Official Protocol Title:	An Open-label, Randomized Phase 3 Study of MK-6482 Versus Everolimus in Participants with Advanced Renal Cell Carcinoma That Has Progressed After Prior PD-1/L1 and VEGF-Targeted Therapies
NCT number:	NCT04195750
Document Date:	14-NOV-2024

TITLE PAGE

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Protocol Title: An Open-label, Randomized Phase 3 Study of MK-6482 Versus Everolimus in Participants with Advanced Renal Cell Carcinoma That Has Progressed After Prior PD-1/L1 and VEGF-Targeted Therapies

Protocol Number: 005-09

Compound Number: MK-6482

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

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

NCT	NCT04195750
EU CT	2023-506635-15
EudraCT	2019-003444-72
WHO	Not applicable
UTN	Not applicable
IND	132,120
jRCT	jRCT2080225166

Approval Date: 14 November 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
6482-005-09	14-NOV-2024	To incorporate revised ECI guidelines within the protocol as Appendix 8. This replaces the previous standalone ECI Guidance document.
6482-005-08	19-MAR-2024	To add text to describe that PRO administration is no longer required as of 15-APR-2024.
6482-005-07	13-Jul-2022	Japan-specific amendment: To update the timing of statistical analyses, given longer than planned accrual and reduce the total number of interim analyses in the study.
6482-005-06	13-Jul-2022	To update the timing of statistical analyses, given longer than planned accrual and reduce the total number of interim analyses in the study.
6482-005-05	16-Feb-2021	Japan-specific amendment: To update contraception appendix to align with program wide requirements.
6482-005-04	16-Feb-2021	To update contraception appendix to align with program wide requirements.
6482-005-03	02-Jun-2020	Japan-specific amendment: To revise the Japan-specific safety run-in to gain a better understanding of PK exposure and safety in a larger sample size.
6482-005-02	14-May-2020	To provide an update of the preclinical toxicology section to reflect recent preclinical toxicology findings, provide inclusion/exclusion criteria clarifications and/or refinement, provide clarifications on the Schedule of Assessment procedures, and enact minor language changes throughout the protocol to provide clarifications and ensure consistency in language.
6482-005-01	18-Dec-2019	Japan-specific amendment: To add a safety run-in component for Japan to ensure the correct dose of belzutifan is used in that participant population.
Original Protocol	30-SEP-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 09

Overall Rationale for the Amendment:

To incorporate revised ECI guidelines within the protocol as Appendix 8. This replaces the previous standalone ECI Guidance document.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 10.8, Appendix 8: Belzutifan ECI Guidance	Added new appendix regarding belzutifan ECI guidance.	Strategy change: To incorporate revised belzutifan ECI guidelines within the protocol as Appendix 8. This replaces the previous standalone ECI Guidance document.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Throughout	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.
Section 4.4, Beginning and End-of-Study Definition	Added that the last participant enrolling in an extension study also is considered end of study.	To include if an extension study becomes available to transfer participants onto.
	Added end of study for reporting purposes information.	See rationale above.
	Added beginning of study definition per EEA requirements.	See rationale above.
Section 6.5, Concomitant Therapy	Added text that inhibitors of UGT2B17 or CYP2C19 may increase plasma exposure of belzutifan and may impact hormonal contraceptives.	Inhibitors of these pathways could potentially increase plasma exposure of belzutifan.
	Added text that inhibitors of UGT2B17 or CYP2C19 may increase plasma exposure of belzutifan.	See rationale above.
Section 6.6.1, Belzutifan Dosing Modifications	Updated reference from ECI guidance document to Appendix 8.	See rationale for primary reason for amendment.
	Table 3 (Other nonlaboratory toxicity) – added that weight increased is not included as a Grade 3 toxicity requiring dose modification.	To align with prescribing information in which weight gain is a belzutifan ADR and does not require dose modification for Grade 3.
Section 6.6.1.1, Management of Anemia	Specified that transfusion can also be used to manage anemia in participants receiving belzutifan.	Anemia is an ADR of belzutifan; text added to provide greater clarification on potential options to manage anemia.

Section Number and Name	Description of Change	Brief Rationale
Section 6.6.1.2, Management of Hypoxia	Deleted NCI CTCAE v5.0 definition of hypoxia.	To remove unneeded text.
	Added text regarding diagnosis and management of hypoxia which should follow CTCAE v5 and the guidance in Table 3 and ECI guidance in Appendix 8.	To provide further details on resources for hypoxia diagnosis and management.
Section 8.4.3, Follow-up of AE, SAE, and Other Reportable Safety Event Information	Removed text indicating that all AEs require follow-up until resolution.	Revised for clarity as only AEs meeting certain criteria must be followed until resolution.
Section 8.4.4, Regulatory Reporting Requirements for SAE	Added text regarding reporting of SUSARS by the Sponsor in compliance with CTR 536/2014.	Per HA requirements.
Section 8.4.7, Events of Clinical Interest	Clarified that the events listed in ECI #b are DILI events.	To ensure that the laboratory abnormality events in ECI #b are captured correctly as DILI events.
	ECI Criterion #c: Grade level revised to Grade ≥3.	To align with ECI guidelines in new Appendix 8.
	ECI Criterion #d: Grade level revised to Grade ≥3	See rationale above for ECI Criterion #c.
	ECI Criterion #e (dyspnea): removed.	See rationale above for ECI Criterion #c.
	Former ECI criterion #f renumbered to current criterion #e.	To align numbering after removal of ECI Criterion #e.
	ECI Criterion #g (former numbering; ≥Grade 4 AEs all causality): removed.	See rationale above for ECI Criterion #c.
Section 8.5, Treatment of Overdose	Revised wording to remove that belzutifan interruption is required.	Belzutifan interruption is not always required in the event of overdose.
Section 10.1.3, Data Protection	Changed his/her to their.	To use gender neutral language
	Added that Sponsor also adheres to EU privacy rules.	See rationale for Section 8.4.4.
Section 10.1.6 Compliance with Study Regulation and Results Posting Requirements	Updated text pertaining to EU compliance regulation.	See rationale for Section 8.4.4.
Section 10.1.8, Data Quality Assurance	Added example of EU CTR retention period.	See rationale for Section 8.4.4.
Section 10.9, Appendix 9: Abbreviations	Former Appendix 8 renumbered to current Appendix 9.	Due to addition of new Appendix 8.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-label, Randomized Phase 3 Study of MK-6482 Versus Everolimus in Participants with Advanced Renal Cell Carcinoma That Has Progressed After Prior PD-1/L1 and VEGF-Targeted Therapies

Short Title: An Open-label, Randomized Phase 3 Study of Belzutifan Versus Everolimus in Participants With Advanced Renal Cell Carcinoma After Prior Therapy

Acronym: MK-6482-005

Hypotheses, Objectives, and Endpoints:

This study will be conducted in male and female participants with advanced clear cell RCC.

Primary Objectives	**Primary Endpoints**
To compare belzutifan to everolimus with respect to PFS per RECIST 1.1 as assessed by BICR. Hypothesis (H1): Belzutifan is superior to everolimus with respect to PFS per RECIST 1.1 by BICR.	PFS: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Objective: To compare belzutifan to everolimus with respect to OS. Hypothesis (H2): Belzutifan is superior to everolimus with respect to OS.	OS: the time from randomization to death due to any cause
Secondary Objectives	**Secondary Endpoints**
Objective: To compare belzutifan to everolimus with respect to ORR based on RECIST 1.1 as assessed by BICR. Hypothesis (H3): Belzutifan increases ORR according to RECIST 1.1 by BICR compared to everolimus.	OR: CR or PR
Objective: To evaluate the 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 safety and tolerability of belzutifan compared to everolimus.	• AEs • Study intervention discontinuation due to AEs

Objective: To evaluate TTD and change from baseline in HRQoL using the EORTC QLQ-C30 and the FKSI-DRS.	PRO scores for the following domains: • EORTC QLQ-C30 global health status/HRQoL (Items 29 and 30) • EORTC QLQ-C30 physical functioning (Items 1-5) • FKSI-DRS Subscale (Items 1-9)
Objective: To characterize health utility as measured using the EuroQoL EQ-5D-5L.	Health utility scores from the EQ-5D-5L

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Renal cell carcinoma
Population	Participants with unresectable, locally advanced, or metastatic RCC after prior therapy
Study Type	Interventional
Intervention Model	Parallel This is a multisite study.
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5.5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 736 participants will be randomized.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use
Belzutifan	Belzutifan	40 mg tablet	120 mg	Oral	QD	Test Product
Everolimus	Everolimus	10 mg tablet	10 mg	Oral	QD	Comparator

Abbreviations: QD=once daily.
Belzutifan: 120 mg dose should be made up of 3 × 40 mg tablets.
Everolimus: 2.5 mg and 5 mg tablets are provided for dose reductions as outlined in Section 6.6.2.

