Official Protocol Title:	Protocol/Amendment No.: 013-02 Phase 2 Study of MK-6482 in Participants With Advanced Renal Cell Carcinoma
NCT number:	NCT04489771
Document Date:	30 June 2022

Title Page

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Protocol Title: Phase 2 Study of MK-6482 in Participants With Advanced Renal Cell Carcinoma

Protocol Number: 013-02

Compound Number: MK-6482

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	132,120
EudraCT	2020-001907-18

Approval Date: 30 June 2022

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 2	30-JUN-2022	To add an optional tumor tissue sample collection after receiving belzutifan treatment to enable exploratory biomarker research on the mechanisms of response and/or resistance to belzutifan treatment.
Amendment 1	22-FEB-2021	To update contraception language to align with program wide requirements.
Original Protocol	09-MAY-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

To add an optional tumor tissue sample collection after receiving belzutifan treatment to enable exploratory biomarker research on the mechanisms of response and/or resistance to belzutifan treatment.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Added an optional tumor tissue sample collection after receiving belzutifan.	To add an optional tumor tissue sample collection after receiving belzutifan treatment to enable exploratory biomarker research on the mechanisms of response and/or resistance to belzutifan treatment.
1.3 Schedule of Activities	Added an optional ICF for biomarker tissue collection.	To obtain consent for optional biopsy.
3 Hypotheses, Objectives, and Endpoints	Updated tertiary biomarker endpoint to include new optional tissue collection after receiving belzutifan treatment.	Clarification.
Title Page Section 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

Section # and Name	Description of Change	Brief Rationale
8.1.9.1 Withdrawal From Future Biomedical Research 10.6 Appendix 6: collection and Management of Specimens for Future Biomedical Research	Sponsor email address change from "@merck" to "@MSD.com".	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA.
1.3 Schedule of Activities	Added that starting at Week 9 Day 1 and thereafter, blood samples for ctDNA analyses do not need to be collected predose.	Clarification on timing of blood sample collections.
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events	Added text that SAEs associated with medication errors, misuse, or abuse are to be documented.	Per REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL.
10.3.1 Definitions of Medication Error, Misuse, and Abuse	Added new section with definitions for medication errors, misuse, or abuse are to be documented. Renumbered subsequent sections accordingly.	Per REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
1.3 Schedule of Activities 8.11.3.3 Survival Follow-up	Changed survival status to vital status.	To align with terminology updates previously approved and ensure consistency throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 8.11.3.2 Imaging Follow-up	Added "end of the study" to list of reasons for discontinuation of imaging, or revised study termination to this wording.	To align with Section 8.2.1.2.
4.2.1.5 Planned Exploratory Biomarker Research	Changed Tumor and RNA collection to Tumor and/or RNA in subsection title and in text. Changed "belzutifan and other therapies" to "antitumor therapies".	To ensure exploratory biomarker section allows flexibility.
6.1 Study Intervention(s) Administered	Changed IMP/NIMP to IMP or NIMP/AxMP Changed use designation from "experimental" to "test product".	To align with EU Clinical Trials Registration.
6.4 Study Conduct Compliance 8.1.1.1 General Informed Consent 10.3.5 Recording of AE and SAE	Changed "his/her" to "their".	Gender references are not necessary.
8.1.4 Medical History	Changed the description of what medical history will be collected from clinically significant to clinically important.	For consistency of terminology and to add clarity to baseline medical conditions.

Section # and Name	Description of Change	Brief Rationale
8.1.11 Tissue Collection	Added that a tumor lesion is inclusive of fresh tissue collected after receiving study intervention.	Clarity.
8.2.1 Tumor Imaging and Assessment of Disease	Revised wording to better explain handling of unscheduled scans.	Clarity.
8.2.1.2 Tumor Imaging During the Study	Deleted ambiguous statement "or notification by the Sponsor." Changed format of list items for reasons to discontinue scans from paragraph to bullets and revised "or notification by the Sponsor" to "end of the study."	Clarity. To align with text in Section 8.2.1.3.
8.2.1.3 RECIST 1.1 Assessment of Disease	Revised to give more specific instructions on when scans are to be collected "(the next scheduled scan should be ≥4 weeks from the most recent scan acquired)".	Clarity.
8.2.2 End of Treatment and Follow-up Tumor Imaging	Changed format of list items for reasons to discontinue scans from paragraph to bullets and revised study conclusion/early termination to "end of the study."	To align with text in Section 8.2.1.3.
8.8 Biomarkers	Changed tissue sample description from archival or newly obtained to tumor tissue.	Per biomarker group guidance to use broader terminology.
10.2 Appendix 2 Clinical Laboratory Tests	Added time period for continuation of pregnancy testing after study intervention termination.	To ensure consistency with Section 5.1 and Section 8.4.1.

Section # and Name	Description of Change	Brief Rationale
Throughout Document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: Phase 2 Study of MK-6482 in Participants With Advanced Renal Cell Carcinoma

Short Title: Phase 2 Study of MK-6482 in Participants With Advanced Renal Cell Carcinoma

Acronym: MK-6482-013

Hypotheses, Objectives, and Endpoints:

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

This study will be conducted in male and female participants with previously treated advanced renal cell carcinoma (RCC) with clear cell component.

Objectives	Endpoints
Objectives	Endpoints
Primary	
• Objective: To compare the 120 mg once daily (QD) dose and 200 mg QD dose of belzutifan with respect to objective response rate (ORR) based on Response Criteria in Solid Tumors (RECIST) 1.1 as assessed by blinded independent central review (BICR). • Hypothesis (H1): Belzutifan 200 mg QD is superior to belzutifan 120 mg QD in terms of ORR per RECIST 1.1 by BICR.	Objective response (OR): complete response (CR) or partial response (PR).
Secondary	
• Objective: To evaluate the 120 mg QD dose and 200 mg QD dose of belzutifan with respect to progression-free survival (PFS) as assessed by BICR according to RECIST 1.1.	• PFS: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

Objectives	Endpoints
• Objective: To evaluate the 120 mg QD dose and 200 mg QD dose of belzutifan with respect to duration of response (DOR) as assessed by BICR according to RECIST 1.1.	• DOR: the time from first documented evidence of CR or PR until either disease progression or death due to any cause, whichever occurs first.
• Objective: To evaluate the 120 mg QD dose and 200 mg QD dose of belzutifan with respect to clinical benefit rate (CBR) as assessed by BICR according to RECIST 1.1.	• Clinical benefit: stable disease ≥6 months or CR or PR based on assessments by BICR per RECIST 1.1.
• Objective: To evaluate the 120 mg QD dose and 200 mg QD dose of belzutifan with respect to overall survival (OS).	• OS: the time from randomization to death due to any cause.
• Objective: To evaluate the safety and tolerability of the 120 mg QD dose compared with the 200 mg QD dose of belzutifan.	• Adverse events (AEs). • Study intervention discontinuation due to AEs.
• Objective: To evaluate the pharmacokinetics (PK) of the 120 mg QD dose and 200 mg QD dose of belzutifan administered orally as monotherapy.	• Maximum concentration (C_{max}), trough concentration (C_{trough}).

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Renal cell carcinoma with clear cell component
Population	Participants with locally advanced or metastatic RCC after prior therapy
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	None

Study Blinding	Unblinded Open-label
Blinding Roles	Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 4 years 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 150 participants will be randomized.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admini-stration	Regimen/ Treatment Period
Belzutifan 120 mg QD	Belzutifan	120 mg	QD	oral	Until progressive disease or discontinuation
Belzutifan 200 mg QD	Belzutifan	200 mg	QD	oral	Until progressive disease or discontinuation

QD=once daily.

Other current or former name(s) or alias(es) for study intervention are as follows: MK-6482, formerly PT2977 (belzutifan).

Total Number of Intervention Groups/ Arms: 2 arms

Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final contact. After a Screening Phase of up to 28 days, each participant will receive belzutifan until: disease progression is radiographically documented per RECIST 1.1, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, or administrative reasons requiring cessation of treatment (Section 7.1). Treatment beyond disease progression may be allowed (Section 4.1). After the end of treatment, each participant will be followed for the occurrence of AEs and other reportable safety events as described under Section 8.4. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, initiation of a new anticancer treatment, withdrawal of consent, pregnancy, death, loss to follow-up, or end of the study. All participants will be followed for OS until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Scientific Advisory Committee	Yes
Study governance considerations are outlined in Appendix 1.	

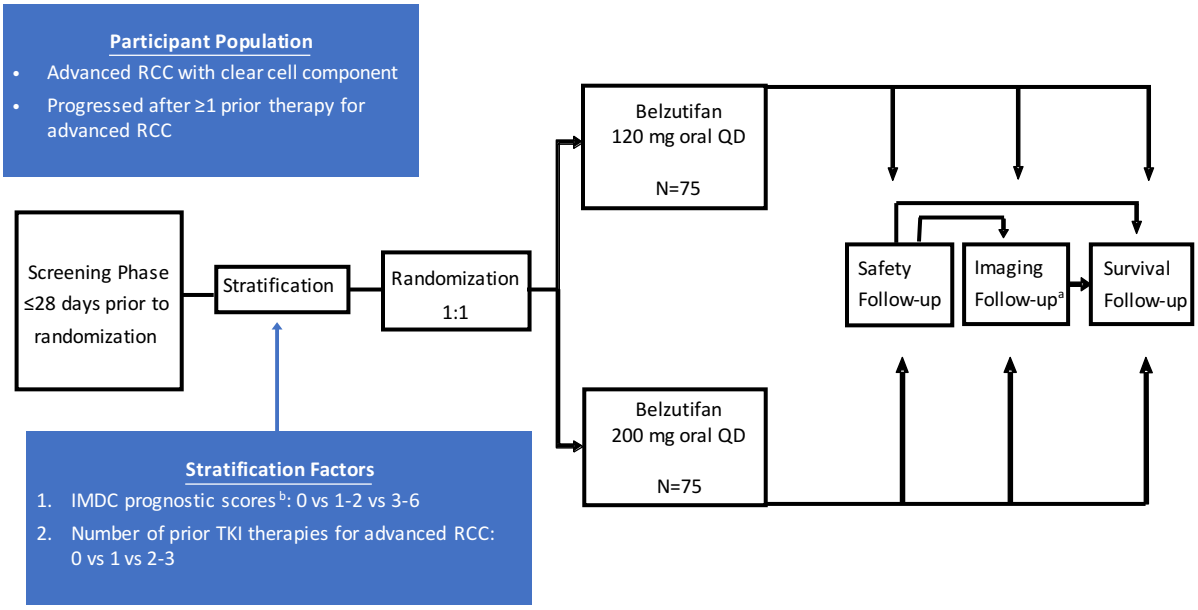
Study Accepts Healthy Volunteers: No

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

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; QD=once daily; RCC=renal cell carcinoma; TKI=tyrosine-kinase inhibitor.

a. Participants who discontinue study treatment for reasons other than disease progression should continue with imaging assessments per the protocol-defined schedule until disease progression, initiation of a new anticancer treatment, death, pregnancy, withdrawal of consent, or end of the study, whichever occurs first.

b. [Cella, D. 2011] [Heng, D. Y., et al 2013]

1.3 Schedule of Activities

Study Period	**Screen-ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen-ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Administrative Procedures													
ICF	X												Consent must be obtained before performing any protocol-specific procedures. If the investigator plans to treat beyond the initial radiologic disease progression, per RECIST 1.1, additional consent is required at initial radiographic disease progression.
Future Biomedical Research ICF (optional)	X												Participants can still participate in the study if they decline to sign the Future Biomedical Research ICF.
Consent for optional tissue collection		←						→					Optional consent
Inclusion/ exclusion criteria	X												

Study Period	**Screen-ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen-ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Participant ID card	X	X											At Week 1, site personnel should add the allocation number to the Participant ID card.
Demographics and medical history	X												Medical history includes alcohol and tobacco use, history of cardiac and respiratory disease/abnormal conditions, and surgical history.
RCC disease history	X												
Prior/ con-comitant medication review	X	X	X	X	X	X	X		X	X	X		Include blood transfusions and supplemental oxygen administration during review of concomitant medication. Concomitant medications administered >30 days after the last dose of study intervention will be recorded for SAEs as outlined for AE monitoring timeframes below.

