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Protocol Title: Phase 1b Open-label Study of MK-8353 in Combination with Selumetinib (MK-5618) in Participants with Advanced/Metastatic Solid Tumors

Protocol Number: 014-01

Compound Number: MK-8353

Sponsor Name:

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

Legal Registered Address:

One Merck Drive

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Regulatory Agency Identifying Number(s):

IND	140238

Approval Date: 19-December-2018

Sponsor Signatory

Typed Name: Date
Title:

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: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 01	19-DEC-2018	Amendment 01 was issued to address Agency feedback.
Original protocol	05-OCT-2018	Original protocol.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendments:

This amendment was issued to address Agency feedback.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1. Protocol Summary Intervention Groups	DL5: Reduced the maximum MK-8353 dose from 300 mg to 250 mg, which is a 25% increment from the previous dose. Edited the text in the description of Intervention Groups.	This modification was applied throughout the protocol to address an Agency request to decrease the increment between Dose Levels 4 and 5. The text was edited to improve consistency within the protocol.
1.2. Schema Figure 1 and associated footnotes	Reduced the maximum MK-8353 dose from 300 mg to 250 mg. Revised Figure 1 to add Figure 1A: Schema to Potential Diagonal MTD① Added Figure 1B: Schema to Potential MTD② and MTD③ Added Table 1: Starting Doses for ERKi and MEKi Escalation to Potential MTD② and MTD③	This modification was applied throughout the protocol to address an Agency request as provided in Section 1.0. The figures were revised to incorporate single agent escalation above DL3 in accordance with the Agency request, and to provide clarity regarding the steps for dose escalation.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 1.3.1 Dose Escalation Phase: Screening and Treatment Cycles	Added visits to treatment Cycles 1 through 4 for additional safety monitoring via chemistry panel assessments; 5 visits were added. The SoA was separated into 2 tables as reflected in subsections 1.3.1 and 1.3.2. Additional modifications were made to the 'Notes' column to align with the differentiation between the 2 tables.	Visits were added to address an Agency request to increase safety monitoring. The SoA was separated into 2 tables to accommodate the increased size of the table and maintain legibility. Additional modifications were made to the 'Notes' column to align with the differentiation between the 2 tables.
1.3 Schedule of Activities 1.3.2 Dose Escalation Phase: End of Treatment and Post-Treatment	The SoA was separated into 2 separate tables as reflected in subsections 1.3.2 and 1.3.2. Additional modifications were made to the 'Notes' column to align with the differentiation between the 2 tables.	Additional modifications were made to the 'Notes' column to align with the differentiation between the 2 tables.
2.2.3.1 MK-8353 and Selumetinib Preclinical Studies	Inserted a paragraph at end of the section to highlight data provided in the IB regarding the elevation of serum creatinine and the assessment of cystatin C.	This modification was applied to address an Agency request to provide guidelines for triggering an assessment of cystatin C.
4.1 Overall Design	Reduced the maximum MK-8353 dose from 300 mg to 250 mg. Revised text to align with new Schema depicted in Figures 1A and 1B; added Table 1 with starting doses for off-diagonal sequences.	This modification was applied to address an Agency request as provided in section 1.0.

Section # and Name	Description of Change	Brief Rationale
4.3.2 Maximum Dose/Exposure for This Study	Reduced the maximum MK-8353 dose from 300 mg to 250 mg.	This modification was applied to address an Agency request as provided in section 1.0.
4.3.3 Rational for Dose Interval and Study Design	Reduced the maximum MK-8353 dose from 300 mg to 250 mg.	This modification was applied to address an Agency request as provided in section 1.0.
5.2 Exclusion Criteria	#13: Added text to include "other cognitive disorders."	This modification was applied to address an Agency recommendation to ensure enrolled participants can meet the requirements of the study.
6.1 Study Intervention(s) Administered	Applied a modification to 'Dosage Level(s)' for MK-8353: Reduced the maximum MK-8353 dose from 300 mg to 250 mg.	This modification was applied to address an Agency request as provided in section 1.0.
6.5.2 Prohibited Concomitant Medications	Table 5 (former Table 4): Removed an incorrect header from the 2nd page of the table.	The incorrect header was removed thus providing clarity to the table.
6.5.3.1 MK-8352 Supportive Care	Diarrhea: Revised text in the last sentence to indicate that supportive care should be based in institutional guidelines as permitted while maintaining compliance with guidance for prohibited medications.	Revised the text for clarity and alignment with other sections in the protocol.

Section # and Name	Description of Change	Brief Rationale
6.6.2 Definition of Dose Limiting Toxicity	#3: Incorporated a time limit of <72 hours.	These modifications were applied to address an Agency request to modify the definition of Dose Limiting Toxicities.
	#4: Reduced the time interval to ≥72 hours	
	#6: Inserted new criterion to provide clarity regarding AST and ALT laboratory values.	
	#13: Eye Disorders Retinal: Revised the Grade of the event Other: Deleted the Grade ≥3 criteria	
6.6.4.1 Dose Modification for MK-8353 and Selumetinib	Figure 4: Revised figure to reflect reduction in the maximum MK-8353 dose from 300 mg to 250 mg	This modification was applied to address an Agency request as provided in section 1.0.
	Table 6 (former Table 5): Revised figure to reflect reduction in the maximum MK-8353 dose from 300 mg to 250 mg	This modification was applied to address an Agency request as provided in section 1.0.
	Table 7 (former Table 6): Eye disorders, Grade 3: Revised to indicate that study treatment may be restarted at a reduced dose level.	This modification was applied to address an Agency request.
	Rash, Grade 3: Revised to indicate that study treatment may be restarted at a reduced dose level.	This modification was applied to address an Agency request.

Section # and Name	Description of Change	Brief Rationale
9.9 Sample Size and Power Calculations	Reduced the maximum MK-8353 dose from 300 mg to 250 mg. Edited other existing text to align with revisions to the study design.	This modification was applied to address an Agency request as provided in section 1.0.
10.2 Appendix 2: Clinical Laboratory Tests	Comprehensive Chemistry Panel: Added creatine kinase	Revised to address required safety monitoring.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: Phase 1b Open-label Study of MK-8353 in Combination with Selumetinib (MK-5618) in Participants with Advanced/Metastatic Solid Tumors

Short Title: A Phase 1b Study of MK-8353 + Selumetinib in Advanced/Metastatic Solid Tumors

Acronym:

Hypotheses, Objectives, and Endpoints:

There are no hypotheses for the study.

This study is to be conducted in male and female participants with advanced/metastatic solid tumors.

Primary Objectives	Primary Endpoints
- To determine the safety and tolerability and to establish preliminary RP2D(s) for the MK-8353 and selumetinib combination in participants with advanced/metastatic solid tumors	- DLTs - AEs - Study drug discontinuations due to an AE
Secondary Objectives	Secondary Endpoints
- To evaluate the pharmacokinetics (PK) of MK-8353 and selumetinib	- Pharmacokinetic parameters, including AUC, Cmin and Cmax

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Advanced/Metastatic Solid Tumors
Population	Participants with advanced solid tumors
Study Type	Interventional
Intervention Model	Sequential This is a multi-site study.
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 48 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 80 participants will be enrolled in this dose escalation study, as described in Section 9; the overall sample size will be at most 140 participants.

Intervention Groups and Duration:

Intervention Groups	This is a dual dose escalation study using the modified toxicity probability interval (mTPI) design to evaluate the safety, tolerability, and efficacy of the combination of MK-8353 and selumetinib (MK-5618). Up to five dose levels for each drug will be evaluated in combination: • MK-8353 (ERKi): 50, 100, 150, 200, and 250 mg • MK-5618 (selumetinib, MEKi): 25, 50, 75, 100, and 125 mg
Total Number	There is 1 intervention group (MK-8353 + selumetinib) in this dose escalation study.
Duration of Participation	Each participant will participate in the study from the time the participant signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will receive the assigned intervention until disease progression is radiographically documented and confirmed by the site per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1); unacceptable AEs; intercurrent illness that prevents further administration of treatment; investigator's decision to withdraw the participant; participant withdrawal of consent; pregnancy of the subject; noncompliance with study treatment or procedure requirements, or administrative reasons requiring cessation of treatment. After the end of treatment, participants are to be followed up for safety for at least 30 days following the last study dosing and until recovery or stabilization of all related toxicities. During the first year in the study, tumor measurements will continue to be made every 9 weeks until progressive disease is observed, and each participant will be followed for survival. After 12 months on study, imaging will be performed every 12 weeks from first dose or as clinically indicated. Upon identification of the preliminary RP2D(s) for the MK-8353 and selumetinib combination, additional participants with solid tumors will be enrolled in a future dose expansion phase of this trial. Participants in the planned expansion phase of this study will receive MK-8353 in combination with selumetinib as dual therapy.

Study Governance Committees:

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

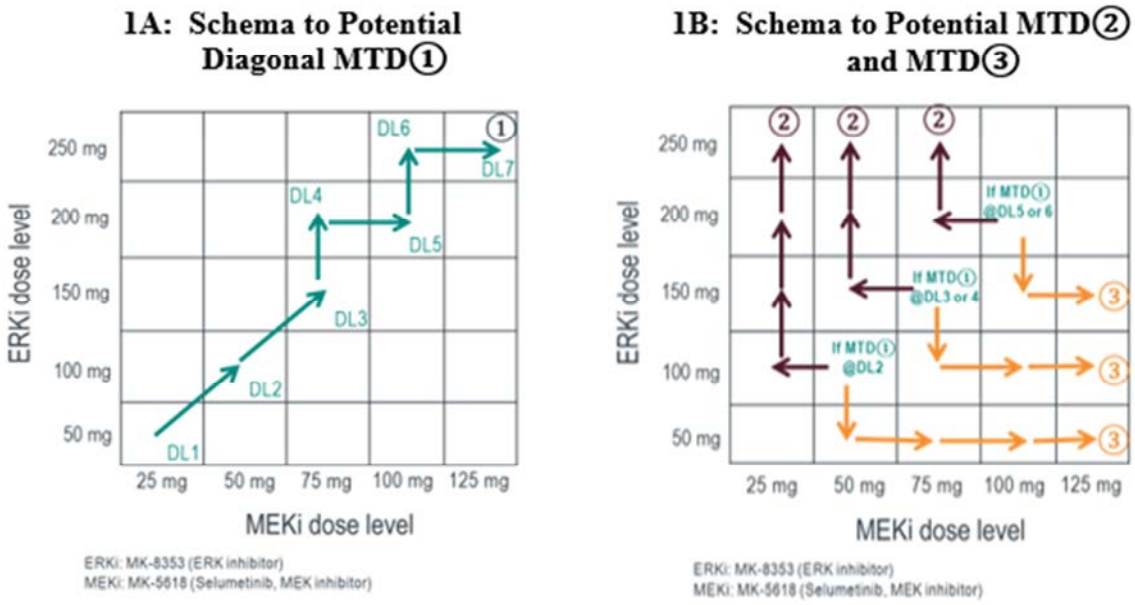
Study governance considerations are outlined in Appendix 1

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The dual dose escalation and conformation plan and schema are depicted in Figure 1 and the study design is shown in Figure 2.



ERK = extracellular signal-regulated kinase; MEK = mitogen activated protein kinase

Dose:

- MK-8353 (ERKi): 50, 100, 150, 200, and 250 mg
- MK-5618 (selumetinib, MEKi): 25, 50, 75, 100, and 125 mg

This grid illustrates 25 possible dose combinations formed by 5 unique MK-8353 (ERKi) doses and 5 unique MK-5618 (selumetinib, MEKi) doses. Using the modified toxicity probability interval (mTPI) design, the dose escalation will start by identifying the maximum tolerated dose (MTD) in the sequence of dose combinations formed along the diagonal of the grid, denoted by ①s shown in Figure 1A. If following the mTPI design the dose escalation along the diagonal of the dose combination grid concludes at either the starting dose, (MK-8353 50 mg + selumetinib 25 mg), or the last dose on the diagonal sequence, (MK-8353 250 mg + selumetinib 125 mg), the study will end with 1 MTD only.

If the dose escalation in the diagonal sequence is concluded at either (DL2, MK-8353100 mg + selumetinib 50 mg), (DL3, MK-8353 150 mg + selumetinib 75 mg), (DL4, MK-8353 200 mg + selumetinib 75 mg) or (DL5 MK-8353 200 mg + selumetinib 100 mg), 2 separate dose de-escalations will be initiated simultaneously along 2 off-diagonal dose combination sequences denoted by ② and ③, to identify additional potential MTDs as shown in Figure 1B.

If following the mTPI design decision rules, the initial dose escalation is concluded at DL6, only one additional sequence will be explored: MK-8353 150 mg/100 mg selumetinib and MK-8353 150 mg/125 mg selumetinib (See Table 1).

Figure 1 Dual Dose Escalation of MK-8353 and Selumetinib; (1A) Schema to Potential Diagonal MTD①; and (1B) Schema to Potential MTD② and MTD③

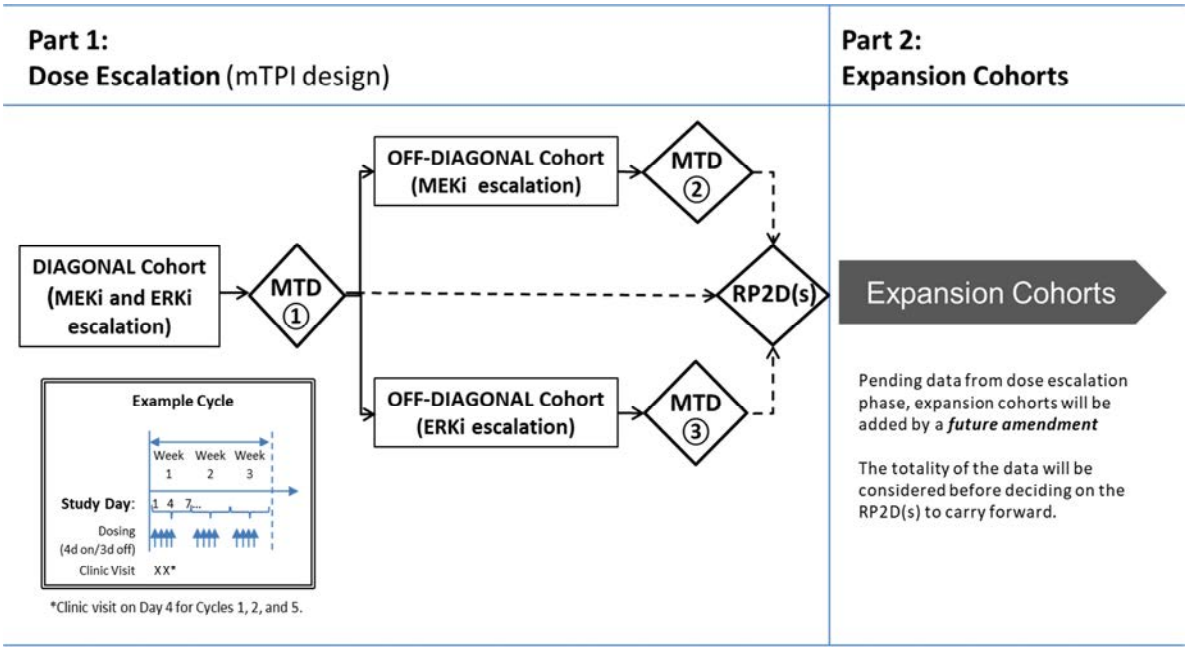


Figure 2 Study Flow Chart

1.3 Schedule of Activities (SoA)

1.3.1 Dose Escalation: Screening and Treatment Phase

Study Period: Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)																Notes
Treatment Cycle (C) / Visit:	Screening (Visit)	C1				C2			C3		C4		C5		C6	C7	C8 and beyond	
Collection Timepoint (Study Day [D]):		D1	D 4	D 8	D 15	D1	D 4	D 15	D1	D 15	D1	D 15	D1	D 4	D1	D1	D1	
Scheduling Window(Days):	-28 to -1		-1	±3	±3	±3	-1	±3	±3	±3	±3	±3	±3	-1	±3	±3	±3	
Administrative Procedures																		
Informed Consent	X																	
Informed Consent for Optional On-treatment Tumor Biopsy	X																	
Informed Consent for FBR	X																	Participating in FBR is optional for study participants.
Participant Identification Card	X																	
Inclusion/Exclusion Criteria	X																	
Demographics and Medical History	X																	
Cancer Disease Status and Prior Treatment History	X																	
Prior and Concomitant Medication Review	X	X	X			X	X		X		X		X	X	X	X	X	
MK-8353 Administration		X ◄															► X	Administered BID 4 days on/3 days off. Escalation/dosing schedule (eg. direction of dose escalation, BID vs. QD, on/off intermittent dosing schedule) may be adjusted based on totality of data (PK, pharmacodynamic, and safety).
Selumetinib Administration		X ◄															► X	Administered BID 4 days on/3 days off. Escalation/dosing schedule (eg. direction of dose escalation, BID vs. QD, on/off intermittent dosing schedule) may be adjusted based on totality of data (PK, pharmacodynamic, and safety).