Other current names for study interventions are as follows: belzutifan/PT2977/MK-6482/ and everolimus/Afinitor®.

Total Number of Intervention Groups/Arms	2
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 or everolimus 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). 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, lost to follow-up, or the 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:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Scientific Advisory Committee	Yes

Study governance considerations are outlined in Appendix 1.

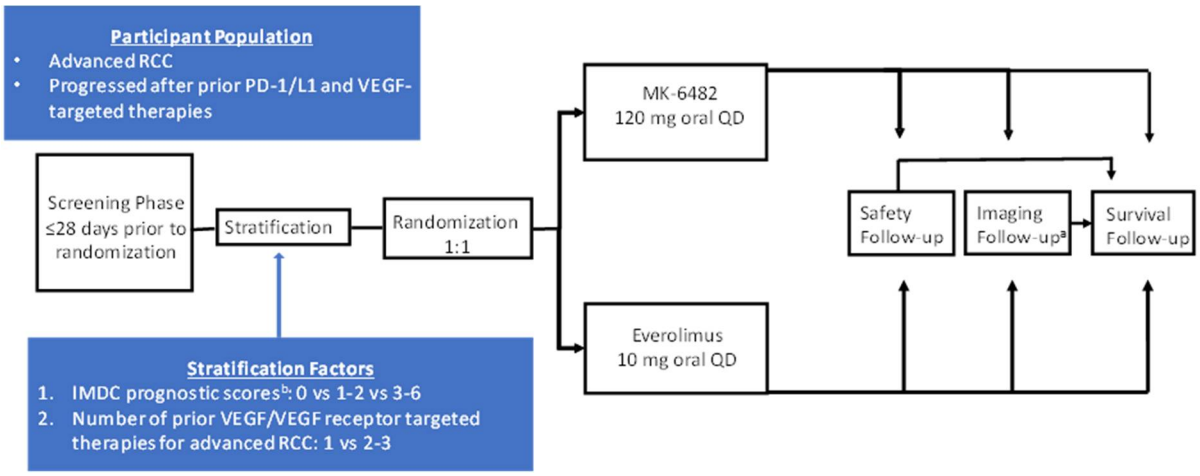
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1. Refer to Appendix 7 for country-specific requirements.

Figure 1 Study Design



Abbreviations: BICR = blinded independent central review; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; QD = once daily; RCC = renal cell carcinoma; VEGF = vascular endothelial growth factor.

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

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

1.3 Schedule of Activities

Study Period	**Screening**	**Treatment Period**					**EOT**	**Posttreatment**			**Notes**
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
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.
Inclusion/ exclusion criteria	X										
Participant ID card	X	X									At Week 1, site personnel should add the allocation number to the Participant ID card.

Study Period	**Screening**	**Treatment Period**					**EOT**	**Posttreatment**			**Notes**
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
Demographics and medical history	X										Medical history includes smoking, alcohol, and surgical history.
Cancer history	X										
Prior/concomitant medication review	X	X	X	X	X	Q4W	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 should be recorded for SAEs as outlined for AE monitoring timeframes below.
Randomization		X									Participants may be randomized up to 3 days prior to initiation of study intervention[a] and after confirmation of eligibility. All procedures and assessments performed on Week 1 Day 1 should be performed after randomization.

Study Period	**Screening**	**Treatment Period**					**EOT**	**Posttreatment**			**Notes**
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
Subsequent antineoplastic therapy status							X	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.
Survival status		<----------				---------->				X	Continued after investigator determined disease progression or start of new anticancer treatment. In addition, on Sponsor request, participants may be contacted for survival status at any time during the study.

Study Period	**Screening**	**Treatment Period**					**EOT**	**Posttreatment**			**Notes**
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
Administration of Study Intervention											
Belzutifan dispensing		X		X	X	Q4W					Participants will hold dosing of belzutifan on regularly scheduled clinic visit days until after completion of blood collection. The time of ingestion of belzutifan will be recorded and subsequent time-dependent procedures should be performed relative to the ingestion time.
Everolimus dispensing		X		X	X	Q4W					
Review study intervention compliance			X	X	X	Q4W	X				At Week 3 Day 1, a tablet count will not be performed.

Study Period	**Screening**	**Treatment Period**					**EOT**	**Posttreatment**			**Notes**
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
Efficacy Procedures											**Imaging should continue to be performed until disease progression is documented by the investigator and verified by BICR, initiation of new anticancer treatment, withdrawal of consent, pregnancy, death, or the 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 prior to randomization. First on-study imaging should be performed at 8 weeks from randomization (±7 days) then Q8W through Week 49 then Q12W (±7 days) thereafter (Section 8.2.1.2). All imaging visits on study will have a visit window of ±7 days (± 14 days after Week 109) Refer to Section 8.2.1.2.

Study Period	**Screening**	**Treatment Period**					**EOT**	**Posttreatment**			**Notes**
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
Bone imaging[e]	X[e]	X[e]					X[e]		X[e]		Screening images are to be captured within 28 days prior to randomization[e]. All imaging visits on study will have a visit window of ±7 days.
Brain imaging[f]	X[f]	X[f]					X[f]				Screening images are to be captured within 28 days prior to 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	Screening	Treatment Period					EOT	Posttreatment			Notes
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
Safety Procedures											
AE monitoring	X	X	X	X	X	Q4W	X	X	X		Any AEs noted prior to ICF should be recorded as medical history. AEs that occur within 30 days of the end of treatment or before initiation of a new anticancer treatment should be followed and recorded. SAEs should be reported from the time of intervention allocation through 90 days after cessation of study intervention or 30 days following 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	**Screening**	**Treatment Period**					**EOT**	**Posttreatment**			**Notes**
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
Directed physical examination		X	X	X	X	Q4W		X			Directed physical examination performed as clinically indicated prior to 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	Q4W	X	X			Vital signs will be obtained prior to study intervention administration on Week 1 Day 1. Pulse oximetry will be measured each time vital signs are taken, using a Sponsor supplied pulse oximeter. If Sponsor-provided pulse oximeter is unavailable, a local device may be used. All blood pressure measurements should be taken after the participant has rested in a seated position for at least 3 minutes.

Study Period	**Screening**	**Treatment Period**					**EOT**	**Posttreatment**			**Notes**
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
12-lead ECG	X	X	X	X	X	Q8W	X	X			Single 12-lead ECG. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. All ECGs should be prior to or no less than 60 minutes after blood draw. Additional assessments should be performed if clinically indicated.
EPO	X										EPO levels will be measured ≤10 days prior to randomization in all participants and should be measured prior to initiating EPO replacement therapy. EPO level to be measured by local laboratory.
Hematology	X	X	X	X	X	Q4W	X	X			All screening laboratory tests should be performed within 10 days prior to randomization. All tests should be performed by the central laboratory.

Study Period	**Screening**	**Treatment Period**					**EOT**	**Posttreatment**			**Notes**
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
Chemistry	X*	X*	X	X	X*	Q4W	X	X			All screening laboratory tests should be performed within 10 days prior to randomization. All tests should be performed by the central laboratory. *Fasting for ≥8 hours at screening, Week 1 Day 1, and every 8 weeks thereafter. There are no fasting restrictions for assessments at other time points.
Urinalysis	X				X	Q8W	X	X			To be performed locally.
Karnofsky performance status	X										KPS performance status is collected at screening only and should be within 10 days prior to randomization.
ECOG performance status	X	X	X	X	X	Q4W	X	X			ECOG performance status at screening should be within 10 days prior to randomization.
HBV, HCV, and HIV testing	X										Not required unless mandated by local health authorities. If mandated, conduct locally.