Study Period	**Screen-ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen-ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Randomizat-ion		X											Participants may be randomized up to 3 days before initiation of study intervention[a] and after confirmation of eligibility. All procedures and assessments performed on Week 1 Day 1 are to be performed after randomization.
Subsequent antineoplastic therapy status									X	X		X	All anticancer therapy will be recorded until time of death or termination of survival follow-up. If a clinic visit is not feasible, follow-up information may be obtained by telephone or email.

Study Period	**Screen -ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen -ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Vital status			◄———	———	———	———	———	———►				X	Continued after investigator determined disease progression or initiation of new anticancer treatment. In addition, on Sponsor request, participants may be contacted for vital status at any time during the study.
Administration of Study Intervention													
Belzutifan dispensing		X		X		X	X						Participants will hold dosing of belzutifan on clinic visit days at Weeks 1, 3, and 5 until after completion of blood collection. The time of ingestion of belzutifan will be recorded and subsequent time-dependent procedures will be performed relative to the ingestion time.
Review study intervention compliance				X		X	X		X				

Study Period	**Screen -ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen -ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Efficacy Procedures													Imaging will continue to be performed until disease progression is documented by the investigator, the initiation of new anticancer treatment, withdrawal of consent, pregnancy, death, or end of the study, whichever occurs first.
Tumor imaging (chest, abdomen, pelvis)	X[d]		X[d]						X[d]		X[d]		Screening images are to be captured within 28 days before randomization. First on-study imaging should be performed at Week 9 Day 1 (±7 days) then Q8W (every 56 days ±7 days) through Week 49 then Q12W (±7 days; (±14 days after Week 109) thereafter (Section 8.2.1.2). Imaging timing is to follow calendar days and is not to be adjusted for delays in study intervention.

Study Period	**Screen-ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen-ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Bone imaging[e]	X[e]		X[e]						X[e]		X[e]		Screening images are to be captured within 28 days before randomization.[e] All imaging visits on study will have a visit window of ±7 days (±14 days after Week 109).
Brain imaging[f]	X[f]		X[f]						X[f]				Screening images are to be captured within 28 days before randomization. All imaging visits on study will have a visit window of ±7 days. Perform at baseline ONLY for participants with previously documented brain metastases (to confirm stability) or who are clinically symptomatic.

Study Period	**Screen-ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen-ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Safety Procedures													
AE/SAE review	X	X	X	X	X	X	X		X	X			Any AEs noted before ICF are to be recorded as medical history. AEs that occur within 30 days of the end of treatment are to be followed and recorded. SAEs are to be reported from the time of intervention allocation through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier. Details are provided in Section 8.4.1.
Complete physical examination including height	X								X				Height at screening only.

Study Period	**Screen-ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen-ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Directed physical examination		X	X	X	X	X	X			X			Directed physical examination performed as clinically indicated before treatment administration and at Safety Follow-up.
Vital signs (weight, systolic and diastolic blood pressure, respiratory rate, heart rate, and pulse oximetry)	X	X	X	X	X	X	X		X	X			Vital signs will be obtained before study intervention administration on Week 1 Day 1. All blood pressure measurements are to be taken after the participant has rested in a seated position for at least 3 minutes.
12-lead ECG	X	X	X	X	X	X		X	X				Single 12-lead ECG. Participants must be in the recumbent position for a period of 5 minutes before the ECG. All ECGs are to be before blood draw or at least 60 minutes after. Additional assessments are to be performed if clinically indicated.

Study Period	**Screen-ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen-ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Karnofsky performance status	X												KPS performance status is collected at screening only and is to be ≤10 days before the first dose of study intervention.
ECOG performance status	X	X	X	X	X	X	X		X	X			ECOG performance status at screening is to be ≤10 days before the first dose of study intervention.
Safety Laboratory Procedures/Assessment: Analysis Performed by LOCAL Laboratory													
EPO	X												EPO levels will be measured ≤10 days before the first dose of study intervention in all participants and will be measured before initiating EPO replacement therapy.
Hematology	X	X	X	X	X	X	X		X	X			All screening laboratory tests are to be performed ≤10 days before the first dose of study intervention.
Chemistry	X	X	X	X	X	X	X		X	X			All screening laboratory tests are to be performed ≤10 days before the first dose of study intervention.

Study Period	**Screen -ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen -ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Urinalysis	X	X				X		X	X	X			
HBV, HCV, and HIV testing	X												Not required unless mandated by local health authorities (Refer to Appendix 7 for country-specific requirements).
Urine or serum hCG - WOCBP only	X	X		X		X	X		X	X			WOCBP require negative test before randomization. If more than 24 hours have elapsed before first dose of study intervention, another pregnancy test is required before starting study intervention. Thereafter, pregnancy tests will be conducted monthly.

Study Period	**Screen-ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen-ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
PT or INR and aPTT	X	X				X		X	X	X			Screening samples collected before obtaining allocation number and ≤10 days before the first dose of study intervention. Test Q8W (every 56 days ±7 days) after Week 9 through Week 49 then Q12W (±7 days) thereafter. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.

Study Period	**Screen -ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen -ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Pharmacokinetics/ Pharmacodynamics/ Biomarkers: Analyses Performed by CENTRAL Laboratory													
Blood for PK analyses[g]		X	X	X									On days of PK blood sample collection, perform ECG before blood draw.
Blood for genetic analyses		X											Collect predose only on Week 1 Day 1.
CCI [redacted]													

Study Period	Screen-ing	Treatment Period							EOT	Post-treatment			Notes
Visit:	Screen-ing[a]	Wk 1 Day 1[a]	Wk 3 Day 1	Wk 5 Day 1	Wk 7 Day 1	Wk 9 Day 1	Wk 13+ Day 1[b]		DC	Safety Follow-up	Imaging Follow-up Visits	Survival Follow-up[c]	
Scheduling Window (Days):	–28 to –1	+3	±3	±3	±3	±3	Q4W ±5	Q8W ±5	At time of DC	30 Days After Last Dose (+7 days)	Q8W or Q12W (±7 days)	Q12W (±7 days)	
CCI													

Study Period	**Screen -ing**	**Treatment Period**							**EOT**	**Post-treatment**			**Notes**
Visit:	**Screen -ing[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**		**DC**	**Safety Follow-up**	**Imaging Follow-up Visits**	**Survival Follow-up[c]**	
Scheduling Window (Days):	**–28 to –1**	**+3**	**±3**	**±3**	**±3**	**±3**	**Q4W ±5**	**Q8W ±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Archival or newly obtained tissue collection	X												Submit an archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. Details pertaining to tumor tissue submission can be found in the laboratory manual.
Optional newly obtained tissue collection		←						→					Separate consent required before collecting tissue for optional biomarker research. Details pertaining to tumor tissue submission can be found in the laboratory manual.

AE=adverse event; aPTT=activated partial thromboplastin time; hCG=human chorionic gonadotropin; BICR=blinded independent central review; CBC=complete blood count; CR=complete response; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; EPO=erythropoietin; HBV=hepatitis B virus; HBsAg=Hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; ID=identification; INR=International normalized ratio; KPS=Karnofsky performance status; MRI=magnetic resonance imaging; PK=pharmacokinetics; PT=prothrombin time; PTT= partial thromboplastin time; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; QD=once daily; QOL=quality of life; RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; SAE=serious adverse event; SoA=schedule of activities; Wk=week; WOCBP=women of childbearing potential.

a. Week 1 Day 1 denotes the first dose of study intervention, which should be on the date of randomization, but can be ≤3 days after randomization. Every effort should be made to ensure the participants receive the first dose of study intervention on the day of randomization.

b. Clinic visits after Week 13 are Q4W.

c. Long-term follow-up may be accomplished via an in-person visit, telephone contact, chart review, etc. Participant status information includes vital status and subsequent antineoplastic therapies for RCC.

d. Tumor assessment including CT or MRI of chest, abdomen, and pelvis should follow the schedule per the SoA until disease progression is documented by the investigator. Imaging visit window may be ±14 days after Week 109. Unscheduled imaging can be performed as clinically indicated. Imaging anatomic coverage should be the same as that at screening; see Section 8.2.1.1 for details. Participants who discontinue treatment for reasons other than disease progression should continue with imaging assessments per the protocol-defined schedule until: 1) disease progression, 2) initiation of a new anticancer treatment, 3) death, 4) pregnancy, 5) withdrawal of consent, or 6) end of the study, whichever comes first.

e. Baseline bone scan is required for all participants at screening. Bone scans are not required to be repeated at screening if performed ≤42 days before randomization. If a participant has a positive baseline bone scan, after randomization, bone scans will be performed at Week 17 (±7 days) and should continue to be performed Q16W (±7 days) through Week 49, subsequently Q24W (±7 days; ±14 days after Week 109) until disease progression. The timing of imaging assessments should follow calendar days and should not be adjusted for delays in study intervention. Bone scans must be performed for confirmation of CR for participants with a positive bone scan at baseline.

f. A brain scan will be performed during screening for participants with brain metastases to ensure participant is stable. After randomization, brain imaging should be performed as clinically indicated in participants with previously documented brain metastases or who are clinically symptomatic, and to confirm a CR in participants with brain metastases at baseline.

g. On Week 1 Day 1, Week 3 Day 1, and Week 5 Day 1, participants will hold dosing of belzutifan tablets, which will be administered in the clinic. The Week 1 Day 1 and Week 3 Day 1 dose should be taken fasted (at least 2 hours after a meal); food should be withheld for 1-hour postdose. To ensure appropriate PK sample collection, it is recommended that study intervention be taken in the morning for the first month of dosing (ie, until Week 5 Day 1). A blood sample for PK assessments will be obtained on Week 1 Day 1 and Week 3 Day 1 at predose, 1, 2 and 4 hours postdose. On Week 5 Day 1 a blood sample will be collected predose. A window of 30 minutes is permitted for all time points at which samples are collected. If a participant has a treatment interruption or discontinues treatment before Week 5, every effort should be taken to collect the PK sample for the Week 5 time point at the time of treatment interruption or discontinuation.

h. On Week 1 Day 1, Week 3 Day 1, and Week 5 Day 1, participants will hold dosing of belzutifan tablets, which will be administered in the clinic. The Week 1 Day 1 and Week 3 Day 1 dose should be taken fasted (at least 2 hours after a meal); food should be withheld for 1-hour postdose. A blood sample for pharmacodynamic assessments will be obtained on Week 1 Day 1 and Week 3 Day 1 at predose, 1, 2 and 4 hours postdose. On Week 5 Day 1 a blood sample will be collected predose. A window of 30 minutes is permitted for all time points at which samples are collected. If a participant has a treatment interruption or discontinues treatment before Week 5, every effort should be taken to collect the pharmacodynamics sample for the Week 5 time point at the time of treatment interruption or discontinuation.

2 INTRODUCTION

This study will evaluate the efficacy and safety of the 120 mg QD dose compared with the 200 mg QD dose of the HIF-2α inhibitor, belzutifan (also known as MK-6482, formerly PT2977), in participants with advanced RCC with clear cell component after prior therapy.