Study Period: Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)																Notes
Treatment Cycle (C) / Visit:	Screening (Visit)	C1				C2			C3		C4		C5		C6	C7	C8 and beyond	
Collection Timepoint (Study Day [D]):		D1	D 4	D 8	D 15	D1	D 4	D 15	D1	D 15	D1	D 15	D1	D 4	D1	D1	D1	
Scheduling Window(Days):	-28 to -1		-1	±3	±3	±3	-1	±3	±3	±3	±3	±3	±3	-1	±3	±3	±3	
Efficacy Assessments																		
Tumor Imaging	X	X ◄															► X	Screening: Imaging must be performed within 28 days prior to the date of Cycle 1 Day 1 (C1D1). For the first 12 months on study: Imaging will be performed Q9W (63 days ± 7 days) calculated from the date of the first dose. After 12 months on study: Imaging will be performed Q12W (± 14 days) from first dose or as clinically indicated.
Clinical Procedures/Assessments																		
Review Adverse Events	X	X ◄															► X	AEs that occur after the ICF is signed but before treatment allocation must be reported if: • Event causes participant to be excluded from the study, or • Event is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy or a study procedure
Full Physical Examination	X																	
Directed Physical Examination	X	X				X			X		X		X		X	X	X	Can be obtained within 3 days prior to C1D1.
Full Ophthalmic Examination	X					X ◄											► X	Performed at the Screening Visit, C2D1 and then every 8 weeks ±7 days) from C2D1 and EoT.
Height, Weight, and Vital Signs	X	X				X			X		X		X		X	X	X	Height will be measured at the Screening Visit only. Vital signs: temperature, pulse, respiratory rate, and blood pressure • C1D1: Can be obtained within 3 days prior • C1D1: It is not necessary to repeat C1D1 testing if the Screening Visit assessment was performed within 7 days prior to C1D1.
12-Lead Electrocardiogram	X					X			X		X		X		X	X	X	Screening: ECG will be performed in triplicate to confirm QTcF interval. C2 and beyond: ECGs will be performed predose, every cycle.

Study Period: Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)															Notes
Treatment Cycle (C) / Visit:	Screening (Visit)	C1				C2			C3		C4		C5		C6	C7	C8 and beyond	
Collection Timepoint (Study Day [D]):		D1	D 4	D 8	D 15	D1	D 4	D 15	D1	D 15	D1	D 15	D1	D 4	D1	D1	D1	
Scheduling Window(Days):	-28 to -1		-1	±3	±3	±3	-1	±3	±3	±3	±3	±3	±3	-1	±3	±3	±3	
Echocardiogram/ MUGA scan (Q12W)	X					X							X		X	X	X	Obtain scans as follows: • Screening Visit • Treatment: C2D1 and C5D1, then every 12 weeks
ECOG Performance Scale	X	X				X			X		X		X		X	X	X	C1D1: • Can be obtained within 3 days prior • It is not necessary to repeat C1D1 testing if the Screening Visit assessment was performed within 7 days prior to C1D1.
Survival Status		X ◄———															X	All participants will be followed up for survival every 12 weeks (± 14 days) after discontinuation (unless consent is withdrawn). In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study.
LOCAL Laboratory Assessments																		
Pregnancy Test – Urine or Serum β-hCG, if applicable	X	X																Pregnancy tests may be performed if clinically warranted, or as defined by local regulations. Monthly pregnancy testing should be conducted as per local regulations where applicable.
PT/INR and aPTT/PTT	X																	
CBC with Differential	X	X				X			X		X		X		X	X	X	C1D1: Does not need to be obtained if Screening Visit samples were obtained within 3 days prior to C1D1.
Chemistry Panel	X	X		X	X	X		X	X	X	X	X	X		X	X	X	Specific to creatinine: Cystatin C could be evaluated if creatinine is abnormal (≥10% increase from baseline). Cystatin C may be conducted by central vendor only if analysis was not available from local study site laboratory. C1D1: Does not need to be obtained if Screening Visit samples were obtained within 3 days prior to C1D1.
Fasting Glucose	X						X											C2D4: Obtain pre-dose prior to FDG-PET scan; performed only in participants enrolled in the MTD levels
Urinalysis	X					X					X				X		X	To be performed at the Screening Visit and every other cycle starting at C2.
Serum Tumor Markers		X ◄———															X	Collected Q3W starting at C1, as appropriate for tumor type.

Study Period: Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)																Notes
Treatment Cycle (C) / Visit:	Screening (Visit)	C1				C2			C3		C4		C5		C6	C7	C8 and beyond	
Collection Timepoint (Study Day [D]):		D1	D 4	D 8	D 15	D1	D 4	D 15	D1	D 15	D1	D 15	D1	D 4	D1	D1	D1	
Scheduling Window(Days):	-28 to -1		-1	±3	±3	±3	-1	±3	±3	±3	±3	±3	±3	-1	±3	±3	±3	
CENTRAL Laboratory Assessments																		
MK-8353 Pharmacokinetics		X	X			X	X						X	X				• C1D1: Pre-dose samples will be collected (within 24 hours prior to pre-dose). Morning dose(s) should be withheld until sample has been drawn. Post-dose samples will be collected at hours 1 (± 10 minutes), 2 (± 10 minutes), 4 (± 10 minutes), 6 (± 10 minutes), and 1 sample any time between 8 and 12 hours (prior to PM dosing for BID regimen). • C1D4: Pre-dose/trough samples will be collected at time 0 (within -10 minutes prior to pre-dose). Morning dose(s) should be withheld until sample has been drawn. Post-dose samples will be collected at hours 1 (± 10 minutes), 2 (± 10 minutes), 4 (± 10 minutes), 6 (± 10 minutes), and 1 sample any time between 8 and 12 hours (prior to PM dosing for BID regimen). • Additional samples will be collected at C2D1, C2D4, C5D1 and C5D4: Pre-dose/trough: Collect at time 0 (within -10 minutes prior to pre-dose). Morning dose(s) should be withheld until sample has been drawn, and Post-dose: Hours 1 (± 10 minutes) and 4 (± 10 minutes). The exact time of sample collection and time of administration of MK-8353 will be recorded.

Study Period: Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)															Notes
Treatment Cycle (C) / Visit:	Screening (Visit)	C1				C2			C3		C4		C5		C6	C7	C8 and beyond	
Collection Timepoint (Study Day [D]):		D1	D 4	D 8	D 15	D1	D 4	D 15	D1	D 15	D1	D 15	D1	D 4	D1	D1	D1	
Scheduling Window(Days):	-28 to -1		-1	±3	±3	±3	-1	±3	±3	±3	±3	±3	±3	-1	±3	±3	±3	
Selumetinib Pharmacokinetics		X	X			X	X						X	X				• C1D1: Pre-dose samples will be collected (within 24 hours prior to pre-dose). Morning dose(s) should be withheld until sample has been drawn. Post-dose samples will be collected at hours 1 (± 10 minutes), 2 (± 10 minutes), 4 (± 10 minutes), 6 (± 10 minutes), and 1 sample any time between 8 and 12 hours (prior to PM dosing for BID regimen). • C1D4: Pre-dose/trough samples will be collected at time 0 (within -10 minutes prior to pre-dose). Morning dose(s) should be withheld until sample has been drawn. Post-dose samples will be collected at hours 1 (± 10 minutes), 2 (± 10 minutes), 4 (± 10 minutes), 6 (± 10 minutes), and 1 sample any time between 8 and 12 hours (prior to PM dosing for BID regimen). • Additional samples will be collected at C2D1, C2D4, C5D1 and C5D4: Pre-dose/trough: Collect at time 0 (within -10 minutes prior to pre-dose). Morning dose(s) should be withheld until sample has been drawn, and Post-dose: Hours 1 (± 10 minutes) and 4 (± 10 minutes). The exact time of sample collection and time of administration of selumetinib will be recorded.
Blood for Genetic Analysis		X																Collect pre-dose.
Blood for RNA Analysis		X	X				X							X				Samples will be collected: • Pre-dose: C1D1, C1D4, C2D4, and C5D4
Blood for Plasma Biomarker Analysis		X	X				X							X				Samples will be collected: • Pre-dose: C1D1, C1D4, C2D4, and C5D4
Blood for Serum Biomarker Analysis		X	X				X							X				Samples will be collected: • Pre-dose: C1D1, C1D4, C2D4, and C5D4
Blood For ctDNA		X	X				X							X				Samples will be collected: • Pre-dose: C1D1, C1D4, C2D4, and C5D4

Study Period: Study Period:	Screening Phase	Treatment Cycles (3-week Cycles)																Notes
Treatment Cycle (C) / Visit:	Screening (Visit)	C1				C2			C3		C4		C5		C6	C7	C8 and beyond	
Collection Timepoint (Study Day [D]):		D1	D 4	D 8	D 15	D1	D 4	D 15	D1	D 15	D1	D 15	D1	D 4	D1	D1	D1	
Scheduling Window(Days):	-28 to -1		-1	±3	±3	±3	-1	±3	±3	±3	±3	±3	±3	-1	±3	±3	±3	
Blood for pERK		X	X			X	X						X	X				Samples will be collected C1D1: • Pre-dose: Collect at time 0, within 24 hours prior to pre-dose); morning dose(s) should be withheld until sample has been drawn, and Samples will be collected C1D4, C2D1, C2D4, C5D1, C5D4: • Pre-dose: Collect at time 0 (within 10 minutes prior to pre-dose); morning dose(s) should be withheld until sample has been drawn, and Post-dose: Hours 1 (± 10 minutes) and 4 (± 10 minutes)
Exploratory Imaging																		
FDG-PET Scan	X						X											Obtain in participants enrolled in the MTD levels. Screening Visit: The baseline scan will be performed between -14 to -1 days prior to C1D1. C2D4: Scan will be performed predose
Tumor Tissue Collection																		
Archival or Newly Obtained Tumor Tissue Collection	X																	
On-treatment Tumor Biopsy (Optional)						X												

Abbreviations: aPTT/PTT= activated prothrombin time/partial thromboplastin time; β-hCG=human chorionic gonadotropin; BID=twice daily; CBC=complete blood count; ctDNA=circulating tumor DNA; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EoT=end of treatment; ERK=extracellular signal-regulated kinase; FBR=future biomedical research; FDG-PET=^{18}F-flourodeoxyglucose-positron emissions tomography;FT3=free triiodothyronine; FT4=free thyroxine; hr = hour; ICF = informed consent form; IHC= immunohistochemistry; IV=intravenous; MSI/MMR= microsatellite instability/mismatch repair; MUGA= multigated acquisition; PD = progressive disease; pERK= phosphorylation of ERK; PK= pharmacokinetic; PT/INR = prothrombin time/International Normalized Ratio; PT/PTT=prothrombin time/partial thromboplastin time;Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W= every 12 weeks; QD = once daily; QTcF = Fridericia's Q-T interval corrected formula; RNA=ribonucleic acid.

1.3.2 Dose Escalation: End of Treatment and Post-Treatment

Study Period:	End of Treatment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Discontinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Collection Timepoint: (Study Day [D])	At time of Treatment Discontinuation	30 days Post-last dose	Every 9 or 12 weeks Post-discontinuation	Every 12 weeks Post-last dose	
Scheduling Window (Days):	+7	+14	±7	±14	
Administrative Procedures					
Prior and Concomitant Medication Review	X	X			
Efficacy Assessments					
Tumor Imaging	X		X		In participants who discontinue study therapy without documented PD, tumor imaging should continue in Post-treatment Follow-up Visits, following the same imaging schedule from the treatment phase; and as clinically indicated.
Clinical Procedures/Assessments					
Review Adverse Events	X	X	X		Follow-up Visits: AEs will be collected when participant is in the clinic for tumor imaging assessment.
Full Physical Examination	X				
Full Ophthalmic Examination	X	X			Performed at the EoT. An ophthalmic examination at the Safety Follow-up Visit is only required if there was a clinically significant abnormality noted at EoT
Weight and Vital Signs	X				Vital signs: temperature, pulse, respiratory rate, and blood pressure
12-Lead Electrocardiogram	X	X			
Echocardiogram/ MUGA scan (Q12W)	X				
ECOG Performance Scale	X	X			
Post-study Anticancer Therapy Status			X	X	
Survival Status	X	X	X	X	All participants will be followed up for survival every 12 weeks (± 14 days) after discontinuation (unless consent is withdrawn). In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study.

Study Period:	End of Treatment (EoT)	Post-treatment			Notes
Treatment Cycle (C) / Visit:	Discontinuation	Safety Follow-up	Follow-up Visits	Survival Follow-up	
Collection Timepoint: (Study Day [D])	At time of Treatment Discontinuation	30 days Post-last dose	Every 9 or 12 weeks Post-discontinuation	Every 12 weeks Post-last dose	
Scheduling Window (Days):	+7	+14	±7	±14	
LOCAL Laboratory Assessments					
CBC with Differential	X	X			
Chemistry Panel	X	X			Specific to creatinine: Cystatin C could be evaluated if creatinine is abnormal. Cystatin C may be conducted by central vendor only if analysis was not available from local study site laboratory.
Urinalysis	X	X			
Serum Tumor Marker	X	X			Collected as appropriate for tumor type.
CENTRAL Laboratory Assessments					
Blood for RNA Analyses	X				
Blood for Plasma Biomarker Analyses	X				
Blood for Serum Biomarker Analyses	X				
Blood for ctDNA	X				

Abbreviations: ctDNA=circulating tumor DNA; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EoT=end of treatment; hr = hour; MUGA= multigated acquisition; PD = progressive disease; Q12W= every 12 weeks; QTcF = Fridericia's Q-T interval corrected formula; RNA=ribonucleic acid.

2 INTRODUCTION

MK-8353 is a highly selective, orally available, adenosine triphosphate competitive small molecule inhibitor of extracellular signal-regulated kinase (ERK). MK-8353 not only inhibits the kinase activity of ERK, but induces a conformational change in ERK that prevents its phosphorylation and activation by mitogen-activated protein/extracellular signal-regulated kinase (MEK). Selumetinib (also known as MK-5618, AZD6244, or ARRY-142886) is a potent, selective, adenosine triphosphate non-competitive, allosteric inhibitor of MEK, thereby inhibiting the phosphorylation of ERK by MEK. MK-8353 is under study for the treatment of solid tumors in combination therapy with selumetinib. This is a Phase 1b dose-escalation, and dose-finding trial to assess the safety and tolerability of MK-8353 in combination therapy with selumetinib. Refer to the MK-8353 and selumetinib Investigator's Brochure (IB) for further information.

2.1 Study Rationale

2.1.1 Rationale for the Study and Selection Participant Population

MK-8353 is a potent ERK inhibitor that has demonstrated antitumor activity in preclinical cancer cell lines and in xenograft and syngeneic animal tumor models, both as a single agent and in combination with other therapeutic agents, including anti PD-1 therapy. A Phase 1 study of MK-8353 was conducted in subjects with advanced solid tumors to evaluate its safety and preliminary efficacy as a single agent, and a Phase 1b study of MK-8353 is ongoing as of 25-SEP-2018 to evaluate its safety and preliminary efficacy in combination with pembrolizumab. Selumetinib is a MEK inhibitor, under clinical evaluation in multiple indications, and has been shown to inhibit growth and/or the survival of selected tumor cell lines in vitro and xenograft growth in vivo either as monotherapy or in combination with established chemotherapies. Emerging data suggests that the combining ERK and MEK inhibitors reduces resistance, and may result in deeper and more durable suppression of the mitogen activated protein kinase (MAPK) signaling pathway compared with single agent targeting of the pathway [Xue, Y., et al 2017] [Merchant, M., et al 2017] (Section 2.1.2 Rationale for Combination of MK-8353 and Selumetinib).

The combination of MK-8353 and selumetinib will be evaluated in participants with any advanced solid tumor for which no curative therapy is available, and thus, suitable for an investigational treatment. Approximately 80 participants will be enrolled (see Section 9.9 for additional details).

2.1.2 Rationale for Combination of MK-8353 and Selumetinib

Emerging data suggest that inhibition of either MEK or ERK alone only transiently inhibits the MAPK pathway due to feedback reactivation. Simultaneous targeting of both MEK and ERK results in deeper and more durable suppression of MAPK signaling that is not achievable with any dose of the single agents, in tumors where feedback reactivation occurs. Combined MEK and ERK inhibition is synergistic in RAS mutant models but, where the RAF complex is dissociated from RAS and thus feedback productivity is disabled. Pathway reactivation in RAS mutant models occurs at the level of CRAF with combination treatment

resulting in a markedly more active pool of CRAF. However, distinct from single node targeting, combining MEK and ERK inhibitor treatment effectively blocks the downstream signaling as assessed by transcriptional signatures and phospho-p90RSK. Importantly, these data reveal that MAPK pathway inhibitors whose activity is attenuated due to feedback reactivation can be rescued with sufficient inhibition by using a combination of MEK and ERK inhibitors. The MEK and ERK combination significantly suppresses MAPK pathway output and tumor growth in vivo to a greater extent than the maximum tolerated doses of single agents, and results in improved anti-tumor activity in multiple xenografts as well as in two KRAS mutant genetically engineered mouse (GEM) models. Collectively, these data demonstrate that combined MEK and ERK inhibition is functionally unique, yielding greater than additive anti-tumor effects and elucidates a highly effective combination strategy in MAPK-dependent cancer, such as KRAS mutant tumors [Merchant, M., et al 2017].