Study Period	Screening	Treatment Period					EOT	Posttreatment			Notes
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
Urine or serum β-hCG - WOCBP only	X	X		X	X	Q4W	X	X			Female participants of childbearing potential will have a serum or highly sensitive urine pregnancy test within 1 day prior to randomization. If more than 1 day has elapsed between the screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed within 24 hours of first dose and must be negative in order for the participant to start receiving study medication. Pregnancy tests will be conducted locally.
PT or INR and aPTT	X	X		X	X	Q4W	X	X			Screening samples will be collected within 10 days prior to randomization. All tests should be performed by the central laboratory. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.

Study Period	Screening	Treatment Period					EOT	Posttreatment			Notes
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
Patient-reported Outcomes											**PROs are to be administered in the order listed, prior to all assessments/procedures**
FKSI-DRS		X	X	X	X	Q4W	X	X			Every effort should be made to administer PRO surveys on site prior to dosing and before other assessments and procedures. As of 15-APR-2024, PROs will no longer be required.
EORTC QLQ-C30		X	X	X	X	Q4W	X	X			
EuroQoL EQ-5D-5L		X	X	X	X	Q4W	X	X			
Pharmacokinetics/ Pharmacodynamics/ Biomarkers											
CCI [redacted]											

Study Period	Screening	Treatment Period					EOT	Posttreatment			Notes
Visit:	Screening[a]	Wk 1 Day 1[a]	Wk 3 Day 1	Wk 5 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	±5	At time of DC	30 Days After Last Dose (+7 days)	Q8W or Q12W (±7 days)	Q12W (±7 days)	Refer to Appendix 7 for country-specific requirements
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Study Period	Screening	Treatment Period					EOT	Posttreatment			Notes
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	**Refer to Appendix 7 for country-specific requirements**
Archival or newly obtained tissue collection	X										Tumor tissue (archival or newly acquired core or excisional biopsy) will be obtained at screening. Tumor blocks are preferred over cut slides (refer to the study laboratory manual for important details regarding tumor tissue submission time window and process). If submitting unstained cut slides, newly cut slides will be submitted to the testing laboratory (details pertaining to tumor tissue submission can be found in the study laboratory manual).

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; β-hCG = β-human chorionic gonadotropin; BICR = blinded independent central review; CBC = complete blood count; CR = complete response; CT = computed tomography; CCI [redacted]; DC = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire 30; EOT = end-of-treatment; EQ-5D-5L = EuroQoL-5 dimensions-5 levels; FKSI-DRS = Functional Assessment of Cancer Therapy – Kidney Symptom Index-disease-related symptoms; 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; PRO = patient-reported outcome; PT = prothrombin 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 treatment, which should be on the date of randomization, but can be within 3 days following 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, contact, medical record review, etc. Participant status information includes survival 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 verified by BICR. 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 verified by BICR should continue with imaging assessments per the protocol-defined schedule until: 1) disease progression is verified by BICR, 2) initiation of a new anticancer treatment, 3) pregnancy, 4) death, 5) withdrawal of consent, or 6) the end of the study, whichever occurs first.

e. Baseline bone scan is required for all participants at screening. Bone scans are not required to be repeated at screening if performed within 42 days prior to 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) until disease progression is verified by BICR. 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. Samples for PK analyses will be collected only from participants randomized to belzutifan. The Week 1 Day 1 dose should be taken fasted (minimum of 2 hours fasting predose); food should be withheld for 1-hour postdose. A window of 30 minutes is permitted for all time points at which samples are collected.

   A blood sample for PK assessments will be obtained on:

   - Week 1 Day 1: at predose, 1, 2 and 4 hours postdose.
   - On Week 3 Day 1, and Week 5 Day 1: participants will hold dosing of belzutifan tablets, until taken in the clinic.
     - A blood sample will be collected predose.
     - If a participant has a treatment interruption or discontinues treatment prior to 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. A blood sample for pharmacodynamic assessments will be obtained on:

   - Week 1 Day 1 at predose, 1, 2 and 4 hours postdose (Postdose collections should only be from participants randomized to belzutifan); a window of 30 minutes is permitted.
   - Week 3 Day 1, and Week 5 Day 1, participants will hold dosing of belzutifan tablets, until taken in the clinic.
     - Week 3 and Week 5 Day 1, a blood sample will be collected predose. If a participant has a treatment interruption or discontinues treatment prior to 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 HIF-2α inhibitor, belzutifan, versus everolimus in participants with advanced RCC after prior therapy.

2.1 Study Rationale

2.1.1 Rationale for the Study of Belzutifan in Renal Cell Carcinoma

The hypoxia-inducible factor, HIF-2α, is believed to play a critical role in tumorigenesis and tumor progression in RCC. Belzutifan (MK-6482, formerly known as PT 2977) 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 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].

2.2 Background

2.2.1 Renal Cell Carcinoma

Renal cancers will be diagnosed in an estimated 400,000 patients worldwide each year and approximately 175,000 patients are expected to die of the disease [Bray, F., et al 2018]. RCC, an aggressive cancer, accounts for approximately 85% of all kidney cancers [National Comprehensive Cancer Network 2019]. RCC is a heterogeneous disease and comprises many distinct histologies with ccRCC, accounting for approximately 80% of all cases[Leibovich, B. C., et al 2010].

A substantial proportion of patients with RCC progress to advanced stage disease; about one-third of patients with RCC present with unresectable disease or metastases 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%. Prognostic factors for survival among RCC patients include tumor stage, grade, presence of regional or nodal metastases, and evidence of metastases at presentation [National Comprehensive Cancer Network 2019]. Common metastatic sites among patients with RCC include lung, lymph nodes, bone, liver, adrenal gland, and brain [Bianchi, M., et al 2012].

2.2.2 Hypoxia-inducible Factor and Renal Cell Carcinoma

HIF-2α is a transcription factor that regulates the body's response to diminished availability of oxygen. HIF-2α activity is mediated by the activity of prolyl hydroxylase enzymes, which use oxygen to add hydroxyl groups to HIF-2α when oxygen availability is high ("normoxia"). The VHL tumor suppressor protein recognizes this modified form of HIF-2α, binds to it and targets it for degradation. Due to its efficient degradation, HIF-2α protein and activity levels are typically low under normoxia. Under hypoxia, the degradation system is inactive, and HIF-2α transcriptional activity is enhanced. This leads to the expression of a

variety of proteins, including factors associated with the production of new RBCs and the formation of new blood vessels.

In RCC, the VHL tumor suppressor is inactivated in the vast majority of patients. This defect in the ubiquitin-proteasome system results in the abnormal over accumulation and activation of HIF-2α. The aberrant activation of HIF-2α is a key oncogenic driver in RCC as it leads to excessive blood vessel growth, cell proliferation and other ill effects.

Refer to the IB for detailed background information on belzutifan.

2.2.3 Current Treatment Options

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 commonly 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. 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.

2.2.4 Pharmaceutical and Therapeutic Background

Belzutifan is a small molecule inhibitor of HIF-2α.

2.2.4.1 Pharmacology

Belzutifan is a potent and selective inhibitor of HIF-2α both in vitro and in vivo. HIF-2α is known to form a heterodimeric complex with HIF-1β, which is also referred to as ARNT; the heterodimer can then bind to hypoxic response elements in target genes and induce their transcription. The PAS domains of HIF are essential for heterodimerization of the HIF-

2α:HIF-1β subunits, a prerequisite for target gene induction. A unique ligand-binding pocket has been identified in the PAS-B domain of HIF-2α [Scheuermann, T. H., et al 2013]. Belzutifan binds in this pocket, thereby disrupting HIF-2α:HIF-1β heterodimerization and directly inhibiting the function of HIF-2α.

In tumor cells in which HIF-2α is activated, belzutifan blocks the transcription of several genes involved in oncogenesis, including cyclin D1, VEGF-A, and the glucose transporter SLC2A1. CCI

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2.2.5 Preclinical Studies

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2.2.5.2 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.

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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.

A summary of belzutifan nonclinical toxicology is contained in the IB. The IB should be reviewed in conjunction with this study protocol.

2.2.6 Clinical Studies

As of 06-SEP-2019, a total of 34 healthy volunteers and 185 patients had been treated with belzutifan in 5 ongoing 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 and 9 patients with GBM in the dose expansion cohort (Part 1B) 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.