2.1 Study Rationale

The hypoxia-inducible factor, HIF-2α, is believed to play a critical role in tumorigenesis and tumor progression in RCC. Belzutifan is an orally available, small molecule inhibitor of HIF-2α, that selectively disrupts the heterodimerization of HIF-2α with HIF-1β. The safety profile of belzutifan in 55 heavily pretreated advanced RCC participants (median 3 prior regimens) in Study MK-6482-001 (also known as PT2977-101) together with the ORR of 24% suggest that belzutifan may be a treatment option for participants with advanced RCC who have progressed after prior therapy [Jonasch, E., et al 2019]. The rationale for this study is to compare efficacy and safety between the 120 mg and 200 mg doses. If 200 mg shows significant and relevant efficacy and an acceptable safety profile, it may be considered for further development.

2.2 Background

Refer to the IB for detailed background information on belzutifan.

2.2.1 RCC Epidemiology and Current Therapeutic Options

Worldwide, there were 403,262 new cases of kidney cancer and 175,098 deaths due to the disease reported in 2018 [Bray, F., et al 2018]. RCC comprises approximately 3.7% of all cancers, with a median age at diagnosis of 64 years [National Cancer Institute 2016]. Approximately 85% of kidney tumors are RCC, and approximately 70% of these have a clear cell histology [Moch, H., et al 2000] [Leibovich, B. C., et al 2010] [Lipworth, L., et al 2016]. Other less common cell types include papillary, chromophobe, translocation, and Bellini duct (collecting duct) tumors. Smoking, obesity, and hypertension are established risk factors for RCC development. Analysis of the SEER database indicates that RCC incidence has been rising on average 0.6% each year and death rates have been falling on average 0.7% each year from 2006 through 2015 [National Cancer Institute 2016]. The 5-year survival for localized RCC has increased from 88.4% (during 1992 to 1995) to 92.6% (during 2007 to 2013) [Howlader, N., et al 2017]. The most important prognostic determinants of 5-year survival are the tumor stage, grade, local extent of the tumor, presence of regional nodal metastases, and evidence of metastatic disease at presentation [Ficarra, V., et al 2005] [Frank, I., et al 2005] [Zisman, A., et al 2001] [Klatte, T., et al 2007] [Lam, J. S., et al 2007] [Minervini, A., et al 2002] [Dall'Oglio, M. F., et al 2007] [Dall'Oglio, M. F., et al 2007] [Lam, J. S., et al 2005] [Sengupta, S., et al 2005]. RCC primarily metastasizes to the lung, bone, liver, lymph nodes, adrenal gland, and brain [DeVita, et al 2008] [Bianchi, M., et al 2012].

A substantial proportion of patients with RCC progress to advanced stage disease; about one-third of patients with RCC present with unresectable disease or metastasis at diagnosis, and

between 20% to 30% of patients with localized tumors will eventually relapse after nephrectomy [National Comprehensive Cancer Network 2019]. The 5-year survival rate for patients with advanced RCC is 12%.

Treatment options for advanced and metastatic RCC have evolved greatly over the last 2 decades. Early lines of treatment for patients with advanced RCC include VEGF-targeting and immunotherapy agents [Escudier, B., et al 2019]. Recently, combination therapy with the immune checkpoint inhibitor antibodies nivolumab and ipilimumab was shown to be effective in the randomized Phase 3 CheckMate 214 study in participants with treatment-naïve advanced RCC with intermediate or poor IMDC risk [Motzer, R. J., et al 2018]. Two combination regimens of immune checkpoint inhibitors with VEGF-targeted therapies in the first-line setting have also recently reported positive Phase 3 data [Motzer, R. J., et al 2019] [Rini, B. I., et al 2019]. In the KEYNOTE-426 study, the pembrolizumab and axitinib combination prolonged OS (HR 0.53) and PFS (median PFS of 15.1 months for pembrolizumab and axitinib vs 11.1 months for sunitinib), and had an increased ORR (59.3% for pembrolizumab and axitinib vs 35.7% for sunitinib) [Rini, B. I., et al 2019]. Thus, the treatment paradigm for patients with advanced RCC is rapidly evolving, with incorporation of immune checkpoint inhibitor combinations as first-line standard of care, and VEGF-targeting and mTOR inhibitors as subsequent lines of care [McKay, R. R., et al 2018].

There is no evidence-based treatment recommendation for the optimal management of patients in the late-line setting after immunotherapy and VEGF-targeting therapy. Among available agents, everolimus, an mTOR inhibitor, is frequently used in late-line settings in accordance with recently published expert/clinical practice guidelines [Escudier, B., et al 2019] [National Comprehensive Cancer Network 2019]. The NCCN and ESMO strongly recommend clinical study participation for patients, particularly with relapsed disease. Current therapeutic options are outlined in the current ESMO guidelines, released in February 2019 [Escudier, B., et al 2019], and the NCCN guidelines, released in August 2019 [National Comprehensive Cancer Network 2019].

As patients rapidly progress on therapy in late-line settings, improved therapeutic options with superior efficacy are in great need and enrollment into clinical studies investigating promising therapies with new mechanisms of action is recommended.

2.2.2 Pharmaceutical and Therapeutic Background

HIF-2α is a transcription factor that has been established as an oncogenic driver in ccRCC. PT2385 was the first HIF-2α antagonist to be evaluated in clinical development and has showed clinical activity in ccRCC participants who had previously been treated with multiple lines of therapy. There is continuing effort to characterize additional HIF-2α antagonists possessing attributes that may contribute to enhanced clinical activity. The second HIF-2α antagonist to be evaluated, belzutifan, is a potent and selective inhibitor both in vitro and in vivo and inhibits HIF-2α function by disrupting its hetero-dimerization with the ARNT in cells. HIF-2α is believed to have a role in tumorigenesis and tumor progression and epigenetic inactivation of VHL expression has been found in many cancers including multiple myeloma, retinoblastoma, NSCLC, pancreatic endocrine tumors, squamous cell carcinoma, acute myeloid leukemia, myelodysplastic syndrome, and esophageal squamous

cell carcinoma [Nguyen, M. P., et al 2013]. A strong connection has been established between ccRCC, mutations in the *VHL* tumor suppressor gene and the subsequent activation of HIF-2α transcriptional activity [Shen, C. 2013]. More than 90% of ccRCC tumors have defective or modulated VHL function through deletion, mutation, or post-translational modification [Sato, Y., et al 2013]. In tumor cells where HIF-2α is activated, belzutifan blocks the transcription of several genes involved in oncogenesis, including *CCND1*, *VEGFA*, and the glucose transporter *SLC2A1*. CCI

Refer to the belzutifan IB for additional information.

2.2.3 Preclinical Studies

2.2.3.1 Preclinical Pharmacokinetics and Metabolism

PK and TK evaluations characterized the ADME of belzutifan. In vivo PK study assessments were conducted in mice, rats, dogs, and monkeys. Belzutifan has low aqueous solubility and high permeability (BCS Class 2) and is well absorbed after oral administration in animals at clinically relevant doses. The oral bioavailability of belzutifan was shown to be high in mice (>100%), moderate in dogs and monkeys (33% and 53%, respectively), and low in rats (18%).

The volume of distribution of belzutifan was greater than total body water in all species, suggesting extensive tissue distribution.

In vitro and in vivo metabolism studies revealed primarily oxidation and O-glucuronidation biotransformation pathways. The oxidation biotransformation pathways were greatest in rats and similar between humans and dogs. In the ADME study of 14C-belzutifan in rats, belzutifan was primarily metabolized by the liver. The presence of a glycosidic glucuronide metabolite (PT3317) in vivo in rats and dogs led to UGT reaction phenotyping with recombinant UGTs, which suggested that the formation of PT3317 is mediated by UGT2B17, an isoform primarily expressed in the small intestine. PT3317 has no activity against HIF-2α.

In vitro studies assessing the inhibition or induction of CYP metabolic enzymes showed that belzutifan did not inhibit any CYP enzymes by either competitive (7 CYP isoforms) or time-dependent (CYP3A4) mechanisms at concentrations of at least 50 µM. In vitro and physiologically based PK modeling results indicated that belzutifan is a weak inducer of

CYP3A4. Belzutifan is not a substrate of P-gp or BCRP and does not inhibit P-gp or BCRP (IC_{50} >100 μM) at clinically relevant concentrations (~4.67 μM).

Urinary excretion was found to be a minor pathway for elimination of belzutifan (≤4% of dose) and PT3317 (≤13% of dose) for dogs and monkeys.

Refer to the belzutifan IB for additional information.

2.2.3.2 Preclinical Toxicology

Belzutifan was not genotoxic in the in vitro bacterial mutagenicity assay (Ames) and the in vitro micronucleus assay, indicating a low genotoxic risk from belzutifan exposure.

The in vivo safety pharmacology assessments of the cardiovascular, central nervous, and respiratory systems included in general toxicology studies did not yield any adverse findings. The cardiovascular system was assessed by hemodynamic and electrocardiographic parameters in the GLP 28-day and 13-week repeat-dose toxicity studies in dogs, and no change from baseline was observed with belzutifan treatment.

The toxicity of orally administered belzutifan was evaluated in 28-day and 13-week repeat-dose GLP studies in rats and dogs. Effects on the RBC compartment were observed consistently in both species. The magnitude of effect stabilized over time at an approximate 30% reduction in the RBC count, hemoglobin and hematocrit levels, with repeated administration. The effects on the RBC compartment were reversed once belzutifan administration stopped and are considered an “on-target” pharmacologic activity of HIF-2α antagonism on erythropoietin production.

In the rat toxicity studies with belzutifan, off-target organ toxicity was identified in the male reproductive system. The belzutifan related effects involved testes (smaller/soft testes and decreased weight associated with hypospermatogenesis, germ cell degeneration, and multinucleated giant cells), and epididymis (oligospermia), and were not reversible within 26-week recovery periods. These findings were associated with decreased sperm motility and sperm counts, and increased number of abnormal sperms in the sperm analysis. No effects on sperm evaluation and histopathology of testes/epididymides were observed in male dogs. No effects on the female reproductive organs were observed in either rats or dogs.

In a pEFD study where pregnant rats were administered belzutifan, a significant level of post implantation loss indicative of embryo-fetal lethality and/or reduced fetal body weight, reduced ossification, and malformations in surviving fetuses was observed at an exposure close to the clinically relevant exposure at 120 mg/day.

Refer to the belzutifan IB for additional information.

2.2.4 Clinical Studies

As of 06-SEP-2019, a total of 34 healthy volunteers and 185 participants had been treated with MK-6482 in 5 clinical studies: MK-6482-002 (also known as PT2977-103), MK-6482-001 (PT2977-101), MK-6482-004 (PT2977-202), MK-6482-003 (PT2977-201) and MK-6482-006 (PT2977-104):

- 16 healthy adult volunteers in the Phase 1 MK-6482-002 (PT2977-103) food effect study.
- 104 participants in the Phase 1 Study MK-6482-001 (PT2977-101). This included 43 participants with various advanced solid tumors in the dose-escalation cohort (Part 1A) of the study, 52 participants with advanced RCC (Part 1B) and 9 participants with GBM in the dose expansion cohort (Part 2) of the study.
- 61 participants with VHL disease-associated RCC in the Phase 2 Study MK-6482-004 (PT2977-202).
- 20 participants with ccRCC in the Phase 2 Study MK-6482-003 (PT2977-201).
- 18 healthy adult volunteers in the Phase 1 MK-6482-006 (PT2977-104) bioavailability study.