A recent study described that parallel evolutionary tracts enabled the selection and propagation of distinct BRAF-amplified subclones, occurring in the same tumor shortly after drug treatment, allowing the tumor to adapt while maintaining its intratumoral heterogeneity. In this study, a fitness threshold model was derived, where fitness threshold refers to the barrier that subclonal populations need to overcome to regain fitness in the presence of drug treatment. Drugs targeting different nodes of the same pathway have distinct mechanisms of actions and, as a consequence, they exert a different evolutionary selective pressure. As such, the level of $BRAF_{amp}$ that was required to overcome the effect of the drug differed between RAF, MEK, and ERK inhibitors, with tumors treated with the latter able to tolerate higher levels of $BRAF_{amp}$. This model predicts that sequential treatment is ineffective, demonstrated by findings that treatment with a RAFi followed by treatment with an ERKi led to a progressive increase in *BRAF* CN and that patients who were pre-treated with ERK signaling inhibitors did not respond well to subsequent treatment with another inhibitor of the pathway. The model also predicts that at a sufficiently high fitness threshold, a broader range of $BRAF_{amp}$ subclones, including those with high-level amplification, is at a fitness disadvantage and prevented from propagation. One way to achieve this is with concurrent targeting of the RAF, MEK, and ERK kinases, which imposed a sufficiently high fitness threshold to prevent the propagation of subclones with high-level $BRAF_{amp}$. When administered on an intermittent schedule, this treatment inhibited tumor growth in 11/11 PDXs of lung cancer or melanoma without apparent toxicity in mice [Xue, Y., et al 2017].

Based on these emerging data, this study will use a dual inhibition approach, combining MEK (selumetinib) and ERK (MK-8353) inhibitors for concurrent targeting of the MAPK pathway.

2.2 Background

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 MK-8353 Pharmaceutical and Therapeutic Background

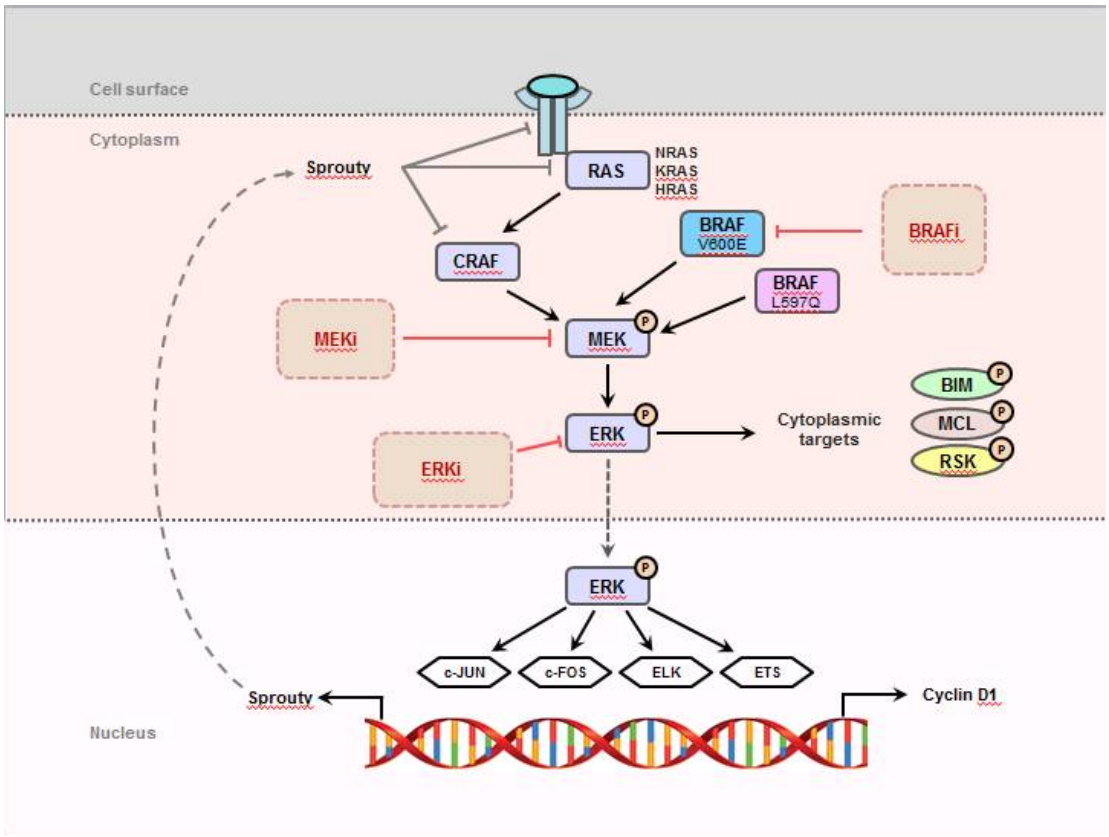
MK-8353 is a potent and selective ERK inhibitor, under clinical evaluation in multiple indications, both as a single agent and in combination with other therapeutic agents. For more details, refer to the MK-8353 IB.

2.2.1.2 Selumetinib Pharmaceutical and Therapeutic Background

Selumetinib is a MEK inhibitor, under clinical evaluation in multiple indications, both as a single agent and in in combination with established chemotherapies, novel targeted agents, and immunotherapy. For more details, refer to the selumetinib IB.

2.2.2 Mechanism of Action

Activation of the MAPK pathway is implicated in contributing to the aberrant growth of ~30% of human cancers particularly those tumors that have activating mutations in RAS and BRAF. While BRAF and MEK inhibitors have shown clinical success in BRAF-mutant melanoma and BRAF-mutant non-small cell lung cancer, they have shown limited activity in RAS-mutant tumors. Emerging preclinical data is showing that this limited activity is due to insufficient pathway suppression and likely pathway reactivation. In preclinical models, simultaneous targeting of both MEK and ERK results in deeper and more durable suppression of MAPK signaling that is not achievable with any dose of either single agent (Figure 3). These encouraging preclinical data lend support to the hypothesis that dual MEK and ERK inhibition may enable stronger sustained anti-tumor activity in MAPK-addicted tumors.



ERK = extracellular signal-regulated kinase; ERKi = extracellular signal-regulated kinase inhibitor; MEK = mitogen activated protein kinase; MEKi = mitogen activated protein kinase inhibitor

Figure 3 Mitogen Activated Protein Kinase Pathway and the Targets

2.2.3 Preclinical and Clinical Trials

2.2.3.1 MK-8353 and Selumetinib Preclinical Studies

In vitro MK-8353 inhibits the growth of cancer cell lines that are mutant for BRAF, KRAS, or NRAS but has limited activity on cell lines wild-type for BRAF and RAS. The antiproliferative effects of MK-8353 on BRAF-mutant cell lines are associated with increased levels of apoptosis. In vivo MK-8353 was shown to inhibit the growth of human tumor xenografts mutant for BRAF, NRAS, and KRAS. In a number of the mutant models MK-8353 induced marked tumor regressions indicative of significant anti-tumor activity.

Preclinically, selumetinib also inhibited the proliferation of human cancer cell lines mutant for BRAF and RAS. Selumetinib also preferentially inhibited the human xenograft models mutant for BRAF and RAS and had limited anti-tumor activity on wild-type models.

The primary toxicological risks associated with preclinical administration of MK-8353 consisted of skin irritation/inflammation in rats, significant body weight loss in dogs with decreased food consumption, and small intestine (enterocyte necrosis) and liver (portal inflammation and necrosis) toxicity in dogs. These findings generally showed complete recovery at the end of the 1-month postdose periods. In early exploratory non-Good Laboratory Practice (GLP) rat and dog studies with an amorphous form of MK-8353, tissue mineralization was noted. In the 1-month rat and dog GLP studies using the salt form, no tissue mineralization was observed but effects of MK-8353 on serum biomarkers (ie, osteocalcin, beta-C-terminal telopeptide, parathyroid hormone, and ionized calcium) were present.

Human absorption, distribution, metabolism, and excretion (ADME) data show that selumetinib is cleared through oxidative metabolism and glucuronidation. Metabolism is mediated primarily by CYP3A4, CYP2C19, UGT1A1 and 1A3. Clinical drug-drug interaction (DDI) data with itraconazole, fluconazole and rifampicin are consistent with these findings. Selumetinib is reported to be a weak inducer of CYPs 3A, 1A and 2C9.

For MK-8353, clearance occurs mostly through oxidative metabolism by CYP3A4, and to a minor extent through glucuronidation by UGT1A3 and 1A4 as determined by enzyme phenotyping. In vitro studies have shown that MK-8353 is a time-dependent inhibitor and competitive inhibitor CYP3A4. RIS data suggested no induction at clinically relevant exposures. Whereas for MK-8353 no clinical DDI data are currently available, based upon the ADME profiles and interaction properties of MK-8353 and selumetinib, a pharmacokinetic (PK) interaction between the two molecules appears possible. Predictions of DDI were conducted using a static model as well as using physiologically-based pharmacokinetic (PBPK) simulations. Simulation results suggest weak DDI upon co-dosing of selumetinib with MK-8353 at 300 mg BID (selumetinib AUC is predicted to increase up to 1.6-fold).

Preclinical data show that MK-8353 is an inhibitor of transporters MATE1 and OCT2 (see IB section 4.2.4.4). These transporters, which are involved in the active tubular secretion component of creatinine, have been shown to contribute to approximately 10-40% of

creatinine clearance [Levey, A. S., et al 1988] [Chu, X., et al 2016]. Therefore, inhibition of these transporters may lead to a rise in serum creatinine that may not be indicative of renal dysfunction. When creatinine increases from baseline ≥10%, monitoring of cystatin C may be used as an alternative marker to evaluate renal function.

2.2.3.2 MK-8353 Clinical Studies

MK-8353 is currently under development evaluation in multiple indications. The initial clinical evaluations of MK-8353 include a single-rising-dose study in healthy volunteers and a multiple-rising-dose study in subjects with advanced cancer [Moschos, S. J., et al 2018]. In the MK-8353 monotherapy dose escalation, the MTD was determined to be 350 mg BID with continuous dosing. Currently, a dose escalation study to evaluate safety and preliminary efficacy of MK-8353 in combination with pembrolizumab is ongoing. Refer to the IB for detailed information on preclinical and clinical experience with MK-8353.

2.2.3.3 Selumetinib Clinical Studies

Selumetinib is under clinical evaluation in multiple indications. More than 3900 participants have been exposed to selumetinib in Phase 1 through Phase 3 studies, including 3 Phase 3 trials (2 completed and 1 ongoing), where a total of 598 participants have been treated. The PK, pharmacodynamics, and safety of selumetinib have been well characterized. Refer to the IB for detailed information on preclinical and clinical experience with selumetinib.

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.

Given the unmet medical need that exists for patients with advanced malignancies, described in Section 2.1, the objective of the current study is to assess the safety and tolerability of the combination study medication. The combination regimen being examined in the current study has a potential to provide improvement of efficacy without increase of toxicity.

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

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

There are no hypotheses for the study.

This study is to be conducted in male and female participants with advanced/metastatic solid tumors.

Objectives	Endpoints
Primary	
• To determine the safety and tolerability and to establish preliminary RP2D(s) for the MK-8353 and selumetinib combination in participants with advanced/metastatic solid tumors	• DLTs • AEs • Study drug discontinuations due to an AE
Secondary	
• To evaluate the pharmacokinetics (PK) of MK-8353 and selumetinib	• Pharmacokinetic parameters, including AUC, C_{min} and C_{max}
Tertiary/Exploratory	
• To evaluate the overall response rate (ORR) and progression-free survival (PFS) based on RECIST 1.1 as assessed by the investigator for each dose level, and overall survival (OS).	• OR (overall response): participants who have a confirmed complete response (CR) or partial response (PR) • PFS: time from the first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first. • OS: time from the first dose of study medication to death due to any cause.
• To evaluate the serum levels of protein biomarkers (eg, carcinoembryonic antigen) before and after administration of MK-8353 in combination with selumetinib	• Determination of molecular/proteomic markers indicative of clinical response, safety or mechanism of action of MK-8353 and selumetinib
• 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-8353 in combination with selumetinib	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and immunohistochemistry (IHC), and other biomarkers (^{18}F-fluoro-deoxy-glucose positron emission tomography [FDG-PET])

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 1b, multicenter, worldwide, open-label study of MK-8353 in combination with selumetinib in participants with histologically or cytologically confirmed diagnosis of advanced solid tumor. This study will evaluate the safety, tolerability, and preliminary efficacy of MK-8353 in combination with selumetinib.

The dose escalation will start in the sequence of dose combinations formed along the diagonal of the dose combination grid denoted by ① in Figure 1A): (DL1, MK-8353 50 mg + selumetinib 25 mg), (DL2, MK-8353 100 mg + selumetinib 50 mg), (DL3, MK-8353 150 mg + selumetinib 75 mg), (DL4, MK-8353 200 mg + selumetinib 75 mg), (DL5, MK-8353 200 mg + selumetinib 100 mg), (DL6, MK-8353 250 mg + selumetinib 100 mg), and (DL7, MK-8353 250 mg + selumetinib 125 mg). The mTPI design with a target dose-limiting toxicity (DLT) rate of approximately 30% will be applied to identify a potential MTD in this sequence of dose combinations. If following the mTPI design the dose escalation along the diagonal of the dose combination grid concludes at either the starting dose, (DL1, MK-8353 50 mg + selumetinib 25 mg), or the last dose on the diagonal sequence, (DL7, MK-8353 250 mg + selumetinib 125 mg), the study will end with one MTD only. Otherwise, the study will simultaneously initiate additional off-diagonal dose combination sequences to identify additional potential MTDs as detailed in Table 1 and Figure 1B (Table 1). Following Table 1 and Figure 1B, if the dose escalation along the diagonal is concluded at either DL2, DL3, DL4, or DL5, two simultaneous off-diagonal dose combination sequences will be initiated with the respective starting doses specified in Table 1. The complete sequence for each possible scenario is found in Figure 1B. Thus, to identify MTD②, MK-8353 will be escalated while keeping selumetinib fixed. To identify MTD③, selumetinib will be escalated while keeping MK-8353 fixed. If the dose escalation along the diagonal is concluded at DL6, only one additional sequence will be explored using the mTPI decision rules by keeping MK-8353 fixed at 150 and escalating selumetinib: MK-8353 150 mg/100 mg selumetinib and MK-8353 150 mg/125 mg selumetinib.

Table 1 Starting Doses for MK-8353 or Selumetinib Escalation to Potential MTD② and MTD③

MTD① per mTPI	**Starting dose for MK-8353 escalation to potential MTD② (see Figure 1B)**	**Starting dose for Selumetinib escalation to potential MTD③ (see Figure 1B)**
DL1	No additional escalation	No additional escalation
DL2	100 mg MK-8353/25 mg selumetinib	50 mg MK-8353/50 mg selumetinib
DL3	150 mg MK-8353/50 mg selumetinib	100 mg MK-8353/75 mg selumetinib
DL4	150 mg MK-8353/50 mg selumetinib	100 mg MK-8353/75 mg selumetinib
DL5	200 mg MK-8353/75 mg selumetinib	150 mg MK-8353/100 mg selumetinib
DL6	No additional escalation[a]	150 mg MK-8353/100 mg selumetinib
DL7	No additional escalation	No additional escalation

[a] ERKi escalation per Figure 1B is not required because highest dose of ERKi is tolerable at DL6.

The rationale for conducting the dose escalation along these sequences is given in Section 4.2.1.

In each of the off-diagonal sequences, the mTPI design with a target DLT rate of approximately 30% will be applied to identify a potential MTD. Based on the emerging safety and/or efficacy signals, other dose levels may also be explored in consultation and agreement with the investigators and Sponsor.

The DLT rates across different dose combinations, in each dose combination sequence, will be estimated using isotonic regression under the assumption of monotonicity between the DLT rates and dose levels in each row and in each column of the dose combination grid [Dykstra, R. L. 1982]. This dose escalation study may yield multiple MTDs. The totality of the data will be considered before deciding on the dose combinations(s) to carry forward to further development (ie, preliminary RP2D).

Upon identification of the preliminary RP2D(s) for the MK-8353 and selumetinib combination, additional participants with solid tumors will be enrolled in the dose expansion

phase of this trial. Participants in the expansion phase of this study will receive MK-8353 in combination with selumetinib as dual therapy.

Preliminary efficacy will be evaluated using objective response rate (ORR) and progression-free survival (PFS) assessed by the investigator based on the RECIST Version 1.1 as exploratory objectives. Overall survival (OS) will also be evaluated as an exploratory objective.