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. 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, 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 t1/2 in the 120 mg QD expansion cohort (Part 1B) on Day 15 was 15.4 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 estimated Vz/F was 106 to 266 L, which suggests extensive distribution to peripheral tissues. The CV was 32 to 59% for C_{max} and 24 to 48% for AUC after a single dose, and 27 to 56% for C_{max} and 30 to 64% for AUC at steady state. 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 11 participants (20%) with PR and 32 participants (58%) with SD as assessed by RECIST v1.1.

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.

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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).

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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.

Preclinical toxicology results for belzutifan are summarized in Section 2.2.5.2. Recent preclinical findings in rats suggest that belzutifan may cause embryo-fetal lethality in humans. 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 in Section 10.5 through 10.5.2 (Appendix 5).

The proposed study will enroll participants with advanced RCC who have progressed after prior therapy. As described in Section 2.2.4.1, belzutifan is a potent and selective inhibitor of HIF-2α in preclinical studies and clinical data as described in Section 2.2.6 show antitumor activity of belzutifan, which warrants further investigation. As described in Section 2.2.6, the most common AE of ≥Grade 3 toxicity occurring in 5% or more of the participants studied have been fatigue, anemia, and hypoxia. These AEs have frequently occurred in conjunction with acute comorbid conditions such as pneumonia, pleural effusion, etc. and have responded to appropriate management. Further guidance on the management of these AEs and dosing is provided in Sections 6.6.1, 6.6.1.1, and 6.6.1.2.

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.

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

This study will be conducted in male and female participants with advanced clear cell RCC.

Primary Objectives	**Primary Endpoints**
To compare belzutifan to everolimus with respect to PFS per RECIST 1.1 as assessed by BICR. Hypothesis (H1): Belzutifan is superior to everolimus with respect to PFS per RECIST 1.1 by BICR.	PFS: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Objective: To compare belzutifan to everolimus with respect to OS. Hypothesis (H2): Belzutifan is superior to everolimus with respect to OS.	OS: the time from randomization to death due to any cause
Secondary Objectives	**Secondary Endpoints**
Objective: To compare belzutifan to everolimus with respect to ORR based on RECIST 1.1 as assessed by BICR. Hypothesis (H3): Belzutifan increases ORR according to RECIST 1.1 by BICR compared to everolimus.	OR: CR or PR
Objective: To evaluate the 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 safety and tolerability of belzutifan compared to everolimus.	• AEs • Study intervention discontinuation due to AEs
Objective: To evaluate TTD and change from baseline in HRQoL using the EORTC QLQ-C30 and the FKSI-DRS.	PRO scores for the following domains: • EORTC QLQ-C30 global health status/HRQoL (Items 29 and 30) • EORTC QLQ-C30 physical functioning (Items 1-5) • FKSI-DRS Subscale (Items 1-9)
Objective: To characterize health utility as measured using the EuroQoL EQ-5D-5L.	Health utility scores from the EQ-5D-5L

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
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4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, open-label, multicenter, randomized, active-controlled study to compare the efficacy and safety of belzutifan with that of everolimus in participants with advanced RCC that has progressed after prior PD-1/L1 and VEGF-targeted therapies.

Approximately 736 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 belzutifan or everolimus (~368 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 within 28 days before randomization, but can occur earlier 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 VEGF/VEGF receptor targeted therapies for advanced RCC: 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 48 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 BICR-verified 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 confirmed disease progression will continue with all protocol-required assessments and procedures.

Crossover between treatment arms is not planned.

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 following 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 following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier.

Study intervention will continue until documented disease progression (BICR-verified disease progression), unacceptable AEs, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, participant withdrawal of consent, pregnancy of the participant, 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 BICR-verified disease progression should continue with imaging assessments as described in the SoA and Section 8.2.2. Following verification of disease progression, all participants will be followed for survival (in-person visit, telephone contact, medical record review, etc.) until death, withdrawal of consent, lost to follow-up, or until the study is concluded or terminated early, whichever occurs first.

Two IAs are planned in addition to the FA for this study. The analyses planned, endpoints evaluated, and drivers of timing are summarized in Section 9.7.

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

Refer to Appendix 7 for country-specific requirements.

4.2 Scientific Rationale for Study Design

This study uses an open-label design similar to what has been used in 2 pivotal randomized Phase 3 studies in advanced RCC, which compared axitinib to sorafenib (AXIS) and cabozantinib to everolimus (METEOR) [Rini, B. I., et al 2011] [Choueiri, T. K., et al 2016].

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. Investigators are to continue study treatment, to repeat radiographic studies at the next scheduled time, and to delay determination of progression until the findings indicating progression are unequivocal per BICR assessment.

Belzutifan and everolimus each have unique safety profiles that may result in the participants experiencing different AEs that may disclose the treatment invention received if the study was blinded.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The dual primary objectives of this study are to evaluate the efficacy of belzutifan compared with everolimus for the treatment of advanced RCC as assessed by PFS as determined by

BICR and by OS. A meta-analysis of 31 studies including 10,943 patients that studied the relationship between PFS and OS in metastatic RCC concluded that in RCC, the treatment effects on PFS are strongly associated with treatment effects on OS [Delea, T. E., et al 2012]. To ensure that PFS is rigorously evaluated, PFS will be determined by a BICR that will review all radiographic studies. The BICR will be blinded to study treatment.

This study will also use ORR and DOR as secondary endpoints. Efficacy will be evaluated using RECIST 1.1 for PFS, ORR, and DOR, determined by BICR.

PFS and ORR are acceptable measures of clinical benefit for a late stage 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 PFS and ORR 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. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Expedited verification of radiologic progression as determined by central review will be communicated to the site.

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

DOR is considered an acceptable measure of clinical benefit when considered with ORR.

4.2.1.2 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the investigator when determining eligibility and for all protocol guidelines related to disease status (eg, discontinuation of study intervention). The RECIST 1.1 assessment of disease progression is used as a basis for discontinuation of treatment.

4.2.1.3 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 CTCAE, Version [5.0].

4.2.1.4 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. As part of the analyses for this study, HRQoL and disease-related symptoms will be investigated among all participants via the FKSI-DRS, EORTC QLQ-C30, and EuroQoL EQ-5D-5L questionnaires. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and study intervention tolerability. The EQ-5D-5L will also be used to calculate health utilities for health economic models.

FKSI-DRS

The FKSI-DRS is a patient-reported instrument that measures whether the patient has experienced any of the following 9 kidney cancer-related symptoms: lack of energy, fatigue, weight loss, pain (general), bone pain, shortness of breath, cough, fever, or blood in the urine [Cella, D., et al 2007]. Each item is scored by using the following 5 response categories: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much. All 9 questions are negatively stated items; according to the scoring manual, the score for each item must be reversed by subtracting the response from "4". Participant responses to all FKSI-DRS items are summed to generate a summary symptom score ranging from 0 to 36, with higher scores indicating improved (more favorable) symptom status. The FKSI-DRS is a reliable, valid, and responsive brief index of the most important symptoms associated with advanced kidney cancer.

EORTC QLQ-C30

The EORTC QLQ-C30 was developed to assess the QoL of participants with cancer. It has been translated and validated in over 100 languages and used in more than 3000 studies worldwide. It contains 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single symptom items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) [Aaronson, N. K., et al 1993]. It is scored on a 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). The EORTC QLQ-C30 instrument also contains 1 global health status/QoL scale that uses a 7-point scale scoring with anchors (1=very poor and 7=excellent).

EuroQoL EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome. The EQ-5D-5L will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions addressed in this instrument are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EuroQoL EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.5 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 steady state C_{trough} values. 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.

4.2.1.6 Pharmacodynamic Endpoints

Assessment of serum EPO levels and other pharmacodynamic markers will be performed by the Sponsor or designee using a validated method.

4.2.1.7 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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[redacted]

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 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. Ct DNA and/or RNA may also be evaluated from blood samples.

Tumor and blood RNA analyses

CCI [redacted]

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 only from participants randomized to belzutifan. Pharmacodynamic biomarkers to be assessed include, but are not limited to, levels of EPO.