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MK-6482-001 (PT2977-101) is an ongoing Phase 1 study designed to assess the tolerability, safety, PK, and pharmacodynamic properties of belzutifan in participants with various advanced solid tumors. As of 06-SEP-2019 a total of 104 participants had been enrolled, including 43 participants with various advanced solid tumors in the dose-escalation portion (Part 1A) ranging from 20 to 240 mg QD and 120 mg BID. The MTD was not reached and 2 treatment-related DLTs were observed, 1 Grade 4 event of thrombocytopenia in the 240 mg QD cohort, and 1 Grade 3 event of hypoxia in the 120 mg BID cohort. The 120 mg QD dose was selected for further clinical development based on favorable PK, pharmacodynamic, and safety findings. A total of 52 additional participants with advanced RCC were treated in an expansion cohort (Part 1B) at the clinical dose of 120 mg QD. In the combined dose-escalation and expansion cohorts, the most common AEs (occurring in ≥20% of participants) were anemia, fatigue, dyspnea, nausea, hypoxia, and peripheral edema. The most common Grade 3 AEs were anemia and hypoxia (in ≥5% of participants). The median t_{max} for belzutifan was 1 to 2.8 hours and exposure increased with dose. The mean steady state $t_{1/2}$ in the 120 mg QD expansion cohort (Part 1B) on Day 15 was 15.3 hours, resulting in

a 1.5-fold accumulation from Day 1 to Day 15. The mean steady state C_{max} in the 120 mg QD expansion cohort (Part 1B) on Day 15 was 1.79 µg/mL (4.67 µM). The estimated CL/F was 5.22 to 14.4 L/h. The mean steady state $AUC_{0\text{-}tau}$ of belzutifan was 20.42 h*µg/mL with 50% CV. The estimated CL/F and the Vz/F at the steady state for belzutifan were 7.56 L/h and 138 L, respectively. In total, 55 participants with previously treated advanced RCC have been treated in this study with belzutifan at 120 mg QD (3 participants in the dose-escalation portion of the study and 52 participants in the dose expansion portion of the study). Best response among these 55 participants included 13 participants (24%) with PR and 31 participants (56%) with SD as assessed by RECIST 1.1 [Choueiri, T. K., et al 2020].

During the dose-escalation portion of the MK-6482-001 (PT2977-101) study, the dose of 120 mg BID was well tolerated in the 6-participant cohort with only 1 DLT of Grade 3 hypoxia observed. The BID dosing regimen had a higher steady state plasma exposure compared with other dose levels.

MK-6482-004 (PT2977-202) is a Phase 2, open-label, efficacy, and safety study in participants with VHL disease-associated RCC. As of 06-SEP-2019, 61 participants had been enrolled at a dose of 120 mg QD. Efficacy data are not yet available. Fatigue was the most common AE of ≥ Grade 3 toxicity (reported by ≥5% of participants).

Refer to the belzutifan IB for additional information.

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.

The proposed study will enroll participants with advanced RCC who have progressed after prior therapy. As described in Section 2.2.3, belzutifan is a potent and selective inhibitor of HIF-2α in preclinical studies and clinical data as described in Section 2.2.4 show antitumor activity of belzutifan, which warrants further investigation. In MK-6482-001 (PT2977-101), the ORR for 55 heavily pretreated advanced RCC participants (62% having received ≥3 prior lines of therapy) was 24% (95% CI: 13, 37), with median DOR not yet reached, a median PFS of 11 months (95% CI: 6, 17) and clinical activity seen across IMDC risk categories [Choueiri, T. K., et al 2020]. This compares favorably to the ORR seen with nivolumab in Checkmate 25 (25%, 95% CI: 3.68, 9.72) and cabozantinib in METEOR (17%, 95% CI: 13, 22), both studies in advanced RCC participants with at least 2 prior lines of therapy including post TKI treatment [Motzer, R. J., et al 2015] [Choueiri, T. K., et al 2016]. While there are no data on the efficacy of 200 mg, as described in Section 2.2.4 and 4.3.1, there is potential for benefit at least equal if not exceeding that seen for the 120 mg QD dose. The safety profile seen in MK-6482-006 (PT2977-104) at the 200-mg dose was similar to that seen previously for the 120 mg dosing, with the limitations that it was a single-dose study. Given the high risk of progression of disease in patients with advanced RCC, there is an unmet medical need for more effective and tolerable treatment, and as belzutifan has been shown to be well tolerated across various tumor types, a positive benefit/risk profile is expected.

Recent preclinical findings in rats suggest that belzutifan may cause embryo-fetal lethality in humans (Section 2.2.3.2). However, there are no data in humans on the effects of belzutifan on embryonic or fetal development. Precautions for participants regarding this newly identified risk are implemented in Section 5.1, Section 5.2, and Sections 10.5 through 10.5.2 (Appendix 5).

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

This study will be conducted in male and female participants with previously treated advanced renal cell carcinoma (RCC) with clear cell component.

Objectives	Endpoints
Primary	
• Objective: To compare the 120 mg once daily (QD) dose and 200 mg QD dose of belzutifan with respect to objective response rate (ORR) based on Response Criteria in Solid Tumors (RECIST) 1.1 as assessed by blinded independent central review (BICR). • Hypothesis (H1): Belzutifan 200 mg QD is superior to belzutifan 120 mg QD in terms of ORR per RECIST 1.1 by BICR.	• Objective response (OR): complete response (CR) or partial response (PR).
Secondary	
• Objective: To evaluate the 120 mg QD dose and 200 mg QD dose of belzutifan with respect to progression-free survival (PFS) as assessed by BICR according to RECIST 1.1.	• PFS: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
• Objective: To evaluate the 120 mg QD dose and 200 mg QD dose of belzutifan with respect to duration of response (DOR) as assessed by BICR according to RECIST 1.1.	• DOR: the time from first documented evidence of CR or PR until either disease progression or death due to any cause, whichever occurs first.
• Objective: To evaluate the 120 mg QD dose and 200 mg QD dose of belzutifan with respect to clinical benefit rate (CBR) as assessed by BICR according to RECIST 1.1.	• Clinical benefit: stable disease ≥6 months or CR or PR based on assessments by BICR per RECIST 1.1.
• Objective: To evaluate the 120 mg QD dose and 200 mg QD dose of belzutifan with respect to overall survival (OS).	• OS: the time from randomization to death due to any cause.
• Objective: To evaluate the safety and tolerability of the 120 mg QD dose compared with the 200 mg QD dose of belzutifan.	• Adverse events (AEs). • Study intervention discontinuation due to AEs.

Objectives	Endpoints
• Objective: To evaluate the pharmacokinetics (PK) of the 120 mg QD dose and 200 mg QD dose of belzutifan administered orally as monotherapy.	• Maximum concentration (C_{max}), trough concentration (C_{trough}).
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4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, open-label, multicenter, randomized, study to compare the safety and efficacy of the 120 mg QD dose and the 200 mg QD dose of belzutifan in participants with advanced RCC that has progressed after a maximum of 3 prior systemic therapies.

Approximately 150 eligible participants who meet all inclusion criteria and none of the exclusion criteria will be randomly assigned in a 1:1 ratio to receive either 120 mg QD or 200 mg QD of belzutifan (~75 participants in each arm).

The study will include a Screening Phase, a Treatment Phase, and a Posttreatment Follow-up Phase.

The Screening Phase assessments must be performed ≤28 days before randomization unless otherwise specified. Potential participants will be screened to determine if they meet the required eligibility criteria.

At randomization, participants will be stratified by the following factors (Section 6.3.2):

- IMDC prognostic scores [Cella, D. 2011] [Heng, D. Y., et al 2013]: 0 vs 1-2 vs 3-6
- Number of prior TKI therapies for advanced RCC: 0 vs 1 vs 2-3

During the Treatment Phase, randomized participants will receive their assigned study intervention and undergo assessments according to the SoA (Section 1.3). Participants will be evaluated radiologically at Week 9 then Q8W thereafter for the first 49 weeks and then Q12W thereafter. Treatment may continue after radiographic progression of RCC per RECIST 1.1, as long as the investigator believes that the participant is still receiving clinical benefit from study intervention and that the potential benefit of continuing study intervention outweighs potential risks. Treatment beyond disease progression requires Sponsor consultation and approval. If approved by the Sponsor, continued participation requires additional consent (Section 8.1.1). Participants who continue treatment beyond disease progression will continue with all protocol-required assessments and procedures.

Crossover between treatment arms is not allowed.

AE monitoring will be ongoing throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE v5. AEs will be reported by the investigator or delegate from informed consent through 30 days after cessation of study intervention (Section 8.4.1). SAEs will be reported by the investigator or delegate from the time of intervention allocation through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier.

Study intervention will continue until documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, participant withdrawal of consent, interruption of study intervention for >28 days without Sponsor consultation, required use of prohibited medication, pregnancy of the participant, noncompliance, or administrative reasons requiring cessation of study intervention (Section 7.1).

The Posttreatment Follow-up Phase includes a Posttreatment Safety Follow-up Visit to occur 30 days after the date of discontinuation of study intervention. Participants who discontinue study treatment for reasons other than disease progression should continue with imaging assessments as described in the SoA and Section 8.2.2. All participants will be followed for survival (in-person visit, telephone contact, chart review, etc.) until death, withdrawal of consent, loss to follow-up, or until the study is concluded or terminated early, whichever comes first.

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

The open-label study design enables appropriate dose modifications for AEs in both study intervention treatment groups. Specific measures have been taken to ensure that PFS and ORR are evaluated rigorously in this study. For determination of the study endpoints of PFS and ORR, a BICR will review all radiographic images. The BICR will be blinded to treatment identity and to clinical data that may lead to inadvertent unblinding.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary objective of this study is to evaluate the efficacy of the 120 mg QD dose of belzutifan compared with the 200 mg QD dose of belzutifan for the treatment of advanced RCC as assessed by ORR as determined by BICR per RECIST 1.1. This study will use PFS, DOR, and CBR as determined by BICR per RECIST 1.1, and OS, as secondary efficacy endpoints.

ORR and PFS are acceptable measures of clinical benefit for a study that demonstrates efficacy of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess ORR and PFS is typically considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by BICR, an independent central review blinded to treatment assignment to minimize bias in the response assessments.

DOR and CBR are considered acceptable measures of clinical benefit when considered with ORR.

OS is standardly used to show benefit in oncology clinical studies.

4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by NCI CTCAE v5.

4.2.1.3 Pharmacokinetic Endpoints

The plasma concentration of belzutifan will be analyzed by the Sponsor or designee using a validated bioanalytical method. Descriptive statistics will be used to describe the concentration-time data including the C_{max} and C_{trough}. The concentration data from the present study and other studies may be pooled together to perform population PK data analysis and the results would be reported in a separate report.

4.2.1.4 Pharmacodynamic Endpoints

Blocking HIF-2α leads to downregulation of EPO. Therefore, EPO levels will be assessed by dose level using descriptive statistics. Assessment of serum EPO levels and other pharmacodynamic markers will be performed by the Sponsor or designee using a validated method.

4.2.1.5 Planned Exploratory Biomarker Research

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

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Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest in oncology drug development include the mutational burden of tumors. Increased mutational burden (sometimes called a 'hyper-mutated' state) may generate neoantigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Besides mutational burden, DNA analysis could assist in determining genomic status of drug metabolizing enzymes and other hypoxia pathway components that may influence drug exposure and/or response to belzutifan treatment. Note that to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. ctDNA and/or RNA may also be evaluated from blood samples.

Tumor and/or blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that correlate to clinical response to treatment with antitumor therapies. MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and IHC using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, IHC). Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for belzutifan therapy. In addition to expression on the tumor tissue, tumor derived proteins can be shed from tumor and released into the blood. Assays such as ELISA measure such proteins in serum. Correlation of expression with response to belzutifan therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. Samples for pharmacodynamic analyses will be collected from all participants. Pharmacodynamic biomarkers to be assessed include, but are not limited to, levels of EPO.

