be conducted. • Anti-HCV • HCV viral load • HCV genotype FSH: PONCBP only.
Assessments Conducted at Screening and During the Study	
Hematology	Hematocrit Hemoglobin Platelet count WBC (total and differential) RBC count RBC indices • MCV[a] • MCH[a] • MCHC Reticulocytes (percent)[a]

Chemistry	Albumin Alkaline phosphatase ALT/SGPT AST/SGOT Bicarbonate (CO_2) BUN/Urea[b] Calcium Chloride Creatinine Fasting or nonfasting glucose Phosphorus Potassium Sodium Total bilirubin Total protein If total bilirubin >ULN: Direct bilirubin
Routine Urinalysis	Specific gravity pH Glucose Protein Blood Ketones By dipstick or alternative, locally available test: Bilirubin Urobilinogen Nitrite Leukocyte esterase If blood or protein is abnormal: Microscopic examination
Other	HIV (eg, HIV RNA level, CD4+ T-cell count): Only for participants with known history of HIV infection or if mandated by local health authority (see Appendix 7 for country-specific requirements), with retesting during the study as clinically indicated for applicable participants (see Sections 5.1 and 8.1.13 for more details). Serum hCG or highly sensitive urine pregnancy tests: As needed for POCBP. Coagulation (PT/INR and aPTT/PTT): At screening for all participants, with retesting during the study as clinically indicated for those on anticoagulants. Glycosylated hemoglobin: Only for diabetic participants.

ALT=alanine aminotransferase; Anti-HBc=antibody to hepatitis B core antigen; Anti-HBe=antibody to hepatitis B e antigen; Anti-HBs=antibody to hepatitis B surface antigen; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GEJ=gastroesophageal junction; HBeAg=hepatitis B e antigen; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HER2=human epidermal growth factor receptor 2; HIV=human immunodeficiency virus; IgM=immunoglobulin M; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; POCBP=participants of childbearing potential; PONCBP=participants of nonchildbearing potential; PT/INR=prothrombin time/international normalized ratio; PTT=partial thromboplastin time; RBC=red blood cell; RNA=ribonucleic acid; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell

[a] To be conducted only if considered standard of care at site/country.

[b] BUN is preferred. If not available, urea may be tested.

- Report the results in the same manner throughout the study. Refer to the Laboratory Manual.
- Pregnancy tests must be conducted as described in Sections 1.3, 5.1, and 8.3.6 or as required by local regulations.

See Appendix 7 for country-specific requirements.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

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

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

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

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

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency 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.

10.3.4 Additional Events Reported

Additional events that require reporting

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

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

10.3.5 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 5.0. 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 study intervention cause the AE?

- The determination of the likelihood that the study intervention 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 study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention 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 study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the study intervention 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 study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose drug study; or (3) study intervention (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 STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION 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 IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant 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.

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

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

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal
  - 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 participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
• IUS [b, c] • Progestogen-only subdermal contraceptive implant [a, c] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with partner(s) capable of producing sperm 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] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [b] IUS is a progestin-releasing IUD. [c] Penile/external condoms must be used in addition to POCBP's hormonal contraception. Note: • Tubal occlusion includes tubal ligation

See Appendix 7 for country-specific requirements.

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

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

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

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

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

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

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

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

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

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

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

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

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

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

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

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

7. Retention of Specimens[3, 4]

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

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

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 China

Title page

Apart from Merck Sharp & Dohme LLC as a sponsor, MSD R&D (China) Co. Ltd is also a sponsor in China.

Sponsor Name: MSD R&D (China) Co. Ltd

Legal registered address: L2-13F, Building 21 Rongda Road, Chaoyang District, Beijing, China

Throughout

Biospecimen collection, testing, and analysis as described in the following sections will be dependent on approval by the HGRAC for participants enrolled in China:

- Section 1.3: Schedule of Activities
- Section 4.2.1.5: Planned Exploratory Biomarker Research
- Section 5: Inclusion Criteria, Exclusion Criteria
- Section 8.2: Efficacy Assessments
- Section 8.6: Pharmacokinetics
- Section 8.1.12: Tumor Tissue for Biomarker Status
- Section 8.8: Biomarkers

Future Biomedical Research will not be conducted in China.