Participants will be monitored carefully for the development of AEs and for clinical and/or radiographic evidence of disease progression according to RECIST 1.1. In participants who have initial evidence of radiological progressive disease (PD) by RECIST 1.1, it will be at the discretion of the investigator whether to continue a participant on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

Adverse events will be evaluated by the investigator, according to criteria outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0, to establish the safety and tolerability of MK-8353 in combination with selumetinib as per the primary objective of this study. The definition of DLTs and criteria for dose modification are outlined in Section 6.6.2 and Section 6.6.3.

Participants may receive study treatment until disease progression is radiographically documented and confirmed by the site per RECIST 1.1, unacceptable toxicity (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, participant withdrawal of consent, pregnancy of the subject, noncompliance with study treatment or procedure requirements, or administrative reasons requiring cessation of treatment, at which point they will be discontinued from the study. After the end of treatment (EoT), participants are to be followed up for safety for at least 30 days following the last study dosing and until recovery or stabilization of all related toxicities. Tumor measurements will continue to be made every 9 weeks until PD is observed, and each participant will be followed for survival. Imaging will not be collected during the Survival Follow-up Visit(s).

Participants may also agree to provide an optional on-treatment biopsy for biomarker analysis as outlined in the Scheduled of Activities (SoA; Section 1.3).

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

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Dose Combination Sequences

Because this is a dual dose escalation study, more than one dose combination level may satisfy the target DLT rate. Therefore, dose escalation along multiple dose combination sequences may need to be conducted. Initiating the dose escalation along the diagonal of the dose combination grid of Figure 1A (DL1, DL2 and DL3) is motivated by the potential for a more efficient study; beyond DL3 to DL7 each drug is escalated individually to mitigate the potential for overlapping toxicities (Figure 1A).

Consistent with the mTPI design, this study assumes nondecreasing toxicity with increasing dose levels. This assumption is made in each row and in each column of the dose combination grid, which implies the same relationship holds along the diagonal as well. Due to this assumption and the dose escalation decisions under the mTPI design, the simultaneous off-diagonal sequences outlined in Figure 1B will not start at the dose combinations immediately above and immediately to the right of the dose combination that concludes the dose escalation along the diagonal sequence. Instead, these sequences will start at the dose combinations immediately to the left and below this dose combination in the case of DL2, DL3 and DL5 (Figure 1B). If the dose combinations that conclude the escalation along the diagonal sequence are DL4 or DL6, the starting doses in the off-diagonal sequence(s) may be even more conservative (Figure 1B).

4.2.2 Rationale for Endpoints

4.2.2.1 Efficacy Endpoints

Exploratory Efficacy endpoints in this study include ORR and PFS, which are based on RECIST 1.1 as assessed by investigator. RECIST 1.1 is a validated tool in assessing anti-cancer activity of an investigational agent. Overall survival is also an exploratory endpoint.

An imaging contract research organization will be used to collect, clean, and hold tumor imaging. Images will be collected for possible analysis by blinded, independent central review (BICR).

4.2.2.1.1 Response Rate Assessed by RECIST 1.1

RECIST 1.1 will be used by the principal investigator to determine the objective response.

4.2.2.2 Safety Endpoints

The primary safety endpoint is the incidence of DLTs and number of discontinuations of study treatment due to an AE. Safety and tolerability will be assessed by clinical review throughout the trial. The toxicities and grades experienced by participants who have received study treatment, including AEs, serious AEs (SAEs) and events of clinical interest (ECIs) will be summarized. Other safety measures evaluated in study include laboratory tests,

electrocardiograms (ECGs), echocardiogram/multigated acquisition), vital signs, physical examinations, and eye examination.

4.2.2.3 Pharmacokinetic Endpoints

A secondary objective of this trial is to characterize the PK profile of MK-8353 and selumetinib (and their metabolites). The PK concentrations of MK-8353 and selumetinib (and its metabolites) will be used to derive PK parameters of the agents. Furthermore, the results of these analyses will be potentially used in conjunction with the pharmacodynamics, safety, and exploratory endpoint data to help assess future dosing strategies for MK-8353 and selumetinib.

4.2.2.4 Planned Exploratory Biomarker Research

4.2.2.4.1 Biospecimens

It is important to investigate the determinants of response or resistance to cancer treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/PD biomarkers and generate information that may better guide single-agent and combination therapy. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

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

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

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and blood RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that

correlate to clinical response to treatment. Specific MEK signaling-related gene sets may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated. MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and immunohistochemistry (IHC) using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses. Tumor or blood-derived proteins may correlate with response to treatments. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays detecting pERK and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for treatments.

Other blood-derived 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 enzyme-linked immunoassay (ELISA) measure such proteins in serum. Correlation of expression with response to treatment may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

4.2.2.4.2 Imaging

For MEK inhibitors, it has been observed that decrease in FDG uptake is primarily related to decrease in GLUT1 mediated by drug-induced changes in MAPK signaling pathways [Baudy, A. R., et al 2012]. In clinical studies with MEK inhibitors, FDG was able to identify early nonresponding patients with a high negative predictive value [Kraeber-Bodere, F., et al 2012] [Zimmer, L., et al 2014] [Rosen, L. S., et al 2016]. Early changes in FDG PET parameters in the tumor may be indicative of biological and pharmacodynamic activities related to mode of action and thus contribute towards selection of optimum dosing regimen of MK-5618 and MK-8353. This study will evaluate FDG-PET as an exploratory biomarker of pharmacodynamic changes related to mechanism of action of the study drugs at the MTD levels.

4.2.2.5 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for

future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this future biomedical research substudy are presented in Appendix 6.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

In the absence of a reliable pharmacodynamic marker for both ERKi and MEKi, variability in PK alone was also used to guide starting dose.

MK-8353 starting dose will be 50 mg BID with 4 days on/3 days off intermittent dosing schedule. This was selected based on PK simulations of MK-8353 indicated that 50 mg BID would be the highest dose where there is no overlap in the interquartile range of exposure from the 350 mg BID dose could be expected (MTD of MK-8353 monotherapy was 350 mg BID with continuous dosing [PN001]).

The starting dose for selumetinib is planned to be 25 mg BID with 4 days on/3 days off intermittent dosing schedule. PK simulations indicated that the interquartile range of exposures at 25 mg BID would have a separation from exposures at 75 mg BID dose (monotherapy selumetinib MTD = 75 mg BID continuous dosing).

In addition, in the clinical evidence of cobimetinib (MEKi) + GDC-0994 (ERKi) trial, [Weekes, C. D., et al 2017] started at 2/3 cobimetinib and 1/2 of GDC-0994 of the RP2D with 21 days on and 7 days off dosing schedule, and had 1 DLT observed [Weekes, C. D., et al 2017]. Therefore, a more conservative approach is to have a starting dose at 1/5 of the MTD of MK-8353 and 1/3 of the MTD of selumetinib with an intermittent dosing of 4 days on/3 days off.

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose of MK-8353 for this study will be 250 mg administered orally BID, on a 4 days on followed by 3 days off schedule (maximum 500 mg total per day). The Phase 2 dose for MK-8353 monotherapy is 350 mg BID administered continuously. This will provide a total dose of 6000 mg per 3-week cycle which is less than monotherapy dose per 3-week cycle (14700 mg).

The maximum dose of selumetinib for this study will be 125 mg administered orally BID, on a 4 days on followed by 3 days off schedule (maximum 250 mg total per day). The Phase 2 dose for selumetinib monotherapy is 75 mg BID administered continuously. This will provide a total dose of 3000 mg per 3-week cycle which is less than monotherapy dose per 3-week cycle (3150 mg).

Inhibition of both MEK and ERK may exacerbate toxicity of either inhibitor alone. However, intermittent dosing schedules of both MK-8353 and selumetinib (4 days on followed by 3

days off schedule) is likely to be better tolerated than continuous dosing and short half-lives (approximately 8 hours) would reduce concerns over toxicity while maintain anti-tumor activity [Xue, Y., et al 2017].

4.3.3 Rationale for Dose Interval and Study Design

MK-8353 will have 50 mg incremental dose levels up to 250 mg (50, 100, 150, 200, 250 mg BID). Selumetinib will have 25 mg incremental dose levels up to 125 mg (25, 50, 75, 100, and 125 mg BID). These follow incremental increases of 100%, 50%, 33% and 25%. The smaller increases at higher doses take into consideration the risk for greater overlapping toxicity.

An alternate dose level, frequency drug administration and dosing schedule may be explored, and an optimal dose will be selected based on totality of data (PK, pharmacodynamic, and safety) emerging throughout the trial. The protocol will be amended as required.

The 4 days on/3 days off schedule was selected based on 1) a preclinical evidence that 4 days on/3 days off with vemurafenib (RAFi), trametinib (MEKi), SCH984 (ERKi) which was shown to ameliorate toxicity and sustain efficacy [Xue, Y., et al 2017]. In this study, continuous MEK/ERK/BRAFi administration was toxic and sequential ERK/MEK inhibition fosters resistance and was less effective, 2) the most common safety signal we see for MAPK pathway is skin rash, usually start seeing early time like from approximately 7 days after the treatment and within 3 month [Wang, D., et al 2007], 3) the short half-life of selumetinib and MK-8353 (approximately 8 hours) suggests that selumetinib and MK-8353 would be eliminated in as long as 2 days after stopping treatment, therefore, have the potential advantage to exploit intermittent schedules that have (preclinically) been shown to ameliorate toxicity but maintain anti-tumor activity [Xue, Y., et al 2017].

4.3.4 Dose Finding Using a Modified Toxicity Probability Interval Design

The modified toxicity probability interval (mTPI) design [Ji Y, Li Y, Bekele BN 2007] with a target DLT rate of approximately 30% will be applied to identify the MTD in each of the studied dose combination sequences described above.

In each dose combination sequence separately, dose escalation and de-escalation decisions will be based on the mTPI design and will depend on the number of participants enrolled and number of DLTs observed at the current dose combination level. The number of DLTs will be based on the DLT evaluable population which consists of participants who finished Cycle 1. See Section 5.6 and Section 9.5.1 for details.

A minimum of 3 participants will be required at each dose combination level. However, depending on the accrual rate, 3, 4, 5, or 6 participants may be enrolled at each new dose combination level. In Table 2, the columns indicate the numbers of participants treated at the current dose combination level, and the rows indicate the numbers of participants experiencing DLT. The entries of the table are the dose-finding decisions: E, S, D, and DU represent escalating the dose, staying at the same dose, de-escalating the dose, and excluding the dose from the trial due to unacceptable toxicity, respectively. For example, if 0 out of

3 participants at a given dose combination level develop a DLT, then the dose can escalate to the next level. If 2 participants out of 3 develop a DLT, the dose will be de-escalated to the next lower dose level. If 3 out of 3 participants develop a DLT, this indicates an unacceptable toxicity at this dose combination. The dose combination should be de-escalated, and the current dose combination will not be explored further. If 1 out of 3 participants at a given dose combination level develops a DLT, then additional participants should be enrolled at that dose combination level following the rules below.

When adding participants to a dose combination level in response to a "stay" decision, the number of additional participants to be enrolled is capped to minimize the exposure to a dose combination that may be unacceptably toxic (denoted as DU in Table 2). Secondly, to determine how many more participants can be enrolled at the dose combination 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 combination level, no more than an additional 3 participants should be enrolled at this dose combination level until additional DLT data are available. This is because this dose combination level would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (ie, 4/6 participants with DLT in Table 2). The same principles will be applied whether 3, 4, 5, or 6 participants are initially enrolled at that dose combination level.

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

Dose finding will end after 14 participants have been enrolled at any of the tested dose combinations, in each sequence separately, regardless of subsequent dose escalation decision.

The DLT rates across dose combination levels will be estimated under the assumption of a monotonic relationship between toxicity and dose in each column, in each row and along the main diagonal of the dose combination grid. In each dose combination sequence, the dose combination with an estimated DLT rate closest to 30% 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 into the planned expansion phase, and the escalation schedule may be adjusted based on PK, pharmacodynamic, and safety data emerging throughout the trial.

Note that although 30% was the target toxicity rate used to generate the guidelines in Table 2, the observed rates of participants with DLTs at the MTD(s) may be slightly above or below 30%.

Dose escalation decisions will be made upon ongoing review of available PK, pharmacodynamic, and safety data at the current dose level.

Based on the emerging safety and/or efficacy signals, lower, intermediate or higher dose combination levels may also be explored in consultation and agreement with the investigators and Sponsor. The exact additional dose combinations in each sequence during dose escalation is not predetermined, which will allow for flexibility in dose escalation based on emerging safety data in the clinical trial. The protocol will be amended as necessary.

Table 2 Dose-finding Rules per mTPI Design

	Number of Participants Evaluable for DLT at Current Dose											
Number of participants with at least 1 DLT	3	4	5	6	7	8	9	10	11	12	13	14
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	S	E	E	E	E
3	DU	DU	D	S	S	S	S	S	S	S	S	S
4		DU	DU	DU	D	D	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	D	S	S	S	S
6				DU	DU	DU	DU	DU	DU	D	S	S
7					DU	DU	DU	DU	DU	DU	DU	D
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 = De-escalate to the next lower dose; DU = The current dose is unacceptably toxic; E = Escalate to the next higher dose; S = Stay at the current dose
Target toxicity rate = 30%.
Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.03[Ji Y, Li Y, Bekele BN 2007], [Ji, Y. and Wang, S.-J. 2013]

4.4 Beginning and End of Study Definition

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

4.4.1 Clinical Criteria for Early Study Termination

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

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

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

3. Quality or quantity of data recording is inaccurate or incomplete

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-8353 or selumetinib.

5 STUDY POPULATION

Male/female participants at least 18 years of age with advanced/metastatic solid tumor(s) will be enrolled in the study.

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Have a histologically- or cytologically-documented, locally-advanced or metastatic solid tumor by pathology report and have received, or been intolerant to, all treatment known to confer clinical benefit.

2. Provide an archival or newly obtained tumor tissue sample and blood samples for assessment of RAS/RAF mutation and for biomarker analysis.

3. Have at least 1 measurable lesion as defined by RECIST 1.1 on imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) as assessed by the investigator/local radiology review. Cutaneous lesions and other superficial lesions that are detectable only by physical examination and subcutaneous lesions detectable by CT are not considered measurable lesions for the purposes of this protocol, but may be considered as nontarget lesions.

4. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale. (Obtain within 7 days prior to first dose of study treatment.)

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

6. Demonstrate adequate organ function as defined in Table 3

   Note: All screening evaluations should be performed within the Screening period, and labs are to be obtained within 7 days of initiation of treatment.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	>1,500/mcL (>1,000/mcL)
Platelets	>100,000/mcL
Hemoglobin	>9 g/dL or >5.6 mmol/L[a]
Renal	
Serum creatinine or creatinine clearance (CrCl) (measured or calculated)[b] or Glomerular Filtration Rate (GFR) in place of CrCl	≤1.5 X ULN or ≥60 mL/min for participant with creatinine levels >1.5 X ULN
Hepatic	
Total bilirubin (serum)	≤1.5 X ULN or Direct bilirubin <ULN for participants with total bilirubin levels >1.5 X ULN
AST (SGOT) and ALT (SGPT)	<2.5 X ULN or ≤5 X ULN for participants with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	< 1.5 X ULN unless participant is receiving anticoagulant therapy < 1.5 X ULN unless participant is receiving anticoagulant therapy

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

[a] Criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

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

Demographics

7. Is Male or Female and a minimum of 18 years of age inclusive, at the time of signing the informed consent.

Male Participants

8. Must agree to use a contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 120 days after the last dose of study intervention and refrain from donating sperm during this period.

Female Participants

9. Eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:

    a) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

        OR

    b) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 120 days, after the last dose of study intervention.

Informed Consent

10. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Have had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) prior to the first dose of study treatment, or has not recovered to CTCAE Grade 1 or better from any AEs that were due to cancer therapeutics administered more than 4 weeks earlier (this includes participants with previous immunomodulatory therapy with residual immune-related AEs). Participants receiving ongoing replacement hormone therapy for endocrine immune-related AEs will not be excluded from participation in this study.

2. Have a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years.

    Note: The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer or in situ cervical cancer, or other in-situ cancers.

3. Have clinically active central nervous system metastases and/or carcinomatous meningitis. Participants with previously-treated brain or meningeal metastases may participate and be eligible for treatment provided they are stable and asymptomatic (without evidence of progression by MRI scan of the brain separated by at least 4 weeks after treatment), have no evidence of new or enlarging brain metastases, are evaluated within 4 weeks prior to first study treatment administration, and are off immunosuppressive doses of systemic steroids at least 2 weeks prior to enrollment

4. Have an active infection requiring therapy.

   Note: Rescreening is possible after the infection resolves.

5. Have known human immunodeficiency virus (HIV) and/or Hepatitis B or C infections, or known to be positive for Hepatitis B antigen (HBsAg)/ Hepatitis B virus (HBV) DNA or Hepatitis C Antibody or RNA. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative hepatitis C virus RNA results greater than the lower limits of detection of the assay.