4.2.1.6 Future Biomedical Research

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

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

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

The doses of belzutifan used in this study are 120 mg QD and 200 mg QD, based on previous clinical study experience as described in Section 2.2.4. Based on favorable PK, pharmacodynamic, safety, and efficacy findings in MK-6482-001 (PT2799-101) Parts 1A and 1B in participants with advanced tumor types including RCC, the 120-mg dose was chosen for continued evaluation in the population of previously treated participants with

advanced RCC. CCI [redacted]

4.3.2 Maximum Dose/Exposure for This Study

There is no maximum duration of treatment for belzutifan.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

Male and female participants with advanced RCC with clear cell component who are at least 18 years of age will be randomized in this 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

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

Type of Participant and Disease Characteristics

1. Must have a histologically confirmed diagnosis of locally advanced/metastatic RCC with clear cell component (with or without sarcomatoid features), ie, Stage IV RCC per AJCC (8th Edition).

2. Has measurable disease per RECIST 1.1 as assessed by BICR.

3. Submit an archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. Details pertaining to tumor tissue submission can be found in the laboratory manual.

Prior Therapy

4. Has experienced disease progression on or after systemic treatment with an anti-PD-1/L1 therapy for locally advanced or metastatic RCC. The anti-PD-1/L1 therapy may be monotherapy or in combination with other agent(s) such as CTLA4 or VEGF targeted-TKI. The immediately preceding line of treatment has to have been an anti-PD-1/L1 therapy.

    - Treatment progression is defined by meeting ALL of the following criteria:

        - Has received at least 2 doses of an anti-PD-1/L1 mAb.

        - Has demonstrated radiographic disease progression during or after an anti-PD-1/L1 mAb as assessed by investigator.

5. Has received no more than 3 prior systemic regimens for locally advanced or metastatic RCC.

6. Has received only 1 prior anti-PD-1/L1 therapy for locally advanced or metastatic RCC.

7. Has recovered from all AEs due to previous therapies to ≤Grade 1 or baseline, with the exception of ≤Grade 2 neuropathy or endocrine-related AEs ≤Grade 2 requiring treatment or hormone replacement.

Demographics

8. Is male or female, who is at least 18 years of age at the time of signing the informed consent.

9. Has a KPS score of at least 70% [Karnofsky, D. A., et al 1948] assessed within 10 days prior to the first dose of study intervention.

Male Participants

10. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after the last dose of study intervention:

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

    OR

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

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

  - Male participants must also agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.

- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

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

- Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 30 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

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

Additional Categories

13. Has adequate organ function, as detailed in Table 1; all screening laboratory tests should be performed within 10 days prior to the first dose of study intervention.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500 cells/µL
Platelets	≥100 000 cells/µL
Hemoglobin	≥10.0 g/dL or ≥6.2 mmol/L[a]
Renal	
Creatinine AND[b]/OR Measured or calculated[c] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN AND[b]/OR ≥30 mL/min for participant with creatinine levels >1.5 × ULN
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
INR OR PT and aPTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

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

[a] Criteria must be met without erythropoietin dependency and without pRBC transfusion within last 28 days.

[b] Applicable only when local guidelines require both assessments.

[c] 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 for the administration of specific chemotherapies.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has any of the following:

   - Hypoxia as defined by a pulse oximeter reading <92% at rest, or
   - Requires intermittent supplemental oxygen, or
   - Requires chronic supplemental oxygen.

2. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

3. Has known CNS metastases and/or carcinomatous meningitis.

   Note: Participants with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of progression) for at least 4 weeks (28 days) by repeat imaging (repeat imaging should be performed during study screening), clinically stable, and without requirement for steroid treatment for at least 14 days prior to the first dose of study intervention.

4. Has clinically significant cardiac disease, including unstable angina, acute myocardial infarction ≤6 months from Day 1 of study drug administration, or New York Heart Association Class III or IV congestive heart failure. Medically controlled arrhythmia stable on medication is permitted.

5. Has moderate to severe hepatic impairment (Child-Pugh B or C).

6. Received colony-stimulating factors (eg, G-CSF, GM-CSF or recombinant EPO) ≤28 days prior to the first dose of study intervention.

7. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.

8. Is unable to swallow orally administered medication or has a gastrointestinal disorder affecting absorption (eg, gastrectomy, partial bowel obstruction, malabsorption).

9. Has known hypersensitivity or allergy to the active pharmaceutical ingredient or any component of the study intervention (belzutifan) formulations.

Prior/Concomitant Therapy

10. Has received prior treatment with belzutifan or another HIF-2α inhibitor.

11. Has received any type of small molecule kinase inhibitor (including investigational kinase inhibitor) ≤2 weeks before randomization.

12. Has received any type of systemic anticancer antibody (including investigational antibody) ≤4 weeks before randomization.

13. Has received prior radiotherapy ≤2 weeks prior to first dose of study intervention. Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout is required for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

14. Has had major surgery ≤3 weeks prior to first dose of study intervention. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.

15. Is currently receiving either strong (phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate (eg, bosentan, efavirenz, modafinil) inducers of CYP3A4 that cannot be discontinued for the duration of the study.
    Note: A current list of strong/moderate inducers of CYP3A4 can be found at the following website:

    https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Prior/Concurrent Clinical Study Experience

16. Is currently participating in a study of an investigational agent or is currently using an investigational device.

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

Diagnostic Assessments

17. Has an active infection requiring systemic therapy.

18. Has active TB.

19. Has a diagnosis of immunodeficiency.

20. Has a known history of HIV infection.

Note: Testing for HIV at screening is only required if mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

21. Has a known history of HBV (defined as HBsAg reactive) or known active HCV (defined as HCV RNA [qualitative] is detected) infection.

    Note: Testing for HBV and HCV is only required if mandated by local health authority.

Other Exclusions

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should avoid grapefruit, grapefruit juice, Seville oranges, Seville orange juice, and St. John's Wort (tablet or tea) while receiving study intervention. Otherwise, participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2 Tobacco Use

Participants should discuss tobacco use with their study physician as it is important to understand the pulmonary and cardiac health of study participants. It is not known whether prior tobacco use will impact the incidence of hypoxia, an Event of Clinical Interest for belzutifan.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Inter-vention Name	Inter-vention Type	Dose Formula-tion	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen / Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Belzutifan 120 mg	Experimental	Belzutifan	Drug	Tablet	40 mg tablet	120 mg	Oral	QD	Test Product	IMP	Central
Belzutifan 200 mg	Experimental	Belzutifan	Drug	Tablet	40 mg tablet	200 mg	Oral	QD	Test Product	IMP	Central

NIMP/AxMP=noninvestigational/auxiliary medicinal product; QD=once daily.

The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Belzutifan tablets are supplied by the Sponsor as an immediate-release tablet in 1 dose strength, 40 mg, for oral administration.

The 40-mg strength tablets will be supplied in HDPE bottles with induction-seal liners and a child-resistant closure.

The Pharmacy Manual contains additional information.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to 120 mg QD belzutifan study intervention and 200 mg QD belzutifan study intervention, respectively.

6.3.2 Stratification

Randomization will be stratified by the following factors:

- IMDC prognostic scores [Cella, D. 2011] [Heng, D. Y., et al 2013]: 0 vs 1-2 vs 3-6
- Number of prior TKI therapies for advanced RCC: 0 vs 1 vs 2-3

The IMDC prognostic factors are the following:

- Clinical Risk Factors
  - Low KPS score (<80%) [Karnofsky, D. A., et al 1948]
  - Time from diagnosis to initiation of first-line treatment <1 year
- Laboratory Risk Factors
  - Low hemoglobin (<LLN)
  - High corrected serum calcium (>ULN)
  - High neutrophils (>ULN)
  - High levels of platelets (>ULN)

Prognosis is based on the number of IMDC factors present and determined as follows:

- Favorable prognosis: 0 risk factors
- Intermediate prognosis: 1-2 risk factors
- Poor prognosis: ≥3 risk factors

The most recent evaluations used to establish eligibility should be used to determine the IMDC category for stratification.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment for >28 days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

The investigator or their designated and qualified representatives will dispense study intervention only to participants enrolled in the study in accordance with the protocol. The study intervention must not be used for reasons other than that described in the protocol.

Participants should be given clear instructions on how and when to take their study intervention. Participants will self-administer belzutifan, except at on Day 1 of Weeks 1, 3, and 5 when belzutifan dosing will occur during the clinic visit.

All participants must return their bottle(s)/packages of belzutifan at the appropriate scheduled visit, when a new bottle/package will be dispensed. Participants will be instructed to notify study site personnel of missed doses.

Study site staff will make tablet counts at clinic when tablets are returned, the remaining tablets will not be returned to the participant, but will be retained by the investigative site until reconciliation is completed by the study monitor.

Compliance should be based on participant reporting and confirmed by tablet count where possible. Issues with compliance should be discussed with the participant and addressed as deemed appropriate by the investigator.

Participants who fail to comply with the dosing requirements of the study may be withdrawn from the study.

6.5 Concomitant Therapy

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

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

In vitro and physiologically based PK modeling results indicated that belzutifan may be a weak inducer of CYP3A4 enzyme. Belzutifan may, therefore, decrease the exposure of concomitant medications that are mainly metabolized by CYP3A4; however, the magnitude and clinical relevance of these effects is not clear. Thus, participants taking medications metabolized by CYP3A4 with narrow therapeutic index should be monitored carefully for potential decreases in drug effect.

Belzutifan exposures may increase with strong CYP3A4 inhibitors in certain subpopulations of participants who have poor metabolizer phenotypes for both UGT2B17 and CYP2C19 enzymes; however, the clinical relevance of these effects is not clear.

6.5.1 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria (Section 5.2) are not allowed during screening and during the study intervention phase of the ongoing study, unless noted below. If there is a clinical indication for any medication or vaccination 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.

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

1. Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.

2. Investigational agents other than belzutifan.

3. Radiation therapy for disease control.

    - Note: Palliative radiation therapy to a symptomatic nontarget lesion or to the brain is allowed after Sponsor consultation.

4. As a precaution, it is recommended that strong inhibitors of CYP3A4 be avoided in participants receiving belzutifan If it is not possible to avoid strong inhibitors of CYP3A4, careful monitoring should be applied for enhanced drug effect with belzutifan.

    Note: A current list of strong/moderate inhibitors of CYP3A4 can be found at the following website:

    https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

5. Chronic use of strong or moderate inducers of CYP3A4.

   Note: A current list of strong/moderate inducers of CYP3A4 can be found at the following website:

   https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

There are no prohibited therapies during the Posttreatment Phase.

6.5.2 Rescue Medications and Supportive Care

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

6.6 Dose Modification

Guidelines for dose modification for belzutifan are listed in Table 3. Specific dose reduction levels are listed in Table 4 for the 120 mg QD starting dose and Table 5 for the 200 mg QD starting dose.

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruption):

- As a general approach, all AEs should be managed with supportive care at the earliest signs of toxicity if considered related to belzutifan treatment. Should this be ineffective, dose reductions or interruptions are to be considered to prevent worsening of toxicity.

- Dose reductions and/or interruptions, at any time while on study, should be implemented for unacceptable toxicity.

- Dose modifications or interruptions may also occur in the setting of lower grade toxicity than defined in Table 3, if the investigator feels it is in the interest of a participant's safety and will optimize drug tolerability.

- Interruption of belzutifan treatment for AEs may occur at any time per investigator discretion. An interruption for >28 days will require Sponsor approval before treatment can be resumed.