4.2.1.8 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator

Everolimus is indicated for advanced RCC after failure of treatment with sunitinib or sorafenib. In the Phase 3 randomized RECORD-1 study comparing everolimus or placebo in participants with metastatic RCC after treatment with sunitinib and/or sorafenib, everolimus was superior for PFS (4.9 months for everolimus vs 1.9 for placebo); there was no significant difference in OS between treatments. An analysis of data from an international consortium of 25 cancer centers that provided data on 1,012 patients who had received third-line targeted therapy showed that, although a wide spectrum of targeted therapies was used in the third-line setting, everolimus was the most prevalent third-line therapy used in 28% of patients [Wells, J. C., et al 2017]. Other agents included sunitinib, sorafenib, pazopanib,

temsirolimus, and axitinib, which were used in between 9% and 13% of patients. Based on the findings that everolimus is frequently used in late-line settings including the intended patient population for this study, everolimus was chosen as the appropriate comparator in this Phase 3 study. Use of everolimus as the comparator allows treatment by agents with different therapeutic targets (ie, HIF-2α or mTOR) than the patient's prior therapies that have targeted the immune system and VEGF/VEGF receptor. The use of everolimus in this study's participant population is in accordance with established clinical practice guidelines [Escudier, B., et al 2019] [National Comprehensive Cancer Network 2019].

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

The dose of belzutifan used in this study is 120 mg QD and is the optimum dose based on previous clinical study experience as described in Section 2.2.6.

The dose of everolimus used in this study is 10 mg QD and is the current approved dose.

4.3.2 Maximum Dose Exposure for This Study

There is no maximum duration of exposure for belzutifan or everolimus.

4.4 Beginning and End-of-Study Definition

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

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

4.4.1 Clinical Criteria for Early Study Termination

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 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. Has unresectable, locally advanced or metastatic clear cell RCC.
2. Has measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions.

Prior Therapy

3. Has had disease progression on or after having received systemic treatment for locally advanced or metastatic RCC with both: PD-1/L1 checkpoint inhibitor and VEGF-TKI in sequence or in combination.
   - PD-1/L1 checkpoint inhibitor 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 PD during or after an anti-PD-1/L1 mAb
   - VEGF-TKI treatment progression is defined by meeting the following criteria:
     - Has demonstrated radiographic PD during or after a treatment with a VEGF-TKI
4. Has received no more than 3 prior systemic regimens for locally advanced or metastatic RCC.
5. For the most recently received regimen, has demonstrated radiographic disease progression.

Demographics

6. Is male or female, who is at least 18 years of age at the time of signing the informed consent.
7. Has a KPS score of at least 70% assessed within 10 days prior to randomization.

Male Participants

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

8. 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.

Female Participants

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

9. 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 for those randomized to the belzutifan study intervention and for at least 8 weeks after last dose of study intervention for those randomized to the everolimus arm. 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) 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 test is positive.
   - Additional requirements for pregnancy testing during and after study intervention are in the Schedule of Activities.
   - 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.

Informed Consent

10. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the main study without participating in FBR. Refer to Appendix 7 for country-specific requirements.

Additional Categories

11. Has adequate organ function, as detailed in Table 1; all screening laboratory tests should be performed within 10 days prior to randomization. Screening laboratory tests should be fasting for >8 hours. Note: Participant cannot have received colony-stimulating factors (eg, G-CSF, GM-CSF or recombinant EPO) or packed RBC transfusion ≤28 days prior to hemoglobin assessment. Refer to Appendix 7 for country-specific requirements.

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
Renal	
Serum creatinine or estimated CrCl using the Cockcroft-Gault equation, or based on a 24-hour urine test[a] (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥51 mL/min for participants with creatinine levels >1.5 x 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
Fasting serum triglycerides and total cholesterol	≤2.5 x ULN AND total cholesterol ≤300 mg/dL (≤7.75 mmol/L). Lipid-lowering medication is allowed
Fasting Glucose	a fasting glucose ≤160 mg/dL (≤8.9 mmol/L) is required

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. Estimated creatinine clearance using Cockcroft-Gault:

$$\frac{(140\text{-age [years]} \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} \quad (\times F)^*$$

*where F = 0.85 for females and F = 1 for males

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 meets any of the following criteria:

Medical Conditions

1. A WOCBP who has a positive urine pregnancy test within 24 hours prior to randomization (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
   Note: If more than 1 day has elapsed between the screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed within 24 hours before the first dose of study intervention and must be negative in order for the participant to start receiving study medication.
2. Has any of the following:
   - Hypoxia as defined by pulse oximeter reading <92% at rest, OR
   - Requires intermittent supplemental oxygen, OR
   - Requires chronic supplemental oxygen.
3. 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.
4. 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 randomization.
5. Has clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study medication administration, or New York Heart Association Class III or IV congestive heart failure. Medically controlled arrhythmia stable on medication is permitted.
6. Has poorly controlled hypertension defined as SBP ≥150 mm Hg and/or DBP ≥90 mm Hg.
7. Has moderate to severe hepatic impairment (Child-Pugh B or C).
8. Received colony-stimulating factors (eg, G-CSF, GM-CSF or recombinant EPO) within 28 days prior to randomization.
9. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.
10. Is unable to swallow orally administered medication or has a gastrointestinal disorder affecting absorption (eg, gastrectomy, partial bowel obstruction, malabsorption).

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

Prior/Concomitant Therapy

12. Has received prior treatment with belzutifan or another HIF-2α inhibitor.
13. Has received any prior treatment with everolimus or any other specific or selective TORC1/PI3K/AKT inhibitor (eg, temsirolimus) in the advanced disease setting.
14. Has received any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before randomization.
15. Has received any type of systemic anticancer antibody (including investigational antibody) within 4 weeks before randomization.
16. Has received prior radiotherapy within 2 weeks prior to randomization. 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.
17. Has had major surgery within 3 weeks prior to randomization. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
18. Has received a live vaccine within 30 days prior to the randomization of study medication. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®/Fluenz Tetra) are live attenuated vaccines and are not allowed.
19. Is currently receiving either strong (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) inhibitors of CYP3A4 that cannot be discontinued for the duration of the study.

    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

20. 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

21. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
22. Is currently receiving a drug that is an inhibitor of P-gp (eg, cyclosporin, elacridar, ketoconazole, quinidine, reserpine, ritonavir, tacrolimus, valspodar, verapamil, zosuquidar) that cannot be discontinued for the duration of the study.

    Note: A current list of inhibitors of P-gp can be found at the following website: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Prior/Concurrent Clinical Study Experience

23. 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 or 5 half-lives, whichever is longer (investigational antibody only requires 4 weeks after last dose).

Diagnostic Assessments

24. Has an active infection requiring systemic therapy.
25. Has active TB.
26. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior randomization. Exception: Replacement corticosteroid therapy for adrenal or pituitary insufficiency is allowed.
27. 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.

28. 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. Refer to Appendix 7 for country-specific requirements.

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.

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

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 (study intervention(s) provided by the Sponsor; local supply as needed) 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 interventions to be used in this study are outlined in Table 2.

Country-specific requirements are noted in Appendix 7.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Levels	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Belzutifan	Experimental	Belzutifan	Drug	Tablet	40 mg tablet	120 mg	Oral	QD	Test Product	IMP	Central
Everolimus	Active Comparator	Everolimus	Drug	Tablet	10 mg tablet	10 mg	Oral	QD	Comparator	IMP	Central; local supply as needed

Abbreviations: EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; QD=once daily.
Belzutifan: 120 mg dose should be made up of 3 × 40 mg tablets.
Everolimus: 2.5 mg and 5 mg tablets are provided for dose reductions as outlined in Section 6.6.2.
Note: The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

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

6.2.1.1 Belzutifan

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. Each bottle of study intervention will contain 90 tablets of a single strength of belzutifan (40 mg) and a desiccant insert.

The Pharmacy Manual contains additional information.

6.2.1.2 Everolimus

Everolimus will be available as 10-mg, 5-mg, and 2.5-mg tablets. Refer to the package insert for additional information. Everolimus is to be administered as the tablet formulation only; the suspension formulation is not to be used.

All dosages of everolimus (10-mg, 5-mg, and 2.5-mg) will be available in commercial packaging if locally sourced.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Treatment allocation will occur centrally using an IRT system. There are 2 study intervention treatment groups. Participants will be assigned randomly in a 1:1 ratio to belzutifan study intervention or everolimus study intervention.