6. Have undergone major surgery and has not fully recovered from any effects of major surgery without significant detectable infection and/or toxicity.

   Note: Surgeries that required general anesthesia must be completed at least 2 weeks before first study intervention administration.

   Note: Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before first study intervention administration and participants should be recovered.

7. Have clinically significant cardiovascular disease as defined by the following:

   a) Uncontrolled hypertension (at screening/baseline: systolic BP ≥150 mmHg or diastolic BP ≥95 mmHg, despite optimal therapy)

   b) LVEF <55% measured by echocardiography (or multigated acquisition scan)

   c) Symptomatic heart failure (New York Heart Association grade II-IV), prior or current cardiomyopathy, or severe valvular heart disease

   d) Uncontrolled angina (Canadian Cardiovascular Society grade II-IV despite medical therapy)

   e) Clinically significant cardiac arrhythmia and/or conduction abnormality ≤6 months prior to start of study treatment

   f) Myocardial infarction (MI) or acute coronary syndrome (ACS) ≤6 months prior to start of study treatment

   g) Mean QTcF interval >470 ms (based on mean of 3 measurements corrected for heart rate based on Fridericia's formula)

8. Have a history of thromboembolic or cerebrovascular events within 6 months prior to treatment start, including transient ischemic attacks (TIAs), cerebrovascular accidents (CVAs), deep vein thrombosis, or pulmonary embolism.

9. Have neuromuscular disorders associated with an elevated creatine kinase (eg, inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy.

10. Have one or more of the following ophthalmological findings/conditions:

    a) Intraocular pressure >21 mmHg, or uncontrolled glaucoma (irrespective of intraocular pressure)

    b) Current or past history of central serous retinopathy or retinal vein occlusion

    c) Retinal degenerative disease

11. Have a known history of Gilbert's Syndrome.

12. Have a history or current evidence of a gastrointestinal (GI) condition (eg, inflammatory bowel disease, Crohn's disease, ulcerative colitis) or impaired liver function or diseases that in the opinion of the investigator may significantly alter the absorption or metabolism of oral medications.

13. Have a known psychiatric or substance abuse disorder, or any other cognitive disorder per the opinion of the investigator, that would interfere with the participant's ability to cooperate with the requirements of the study.

14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 120 days after the last dose of study treatment.

Prior/Concomitant Therapy

15. Received prior therapy with a MEK inhibitor (eg, cobimetinib, trametinib), or an ERK inhibitor (eg, MK-8353, GCD-0994, ulixertinib), or a BRAF inhibitor (eg, dabrafenib, vemurafenib).

16. Received any herbal medications/supplements or any medications or foods that are strong or moderate inhibitors or inducers of CYP2C19 and CYP3A4 enzymes within 14 days prior to the start of study treatment (Table 5).

Prior/Concurrent Clinical Study Experience

17. Is currently participating and receiving study treatment in a study of an investigational agent or has participated and received study treatment in a study of an investigational agent or has used an investigational device within 28 days of administration of selumetinib.

    Note: Participants who have entered the Post-treatment Follow-up Phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent.

Diagnostic Assessments

Other Exclusions

18. Have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to agents and/or excipients used in the study.

Pregnancy Exclusion

19. A WOCBP who has a positive urine pregnancy test within 24 hours before the first dose of study treatment (see Appendix 5). If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

5.3 Special Considerations for Subjects of Asian Ethnicity

Plasma exposure of selumetinib (C_{max} and AUC) is higher, at a population level, in subjects of Asian ethnicity by approximately 1.5- to 2-fold, compared with Western subjects. However, the PK of selumetinib show considerable variation and there is overlap in the range of exposure experienced by Asian and Western subjects (some individual Asian subjects have similar plasma levels to those in Western subjects). The higher average plasma exposure was not associated with a change in the tolerability profile of single dose selumetinib.

Patients of Asian ethnicity are not excluded from studies evaluating selumetinib. However, when considering enrolling an individual of Asian ethnicity to a selumetinib clinical study, investigators should make a clinical judgment as to whether the potential risk of experiencing higher selumetinib plasma levels outweighs the potential benefit of treatment with selumetinib. Investigators should be aware of the potentially higher risk of adverse events when monitoring patients of Asian ethnicity receiving treatment in clinical studies of selumetinib.

Additional details are available in the selumetinib IB.

5.4 Lifestyle Considerations

5.4.1 Meals and Dietary Restrictions

Selumetinib should be taken on an empty stomach; no food or drink other than water for approximately 2 hours prior to dosing and approximately 1 hour after dosing. The participant must be fasting for the glucose (finger stick) obtained pre-dose on C2D4 visit.

Foods that contain CYP3A inhibitors must not be consumed during the study. Grapefruit juice and other fruit juices are known to be CYP3A inhibitors, and should not be consumed for 2 weeks before the first dose of MK-8353 and for the entire duration of the study. Consumption of CYP3A4 inhibitors, such as grapefruit juice, may significantly increase the levels of MK-8353 and cause increased toxicity.

St. John's Wort is a CYP3A inducer, and the consumption of St. John's Wort or products containing St. John's Wort may reduce the levels of MK-8353.

5.4.2 Caffeine, Alcohol, and Tobacco Restrictions

There are no study specific restrictions.

5.4.3 Activity Restrictions

There are no study specific restrictions.

5.5 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 Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.6 Participant Replacement Strategy

In order to adequately evaluate the safety of the doses administered in this study, all participants enrolled must meet the criteria for evaluability for Cycle 1. Participants are considered nonevaluable and will be replaced if:

- They are allocated but not treated.
- They discontinue from the trial prior to completing all the safety evaluations for reasons other than treatment-related AEs.
- They receive less than 75% of the total selumetinib or MK-8353 study treatment in Cycle 1 and did not experience a DLT.

Participants who are not evaluable will be replaced unless accrual to the dose level has stopped. Nonevaluable participants will not be counted toward the total number of participants in the dose level for DLT evaluation.

If a participant experiences a DLT in Cycle 1, study intervention may be discontinued following discussion between the Sponsor and investigator. However, if the participant is deriving clinical benefit from the study intervention, the participant may be allowed to continue after discussion between the Sponsor and the investigator.

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.

Study interventions provided by the Sponsor will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies. Clinical supplies will be labeled with guidance to administer as directed.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 4.

Table 4 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
MK-8353 + MK-5618	Experimental	MK-8353	Drug	Capsule	50 mg, 100 mg	50 mg, 100 mg, 150 mg, 200 mg, 250 mg	Oral	BID 4 days on and 3 days off	Experimental	IMP	Provided centrally by Sponsor
MK-8353 + MK-5618	Experimental	MK-5618 (Selumetinib)	Drug	Capsule	25 mg	25 mg, 50 mg, 75 mg, 100 mg, 125 mg	Oral	BID 4 days on and 3 days off	Experimental	IMP	Provided centrally by Sponsor

BID = Twice daily; IMP = Investigational Medicinal Products; NIMP = Non-investigational Medicinal Product
Alternate dose levels, drug administration frequency and dosing schedule (eg, BID vs. once daily [QD], on/off intermittent dosing schedule) may be explored.

All supplies indicated in Table 4 will be provided per the "Sourcing" row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product per local guidelines unless otherwise instructed by the Sponsor.

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

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

Treatment allocation will occur centrally using an interactive response system / integrated web response system (IRS/IWRS). Participants will first be assigned in a nonrandom fashion to the diagonal dose combination sequence. Once this sequence is closed and in case two additional off-diagonal dose combination sequences are initiated, participants will be allocated by alternate assignment to either off-diagonal sequence. In each sequence, a new dose combination will open for enrollment without delay once the 21-day DLT observation

period of the previous dose combination level is completed. Dose escalation decisions within each sequence will be made independently.

6.3.2 Stratification

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

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Interruptions from the protocol specified treatment plan or procedures >12 weeks will be considered noncompliant. Further, any interruptions of MK-8353 and selumetinib doses for non-drug related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

6.5.1 Acceptable Concomitant Medication

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

All concomitant medications received within 30 days before the first dose of study intervention and 30 days after the last dose of study intervention should be recorded. Concomitant medications administered after 30 days after the last dose of study intervention should be recorded for SAEs and ECIs as defined in Section 8.4.

6.5.2 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication or vaccination. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Participants are prohibited from receiving the following therapies during the Screening and study intervention phase(s):

1. Antineoplastic systemic chemotherapy or biological therapy

2. Immunotherapy not specified in this protocol

3. Chemotherapy not specified in this protocol

4. Investigational agents other than MK-8353 and selumetinib

5. Any supplemental vitamin E. High doses of vitamin E have been reported to cause bleeding and interrupt blood coagulation processes.

   - Selumetinib capsules contain vitamin E in the form of D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS), a water-soluble form of vitamin E, which acts as a formulation excipient.

   - Selumetinib should be administered with caution in participants who are receiving concomitant coumarin anticoagulant medications, eg, warfarin. These participants should have their INR monitored, anticoagulant assessments conducted more frequently, and the dose of the anticoagulant therapy adjusted accordingly.

6. Radiation therapy

   Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion after the DLT observation period in order for the participant to be considered evaluable for DLT.

7. Agents that may affect the metabolism of MK-8353 or selumetinib (eg, strong/moderate inhibitors or inducers of CYP3A4 and CYP2C19), unless considered clinically indicated (Table 5)

   Note: If the PI determines the use of such agent is clinically indicated, caution must be taken when co-administering these agents with MK-8353 and selumetinib.

8. Compounds with a narrow therapeutic index that are substrates for CYP3A4, -2C8, OATP1B1/3, and OCT2 should be avoided (Table 5). Once study treatment is initiated, the participant must not take medications listed in Table 5 during the course of the study.

    - Table 5 is not a comprehensive listing. The investigator must use his/her medical judgment when a participant presents with a medication not on the list or call the Sponsor for clarification as needed. The investigator should consult an actively updated list of drugs that are clinically relevant inducers, or inhibitors of CYP450, including CYP2C19 and CYP3A4, and a narrow therapeutic index that are substrates for CYP3A4, -2C8, OATP1B1/3, and OCT2, as well as the product labeling of these compounds for reference.

Table 5 Examples of CYP3A4 Inducers/Inhibitors and Narrow Therapeutic Index Substrates of CYP3A4, CYP2C8, OATP1B1/3 and OCT2 Prohibited During the Trial

Strong CYP3A4 Inhibitors[a,g]	**Strong CYP3A4 Inducers**[b,g]	**Moderate CYP3A4 Inhibitors**[c,g]	**Moderate CYP3A4 Inducers**[d,g]
Atazanavir Cannabis (oral, IV) Clarithromycin Cobicistat Conivaptan Danoprevir and ritonavir Dasabuvir Elvitegravir and ritonavir Grapefruit juice and other juices[f] Idelalisib Indinavir and ritonavir Itraconazole Ketoconazole Lopinavir and ritonavir Paritaprevir and ritonavir (ombitasvir and/or dasabuvir) Posaconazole Nefazodone Nelfinavir Ritonavir Saquinavir and ritonavir Telithromycin Tipranavir and ritonavir Troleandomycin Voriconazole	Carbamazepine Enzalutamide Mitotane Phenobarbital Phenytoin Rifabutin Rifampin St John's wort[e]	Amprenavir Aprepitant Cimetidine Ciprofloxacin Clotrimazole Crizotinib Cyclosporine Diltiazem Dronedarone Erythromycin Fluconazole Fluvoxamine Fosamprenavir Imatinib Tofisopam Verapamil Grapefruit juice and other juices[f]	Bosentan Efavirenz Etravirine Modafinil
CYP3A4 Substrates with Narrow Therapeutic Index[h]	CYP2C8 Substrates with Narrow Therapeutic Index[h]	OATP1B1/1B3 Substrates with Narrow Therapeutic Index[i]	OCT2 Substrates with Narrow Therapeutic Index[i]
Alfentanil Alprazolam Astemizole Cisapride Ergotamine Diergotamine Cyclosporine Fentanyl (including Duragesic) Hydrocodone Lovastatin Lurasidone Paclitaxel Pimozide Quinidine Rivaroxaban Sirolimus Tacrolimus	Cisapride Repaglinide Paclitaxel	Asunaprevir Atorvastatin Bosentan Danoprevir Docetaxel Glyburide Nateglinide Paclitaxel Pitavastatin Pravastatin Rosuvastatin Simvastatin	Dofetilide Metformin

Strong CYP3A4 Inhibitors[a,g]	Strong CYP3A4 Inducers[b,g]	Moderate CYP3A4 Inhibitors[c,g]	Moderate CYP3A4 Inducers[d,g]

CYP = cytochrome P450; OATP = Organic Anion Transporting Polypeptide; OCT = Organic Cation Transporter

[a] Strong inhibitors are drugs that increase the plasma AUC of sensitive CYP index substrates by ≥5-fold.

[b] Strong inducers are drugs that decrease the plasma AUC of sensitive CYP index substrates by ≥80%.

[c] Moderate inhibitors are defined as causing a ≥2- but <5-fold increase in the AUC values of sensitive CYP index substrates when the inhibitors were given at the highest approved dose and the shortest dosing interval in clinical evaluations.

[d] A moderate inducer decreases the AUC of a sensitive index CYP substrate by ≥50% to 80%.

[e] The effect of St John's wort varies widely and is preparation-dependent.

[f] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

[g] Compiled from the table of substrates, inhibitors and inducers available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm ("Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers").

[h] CYP3A4 and CYP2C8 substrates with narrow therapeutic range refers to drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of CYP3A4 or CYP2C8 inhibitors may lead to serious safety concerns. For specific information, refer to the Classification of Substrates tables, accessible at the following link: https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm (In subsection "CYP Enzymes", select "Clinical substrates").

[i] OATP1B1/1B3 and OCT2 substrates with narrow therapeutic range refers to drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of OATP1B1/1B3 or OCT2 inhibitors may lead to serious safety concerns. For specific information, refer to the Classification of Substrates tables, accessible at the following link: https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm (In subsection "Transporters", select "Clinical substrates").

Based on investigator assessment, participants who require the use of any of the aforementioned treatments for clinical management should be discontinued from study intervention and continue in the Post-treatment Follow-up Phase as outlined in the SoA (Section 1.3). Participants may receive other medications that the investigator deems to be medically necessary.

6.5.3 Supportive Care

6.5.3.1 MK-8353 Supportive Care

Medications required to treat AEs or concurrent illnesses other than those prohibited in Section 6.5.2 are allowed during the study. These include antiemetics, growth factors, and other supportive care medications. Contraceptive medications as described in Appendix 5 are allowed.

Bisphosphonates are allowed for subjects with lytic bone metastases. Antiemetics, including serotonin-receptor antagonists, metoclopramide, prochlorperazine, or thiethylperazine are allowed. Aprepitant is a CYP3A4 inhibitor and should not be used in the study.

Skin rash has been observed in subjects treated with inhibitors of the MAPK pathway and is expected in the current study. It may be representative of an on-target effect of the study medication. Appropriate clinical management of skin rash may be utilized as clinically indicated. An algorithm based on dermatology best practices for other contemporary targeted agents that cause skin toxicity is offered below as guidance to manage skin toxicities seen in subjects being treated on this protocol. The algorithm suggests a step-wise approach to rash management.

- If the rash is NCI CTCAE Grade 1, consider starting with topical steroids (eg, betamethasone), topical antibiotics such as clindamycin gel, or no treatment if the subject is asymptomatic. Use of topical steroid cream with higher potency may be considered early in subjects with moderate rash on the face.

- If the rash is NCI CTCAE Grade 2, continue topical steroid or pimecrolimus cream and consider adding an oral tetracycline or a similar agent.

- If the rash reaches NCI CTCAE Grade 3 or above, dose interruption and/or dose reduction, coupled with the addition of topical steroids is recommended.

- Pruritus of any grade may be treated with an antihistamine, such as diphenhydramine or hydroxyzine hydrochloride.

- Xerosis can be treated with classical emollients.

- Secondary infection may complicate or worsen skin toxicity. To reduce the likelihood of nasal infection, intranasal mupirocin may be considered. Infected rash may be treated with a short course of an oral tetracycline, such as doxycycline. Sun exposure should be avoided in subjects receiving doxycycline or other tetracycline antibiotics.

- If there is a clinical diagnosis of impetigo, or an infection with Staphylococcus aureus is confirmed, topical mupirocin may be used. Infected lesions suspected to be treatment-resistant should be cultured. If there is no improvement after 2 weeks of treatment, therapy for the rash should be considered ineffective and discontinued.

- Additionally, oral antihistamines (nonsedative) may also be considered for the treatment of Grade 1 to 3 rashes. Oral steroids may be considered for Grade 3 rash.

Every medication taken by the subject during the trial and the reason for use must be recorded in the electronic case report form (eCRF). Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an AE of the subject.