The AE profile of belzutifan indicates that anemia and hypoxia have been associated with belzutifan treatment. Guidelines for the management of anemia and hypoxia are provided in Section 6.6.1.1 and Section 6.6.1.2, respectively. ECIs for belzutifan and guidelines for reporting these AEs as ECIs are provided in Section 8.4.7. Please refer to the ECI Guidance document for additional practice guidelines and management recommendations for AEs potentially related to belzutifan treatment.

Table 3 Dose Modification Guidelines for Belzutifan (MK-6482)-related Toxicities

Belzutifan (MK-6482)-Related Toxicity		Action
Anemia	• Grade 4 anemia	• 1st episode: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by 1 level • 2nd episode: Permanently discontinue belzutifan
Neutropenia/Febrile neutropenia	• Grade 3 febrile neutropenia (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), or • Grade 4 neutropenia for >5 days	• 1st and 2nd episodes: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by 1 level • 3rd episode: Permanently discontinue belzutifan
	• Grade 4 febrile neutropenia	• Permanently discontinue belzutifan
Thrombocytopenia	• Grade 3 thrombocytopenia with bleeding	• 1st and 2nd episodes: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by 1 level • 3rd episode: Permanently discontinue belzutifan
	• Grade 4 thrombocytopenia	• 1st episode: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by 1 level • 2nd episode: Permanently discontinue belzutifan
Hypoxia or Dyspnea	• Grade 3 dyspnea • Grade 3 hypoxia (asymptomatic), belzutifan may be continued at the discretion of the investigator • Grade 3 hypoxia (symptomatic)	• 1st and 2nd episodes: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by 1 level • 3rd episode: Permanently discontinue belzutifan
	• Grade 4 dyspnea • Grade 4 hypoxia	• Permanently discontinue belzutifan

Belzutifan (MK-6482)-Related Toxicity		Action
Gastrointestinal	• Grade 3 or 4 nausea, vomiting, or diarrhea if persistent for >48 hours despite optimal antiemetic or antidiarrheal therapy	• 1st and 2nd episodes: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by 1 level • 3rd episode: Permanently discontinue belzutifan
Hepatic	• Grade 3 increase in AST and/or ALT levels, if confirmed on repeat testing within 48 hours	• 1st episode: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by 1 level • 2nd episode: Permanently discontinue belzutifan
	• Grade 4 increase in AST and/or ALT levels, if confirmed on repeat testing within 48 hours, or • Grade 3 or 4 increase in AST and/or ALT levels if accompanied by a Grade 2 increase in bilirubin level and an alkaline phosphatase level <2 × ULN	• Permanently discontinue belzutifan
Cardiovascular, vascular, or thrombotic	• Grade 3 or 4 cardiovascular, vascular or thrombotic events	• Permanently discontinue belzutifan
Other Non-Laboratory Toxicities	• Any other nonlaboratory Grade 3 toxicity	• 1st and 2nd episodes: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by 1 level • 3rd episode: Permanently discontinue belzutifan
	• Any other nonlaboratory Grade 4 toxicity	• Permanently discontinue belzutifan
Other Laboratory Toxicities	• Grade 3 or 4 laboratory toxicity that does not resolve within 48 hours and is considered clinically significant by the investigator	• Permanently discontinue belzutifan
Abbreviations: ANC=absolute neutrophil count; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal. Re-escalation to the next higher dose level may be permitted after Sponsor consultation for a participant who has resumed belzutifan at a given dose level for at least 28 days and original toxicity has not reappeared. Re-escalation of belzutifan will not be permitted for events of Grade 3 symptomatic hypoxia. If Action is "dose reduce by 1 dose level" and participant is already at dose level -2 when a toxicity occurred, belzutifan should be permanently discontinued.		

Table 4 Belzutifan Dose Levels – 120 mg QD Starting Dose

Belzutifan Dose Levels	
Dose Level	**Dose**
Starting Dose	120 mg QD
-1	80 mg QD
-2	40 mg QD
QD=once daily.	

Table 5 Belzutifan Dose Levels –200 mg QD Starting Dose

Belzutifan Dose Levels	
Dose Level	**Dose**
Starting Dose	200 mg QD
-1	120 mg QD
-2	80 mg QD
QD=once daily.	

6.6.1 Management of Anemia

Participants enrolled in the study will have a baseline hemoglobin level of ≥10 g/dL (no transfusion or growth factor support within 4 weeks of the hematology screening assessment). During the study, participants should undergo hematology assessments at each clinic visit (Appendix 2) to monitor their hemoglobin and hematocrit to detect onset or worsening of anemia. If clinically indicated, anemia will be appropriately managed by the investigator. Given that decreased EPO is the etiology of potential anemia with belzutifan treatment, EPO replacement is an effective management strategy for participants who may develop and subsequently require intervention for belzutifan-induced anemia. EPO levels will be measured at baseline in all participants and will be measured before initiating EPO replacement therapy.

6.6.2 Management of Hypoxia

Per the NCI CTCAE v5, hypoxia is defined as pulse oximetry finding of <88%. Participants enrolled in the study will have a baseline pulse oximetry of at least 92% at rest and will not be in need of intermittent or chronic supplemental oxygen. During the study, participants undergo pulse oximetry monitoring at each clinic visit (Section 1.3). If clinically indicated, management of hypoxia should include treating any underlying acute medical conditions and providing supplemental oxygen therapy as necessary.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

For studies using controlled substances, all Federal, State, Province, Country, etc., regulations must be adhered to in regard to their shipping, storage, handling, and dispensing of controlled substances. Additionally, the investigator should have the appropriate controlled drug license(s) as mandated by Federal, State, Province, Country, etc., laws in which the study is being conducted.

6.9.1 Study Site Retention Samples

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 and Section 8.11.3.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Documented radiographic disease progression per RECIST 1.1.

  Note: Participants may be permitted to continue treatment beyond disease progression, after Sponsor consultation, and the participant is tolerating study intervention (Sections 4.1 and 8.2.1.2).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment. Exceptions to second malignancy include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new nonulcerated primary melanoma <1 mm in depth with no nodal involvement, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that undergo potentially curative therapy. Exceptions should be discussed with the Sponsor before continuing therapy.
- Unacceptable AEs or toxicities (Section 6.6).
- The participant interrupts study intervention administration for >28 consecutive days without Sponsor consultation. Participants may continue on study on Sponsor consultation.
- Required use of prohibited medications.
- Intercurrent illness that prevents further administration of study treatment.
- Noncompliance with study treatment or procedure requirements.
- The participant has a confirmed positive serum or urine pregnancy test.
- Sponsor discontinuation of study.

As described in Sections 4.1 and 8.2.1.2, treatment may continue beyond investigator-assessed disease progression, but requires Sponsor consultation and approval. If approved by the Sponsor, continued participation requires additional consent (Section 8.1.1). Participants who continue treatment beyond investigator-assessed disease progression will continue with all protocol-specified assessments and procedures.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

- 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

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

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

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

Treatment beyond disease progression requires Sponsor consultation and approval. If approved by the Sponsor, the participant or their legally acceptable representative will be

asked to provide documented informed consent at the point of initial radiographic disease progression.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. Medical history should include information about alcohol and tobacco use, history of cardiac and respiratory disease/abnormal conditions, and surgical history. Details regarding the disease for which the participant has enrolled in this 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 intervention. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study and up to 30 days after the last dose of study intervention. Concomitant medications administered 30 days after the last dose of study intervention should be recorded for SAEs and ECIs as defined in Section 8.4.7. In the posttreatment follow-up period, information about new anticancer therapies will be collected.

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 randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention should begin on the date of randomization, but can be ≤3 days after randomization. Every effort should be made to ensure the participants receive the first dose of study intervention on the day of randomization.

Study intervention may be administered at home except on clinic visit days on Day 1 of Weeks 1, 3, and 5. Study intervention on these days will occur in the clinic after completion of blood collection. On the Day 1 of Week 1 and Week 3 visits, study drug should be taken fasted (at least 2 hours after a meal; Section 8.6.1) and food should be withheld for 1 hour postdose.

8.1.8.1 Timing of Dose Administration

Participants should be given clear instructions on how and when to take their study intervention. Participants in the 120 mg QD belzutifan dose arm will take three 40-mg tablets of belzutifan orally QD, and participants in the 200 mg QD belzutifan dose arm will take five 40-mg tablets of belzutifan orally QD, with doses taken at approximately the same time of day. To ensure appropriate PK sample collection, it is recommended that study intervention be taken in the morning for the first month of dosing (ie, until Week 5 Day 1). Belzutifan can be taken without regard to food, except when it should be taken fasted on Day 1 of Week 1 and Week 3 as described in Section 8.6.1.

Missed doses may be made up if taken within 6 hours after the scheduled administration time. Participants who vomit after study drug administration should not retake that study drug dose, but should resume taking study drug with the next scheduled dose.

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 as outlined in the SoA and Section 8.11.3.

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

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for 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 Tissue Collection

A tumor specimen for biomarker assessment will be provided or collected before randomization in the study.

A core or excision biopsy of a tumor lesion (inclusive of fresh tissue collected after receiving study intervention) is preferred. Submission of either FFPE tumor blocks or unstained slides is acceptable; FFPE tumor blocks are preferred.

Participants must sign the main study ICF before submitting existing tissue samples and/or undergoing a new biopsy.

CCI [redacted]

Details for the collection, processing, storage and shipment of tissue samples can be found in the study laboratory manual.

8.1.12 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

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

The process for scan collection and transmission to the iCRO can be found in the SIM. In general, scans should include the chest, abdomen, and pelvis. Tumor scan 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. Contrast-enhanced MRI is the strongly preferred modality for scan of the brain. Scan of any anatomy that shows disease either at screening or in subsequent evaluations will

be required and should be submitted to the iCRO. The same scan 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 scans.

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

All scheduled scans for all study participants from the sites will be submitted to the iCRO. In addition, a scan that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), should also be submitted to the iCRO if it shows progression, or if it is used to support a response assessment.

8.2.1.1 Initial Tumor Imaging

Initial tumor scans at screening must be performed ≤28 days before randomization. The screening scans must be submitted to the iCRO for confirmation of measurable disease per RECIST 1.1 for eligibility before randomization.

Tumor scans performed as part of routine clinical management is acceptable for use as screening tumor scans if it is of diagnostic quality, performed ≤28 days before randomization and can be assessed by the iCRO.

Tumor scans at screening includes the following:

- CT (preferred) or MRI of the abdomen and pelvis, must include IV contrast
- CT of the chest
- Bone scan is required for all participants at screening. Bone scans are not required to be repeated at screening if performed ≤42 days before randomization. Additionally, X-ray or MRI may also be taken for symptomatic sites even if bone scan is negative and there is clinical suspicion for metastatic disease.
- Brain scan is required at screening for those participants with known brain metastases at baseline (ie, to confirm stability) or in those who are clinically symptomatic. MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

8.2.1.2 Tumor Imaging During the Study

The first on-study scan assessment should be performed at Week 9 Day 1 (±7 days) from the date of randomization. Subsequent tumor scans should be performed Q8W (±7 days) through Week 49, or more frequently if clinically indicated. After Week 49 (±7 days), participants who remain on study intervention will have scans performed Q12W (±7 days). The scan visit

window is ±14 days after Week 109. Scan timing should follow calendar days from the date of randomization and should not be adjusted for delays in study intervention. Scans should continue to be performed until disease progression is determined by the investigator (unless the investigator elects to continue treatment after Sponsor approval [Section 7.1]), or until any of these conditions are met:

- The initiation of new anticancer treatment
- Withdrawal of consent
- Pregnancy
- Death
- The end of the study

whichever occurs first. All supplemental scans must be submitted to the iCRO.