Section 4.1 Overall Design

After enrollment of the global study is complete, the study may remain open to enrollment in China until the target number of participants in China has been enrolled to meet local requirements.

Section 6.1 Study Intervention(s) Administered

All study interventions will be administered on an outpatient basis. However, hospitalization is acceptable if it is standard procedure for the local site.

Section 8.2 Efficacy Assessments

Dependent on HGRAC approval, remaining PK and/or ADA samples may be used for validation purposes (eg, Nab, ADA, PK).

Section 8.6 Pharmacokinetics

Dependent on HGRAC approval, remaining PK and/or ADA samples may be used for validation purposes (eg, Nab, ADA, PK).

Appendix 2 Clinical Laboratory Tests

Routine Urinalysis by dipstick: a urine leukocyte count by microscopy is acceptable when the leukocyte esterase by dipstick cannot be performed.

10.7.2 Chile

8.4.5 Pregnancy and Exposure During Breastfeeding

Follow-up of all reported pregnancies and childbirth is mandatory. Additionally, follow-up of the newborns for up to 12 months of age may be mandatory.

10.5.2 Contraception Requirements

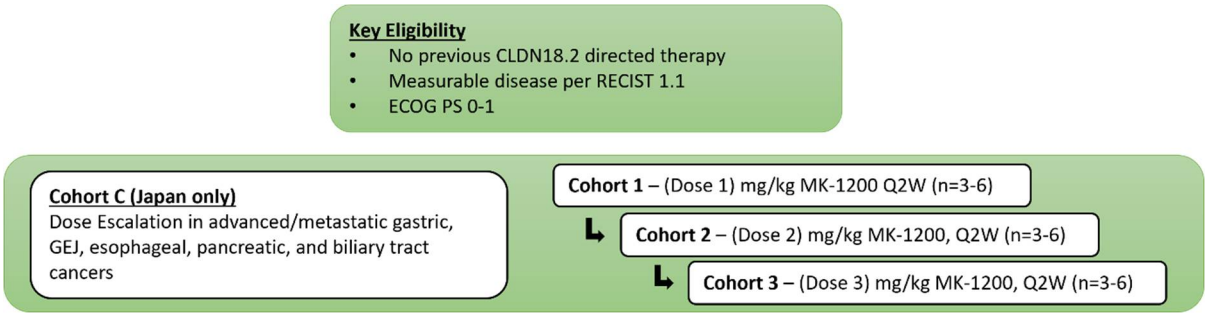
Use of emergency hormonal contraception is permitted for POCBPs who have engaged in unprotected sexual activity.

10.7.3 Japan

Japan has country-specific requirements for the protocol that are summarized below. Further clarification is provided in a separate protocol addendum document titled as "Policies for Enrollment and Evaluation of Tolerability in Japanese Participants in MK-1200-002 study".

Section 1.2 Schema

Figure 2 Part 2 Cohort C Schema (Japan Only)



CLDN18.2=Claudin 18.2; ECOG PS=Eastern Cooperative Oncology Group performance status; GEJ=gastroesophageal junction; Q2W=every 2 weeks; RECIST=Response Evaluation Criteria in Solid Tumors

Section 1.3 Schedule of Activities

For participants in Part 2 Cohort C, blood samples for PK sampling should be collected according to the Part 1 schedule described in Section 1.3 (Table 1 and Table 2), except for Cycle 4. During Cycle 4, PK sampling is only to be performed within 1 hour pre-dose and at

30 min (±15 min) post-dose (the same sampling schedule as Cycles 2-3 and Cycles 5-8 of Part 1).

Section 4.1 Overall Design

In Part 2 of the study, an additional dose escalation cohort (Cohort C) will be enrolled specifically at sites in Japan. The dose levels for escalation will be determined based on the totality of data from the dose escalation in Part 1 of this study.

Section 5.1.1 Japan Cohort Specific Inclusion Criteria

Part 1 specific inclusion criteria described in Section 5.1.1 are also applicable to Part 2 Cohort C.

Section 5.2 Exclusion Criteria

In addition to the exclusion criteria defined in Section 5.2, participants for Part 2 Cohort C must not meet any of the following criteria:

Has received colony-stimulating factors (eg, G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks before intervention allocation.