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 VEGF/VEGF receptor targeted therapies for advanced RCC: 1 vs 2-3

The IMDC prognostic factors are the following:

- Clinical Risk Factors
  - Low KPS score (<80%)
  - 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, and only results from central laboratory testing will be considered for the laboratory factors.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

The investigator or his/her designated and qualified representatives will dispense study intervention (except locally sourced everolimus) 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 Weeks 1, 3, and 5 when belzutifan dosing will occur during the clinic visit.

All participants must bring back to the clinic their bottle(s)/packages of belzutifan/everolimus at the appropriate scheduled visit. 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 (if permitted) until reconciliation is completed by the study monitor, if possible.

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 prior to randomization and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered >30 days after the last dose of study intervention should be recorded for SAEs as 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 should also be included on the eCRF.

In vitro and physiologically based PK modeling results indicated that belzutifan is a weak inducer of CYP3A4. Belzutifan may, therefore, decrease the exposure of concomitant medications that are mainly metabolized by CYP3A4, including hormonal contraceptives; however, the clinical relevance of these effects is not clear. Inhibitors of UGT2B17 or CYP2C19 may increase plasma exposure of belzutifan, which may increase the incidence and/or severity of adverse reactions.

Everolimus is a substrate of CYP3A4 and of the multidrug efflux pump P-gp. Refer to the most current everolimus prescribing information about potential drug interactions and appropriate dosage adjustments.

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 symptomatic lesions or to the brain is allowed following Sponsor consultation.

4. Live vaccines while participating in the study. Refer to Appendix 7 for country-specific requirements.
    - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, intranasal seasonal influenza, rabies, BCG, and typhoid (oral).

      Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed

5. Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE. Corticosteroid replacement therapy for participants with adrenal or pituitary insufficiency is permitted. Note: Inhaled, intranasal, ophthalmologic, intra-articular or intrathecal steroid injections are permitted.
6. Use of strong inhibitors of CYP3A4 is not allowed on treatment. If a moderate CYP3A4 inhibitor or a moderate/strong CYP3A4 inducer is required during the study intervention treatment period for participants randomized to belzutifan consult with the Sponsor Clinical Director; for participants randomized to everolimus, refer to the everolimus package insert for guidance.
    - *Note: a current list of strong/moderate inducers/inhibitors of CYP3A4 can be found at the following website:* https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
7. P-gp inhibitors are not prohibited during the study intervention treatment period for participants randomized to belzutifan. If a P-gp inhibitor is required during the study intervention treatment period for participants randomized to everolimus, refer to the everolimus package insert for guidance.
    - *Note: a current list of P-gp inhibitors 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
8. ACE inhibitors are prohibited for those participants receiving everolimus, however, are not prohibited for participants receiving belzutifan.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from treatment, but continue in study for assessment of disease status and survival.

There are no prohibited therapies during the Survival Follow-up 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

6.6.1 Belzutifan Dosing Modifications

Guidelines for dose modification for belzutifan are listed in Table 3. Specific dose reduction levels are listed in Table 4.

The following should be considered in decisions regarding dose modifications:

- As a general approach, all AEs should be managed with supportive care at the earliest signs of toxicity considered related to belzutifan treatment. Should this be ineffective, dose reductions or interruptions should 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 of study treatment for >28 days will require Sponsor consultation.

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. Refer to the ECI Guidance (Appendix 8) for additional practice guidelines and management recommendations for AEs potentially related to belzutifan treatment.

Table 3 Dose Modification Guidelines for Belzutifan-related Toxicities

Belzutifan-related Toxicity		Action
Anemia	• Grade 4 anemia	• First episode: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by one level. • Second 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 one hour,) or • Grade 4 neutropenia for >5 days	• First and second episodes: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by one level. • Third episode: Permanently discontinue belzutifan.
	• Grade 4 febrile neutropenia	• Permanently discontinue belzutifan.
Thrombocytopenia	• Grade 3 thrombocytopenia with bleeding	• First and second episodes: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by one level. • Third episode: Permanently discontinue belzutifan.
	• Grade 4 thrombocytopenia	• First episode: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by one level. • Second 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)	• First and second episodes: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by one level. • Third episode: Permanently discontinue belzutifan.
	• Grade 4 dyspnea • Grade 4 hypoxia	• Permanently Discontinue belzutifan.
Gastrointestinal	• Grade 3 or 4 nausea, vomiting, or diarrhea if persistent for >48 hours despite optimal antiemetic or antidiarrheal therapy	• First and second episodes: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by one level. • Third episode: Permanently discontinue belzutifan.

Belzutifan-related Toxicity		Action
Hepatic	• Grade 3 increase in AST and/or ALT levels, if confirmed upon repeat testing within 48 hours	• First episode: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by one level. • Second episode: Permanently discontinue belzutifan.
	• Grade 4 increase in AST and/or ALT levels, if confirmed upon 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 Nonlaboratory Toxicities	• Any other nonlaboratory Grade 3 toxicity (excluding weight increased)	• First and second episodes: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by one level. • Third 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; ULN = upper limit of normal; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Re-escalation to the next higher dose level may be permitted after Sponsor Consultation for a participant that 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 one dose level" and participant is already at dose level -2 when a toxicity occurred, belzutifan should be permanently discontinued.

Table 4 Belzutifan Dose Levels

Dose Level	Dose
Starting Dose	120 mg QD
-1	80 mg QD
-2	40 mg QD

6.6.1.1 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. Transfusion can also be used to manage anemia in patients receiving belzutifan.

6.6.1.2 Management of Hypoxia

Participants enrolled in the study will have a baseline pulse oximetry of at least 92% at rest, nor require 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. Diagnosis of hypoxia is to follow CTCAE v5 and management to follow the dose modification Table 3 and ECI guidance in Appendix 8.

6.6.2 Everolimus Dosing Modifications

For participants on the everolimus arm, dose adjustments and the management of AEs should be made as described in the everolimus package insert.

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 (belzutifan and everolimus) 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.
- Radiographic disease progression outlined in Section 8.2.1 (exception if the Sponsor approves treatment continuation following BICR-verified disease progression per RECIST [Section 4.1]).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires treatment.
- Unacceptable AEs or toxicities (Section 6.6).
- The participant interrupts study intervention administration for >28 consecutive days without Sponsor consultation.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum or highly sensitive urine pregnancy test.
- Sponsor discontinuation of study.

As described in Section 4.1, treatment may continue beyond BICR-verified 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 confirmed 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 FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study

protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

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

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

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history. Investigator will discuss use of tobacco or any inhaled agents (vaping) with study participants as it is important to understand the pulmonary and cardiac health of study participants. It is not known whether prior use of these agents will impact the incidence of hypoxia, an ECI for this study. Refer to Appendix 7 for country-specific requirements.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication/vaccination use, including any protocol-specified washout requirement, and record prior medication/vaccination taken by the participant within 28 days before randomization.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after treatment allocation. Once a 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 randomization number.

8.1.8 Study Intervention Administration

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

8.1.8.1 Belzutifan

Study intervention may be administered at home except on clinic visit days on Day 1 of Weeks 1, 3, 5, and 9. Study intervention on these days will occur in the clinic after completion of blood collection.

8.1.8.2 Everolimus

Study intervention may be administered at home except on clinic visit days of Week 1, 3, 5, and 9.

8.1.8.3 Timing of Dose Administration

Participants should be given clear instructions on how and when to take their study intervention. Three 40-mg tablets of belzutifan or everolimus 10mg will be taken orally QD, with doses taken at approximately the same time of day. Study medication can be taken without regard to food.

Missed doses may be made up if taken within 6 hours after the scheduled administration time. In the event of a missed everolimus dose, refer to the package insert or SmPC. Participants who vomit after study medication administration should not retake that study medication dose but should resume taking study medication with the next scheduled dose.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention 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 FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. The participant's data will be included in any analyses that are in

progress at the time of the request for withdrawal or that have already been performed before the request being received by the Sponsor. The participant's data will not be included in any new analyses generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

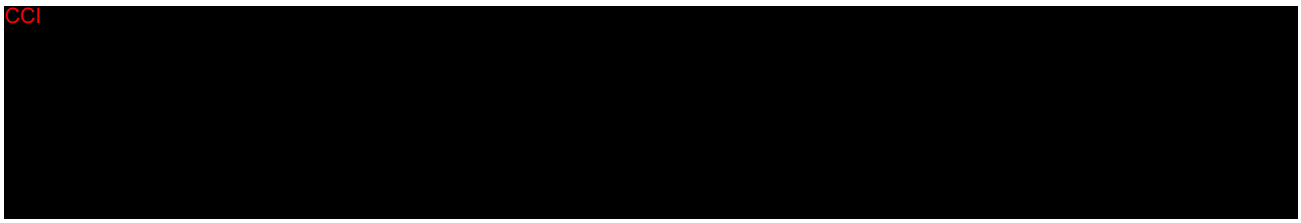
This is an open-label study; there is no blinding in this study.