Subjects will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined below:

- **Diarrhea**: diarrhea should be treated promptly with appropriate supportive care, including loperamide. Subjects should be instructed to begin taking loperamide at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day, or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. The daily dose of loperamide should not exceed 16 mg/day. Loperamide should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious etiology. Subjects should be also advised to drink liberal quantities of clear fluids to help prevent dehydration. Supportive care according to institutional guidelines in the context of standard of care for diarrhea are permitted (except prohibited medications; see Section 6.5.2).

- **Nausea/vomiting:** nausea and vomiting should be treated aggressively. After an initial occurrence of Grade 2 or higher nausea or vomiting, strong consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

- **Anemia:** transfusions and/or erythropoietin may be utilized as clinically indicated per American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) guidelines after the first cycle of combination therapy for the treatment of anemia, but should be clearly noted as concurrent medications.

- **Neutropenia:** colony–stimulating factors including G-CSF, pegylated G-CSF or GM-CSF according to ASCO/ASH guidelines after the first cycle of combination therapy. Colony–stimulating factors can be administered for the management of neutropenia toxicities after Cycle 1.

- **Thrombocytopenia:** transfusion of platelets may be used per ASCO/ASH guidelines if clinically indicated.

- **Anti-infectives**: subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

6.5.3.2 Selumetinib Supportive Care

- **Hypertension:** It is recommended that additional blood pressure monitoring occur for participants who may be at risk (participants with hypertension at baseline) or those with antecedents of hypertension or those treated with antihypertensive medication. Early initiation of treatment is recommended after diagnosis, with aggressive management of emergent hypertension.

- **Nausea and/or vomiting:** Because nausea and vomiting have been reported for selumetinib, it is recommended that participants are educated on the possibility of occurrence of these side effects prior to starting study treatment. Participant education as well as proper management of nausea and/or vomiting at the first sign is important. Clinical judgment and experience of the treating physician should guide the management plan of each participant. Participants experiencing nausea and/or vomiting CTCAE Grade ≥1 should receive antiemetics at the discretion of the treating physician (as per local guideline). It is recommended that participants be provided a prescription for antiemetics, and are instructed on the use of antiemetics on the first day of study drug treatment. Prophylactic antiemetics such as dexamethasone 8 mg, prochlorperazine, or metoclopramide may be administered to participants on an "as needed" basis. Medication use should be recorded accordingly.

  Dose interruption/reduction decisions for nausea and/or vomiting should be based on the CTCAE grade of the toxicity and the guidelines provided in Section 6.6.4.

  As guidance for recommendations on supportive measures for the prevention and/or management of nausea and/or vomiting, the published recommendation from ASCO [Sepulveda, A. R., et al 2017], European Society for Medical Oncology (ESMO) [Van Cutsem, E., et al 2016], and Multinational Association of Supportive Care (MASCC) can be used [Basch, E., et al 2011] [Roila, F., et al 2010].

- **Diarrhea:** Management of diarrhea should be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. All concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications section of the participant record. It is recommended that participants be provided loperamide tablets and are instructed on the use of loperamide on the first day of selumetinib treatment. In addition to the selumetinib -induced diarrhea dosing guidelines, these instructions should be provided at each visit and the site should ensure that the participant understands the instructions.

  For uncomplicated Grade 1/2 diarrhea

  - Stop all lactose-containing products, alcohol and eat frequent small meals that include bananas, rice, applesauce, or toast)

  - Stop laxatives, bulk fiber (ie, Metamucil®) and stool softeners (eg, docusate sodium; Colace®)

- Stop high-osmolar food supplements such as Ensure® Plus and Jevity® Plus (with fiber)

- Drink 8 to 10 large glasses of clear liquids per day (eg, water, Pedialyte®, Gatorade® or broth)

- Consider administration of standard dose of loperamide: initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool

- Discontinue loperamide after 12-hours diarrhea-free (Grade 0) interval

- If uncomplicated Grade 1 to 2 diarrhea persists for more than 24 hours, escalate to high dose loperamide: 2 mg every 2 hours (max. of 16 mg/day) or after each unformed stool.

Note: Oral antibiotics may be started as prophylaxis for infections under the discretion of the physician.

- If uncomplicated Grade 1 to 2 diarrhea persists after 48 hours of treatment with loperamide, discontinue loperamide and begin a second-line agent which can be an opiate (opium tincture or paregoric), octreotide acetate or steroid (budesonide).

For complicated Grade 1/2 diarrhea or any Grade 3 to 4 diarrhea

- The participant must call the investigator immediately

- If loperamide has not been initiated, initiate loperamide immediately. Initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.

- Administer IV fluids and electrolytes as needed. In case of severe dehydration, replace loperamide by octreotide.

- Monitor/continue IV fluids and antibiotics as needed. Intervention should be continued until the participant is diarrhea free for at least 24 hours.

- Hospitalization may need to be considered.

Skin Toxicity: Clinical judgment and experience of the treating physician should guide the management plan of each participant. In general, the following interventions are in addition to the rash dosing adjustment guidelines in Table 6.

- Prophylaxis of skin toxicity to be initiated 24 hours prior to the first treatment with study drug or later as needed.

- Application of topical agents to the most commonly affected skin areas such as face, scalp, neck, upper chest and upper back.

Topical agents include non-oily sunscreen (para-aminobenzoic acid [PABA] free, SPF ≥30, ultraviolet A [UVA]/ultraviolet B [UVB] protection), topical steroids (preferably mometasone cream ie, Elocon®) and topical erythromycin (ie, Eryaknen® or topical pimecrolimus).

Note: Topical agents should be applied on a daily basis starting on Day 1 of study treatment or 24 hours prior to the first dose, and more often as needed.

- Possibly oral doxycycline (100 mg daily) for the first 2-3 weeks of study drug administration.

Other effective medications are antihistamines, other topical corticosteroids, other topical antibiotics and low-dose systemic corticosteroids.

The treatment algorithm based on CTCAE grade is as follows:

Mild rash (CTCAE Grade 1)

- Consider prophylactic rash treatment if not already started.
- Topical or other topical corticosteroid (ie, mometasone cream) and/or topical antibiotic (ie, erythromycin 2%) are recommended.
- The participant should be reassessed within a maximum of 2 weeks or as per investigator opinion.

Moderate rash (CTCAE Grade 2)

- Use of topical erythromycin or clindamycin (1%) plus topical mometasone or pimecrolimus cream (1%) plus oral antibiotics such as: lymecycline (408 mg QD), doxycycline (100 mg BID) or minocycline (50 to 100 mg QD).
- Although there has been no evidence of phototoxicity or photosensitivity in participants being treated with selumetinib, doxycycline (or minocycline as second-line) should be used with thorough UV protection (ie, avoidance of direct exposure to sunlight, use of sunscreen and sunglasses).
- Use of acitretin is not recommended

Severe rash (CTCAE Grade 3-4)

CTCAE Grade 3

- In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day).

- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low doses, ie, 0.3 to 0.5 mg/kg) [Lacouture, M. E., et al 2011].

- Use of acitretin is not recommended.

CTCAE Grade 4

- Immediately discontinue the participant from study drug and treat the participant with oral and topical medications (see recommendation CTCAE Grade 3).

Symptomatic Treatment:

- It is strongly recommended that participants who develop rash/skin toxicities receive symptomatic treatment:

  - For pruritic lesions, use cool compresses and oral antihistaminic agents

  - For fissuring, use Monsel's solution, silver nitrate, or zinc oxide cream. If not sufficient use mild steroid ointments or combinations of steroids and antibiotics such as Fucicort®

  - For desquamation, use emollients with mild pH 5/neutral (best containing urea 10%)

  - For paronychia, antiseptic bath and local potent corticosteroids, use oral antibiotics and if no improvement is seen, refer to a dermatologist or surgeon

  - For infected lesions, obtain bacterial and fungal cultures and treat with topical or systemic antibiotics based on sensitivity of culture

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Dose Administration/Escalation

6.6.1.1 Dose Administration (Preparation)

Details on preparation and administration of MK-8353 and selumetinib are provided in the appropriate Pharmacy/Procedures Manual.

6.6.2 Definition of Dose limiting Toxicity

All toxicities will be graded using NCI CTCAE v4.0 based on the investigator assessment.

The DLT window of observation will be during Cycle 1. The observation window can be modified to encompass Cycle 1 and 2 (and/or additional cycles).

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

1. Grade 4 nonhematologic toxicity (not laboratory).
2. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
    - Grade 4 thrombocytopenia of any duration
    - Grade 3 thrombocytopenia associated with clinically significant bleeding
3. 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 without use of anti-emetics or anti-diarrheals per SOC lasting <72 hours; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per SOC.
4. Any Grade 3 or Grade 4 non-hematologic laboratory value if:
    - Clinically significant medical intervention is required to treat the subject, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for ≥72 hours.
    - The abnormality is consistent with drug-induced liver injury and meeting the protocol Events of Clinical Interest criteria (see Section 8.4.7)

      Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.

5. Febrile neutropenia Grade 3 or Grade 4:

    - Grade 3 is defined as absolute neutrophil count (ANC) <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour

    - Grade 4 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.

6. An elevated AST or ALT laboratory value that is ≥3X the ULN and an elevated total bilirubin laboratory value that is ≥2X the ULN and, at the same time, an alkaline phosphate laboratory value that is <2X the ULN, as determined by the way of protocol-specified laboratory testing or unscheduled laboratory testing.

7. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.

8. Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1.

9. Missing >25% of MK-8353 and/or selumetinib doses as a result of drug-related AE(s) during the first cycle.

10. Grade 5 toxicity.

11. Cardiac disorders

    - Absolute decrease in LVEF >10% compared with baseline and the LVEF is below the institution's lower limit of normal

    - Left ventricular systolic dysfunction Grade ≥3

    - Other cardiac disorders Grade ≥3

12. Vascular disorders

    - Hypertension CTCAE Grade ≥3 requiring more than 1 drug or more intensive therapy

    - Grade 4 hypertension

13. Eye disorders

Retinal:

- Retinopathy or retinal detachment Grade ≥2, confirmed by ophthalmic examination
- Retinal vein disorder including retinal vein occlusion, confirmed by ophthalmic examination

Visual disturbances without ocular (retinal) changes:

- Blurred vision, flashing lights, floaters: Grade ≥3

Other specify:

- Grade 4 confirmed by ophthalmic examination

6.6.3 Timing of Dose Administration

6.6.3.1 Timing of Administration for MK-8353 and Selumetinib

Participants should be instructed to take MK-8353 and selumetinib capsules 12 ± 2 hours apart for BID dosing schedule with a large glass of water (~250 mL) in the morning and in the evening at approximately the same time every day. (If dosing is changed to QD, participants should be instructed to take MK-8353 and selumetinib capsules every 24 ± 2 hours in the morning). Starting on Day 1 of Cycle 1, MK-8353 and selumetinib will be administered 4 days on/3 days off concomitantly at the same time. On clinic days when PK samples are scheduled, dosing should be delayed until arrival at the clinic and until the pre-dose PK sample has been taken.

The reason for any variability in administration of MK-8353 and selumetinib outside of the protocol specified window should be documented in the subject's chart and recorded on the electronic Case Report Forms (eCRFs).

Every effort should be made to begin the first dose of study intervention on the day of treatment assignment, but if this is not achieved, study intervention should be initiated no later than 3 days from the date of treatment assignment. All subsequent cycles of study intervention may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the investigator's judgment. All study interventions will begin on Day 1 of each cycle after all predose study procedures and assessments have been completed as detailed in Section 2, Summary of Activities.

The Pharmacy Manual contains specific instructions for administration of MK-8353 and selumetinib and additional guidance (for example, missed doses).

6.6.4 Guidelines for Dose Modification Due to Adverse Events

6.6.4.1 Dose Modification for MK-8353 and Selumetinib

Adverse events (both nonserious and serious) associated with MK-8353 and selumetinib exposure may occur shortly after the first dose or several months after the last dose of treatment.

The CTCAE v4.0 must be used to grade the severity of AEs for individual participants. The investigator may attribute each toxicity event to MK-8353 alone, to selumetinib alone, or to the combination, but modification of the doses of both drugs must be followed according to Table 7. Examples of dose reduction are as follows:

Example 1:

If a participant is receiving a dose along the MTD① diagonal of the dose combination grid (eg, Dose Level 5, which is MK-8353 200 mg and selumetinib 100 mg) and per Table 7 a dose reduction is indicated, both MK-8353 and selumetinib will have doses reduced to the next lower dose level along the diagonal (eg, to Dose Level 3, which is MK-8353 150 mg and selumetinib 75 mg).

Example 2:

If a participant is receiving a dose along one of the off-diagonal dose sequences and per Table 7 a dose reduction is indicated, both MK-8353 and selumetinib will have doses reduced along the diagonal of the dose combination grid to the next lower dose level sequentially, as shown in Figure 4.

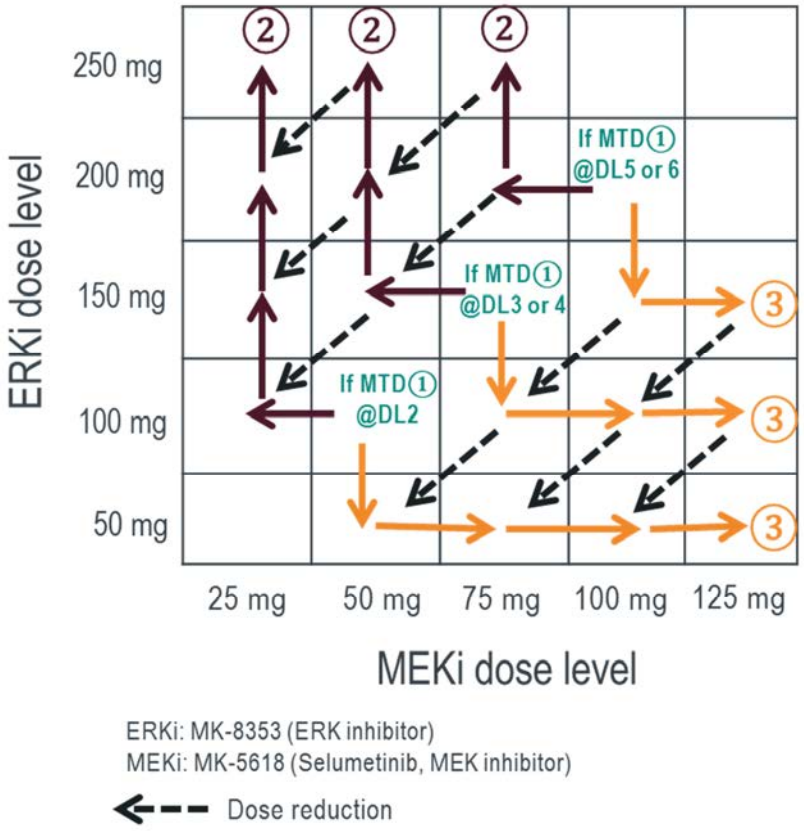


Figure 4 Example of Sequential Dose Reduction Along the Off-Diagonal Sequences

ERK = extracellular signal-regulated kinase;
MEK = mitogen-activated protein/extracellular signal regulated kinase

Example 3:

If a participant is receiving a dose combination where one of the drugs (MK-8353 or selumetinib) is already at their lowest dose level (eg, MK-8353 50 mg or selumetinib 25 mg) and per Table 7 a dose reduction is indicated, then participants should be discontinued.Table 6 provides some examples of what the dose reductions would be for various dose levels.

Table 6 Examples of Maximum Dose Reductions

Selumetinib/MK-8353	Selumetinib/MK-8353 1st dose reduction	Selumetinib/MK-8353 2nd dose reduction
75 mg /250 mg	50 mg/200 mg	25 mg/150 mg
50 mg /250 mg	25 mg/200 mg	off study
75 mg /200 mg	50 mg/150 mg	25 mg/100 mg
50 mg /200 mg	25 mg/150 mg	off study
50 mg /150 mg	25 mg/100 mg	off study
125 mg /150 mg	100 mg/100 mg	75 mg/50 mg
100 mg /150 mg	75 mg/100 mg	50 mg/50 mg
125 mg /100 mg	100 mg/50 mg	off study
100 mg /100 mg	75 mg/50 mg	off study
75 mg /100 mg	50 mg/50 mg	off study

If a dose modification for toxicity occurs with MK-8353 or selumetinib, the dose may not be re-escalated to the dose that preceded the dose modification. Dose modifications will be based on the previous cycle.