Objective response should be confirmed by a repeat scan assessment. Tumor scans to confirm PR or CR should be performed at least 4 weeks (at least 28 days) after the first indication of a response is observed. Participants will then return to regular scheduled scans, starting with the next scheduled scan time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled tumor scan if it is less than 4 weeks (<28 days) later; tumor scans may resume at the subsequent scheduled scan time point.

If a participant has a positive baseline bone scan at screening, after randomization, bone scans will be performed at Week 17 (±7 days) and should continue to be performed Q16W (±7 days) through Week 49, then subsequently Q24W (±7 days; ±14 days after Week 109) until disease progression is determined by the investigator (unless the investigator elects to continue treatment after Sponsor approval [Section 7.1]). The timing of scans assessments should follow calendar days and should not be adjusted for delays in study intervention. Bone scans must be performed for confirmation of CR for participants with a positive bone scan at baseline.

After randomization, brain scans should be performed as clinically indicated and to confirm a CR in participants with brain metastases at baseline.

Participants who have disease progression will discontinue study intervention (unless the investigator elects to continue treatment after Sponsor approval [Section 7.1 and Section 8.2.1.3]). Participants who continue treatment beyond disease progression must sign a separate ICF and will continue with all protocol-specified assessments and procedures.

8.2.1.3 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 intervention). If disease progression is established by the investigator, the process continues as follows:

- Investigator judgment will determine action
- If the participant is clinically stable and study intervention is to continue, communication with the sponsor is required and a reconsent addendum must be signed. In addition, the following are to occur:
    - Continue scans per protocol schedule (the next scheduled scan should be ≥4 weeks from the most recent scan acquired)
    - Send scans to iCRO

For the purpose of this decision process, lack of clinical stability is defined as:

- Unacceptable toxicity
- Clinical signs or symptoms indicating clinically significant disease progression
- Decline in performance status
- Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.

8.2.2 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue study intervention, tumor scans should be performed at the time of treatment discontinuation (±4 week window). If previous scan was obtained ≤4 weeks (28 days) before the date of discontinuation, then scans at treatment discontinuation is not mandatory. For participants who discontinue study intervention due to documented disease progression, this is the final required tumor scan.

Participants who discontinue study treatment for reasons other than disease progression should continue with scan assessments per the protocol-defined schedule until one of the following conditions are met:

- Disease progression
- The start of a new anticancer treatment
- Pregnancy
- Death
- Withdrawal of consent

- The end of the study

whichever occurs first. For participants who discontinue for reasons other than disease progression, scans should be performed using the same imaging schedule used while on treatment calculated from the randomization date (see Section 8.2.1) until disease progression, the initiation of new anticancer treatment, withdrawal of consent, pregnancy, death, or notification by the Sponsor, whichever occurs first.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard and at the time points specified in the SoA (Section 1.3). Height (screening only) 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.

8.3.2 Vital Signs

The investigator or qualified designee will measure vital signs at the time points specified in the SoA (Section 1.3) including weight, systolic and diastolic blood pressure, respiratory rate, heart rate, and pulse oximetry. Height will be measured at screening only.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3). Clinically significant abnormal findings at screening should be recorded as medical history. QTc will be calculated locally using Fridericia's formula. Additional ECGs should be performed when clinically necessary.

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

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

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

8.3.5 KPS and ECOG Performance Status

The investigator or qualified designee will assess KPS and ECOG performance status at screening (≤10 days before the first dose of study intervention) [Karnofsky, D. A., et al 1948] [Oken, M.M., et al 1982]. The investigator or qualified designee will assess ECOG performance status as listed in the SoA (Section 1.3). ECOG performance status will be assessed before the administration of the study intervention or study-related procedures.

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety

events for outcome according to Section 8.4.3. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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

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

- All AEs from the time of intervention randomization through 30 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention 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 intervention through the time required to eliminate systemic exposure after cessation of study intervention as described in Section 5.1 and Appendix 2, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 6.

Table 6 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

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

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

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint that on review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

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

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).
- Any ≥Grade 2 anemia/decreased hemoglobin.
- Any ≥Grade 2 hypoxia.
- Any ≥Grade 2 dyspnea.
- Any ≥Grade 3 AE deemed related to belzutifan by the investigator, including laboratory abnormalities.
- Any ≥Grade 4 AEs (all causality).

8.5 Treatment of Overdose

An overdose will be defined as any dose greater than 240 mg QD. No specific information is available on the treatment of overdose of belzutifan. In the event of overdose, belzutifan should be interrupted 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 Belzutifan

CCI [redacted]

8.7 Pharmacodynamics

Blood samples for analysis of pharmacodynamic effects will be collected as listed in the SoA (Section 1.3). Pharmacodynamic biomarkers to be assessed include, but are not limited to, levels of EPO.

Details for the collection, processing, storage, and shipment of samples for the determination of pharmacodynamic effects and biomarker assessments can be found in the study laboratory manual.

8.8 CCI [redacted]

[redacted]

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

8.8.1 CCI [redacted]

[redacted]

8.9 Future Biomedical Research Sample Collection

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

- Leftover specimens as listed in Section 8.8.

8.10 Medical Resource Utilization and Health Economics

All-cause hospitalizations and emergency room visits must be reported in the eCRF, from the time of treatment allocation/randomization through 90 days after cessation of study intervention, or 30 days after cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

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

From -28 days to -1 day before randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

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

specified time frame. Screening procedures are to be completed ≤28 days before the first dose of study intervention except for the following:

- Laboratory tests are to be performed ≤10 days before the first dose of study intervention. An exception is HIV (if required by local health authority) and hepatitis testing which may be performed up to 28 days before the first dose of study intervention. Refer to Appendix 7 for country-specific requirements.

- Evaluation of KPS and ECOG is to be performed ≤10 days before the first dose of study intervention.

- WOCBP require negative test before randomization. If more than 24 hours have elapsed before first dose of study intervention, another pregnancy test is required before starting study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Screening images are to be captured within 28 days before randomization.

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

8.11.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1. Assessments/procedures will be performed before the administration of study intervention.

8.11.3 Poststudy

8.11.3.1 Posttreatment Safety Follow-up Visit

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

8.11.3.2 Imaging Follow-up

Participants who discontinue study treatment for reasons other than disease progression will continue with imaging assessments per the protocol-defined schedule until: 1) disease progression, 2) initiation of a new anticancer treatment, 3) death, 4) pregnancy, 5) withdrawal of consent, or 6) end of the study, whichever occurs first. Tumor imaging will be performed Q8W (±7 days) through Week 49, or more frequently if clinically indicated. After

Week 49 (±7 days), participants who remain on study intervention will have imaging performed Q12W (±7 days). The imaging visit window is ±14 days after Week 109.

8.11.3.3 Survival Follow-up

Participants who experience documented disease progression or start a new anticancer therapy, will move into the Survival Follow-up Phase and will be followed for survival (vital status) (in-person visit, telephone contact, chart review, etc.) approximately Q12W from the treatment discontinuation visit or from Imaging Follow-up discontinuation. Every effort should be made to assess for vital status until death, withdrawal of consent, or the end of the study, whichever occurs first. Information regarding initiation of a new anticancer treatment will also be collected.

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but before final database lock, will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A randomized, open-label, Phase 2 study of 120 mg QD of belzutifan compared with 200 mg QD of belzutifan in participants with advanced RCC after prior therapy
Treatment Assignment	Participants will be randomly assigned in a 1:1 ratio to receive either belzutifan at 120 mg QD or belzutifan at 200 mg QD. Stratification factors are as follows: • IMDC prognostic scores: 0 vs 1-2 vs 3-6 • Number of prior TKI therapies for advanced RCC: 0 vs 1 vs 2-3
Analysis Populations	Efficacy: ITT Safety: APaT
Primary Endpoints	• ORR

Secondary Endpoints	• PFS • DOR • CBR • OS • AEs and discontinuations due to AEs
Statistical Methods for Key Efficacy Analyses	The primary hypotheses comparing the 120 mg QD dose of belzutifan to the 200 mg QD dose of belzutifan with respect to ORR will be evaluated using the stratified Miettinen and Nurminen method with strata weighted by sample size. PFS and OS will be summarized within each treatment group using the Kaplan-Meier method. For PFS and OS, the HR will be estimated using a stratified Cox regression model.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	No formal interim analysis is planned. Final analysis will be performed at least 6 months after the last participant is randomized.
Multiplicity	No multiplicity adjustment will be applied.
Sample Size and Power	The study will randomize approximately 150 participants in a 1:1 ratio to the belzutifan 120 mg QD and belzutifan 200 mg QD arms. With 75 participants at each dose level, the study has ~83% power to detect a 20% difference in ORR between the 2 doses at the 5% type I error rate (one-sided) assuming that the ORR in the lower dose arm is 24%.

9.2 Responsibility for Analyses/In-house Blinding

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

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IRT.

Although this is an open-label study, analyses or summaries generated by randomized treatment assignment, or actual treatment received will be limited and documented. Further documentation will be provided in the sSAP.

An independent radiologist(s) will perform the central imaging review without knowledge of treatment assignments.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Primary:

ORR – ORR is defined as the proportion of participants in the analysis population who have a best overall response of either confirmed CR or PR per RECIST 1.1 as assessed by BICR.

Secondary:

PFS – PFS is defined as the time from randomization to the first documented disease progression based on RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

DOR – For participants who showed CR or PR, DOR is defined as the time from the first documented evidence of confirmed CR or PR until the first documented date of disease progression or death due to any cause, whichever occurs first. Responses and progression will be assessed using RECIST 1.1 by BICR.

CBR – CBR is defined as the percentage of participants who have achieved SD of ≥6 months or CR or PR based on assessments by BICR per RECIST 1.1.

OS – OS is defined as the time from randomization to death due to any cause.

9.4.2 Safety Endpoints

A description of safety endpoint assessment is provided in Section 4.2.1.2. Assessments include, but not limited to, the incidence of, causality of, and outcome of AEs/SAEs; and changes in laboratory values.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The ITT population will serve as the population for primary efficacy analyses. All randomized participants will be included in this population. Participants will be included in the treatment arm to which they are randomized.

9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population.

At least 1 laboratory or vital sign measurement obtained after 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.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP. If there are a small number of responses/events in 1 or more strata, for the purpose of analysis strata will be combined to ensure sufficient number of responses/events in each stratum. Details regarding the combining of strata will be specified in the sSAP.

9.6.1.1 Objective Response Rate

The stratified Miettinen and Nurminen's method will be used for comparison of the ORR between the 2 belzutifan doses. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported. The stratification factors used for randomization (See Section 6.3.2) will be applied to the analysis.

Sensitivity analyses will be performed to assess ORR based on investigator's assessment.

9.6.1.2 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment arm. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to the stratified Cox model.

Since disease progression is assessed periodically, disease progression can occur any time in the time interval between the last assessment where disease progression was not documented and the assessment when disease progression is documented. The true date of disease progression will be approximated by the earlier of the date of the first assessment at which disease progression is objectively documented per RECIST 1.1 by BICR and the date of death. Death is always considered a confirmed disease progression event.

For the primary analysis, any participant who experiences an event (disease progression or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment before the missed visits. In addition, any participant who initiates new anticancer therapy will be censored at the last disease assessment before the initiation of new anticancer therapy. Participants who do not start new anticancer therapy and who do not experience an event will be censored at the last disease assessment. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

Additional supportive PFS sensitivity analyses may be performed. Details of sensitivity analyses will be provided in the sSAP.

Table 7 Censoring Rules for PFS

Situation	Date of Progression/Death or Censoring
Disease progression or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented disease progression or death
Disease progression or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment before the earlier date of ≥2 consecutive missed disease assessments and new anticancer therapy, if any
No disease progression and no death; new anticancer treatment is not initiated	Censored at last disease assessment
No disease progression and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment
PFS=progression-free survival.	