Section 5.5 Participant Replacement Strategy

To evaluate safety and tolerability, all participants in Cohort C must meet the criteria for DLT evaluability during the DLT evaluation period (28 days from Cycle 1 Day 1).

Participants in Part 2 Cohort C who are not evaluable will be replaced unless accrual has stopped. Unevaluable participants will not be counted toward the total number of participants for DLT evaluation. However, the Sponsor will determine the dose escalation and de-escalation of MK-1200 in Japanese participants while considering all drug safety information, including adverse events that occurred in participants excluded from the DLT evaluation due to reasons other than DLT.

Section 6.1 Study Intervention(s) Administered

Table 5 Study Interventions

Antiemetic (eg, 5-HT3 receptor) used in this study is not categorized as “product(s) used in the clinical trial” in Japan.

10.7.4 All European Economic Area Member States

Section 5.1 Inclusion Criteria

Participants in the EEA must agree to continue contraception for 120 days (participants assigned male sex at birth) or 210 days (participants assigned female sex at birth) after the last dose of study intervention

10.8 Appendix 8: Eastern Cooperative Oncology Group Performance Status

Grade	Performance Status
0	Normal activity. Fully active, able to carry on all predisease 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.

Source: Adapted from [ECOG ACRIN Cancer Research Group 2016]

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
1L	first line
2L	second line
3L	third line
5-FU	5-fluorouracil
5-FU/LV	5-fluorouracil/leucovorin
ADA	antidrug antibodies
ADC	antibody-drug conjugate
ADCC	antibody-dependent cellular cytotoxicity
ADL	activities of daily living
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APaT	All-Participants-as-Treated
ART	antiretroviral therapy
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BICR	blinded independent central review
BLRM	Bayesian logistic regression model
BP	blood pressure
BRCA	BReast CAncer gene
CAPOX	a regimen of capecitabine and oxaliplatin
CCA	cholangiocarcinoma
CDC	complement-dependent cytotoxicity
CEP17	chromosome enumeration probe 17
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration

Abbreviation	Expanded Term
C_{min}	minimum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	Case Report Form
CSF	colony-stimulating factor
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
DILI	drug-induced liver injury
DL	dose level
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	External Data Monitoring Committee
EEA	European Economic Area
EGJ	esophagogastric junction
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency

Abbreviation	Expanded Term
EOT/DC	end of treatment/discontinuation
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FISH	fluorescence in situ hybridization
FLOT	a regimen of 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel
FOLFIRI	a regimen of 5-fluorouracil, leucovorin, and irinotecan
FOLFIRINOX	a regimen of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin
FOLFOX	a regimen of 5-fluorouracil, leucovorin, and oxaliplatin
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GEJ	gastroesophageal junction
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HGRAC	Human Genetic Resource Administration of China
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
iCRO	imaging CRO

Abbreviation	Expanded Term
ID	identification
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
ISH	in situ hybridization
ISOO	International Society of Oral Oncology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
JRCT	Japan Registry of Clinical Trials
LLOQ	lower limit of quantitation
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	a regimen of 5-fluorouracil, leucovorin, and oxaliplatin
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
mTPI-2	modified Toxicity Probability Interval 2
MUGA	multigated acquisition
NALIRIFOX	a regimen of 5-fluorouracil, leucovorin, oxaliplatin, and liposomal irinotecan
NCI	National Cancer Institute
NK-1	neurokinin-1
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate

Abbreviation	Expanded Term
OS	overall survival
OTC	over the counter
PARP	poly ADP-ribose polymerase
PD	progressive disease
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PET-CT	positron emission tomography–computed tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
po	orally
POCBP	participant(s) of childbearing potential
PONCBP	participant (s) of nonchildbearing potential
PR	partial response
PSA	prostate-specific antigen
Q2W	every 2 weeks
Q3W	every 3 weeks
QRS	Q wave, R wave, and S wave
QTc	corrected QT interval
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	respiratory rate
SAE	serious adverse event
SCC	squamous cell carcinoma
SIM	Site Imaging Manual
SLAB	Supplemental laboratory test(s)
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
SpO2	oxygen saturation

Abbreviation	Expanded Term
SUSAR	suspected unexpected serious adverse reaction
TACE	transarterial chemoembolization
ULN	upper limit of normal
US	United States

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