8.1.11 Tissue Collection

A tumor specimen for biomarker assessment will be provided or collected prior to randomization in the study. A new tumor specimen, if obtained as part of normal clinical practice (not solely for the purpose of screening for randomization in this study) is preferred to archival samples.

A core or excision biopsy of a tumor lesion 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 prior to submitting existing tissue samples and/or undergoing a new biopsy.



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

The process for image collection and transmission to the iCRO can be found in the SIM. In general, imaging should include the chest, abdomen, and pelvis. Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. Contrast-enhanced MRI is the strongly preferred modality for imaging the brain. Imaging 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 imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

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

All scheduled images for all study participants from the sites will be submitted to the iCRO. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which captures radiologic progression based on investigator assessment, should also be submitted to the iCRO.

When the investigator identifies radiographic progression per RECIST 1.1, the BICR will perform expedited verification of radiologic disease progression and the results will be communicated to the study site and the Sponsor via email. In clinically stable participants, imaging should continue until disease progression has been verified by BICR (if initial site-assessed disease progression was not verified by BICR, each subsequent scan, if indicating progression, must be submitted to the iCRO with a verification of disease progression request until disease progression has been verified by BICR).

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of randomization. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

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

Tumor imaging 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 within 42 days prior to randomization.
- Brain imaging is required at screening for those participants with brain metastases at baseline (ie, to confirm stability) or 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 imaging assessment should be performed at Week 9 Day 1 (±7 days) from the date of randomization. Subsequent tumor imaging 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 imaging performed Q12W (±7 days). The imaging visit window is ±14 days after Week 109. Imaging timing should follow the imaging scheduling calculator from the date of randomization and should not be adjusted for delays in study intervention. Imaging should continue to be performed until disease progression is BICR-verified (unless the investigator elects to continue treatment following Sponsor approval [Section 7.1]), or until any of the following conditions are met, whichever occurs first:

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

All supplemental imaging must be submitted to the iCRO.

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) until disease progression is verified by BICR. 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.

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

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging 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 imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks (<28 days) later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response does not typically need to be verified in real time by BICR.

On investigator-assessed disease progression, the indicative scan(s) is to be submitted immediately to the iCRO for BICR verification of progression. After submission of the scan(s), the iCRO will email the assessment to the site and the Sponsor. Participants who have unverified disease progression should continue on treatment at the discretion of the investigator until disease progression is BICR-verified provided they are clinically stable. In clinically stable participants, imaging should continue until disease progression has been verified by BICR (if initial site-assessed disease progression was not verified by BICR, each subsequent scan, if indicating progression, must be submitted to the iCRO with a verification of disease progression request until disease progression has been verified by BICR).

If disease progression is not verified, the process continues as follows:

- If participant is clinically stable, continue study intervention per protocol
  - Resume imaging per protocol schedule (Q8W until Week 49, then Q12W)
  - Send scans to iCRO
  - Continue local assessment
  - Do not change investigator assessment of disease progression
  - If subsequent scan(s) indicate progression, submit scan(s) to iCRO to request verification
- If the participant is not clinically stable, best medical practice is to be applied.

Before stopping study intervention or imaging or starting new anticancer therapy in a participant who is clinically stable, communication with the Sponsor is required.

If disease progression is verified, the process continues as follows:

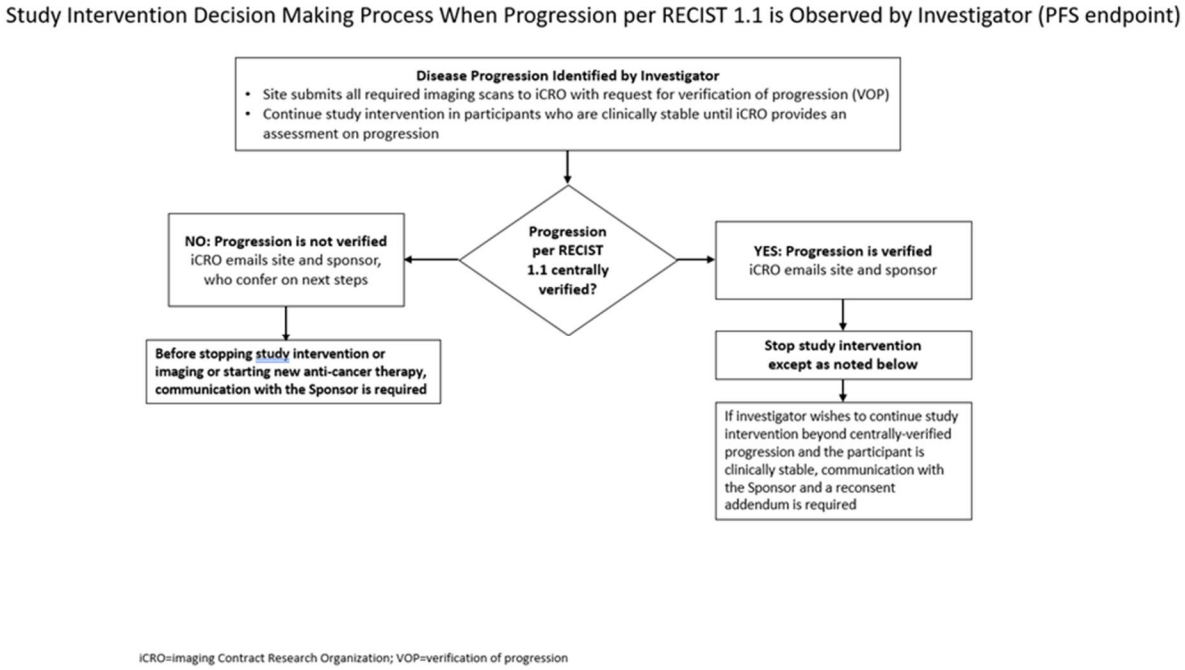
- Investigator judgment will determine action
- If the participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a reconsent addendum must be signed.
  - Obtain scans locally per original protocol schedule
  - Do not send scans to iCRO.

Figure 2 illustrates the study intervention decision process involving verification of disease progression for participants.

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.

Figure 2 Decision-Making Process When Progression Observed by Investigator



iCRO=imaging contract research organization; RECIST=Response Evaluation Criteria in Solid Tumors; VOP=verification of progression.

Participants who continue treatment beyond verified disease progression must sign a separate ICF and will continue with all protocol-specified assessments and procedures.

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

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

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

- Disease progression is BICR-verified
- Start of a new anticancer treatment
- Pregnancy
- Death
- Withdrawal of consent
- End of the study, whichever occurs first.

For participants who discontinue for reasons other than disease progression, imaging 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 is verified by BICR.

8.2.2 Quality of Life Assessments

The PROs will be completed on Day 1 of Weeks 1, 3, 5, and 9, Q4W thereafter, at the treatment discontinuation visit, and at the 30-day Posttreatment Safety Follow-Up Visit. It is estimated that the assessments will take approximately 10 minutes. The FKSI-DRS, EORTC QLQ-C30, and EQ-5D-5L questionnaires will be administered by trained study-site personnel and completed by the participants themselves.

It is strongly recommended that PROs are administered prior to other study procedures and assessments including drug administration, AE evaluation, and disease status notification. The PROs are to be completed in the following order: FKSI-DRS, then EORTC QLQ-C30, then EQ-5D-5L at the time points specified in Section 1.3.

As of 15-APR-2024, PROs will no longer be required.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided throughout Section 8.3. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the laboratory manual.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard 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 using Fridericia's formula locally. 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 laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5 KPS and ECOG Performance Status

The investigator or qualified designee will assess KPS and ECOG performance status at screening (within 10 days prior to randomization). The investigator or qualified designee will assess ECOG performance status on Day 1 of Weeks 1, 3, 5, 9, and Q4W thereafter (Section 1.3). ECOG performance status will also be assessed at the treatment discontinuation visit, and at the 30-day Posttreatment Safety Follow-Up Visit. ECOG performance status [Oken, M. M., et al 1982] will be assessed prior to 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 need to document if an SAE was associated with a medication error, misuse, or abuse.