9.6.1.3 Duration of Response

If sample size permits, the nonparametric Kaplan-Meier method will be used to estimate the DOR curve in each treatment group; estimates of the percentage of participants still in response and 95% CIs at specific duration time points will be provided.

Sensitivity analyses will be performed to assess DOR based on investigator's assessment.

Censoring rules for DOR are summarized in Table 8.

For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responding participants who are alive, have not progressed, have not initiated new anticancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 8 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (Non-event)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (Non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment before ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (Non-event)
Death or progression after ≤1 missed disease assessments and before new anticancer therapy, if any	Disease progression or death	End of response (Event)

DOR=duration of response.

A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.

9.6.1.4 Clinical Benefit Rate

The difference in CBR between the 2 belzutifan doses and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported. The stratification factors used for randomization (See Section 6.3.2) will be applied to the analysis.

9.6.1.5 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the OS curve in each treatment arm. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to the stratified Cox model.

Participants without documented death at the time of analysis will be censored at the date the participant was last known to be alive.

9.6.1.6 Analysis Strategy for Key Efficacy Endpoints

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 9.

Table 9 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method	Analysis Population	Missing data approach
Primary Endpoint			
ORR • RECIST 1.1, BICR	Testing and estimation: stratified Miettinen and Nurminen method	ITT	Participants with missing data are considered nonresponders
Secondary Endpoints			
DOR • RECIST 1.1, BICR	Summary statistics using Kaplan-Meier method	Responders in ITT population	Censored at last assessment date
PFS • RECIST 1.1, BICR	• Estimation: Stratified Cox model with Efron's tie handling method • Summary statistics using Kaplan-Meier method	ITT	Censored at last assessment date
CBR • RECIST 1.1, BICR	Estimation: • Stratified Miettinen and Nurminen method	ITT	Participants with missing data are considered to be participants without CR, PR or SD
OS	• Estimation: Stratified Cox model with Efron's tie handling method • Summary statistics using Kaplan-Meier method	ITT	Censored at last date the participant was known to be alive

BICR=blinded independent central review; CBR=clinical benefit rate; CR=complete response; DOR=duration of response; ITT=intent-to-treat; ORR=objective response rate; CBR=clinical benefit rate; OS=overall survival; PFS=progression-free survival; PR=partial response; RECIST=Response Evaluation Criteria In Solid Tumors; SD=stable disease.

9.6.2 Statistical Methods for Safety Analyses

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

The safety analysis will follow a tiered approach (Table 10). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory and vital signs parameters are either prespecified as Tier-1 endpoints, or will be classified as belong to "Tier 2" or "Tier 3", based on the number of events observed.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute Tier 1 safety endpoints that will be subject to inferential testing for statistical significance.

There are no known AEs associated with participants with RCC for which determination of a p-value is expected to impact the safety assessment. Therefore, there are no Tier 1 events for this protocol.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the Miettinen and Nurminen method, an unconditional, asymptotic method [Miettinen, O. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least 10% of participants in any treatment group show the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups),SAEs (≥5% of participants in 1 of the treatment groups), Grade 2 to 5 anemia/decreased hemoglobin (>0% of participants in 1 of the treatment groups), Grade 2 to 5 hypoxia (>0% of participants in 1 of the treatment groups), and Grade 2 to 5 dyspnea (>0% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

Continuous measures such as changes from baseline in laboratory parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 10 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE (≥10% of participants in one of the treatment groups)	X	X
	Any serious AE (≥5% of participants in one of the treatment groups)	X	X
	Any Grade 3 to 5 AE (≥5% of participants in one of the treatment groups)	X	X
	Grade 2 to 5 anemia/decreased hemoglobin (>0% of participants in 1 of the treatment groups)	X	X
	Grade 2 to 5 hypoxia (>0% of participants in 1 of the treatment groups)	X	X
	Grade 2 to 5 dyspnea (>0% of participants in 1 of the treatment groups)	X	X
Tier 3	AEs, Specific AEs, SOCs		X
	Discontinuation due to AE		X
	Dose interruption due to AE		X
	Change from baseline results (laboratory, ECGs, Vital Signs)		X
AE=adverse event; ECG=electrocardiogram; SOC=system organ class; X=results will be provided.			

9.6.3 Demographics and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

No formal IA is planned.

Final analysis will be performed at least 6 months after the last participant is randomized.

9.8 Multiplicity

There will be no multiplicity adjustments.

9.9 Sample Size and Power Calculations

The study will randomize approximately 150 participants in a 1:1 ratio to the belzutifan 120 mg QD and belzutifan 200 mg QD arms. With 75 participants at each dose level, the study has ~83% power to detect a 20% difference in ORR between the 2 doses of belzutifan at the 5% type I error rate (one-sided) assuming that the ORR in the lower dose arm is 24%. A p-value of 5% approximately corresponds to 12% observed difference in ORR.

The sample size and power calculations were performed using EAST 6.4 and gsDesign 3.6.1 (R package).

9.10 Subgroup Analyses

The treatment effect of the primary endpoint will be estimated and/or plotted within each category of the following classification variables:

- IMDC risk category [IMDC prognostic score] (favorable [0] vs intermediate [1-2] vs poor [3-6]; favorable [0] vs intermediate plus poor [1-6])
- Number of prior TKI therapies: 0 vs 1 vs 2-3
- Geographic region (North America vs Western Europe vs Rest of the World)
- Age category (<65 vs ≥65 years)
- Sex (male vs female)
- Race (white vs non-white)
- Number of prior lines of therapy (1 vs 2 vs 3)

9.11 Compliance (Medication Adherence)

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

For each participant, percent compliance will be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should Be on Therapy}} \times 100\,\%$$

For participants who are followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from the first scheduled intervention day to the last scheduled intervention day. For participants who discontinue from the study permanently, the "Number of Days Should Be on Therapy" is the total number of days from the first scheduled intervention day to the last dose day.

Summary statistics will be provided on percent compliance by treatment group for the APaT population. Details of the calculations will be provided in the sSAP.

9.12 Extent of Exposure

Extent of exposure for a participant is defined as number of days in which the participant receives the study intervention. Summary statistics will be provided on extent of exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus

source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee (SAC)

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.5 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.

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

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

standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted for the time required to eliminate systemic exposure after the last dose of study intervention as noted in Section 5.1. The length of time required to continue pregnancy testing for study intervention is as follows:
    - Belzutifan: at least 30 days after the last dose of study intervention

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

Table 11 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes[a]	WBC count with Differential[a]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN or urea[b]	Potassium	AST/ SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Albumin	CO_2 or bicarbonate[c]	Chloride	Phosphorous
	Creatinine or CrCl[d]	Sodium	ALT/SGPT	Total protein
	Glucose	Calcium[e]	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, (bilirubin, urobilinogen, nitrite, leukocyte esterase) by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle stimulating hormone (as needed in women of nonchildbearing potential only) • Serum or urine hCG pregnancy test (as needed for WOCBP) • Serology (HIV antibody, HBsAg, and HCV antibody) as required by local health authority or institutional regulations. Refer to Appendix 7 for country-specific requirements. • Coagulation factors (PT or INR, and aPTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy.			

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CO_2=carbon dioxide; CrCl=creatinine clearance; GFR=glomerular filtration rate; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; RBC=red blood cell; SoA=Schedule of Activities; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

NOTES:

[a] Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.

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

[c] Performed only if considered the local standard of care.

[d] GFR (measured or calculated) or CrCl can be used in place of creatinine.

[e] Corrected calcium is needed at screening (this is used to determine IMDC criteria).

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

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

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

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

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

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

Events NOT meeting the AE definition

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

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

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

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

- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a 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.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

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

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

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

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

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

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

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

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

  - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

  - **Rechallenge:** Was the participant 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 their best clinical judgment, including consideration of the above elements.

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

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

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

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

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

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

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

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

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable for this study.

10.4.1 Definition of Device Event

Not applicable for this study.

10.4.2 Definition of Adverse Device Event

Not applicable for this study.

10.4.3 Definition of Medical Device Incident (Including Malfunction)

Not applicable for this study.

10.4.4 Documenting Device Events, Adverse Device Events, and Medical Device Incidents

Not applicable for this study.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

10.5.2 Contraception Requirements

Highly Effective Contraception Methods

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

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal from Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.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 before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

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10.7 Appendix 7: Country-specific Requirements

10.7.1 United Kingdom

Study Period	**Screening**		**Treatment Period**						**EOT**	**Notes**
Week	**Screening[a] (Visit 1)**		**Wk 1 Day 1**	**Wk 3 Day 1**	**Wk 5 Day 1**	**Wk 7 Day 1**	**Wk 9 Day 1**	**Wk 13+ Day 1[b]**	**DC**	
Visit Number	**1**		**2**	**3**	**4**	**5**	**6**	**7+**		
Scheduling Window (Days):	**–42 to -1**	**–28 to –1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of DC**	
Safety Procedures										
HIV testing	X									Testing is required.

a. All screening procedures should be performed within 42 days before treatment allocation, unless otherwise noted.

b. After Week 13, visits are to occur approximately every 4 weeks (~28 days) until documented disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

Section 5.2 Exclusion Criteria

20. Participant has a known history of HIV infection. Testing for HIV is required at screening.

Section 8.11.1 Screening

- Laboratory tests are to be performed within 10 days before the first dose of study intervention. An exception is HIV and hepatitis testing which may be performed up to 42 days before the first dose of study intervention.

Appendix 2 Clinical Laboratory Tests

Other Screening Tests: Serology (HIV antibody).

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ADL	activities of daily living
ADME	adsorption, distribution, metabolism, excretion
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APaT	All-Participants-as-Treated
aPTT	activated partial thromboplastin time
ARNT	aryl hydrocarbon receptor nuclear translocator
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BID	twice daily
BUN	blood urea nitrogen
CBR	clinical benefit rate
ccRCC	clear cell renal cell carcinoma
C_{max}	maximum concentration
CI	confidence interval
CL/F	clearance
CNS	central nervous system
CO_2	carbon dioxide
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE v5	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor deoxyribonucleic acid
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C_{trough}	trough plasma concentration
CYP	cytochrome P450
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	end of treatment
EPO	erythropoietin
ESMO	European Society for Medical Oncology
FA	final analysis
FBR	future biomedical research

Abbreviation	Expanded Term
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin embedded
FSH	follicle stimulating hormone
GBM	glioblastoma
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage colony-stimulating factor
GMR	geometric mean ratio
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HDPE	high-density polyethylene
HIF	hypoxia-inducible factor
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
iCRO	imaging CRO
ID	identification
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
KPS	Karnofsky performance status
LAM	lactational amenorrhea method
LLN	lower limit of normal
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	Non-investigational Medicinal Product

Abbreviation	Expanded Term
NSAE	nonserious adverse event
NSCLC	non–small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PD-1	programmed cell-death 1
pEFD	preliminary embryo-fetal development
PFS	progression-free survival
P-gp	P glycoprotein
PK	pharmacokinetic
PR	partial response
pRBC	packed red blood cells
PT	prothrombin time
PTT	partial thromboplastin time
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
Q24W	every 24 weeks
QD	once daily
RCC	renal cell carcinoma
RECIST	Response Criteria in Solid Tumors
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results Program
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIM	Site Imaging Manual
SNP	single-nucleotide polymorphism
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TK	toxicokinetic
TKI	tyrosine-kinase inhibitor
t_{max}	time to maximum concentration
UGT	uridine 5'-diphospho-glucuronosyltransferase-glucuronosyltransferase
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VHL	Von Hippel-Lindau disease
Vz/F	apparent volume of distribution
WBC	white blood cell
Wk	week
WOCBP	woman/women of childbearing potential

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