Participants may have up to 2 dose modifications of MK-8353 and selumetinib throughout the course of the study, as described in Table 7. If further toxicity occurs or the criteria for resuming treatment are not met, the participant must be discontinued from the study treatment. If a participant experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

Table 7 MK-8353 and Selumetinib Dose Modification and Treatment Discontinuation Guidelines for Drug-Related Adverse Events

Eye disorders – Retinal Events (including serous detachment of the retina)	
Grade 1	Maintain dose level of MK-8353 and selumetinib and repeat ophthalmic monitoring including visual acuity assessment and ocular coherence tomography (OCT) within 10 days.
Grade 2	Interrupt MK-8353 and selumetinib dosing and refer the participant to ophthalmologist within 1 week and obtain OCT within 10 days: If resolved to baseline or Grade ≤1 within 10 days, resume treatment at current dose level and continue schedule of visual assessments established per protocol. If not resolved to baseline or Grade ≤1 within 10 days, resume treatment at reduced dose level and continue the schedule of events of visual assessments established per protocol.
Grade 3	Interrupt MK-8353 and selumetinib and refer the participant to ophthalmologist within 1 week and obtain OCT: If resolved to baseline or Grade ≤1 within 7 days, resume treatment at a reduced dose level and continue schedule of visual assessments established per protocol. If not resolved to baseline or Grade ≤1 within 7 days, continue to hold the MK-8353 and selumetinib dose and repeat ophthalmic assessment in 10 days. If resolved to baseline or Grade ≤ 1, resume treatment at reduced dose level and continue schedule of visual assessments established per protocol. If remains Grade 3, permanently discontinue MK-8353 and selumetinib.
Grade 4	Permanently discontinue MK-8353 and selumetinib and immediately follow up with ophthalmic monitoring.
Eye disorder – Retinal Vein Occlusion (RVO)	
Any Grade	Permanently discontinue MK-8353 and selumetinib.
Other Eye Disorders (ie, Non-retinal Events)	
Grade 1-2	Maintain dose level of MK-8353 and selumetinib and increase frequency of ophthalmic monitoring to at least 14 days until stabilization or resolution.
Grade 3	Interrupt MK-8353 and selumetinib and refer participant to ophthalmologist within 1 week: If resolved to Grade ≤1 in ≤21 days, reduce 1 dose level of MK-8353 and selumetinib. If not resolved to Grade ≤1 in ≤21 days, permanently discontinue MK-8353 and selumetinib.
Grade 4	Permanently discontinue MK-8353 and selumetinib.

Liver-related Adverse Events	
Grade 1 AST or ALT (> ULN - 3 × ULN)	Maintain dose level of MK-8353 and selumetinib.
Grade 2 AST or ALT (>3 - 5.0 × ULN) or 3 × baseline value (if liver metastasis) AND blood bilirubin ≤2.0 × ULN	Interrupt dose of MK-8353 and selumetinib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then: • If resolved in ≤14 days, maintain dose level of MK-8353 and selumetinib. • If resolved in >14 days, reduce dose level of MK-8353 and selumetinib. Recurrence: • Interrupt dosing of MK-8353 and selumetinib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then resume treatment at a reduced dose.
Grade 2 AST or ALT (> 3 - 5.0 × ULN) or 3 × baseline value (if liver metastasis) AND blood bilirubin > 2.0 × ULN	Interrupt dose of MK-8353 and selumetinib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then: • If resolved in ≤7 days, resume treatment at a reduced dose of MK-8353 and selumetinib. • If not resolved in ≤7 days, permanently discontinue MK-8353 and selumetinib.
Grade 3 AST or ALT (>5.0 - 8.0 × ULN) AND blood bilirubin ≤2.0 × ULN	Interrupt dose of MK-8353 and selumetinib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then: • If resolved in ≤14 days, maintain dose level of MK-8353 and selumetinib. • If resolved in >14 days, reduce dose level of MK-8353 and selumetinib. Recurrence: • Interrupt dosing of MK-8353 and selumetinib until resolved to Grade ≤1 (or Grade ≤2 in case of liver metastasis), then resume treatment at a reduced dose.
AST or ALT (>8 x ULN) AND blood bilirubin* ≤ 2.0 × ULN	Permanently discontinue MK-8353 and selumetinib.
AST or ALT (>5.0 × ULN) AND blood bilirubin* >2.0 × ULN	Permanently discontinue MK-8353 and selumetinib.
AST or ALT Grade 4 (>20.0 × ULN)	Permanently discontinue MK-8353 and selumetinib.

Cardiac Disorders	
Left ventricular systolic dysfunction Asymptomatic decrease of >10% in LVEF compared to baseline and the LVEF is below the institution's lower limit of normal	Interrupt dose of MK-8353 and selumetinib and repeat evaluation of LVEF within 2 weeks. • If the LVEF recovers (defined as LVEF ≥50% or ≥LLN and absolute decrease ≤10% compared to baseline) ≤3 weeks, reduce 1 dose level after approval of the Sponsor Medical Monitor. Monitor LVEF 2 weeks after restarting on MK-8353 and selumetinib, every 4 weeks for 12 weeks and subsequently as per protocol. • If the LVEF does not recover within 3 weeks, permanently discontinue participant from study treatment. Closely monitor LVEF until resolution (or 16 weeks).
Grade 3-4	Permanently discontinue participant from MK-8353 and selumetinib. Closely monitor LVEF until resolution (or 16 weeks).
CK Elevation	
Grade 1-2	Continue treatment on same dose level. Ensure patient is adequately hydrated. Monitor closely CK and serum creatinine levels. (If total CK ≥3 X ULN, measure isoenzymes and myoglobin in blood and urine).
Grade 3 (>5.0 - 10.0 × ULN) without renal impairment (ie, serum creatinine < 1.5 × ULN or 1.5 × baseline)	If asymptomatic, maintain dose of MK-8353 and selumetinib. Monitor closely and measure isoenzymes and myoglobin in blood and urine. If symptomatic (muscle pain/spasms or muscle weakness), interrupt dose of MK-8353 and selumetinib until resolved to CTCAE Grade ≤1 and monitor closely, then: • If resolved in ≤21 days, reduce 1 dose level of MK-8353 and selumetinib. • If resolved in >21 days, permanently discontinue MK-8353 and selumetinib.
Grade 4 without renal impairment (ie, serum creatinine <1.5 × ULN or 1.5 × baseline)	If asymptomatic, interrupt dose of MK-8353 and selumetinib and monitor closely. Ensure patient is adequately hydrated and monitor and measure isoenzymes and myoglobin in blood or urine, and serum creatinine. • If resolved in ≤21 days, reduce 1 dose level of MK-8353 and selumetinib. • If resolved in >21 days, permanently discontinue MK-8353 and selumetinib. • If symptomatic, permanently discontinue MK-8353 and selumetinib. If symptomatic (muscle pain/spasms), permanently discontinue MK-8353 and selumetinib.
Grade 3 or 4 with renal impairment (ie, serum creatinine ≥1.5 × ULN or 1.5 × baseline)	Interrupt MK-8353 and selumetinib dose until resolved to Grade <1 or baseline level. Ensure patient is adequately hydrated. Monitor isoenzymes and myoglobin in blood or urine, and serum creatinine, then: • If resolved in ≤21 days, reduce 1 dose level of MK-8353 and selumetinib. • If resolved in >21 days, permanently discontinue MK-8353 and selumetinib. Recurrence: • Permanently discontinue MK-8353 and selumetinib

Rash	
Grade 1	Treatment with MK-8353 and selumetinib should be maintained at the current dose. Initiate prophylactic regimen if it was not already and monitor closely.
Grade 2	First occurrence: Treatment with MK-8353 and selumetinib should be maintained at the current dose and rash should be closely monitored. Initiate prophylactic regimen if it was not already started. Reassess within a maximum of two weeks. If rash worsens or does not improve, interrupt dosing until improvement to Grade ≤1. Resume treatment at the same dose level. Second occurrence: Reassess within a maximum of 2 weeks. If rash worsens or does not improve, interrupt dosing until improvement to Grade ≤1. Resume treatment at a reduced dose level. Only one dose reduction is permitted.
Grade 3	First occurrence: Treatment with MK-8353 and selumetinib should be interrupted. Reassess the participant weekly. Consider referral to dermatologist and manage rash per dermatologist's recommendation. Interrupt treatment until improvement to Grade ≤1. Resume treatment with MK-8353 and selumetinib at a reduced dose level. Second occurrence: Interrupt treatment until improvement to Grade ≤1. Resume treatment with MK-8353 and selumetinib at a reduced dose level. If participant is at the lowest dose, participant should be discontinued. Consider referral to dermatologist and manage rash per dermatologist's recommendation.
Grade 4	Permanently discontinue MK-8353 and selumetinib.
Diarrhea	
Uncomplicated Grade 1-2	Consider temporary interruption of MK-8353 and selumetinib until resolved to Grade ≤1. Treatment with MK-8353 and selumetinib may then be resumed at the same dose level.
Complicated Grade 1-2	Temporarily interrupt MK-8353 and selumetinib treatment until resolved to Grade ≤1. Restart MK-8353 and selumetinib at one reduced dose level. If participant is at the lowest dose, participant should be discontinued.
Grade 3-4	Temporarily interrupt MK-8353 and selumetinib treatment until resolved to Grade ≤1. Restart MK-8353 and selumetinib at a reduced dose level. If participant is at the lowest dose, participant should be discontinued.
Nausea/Vomiting	
Grade 1-2	Treatment with MK-8353 and selumetinib should be maintained at the current dose. Promptly institute antiemetic measure.
Grade 3	Temporarily interrupt MK-8353 and selumetinib treatment until resolved to Grade ≤1. Resume treatment with MK-8353 and selumetinib at the same dose if, in the judgment of the investigator, the toxicity is considered to be unrelated to selumetinib, or at one reduced dose level. Note: Interrupt dose for ≥Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).
Grade 4	Permanently discontinue MK-8353 and selumetinib treatment

Interstitial Lung Disease/Pneumonitis	
Grade 1	Maintain dose level of MK-8353 and selumetinib. Monitor weekly.
Grade 2	Withhold MK-8353 and selumetinib for up to 3 weeks. • If improved to Grade 0 or 1, resume treatment at 1 reduced dose level of MK-8353 and selumetinib • If not resolved within 3 weeks, permanently discontinue MK-8353 and selumetinib.
Grade 3-4	Permanently discontinue MK-8353 and selumetinib.
Venous Thromboembolism	
Uncomplicated DVT or PE	Withhold MK-8353 and selumetinib for up to 3 weeks. • If improved to Grade 0 or 1, resume at reduced dose. • If not improved, permanently discontinue.
Life threatening PE	Permanently discontinue MK-8353 and selumetinib.
All other Adverse Events (suspected to be related)	
Grade 1-2	If the event is a persistent Grade 2 AE not responsive to a specific therapy, consider MK-8353 and selumetinib interruption or reduction.
Grade 3	For other AEs, interrupt MK-8353 and selumetinib until resolution to Grade ≤1 or to pre-treatment/baseline level. If the event resolves within 21 days, then MK-8353 and selumetinib may be restarted at a lower dose (one level below that previously received) based upon the Investigator's discretion.
Grade 4	Permanently discontinue study drug (MK-8353 and selumetinib).

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; CTCAE = Common Terminology Criteria for Adverse Events; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; ULN = upper limit of normal

6.7 Intervention After the End of the Study

There is no study-specified intervention following 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, MK-8353 50 mg (or 100 mg) or selumetinib 25 mg, are included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

This section is 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 prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

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.
- The participant interrupts study intervention administration due to treatment-related toxicity for more than 14 consecutive days in cycle 1 or has >25% cumulative missed doses.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Confirmed radiographic disease progression outlined in Section 8.2 (exception if the Sponsor approves treatment continuation).
- Unacceptable adverse experiences as described in Section 8.4.
- Progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.

- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.

- Investigator's decision to discontinue treatment.

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

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

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained 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 signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The total amount of blood/tissue to be drawn/collected over the course of the trial, including approximate blood/tissue volumes drawn/collected by cycle and by sample type per subject can be found in the Procedures Manual.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research .If there are changes to the participant's status during the study (eg, health or age of

majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

8.1.5 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 the first dose of study medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

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

All new anticancer therapy initiated after the study start must be recorded in the eCRF. If a participant initiates another anticancer therapy other than the assigned study treatment(s), the study treatment(s) should be discontinued and the participant will move into the Post-treatment Follow-up Phase; if a participant initiates a new anticancer therapy within 30 days after the last dose of the study treatment, the 30 day Safety Follow-up Visit should occur before the first dose of the new 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 prior to intervention allocation.Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will receive an allocation number (AN). The AN identifies the participant for all procedures occurring after randomization. Once an is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 AN.

8.1.8 Study Intervention Administration

During on-site visits, administration of study medication will be witnessed by the investigator and/or trial staff. The administration, the dose, the time of administration, as well as any immediate reactions at the time of intake will be documented in the eCRF.

For non-visit days, MK-8353 and selumetinib will be taken at home.

When a participant attends a study visit, he/she will bring any unused capsules.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 MK-8353 Administration

MK-8353 is an oral medication, and is supplied as hard-shell capsules in strength of 50 mg or 100 mg. Participants should be instructed to take MK-8353 capsule(s) in the morning and in the evening at approximately the same times every day.

MK-8353 will be taken BID for the repeated schedule of 4 days on followed by 3 days off.

The Pharmacy Manual contains specific instructions for MK-8353 storage and administration.

8.1.8.1.2 Selumetinib Administration

Selumetinib is an oral medication, and is supplied as hard-shell capsules in strength of 25 mg. Participants should be instructed to take selumetinib capsules in the morning and in the evening at approximately the same times every day. Selumetinib should be taken on an empty stomach; no food or drink other than water for approximately 2 hours prior to dosing and approximately 1 hour after dosing.

Selumetinib will be taken BID in a repeating cycle of 4 days on followed by 3 days off.

The Pharmacy Manual contains specific instructions for MK-5618 (selumetinib) storage and administration.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit should be performed (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 future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

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

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 is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the imaging contract research organization can be found in the Site Imaging Manual (SIM). Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast 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 assessment of response or progression based on imaging.

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

Imaging of chest, abdomen, and pelvis is typical. The SIM will include detailed instructions for specific tumor types and clinical scenarios.

Although RECIST 1.1 references to a maximum of 5 target lesions in total and 2 per organ, Merck allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at the Screening Visit must be performed within 28 days prior to the date of allocation.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of allocation.

Participants with previously treated brain metastases may participate provided they have stable brain metastases (ie, without evidence of progression by imaging confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT used at prior imaging) for at least 4 weeks prior to the first dose of study intervention. Any neurologic symptoms must have returned to baseline and participants must have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 28 days prior to study initiation as per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

If brain imaging is performed to document the stability of existing metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

8.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) from the date of allocation. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) for the first 12 months on treatment, or more frequently if clinically indicated. After 12 months on treatment, subsequent tumor imaging should be performed every 12 weeks (84 days ±14 days), or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the

investigator, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 9 weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note that the response does not typically need to be verified in real time by BICR.

8.2.1.3 End of Treatment and Follow-up Imaging

For participants who discontinue study intervention, tumor imaging should be performed at the time of intervention discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at intervention discontinuation is not mandatory. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by radiologic tumor until the start of a new anticancer treatment, documented disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first. The timing for these assessments should continue the same imaging schedule from the treatment phase (9 weeks ± 7 days in the first 12 months, or 12 weeks ± 14 days beyond 12 months – see Section 8.2.1.2); Imaging should occur at any time where there is clinical suspicion of PD.

8.2.2 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by the investigator 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 treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

Participants who show evidence of radiological PD by RECIST 1.1, as determined by the investigator, will be discontinued from the study (see Table 8).

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status

- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from trial treatment at site-assessed first radiologic evidence of PD.

Table 8 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site.	NA	Discontinue treatment
NA = not applicable; PD = progressive disease; PFS = progression-free survival				

8.2.3 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at the Screening Visit, prior to the administration of each dose of study intervention and during the Post-treatment Follow-up Phase as specified in the SoA (Section 1.3).

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/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 Study Procedures 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) as 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.

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

8.3.1.1 Full Physical Examination

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

8.3.1.2 Directed Physical Examination

The investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration at the time points indicated in the SoA (Section 1.3). New clinically significant abnormal findings should be recorded as AEs.

8.3.2 Full Ophthalmic Examination

Full ophthalmic examination, including best corrected visual acuity for distance testing, automated visual field testing, slit lamp examination, intraocular pressure and dilated fundoscopy with attention to retinal abnormalities, especially retinal pigment epithelial detachment (RPED), serous detachment of the retina and RVO, will be performed by an ophthalmologist at the Screening Visit, C2D1 and then every 8 weeks from C2D1 and EoT. An ophthalmic examination at the Safety Follow-up Visit is only required if there was a clinically significant abnormality noted at EoT. For all participants, ophthalmic assessments may be performed more frequently per SOC or if clinically indicated for evaluation of any visual signs or symptoms.

8.3.3 Additional Testing

Participants with clinical suspicion of retinal abnormalities (ie, RPED, serous detachment of the retina, RVO, photopsia, metamorphopsia, impairment of visual acuity), must complete at least one of the following additional assessments:

- For non-vascular abnormalities: optical coherence tomography (OCT) of the macula (spectral domain OCT recommended)
- For vascular abnormalities: fluorescein angiography of the central 30 degrees.
- Images/results of the ophthalmic examinations (at a minimum, OCT and/or fluorescein angiography) should be sent to the study site and be maintained in the participant's source document file. These images/results may be requested to be sent to the Sponsor or designee.

8.3.4 Vital Signs

The investigator or qualified designee will take vital signs at the Screening Visit, prior to the administration of each dose of study intervention and at the EoT Visit as specified in the SoA (Section 1.3). Vital signs include temperature, pulse, respiratory rate, and blood pressure. Height will be measured at the Screening Visit only.

Blood pressure and pulse measurements should be performed with a completely automated device. Manual techniques will be used only if an automated device is not available. The participant should be in a semi-recumbent or supine position for at least 10 minutes prior to having the measurement performed. The correct size of the blood pressure cuff and correct positioning of the participant's arm are essential to the accuracy of the blood pressure measurement.

8.3.5 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECGs is specified in the SoA (Section 1.3). Clinically significant abnormal findings should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

- A standard 12-lead ECG will be performed using local standard procedure.
- The ECG measurement performed at the Screening Visit will be used to determine eligibility.
- The ECG measurement at any time point should be used for AE grading and recommended dose modifications.
- When an ECG is to be performed at the same time point as a blood collection, the ECG is to be performed first.
- ECG will be performed predose at every visit starting at C2D1.

Screening: Triplicate 12-lead ECGs will be obtained at the Screening Visit only.

Three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. Refer to Section 5.2 (Exclusion Criterion 7 for QTcF withdrawal criteria).

8.3.6 Echocardiogram/Multigated Acquisition Scan

Cardiac ejection fraction will be assessed by transthoracic ECHO or MUGA scans at the time points specified in the SoA (Section 1.3). The same method should be used throughout the study. Participants who develop signs/symptoms of CHF at any point during the study are required to have an evaluation of LVEF measurement by ECHO or MUGA.

8.3.7 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 case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), 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 4.

Progression of the cancer under study is not considered an AE unless it results in hospitalization or death as described in Section 8.4.6 and Appendix 3.

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, 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 consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.

- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered drug-related.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 9.

Table 9 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious Adverse Event (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
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (ECI) (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential Drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as

serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

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

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger 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-8353 and/or selumetinib by ≥20% of the indicated single dose. No specific information is available on the treatment of overdose of of MK-8353 and/or selumetinib. In the event of overdose, MK-8353 and selumetinib should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

8.6.1 Blood Collection for Plasma

Sample collection, storage, and shipment instructions for PK samples will be provided in the operations/laboratory manual for both MK-8353 and selumetinib.

Pharmacokinetic samples should be drawn according to the PK collection schedule for all participants. The exact time of sample collection and time of administration of MK-8353 and selumetinib will be recorded.

8.6.1.1 MK-8353 Blood Collection for Plasma

Blood samples for determination of plasma concentrations of MK-8353. Plasma samples for MK-8353 will be obtained from consenting participants. Serial plasma samples for PK analysis of MK-8353 will be collected C1D1 and C1D4 at time 0 (within 24 hours prior to pre-dose for C1D1 or within -10 minutes prior to pre-dose for C1D4 trough sample), post-dose at 1(± 10 minutes), 2 (± 10 minutes), 4(± 10 minutes), 6 (± 10 minutes), and 1 sample any time between 8 and 12 hours (prior to PM dosing for BID regimen). Additional samples will be collected at pre-dose/trough (within -10 minutes prior to pre-dose), hours 1 (± 10 minutes), and hours 4 (± 10 minutes) at C2D1, C2D4, C5D1, C5D4. The exact time of sample collection and time of administration of MK-8353 will be recorded.

8.6.1.2 Selumetinib Blood Collection for Plasma

Blood samples for determination of plasma concentrations of selumetinib and N-desmethyl selumetinib. Other metabolites (eg, selumetinib amide) may also be determined. Plasma samples for selumetinib and N-desmethyl selumetinib will be obtained from consenting participants. Serial plasma samples for PK analysis of selumetinib and N-desmethyl selumetinib will be collected C1D1 and C1D4 at time 0 (within 24 hours prior to pre-dose for C1D1 and within -10 minutes prior to pre-dose for C1D4 trough sample), post-dose at 1(± 10 minutes), 2 (± 10 minutes), 4 (± 10 minutes), 6 (± 10 minutes), and 1 sample any time between 8 and 12 hours (prior to PM dosing for BID regimen). Additional samples will be collected at pre-dose/trough (within -10 minutes prior to pre-dose), hours 1 (± 10 minutes), and hours 4 (± 10 minutes) at C2D1, C2D4, C5D1, C5D4. The exact time of sample collection and time of administration of selumetinib will be recorded.

Based on observed toxicity and severity of toxicity, we may pause the study and analyze PK to assess if there is a need to modify the dose/dosing schedule (eg, lower the dose; change from BID to QD).

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be provided in operations/laboratory manual.

8.8 Future Biomedical Research Sample Collection

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

- Leftover from specimens listed in Section 8.10, Biomarkers.

8.9 Planned Genetic Analysis Sample Collection

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

8.10 Biomarkers

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

- Blood for Genetic Analysis
- Blood for ctDNA
- Blood for RNA Analyses
- Blood for Plasma Biomarker Analyses
- Blood for Serum Biomarker Analyses
- Blood for pERK
- Archival or Newly Obtained Tumor Tissue collection
- On-treatment Tumor Biopsy (Optional)

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

Exploratory FDG-PET:

Exploratory imaging will be used as a biomarker of the study drugs. FDG-PET scans will be obtained from participants at the MTD levels only as specified in the SoA. Details for the collection and storage scans will be provided in the operations/laboratory manual.

8.11 Visit Requirements

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

8.11.1 Screening

Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the participant signing consent as part of routine management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment. An exception is hepatitis testing, which may be done up to 28 days prior to the first dose of trial treatment.
- Evaluation of ECOG is to be performed within 7 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Archival tumor sample collection is not required to be obtained within 28 days prior to the first dose of trial treatment. Newly obtained tumor tissue may be obtained within 90 days of treatment initiation.

8.11.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided above in Section 8 – Study Assessments and Procedures.

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study treatment is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging in post-treatment follow up visits. Imaging will not be collected during Survival Follow-up Visit(s). Visit requirements are outlined in the SoA (Section 1.3). Additional details regarding participant withdrawal and discontinuation are presented in Section 8.1.9 –Discontinuation and Withdrawal. Additional details regarding Post-treatment Follow-up imaging visits are represented in Section 8.2.1.3 – End of Treatment and Follow-up Imaging.

8.11.4 Post-treatment

Participants will be required to return to clinic approximately 30 days after the last dose of study intervention for the post-treatment Safety Follow-up Visit. If a participant initiates a

new anticancer therapy within 30 days after the last dose of study treatment, the Post-treatment Safety Follow-up Visit should occur before the first dose of the new therapy.

After treatment discontinuation, each participant will be followed for up 30 days for AE monitoring. Participants will be monitored for SAEs for 90 days after treatment discontinuation, 30 days if the participant initiates new anticancer therapy less than 30 days after study treatment discontinuation, or until the day new anticancer therapy is initiated if between 30 days and 90 days after study treatment discontinuation. Participants with an ongoing AE of Grade >1 at the time of treatment discontinuation will be followed until resolution of the AE to Grade 0 to 1, until considered stable by the treating physician, or until beginning a new anticancer therapy, whichever occurs first.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by radiologic tumor until the start of a new anticancer treatment, documented disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first. The timing for these assessments should continue the same imaging schedule from the treatment phase (9 weeks ± 7 days in the first 12 months, or 12 weeks ± 14 days beyond 12 months – see Section 8.2.1.2 Tumor Imaging During the Study); Imaging should occur at any time where there is clinical suspicion of progression.

After confirmed disease progression, each subject will be contacted by telephone approximately every 12 weeks (84 ±7 days) for survival until withdrawal of consent to participate in the study, becoming lost to follow-up, death, or end of the study, whichever occurs first as shown in the SoA (Section 1.3).

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

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

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

Study Design Overview	This is a Phase 1b trial of MK-8353 in combination with selumetinib in participants with advanced/metastatic solid tumors. The study applies the mTPI design for dual-agent dose finding.
Treatment Assignment	Participants will be allocated centrally through interactive response technology to MK-8353 coadministered with selumetinib. Nonrandom assignment to dose levels will be used in the diagonal dose combination sequence. In case two additional off-diagonal dose combination sequences are initiated, participants will be allocated by alternate assignment to either off-diagonal sequence.
Analysis Populations	Safety (Primary): All-Participants-as-Treated (APaT) PK (Secondary): Per-Protocol (PP) Efficacy (Exploratory): Full Analysis Set (FAS)
Primary Endpoint(s)	• DLTs • AEs • Study drug discontinuations due to an AE
Secondary Endpoints	PK parameters including AUC, C_{max} and C_{min}
Statistical Methods for Efficacy/ Pharmacokinetic Analyses	Efficacy analyses are documented in the sSAP. PK parameters of study medicines will be summarized by planned visit and time for each dose separately.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate. The DLT rates across different dose combinations, in each dose combination sequence, will be estimated using isotonic regression under the assumption of monotonicity between the DLT rates and dose levels in each row and in each column of the dose combination grid [Dykstra, R. L. 1982]. The estimate of the DLT rate among participants treated at the RP2D for the MK-8353 and selumetinib combination, and the associated 80% Bayesian credible intervals will be provided.
Interim Analyses	No efficacy interim analysis will be performed.
Multiplicity	No multiplicity adjustment is planned in this Phase 1b trial.

Sample Size and Power	The overall sample size for this study depends on the observed DLT profiles of MK-8353 in combination with selumetinib. A target sample size of 80 participants will be used for study planning purposes.

9.2 Responsibility for Analyses/In-house Blinding

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

The trial is open-label, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignment after each participant is enrolled and treatment is assigned.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 3 – Hypothesis, Objectives, and Endpoints.

9.4 Analysis Endpoints

9.4.1 Efficacy/Pharmacokinetics Endpoints

Efficacy endpoints (OR, PFS, OS) are exploratory endpoints in this study. Details of the analysis plan will be documented in the sSAP.

Pharmacokinetic endpoints include plasma concentrations of MK-8353 and selumetinib, as well as derived PK parameters.

9.4.2 Safety Endpoints

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

A description of safety measures is provided in Section 8.3 – Safety Assessments.

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

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

The DLT evaluable population includes APaT participants who meet the criteria for DLT evaluability (eg, finished Cycle 1 without a DLT or experienced a DLT in Cycle 1). See Section 5.6 Participant Replacement Strategy for details.

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

9.5.2 Pharmacokinetic Analysis Populations

The PP population will be used for the analysis of PK data in this study. The PP population consists of the subset of participants who complied with the protocol sufficiently to ensure that their data will be likely to exhibit 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 clinical study report (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 may be included in the PP analysis dataset.

9.5.3 Efficacy Analysis Populations

The FAS population will be used for the analyses of efficacy data in this study. It consists of all participants with a baseline scan that demonstrated measurable disease by the investigator's assessment, and who were administered at least 1 dose of study medicine.

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analysis

The statistical methods for efficacy analyses will be documented in the sSAP.

9.6.2 Statistical Methods for Safety Analysis

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

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

Dose limiting toxicities will be listed and summarized by dose level. The DLT rates across different dose combinations, in each dose combination sequence, will be estimated using isotonic regression under the assumption of monotonicity between the DLT rates and dose levels in each row and in each column of the dose combination grid [Dykstra, R. L. 1982]. The estimate of the DLT rate among participants treated at the RP2D and the 80% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analysis

9.6.3.1 Demographic and Baseline Characteristics

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

9.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

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

9.7 Interim Analyses

No efficacy interim analysis will be conducted.

9.8 Multiplicity

There will be no multiplicity control in this study.

9.9 Sample Size and Power Calculations

With a maximum sample size of 14 at each dose level, the overall sample size for this Phase 1b trial will be at most 140 (the scenario where dose escalation along the diagonal concludes at DL2 and extends to off-diagonal escalation in Figure 1B which has a total of 10 dose combination levels and assumes 14 subjects per dose level). The actual sample size depends on the safety profiles and number of doses studied. For example, if dose escalation along the diagonal concludes at DL3 and then proceeds to the off-diagonal escalations, where there are three dose combination levels in each sequence, the sample size is expected to be approximately 80, assuming 6 subjects in the first two dose levels and 14 subjects at the final dose combination level in each sequence. Alternatively, if dose escalation along the diagonal of the dose combination grid concludes at the last dose on the diagonal sequence, (MK-8353 250 mg, selumetinib125 mg), the sample size is expected to be approximately 50, also assuming 6 subjects in the first six dose levels and 14 subjects at the final dose.

9.10 Subgroup Analyses

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

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) 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 (eg, 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 (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of 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 fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

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

III. Participant Protection

A. Ethics Committee Review (Institutiona Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

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

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

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review 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 (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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 report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); 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 Studies.

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

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

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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 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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10 will be performed by the local laboratory.

- If the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- 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.
- The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Table 10 Protocol-required Safety Laboratory Assessments

Hematology	Comprehensive Chemistry Panel	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)[a]
Hemoglobin	Alkaline phosphatase	Glucose	
Platelet count	Alanine aminotransferase	Protein	PT/INR
WBC (total and differential)[b]	Aspartate aminotransferase	Specific gravity	aPTT or PTT
	Bicarbonate	Microscopic exam, if abnormal results are noted	Anti-HCV
RBC	Calcium		HCV viral load[c]
Absolute lymphocyte count[b]	Chloride		HCV genotype[c]
	Creatinine		anti-HBs[c]
Absolute neutrophil count[d]	Cystatin C[d]		HBsAg
	Glucose		Anti-HBc (total and IgM)[c]
	Phosphorus		HBeAg[c]
	Potassium		anti-HBe[c]
	Sodium		HBV viral load[c]
	Total bilirubin		Anti-HDV [c]
	Creatine kinase		AFP
	Direct bilirubin		CRP
	Total protein		GGT
	Blood urea nitrogen		

a. Perform on women of childbearing potential only 72 hours prior to Day 1 of Cycle 1. Pregnancy tests must be repeated prior to every cycle if required or as specified per local regulatory guidance.
b. Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.
c. If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Procedure Manual.
d. Specific to creatinine: Cystatin C could be evaluated if creatinine is abnormal. Cystatin C may be conducted by central vendor only if analysis was not available from local study site laboratory.

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.7 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

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

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

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

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- 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 Common Terminology for Adverse Events (CTCAE), version 4.0. 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 activities of daily living (ADL).

    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

    - Grade 4: Life threatening consequences; urgent intervention indicated.

    - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

- If yes, this is a positive rechallenge.

- If no, this is a negative rechallenge.

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

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AE, SAE, 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 electronic data collection (EDC) tool.

    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.

  - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP:

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol defined time frame in Section 5.1:

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

- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

  - The following are not acceptable methods of contraception:

    - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).

    - Male condom with cap, diaphragm, or sponge with spermicide.

    - Male and female condom cannot be used together.

  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c] • Intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD) • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
1. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. 2. Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). a) Male condoms must be used in addition to the hormonal contraception. b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c) IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, sympothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment additional pregnancy testing will be performed if clinically warranted and at monthly intervals as defined by local regulations where applicable, during the treatment period plus 30 days (a menstruation cycle) after the last dose of study intervention, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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

- Definitions

9. 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.

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

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

12. DNA: Deoxyribonucleic acid.

13. RNA: Ribonucleic acid.

- **Scope of Future Biomedical Research**

The specimens consented and/or collected in this study as outlined in Section 8.10 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 drugs/vaccines may interact with
- 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.

- **Summary of Procedures for Future Biomedical Research**.

- Participants for Enrollment

  All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research substudy

- 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.

- 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.

- 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.

- **Confidential Participant Information for Future Biomedical Research**

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' 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 gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

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

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

- **Biorepository Specimen Usage**

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

- **Withdrawal From Future Biomedical Research**

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

- **Retention of Specimens**

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being

answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

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

- **Data Security**

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

- **Reporting of Future Biomedical Research Data to Participants**

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

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

- **Future Biomedical Research Study Population**

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

- **Risks Versus Benefits of Future Biomedical Research**

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

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

- **Questions**

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

- **References**

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ADL	activities of daily living
AE	adverse event
AN	allocation number
ANC	absolute neutrophil count
APaT	All Participants as Treated
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AUC	area under the curve
BID	administered twice daily
BP	Blood pressure
C_{max}	maximum concentration
C_{min}	minimum concentration
CR	complete response
CRAF	Cellular protein encoded by the *raf*1 gene
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	drug-induced liver injury
DL	dose level
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
EoT	end of treatment
ERK	extracellular signal-regulated kinase
ERKi	extracellular signal-regulated kinase inhibitor
FDAAA	Food and Drug Administration Amendments Act
FDG-PET	fluorodeoxyglucose-positron emissions tomography
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
MAPK	mitogen activated protein kinase
MEK	mitogen-activated protein kinase
MEKi	mitogen-activated protein kinase inhibitor

Abbreviation	Expanded Term
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	overall response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PP	Per protocol
PR	partial response
QD	once daily
RAS	*ras* proto-oncogene family
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RVO	Retinal vein occlusion
SAE	serious adverse event
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
WOCBP	woman/women of childbearing potential

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