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention 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 after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of intervention randomization through 30 days for belzutifan or 8 weeks for everolimus following cessation of study intervention, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

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

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

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

8.4.7 Events of Clinical Interest

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor. ECIs that are not SAEs should be collected through 30 days following cessation of study intervention and must be reported by the investigator. ECIs that are SAEs should be collected through 90 following cessation of study intervention and must be reported by the investigator.

Events of clinical interest for this study include:

a. An overdose of Sponsor's product, as defined in Section 8.5.
b. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin laboratory value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase laboratory 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).
c. Any ≥Grade 3 anemia
d. Any ≥Grade 3 hypoxia
e. Any ≥Grade 3 AE deemed related to belzutifan by the investigator, including laboratory abnormalities

8.5 Treatment of Overdose

Overdose will be defined as any dose greater than 240 mg QD of belzutifan. No specific information is available on the treatment of overdose of belzutifan. In the event of overdose the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. Overdose is defined as any dose exceeding the prescribed dose of everolimus. No specific information is available on the treatment of overdose of everolimus. In the event of overdose, everolimus 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

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8.7 Pharmacodynamics

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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.

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8.9 Future Biomedical Research Sample Collection

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

- Leftover specimens as listed in Section 8.8.

8.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economic data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- All-cause hospitalizations and emergency department visits, from the time of treatment allocation through 90 days following cessation of study intervention, or 30 days following cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

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

Written 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 within 28 days before randomization except for the following:

- Laboratory tests are to be performed within 10 days prior to randomization. An exception is HIV (if required by local health authority) and hepatitis testing which may be conducted up to 28 days prior to randomization. Refer to Appendix 7 for country-specific requirements.
- Evaluation of KPS and ECOG is to be performed within 10 days prior to randomization.
- For WOCBP, a urine pregnancy test will be performed within 24 hours prior to randomization. If greater than 1 day has elapsed between the screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed within 24 hours of first dose and must be negative in order for participants to start receiving study medication. 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 prior to randomization.

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

8.11.2 Treatment Period

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

8.11.3 Posttreatment

8.11.3.1 Posttreatment Safety Follow-up Visit

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

8.11.3.2 Imaging Follow-up

Participants who discontinue study treatment for reasons other than BICR-verified disease progression should continue with imaging assessments per the protocol-defined schedule

until: 1) disease progression is BICR-verified, 2) initiation of a new anticancer treatment, 3) death, 4) pregnancy, 5) withdrawal of consent, or 6) the end of the study, whichever occurs first. Tumor imaging 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 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 should be followed for survival (in-person visit, telephone contact, medical record review, etc.) approximately Q12W. Every effort should be made to assess for survival 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.

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

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

For participants who completed assessments in Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

To ensure current and complete survival data are available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to, but not limited to an 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 survival status.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to these hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to the exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a sSAP and referenced in the CSR for the study. Posthoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will be included in the sSAP. A separate biomarker analysis plan may be provided as appropriate in the sSAP.

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 3 controlled study of the HIF-2α inhibitor, belzutifan, versus everolimus in participants with advanced renal cell carcinoma after prior therapy
Treatment Assignment	Participants will be randomly assigned in a 1:1 ratio to receive either belzutifan at 120 mg QD or everolimus at 10 mg QD. Stratification factors are as follows: • IMDC prognostic scores: 0 vs 1-2 vs 3-6 • Number of prior VEGF/VEGF receptor targeted therapies for advanced RCC: 1 vs 2-3
Analysis Populations	Efficacy: ITT Safety: APaT
Primary Endpoints	• PFS • OS
Secondary Endpoints	• ORR • DOR • PRO assessment • AEs and discontinuations due to AEs
Statistical Methods for Key Efficacy Analyses	The primary hypotheses comparing belzutifan to everolimus with respect to PFS and OS will be evaluated using a stratified log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The stratified Miettinen and Nurminen method with strata weighted by sample size will be used for analysis of ORR.
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	Two IAs are planned for the study. Results will be reviewed by an external DMC. Details are provided in Section 9.7. CCI [redacted] • Primary purpose: efficacy analyses for PFS, OS, and ORR. Second IA (IA2): CCI [redacted] • Primary purpose: efficacy analysis for OS and PFS (final analysis). FA: CCI [redacted] • Primary purpose: efficacy analysis for OS.
Multiplicity	The overall Type I error rate over the primary and secondary hypotheses is strongly controlled at 2.5% (1-sided), with 0.5% initially allocated to PFS (H1), 1.9% initially allocated to OS (H2) and 0.1% initially allocated to ORR (H3). By using the graphical approach of Maurer and Bretz, if one hypothesis is rejected, the alpha will be shifted to other hypotheses [Maurer, W. and Bretz, F. 2013].
Sample Size and Power	The planned sample size is approximately 736 participants. There will be ~483 deaths at the final OS analysis. With 483 deaths, the study has ~85.4% power for detecting a HR of 0.75 at an initially assigned 0.019 (1-sided) significance level. It is estimated that there will be ~626 events at the final PFS analysis (ie, the second IA of the study). With 626 PFS events, the study has ~96.9% power for detecting a HR of 0.70 at an initially assigned 0.005 (1-sided) significance level. Based on all randomized participants, the power of the ORR testing at the allocated α=0.001 is approximately 99.9% to detect a 15-percentage point difference between an underlying 5% response rate in the control arm and a 20% response rate in the experimental arm.

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:

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.

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

Secondary:

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.

DOR – For participants who demonstrated confirmed 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.

9.4.2 Safety Endpoints

A description of safety endpoint assessment is provided in Section 4.2.1.3. Assessments include, but not limited to, the incidence of, causality of, and outcome of AEs/SAEs; and changes in laboratory values.

9.4.3 Patient-reported Outcome Endpoints

As described in Section 4.2.1.4, the following PRO assessments will be evaluated:

- Scores from the EORTC QLQ-C30:
  - Global health status/QoL scale (items 29 and 30)
  - Physical functioning scale (items 1-5)
- Scores from the FKSI-DRS
- Health Utility Scores from the EQ-5D-5L

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The ITT population will serve as the population for primary efficacy analysis. All randomized participants will be included in this population. Participants will be included in the treatment arm to which they are randomized. The same population will be used for all efficacy analyses unless otherwise specified in the sSAP.

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. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

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.

9.5.3 Patient-reported Outcome Analysis Population

The PRO analyses are based on the PRO FAS population, defined as randomized participants who have at least 1 PRO assessment available and have received at least 1 dose of study treatment.

9.6 Statistical Methods

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

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9.6.1.1 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. 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 both the stratified log-rank test and the stratified Cox model.

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9.6.1.2 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. 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). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and 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.

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9.6.1.3 Objective Response Rate

The stratified Miettinen and Nurminen's method will be used for comparison of the ORR between 2 treatment groups. The difference in ORR and its 95% confidence interval 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.

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9.6.1.4 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 subjects still in response and 95% CIs at specific duration time points will be provided.

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9.6.1.5 Analysis Strategy for Key Efficacy Endpoints

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 8.

Table 8 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis 1			
PFS as assessed by BICR according to RECIST 1.1	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 6)
Primary Hypothesis 2			
OS	Test: stratified log-rank test Estimation: stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Key Secondary Hypothesis 3			
ORR as assessed by BICR according to RECIST 1.1	Testing and estimation: stratified Miettinen and Nurminen method	ITT	Participants with missing data are considered nonresponders

Abbreviations: BICR = blinded independent central review; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.
Note: Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization will be used as stratification factors for analysis.

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.

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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 exhibit 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) and SAEs (≥5% 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 9 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
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
Abbreviations: AE = adverse event; SOC = system organ class; X = results will be provided.			

9.6.3 Statistical Methods for Patient-reported Outcome Analyses

Details of PRO analyses will be included in the sSAP.

9.6.4 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.

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9.7.1 Efficacy Interim Analyses

Two IAs are planned in addition to the FA for this study. For the IAs and FAs, all randomized participants will be included. Results of the IAs will be reviewed by the DMC.

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9.7.2 Safety Interim Analyses

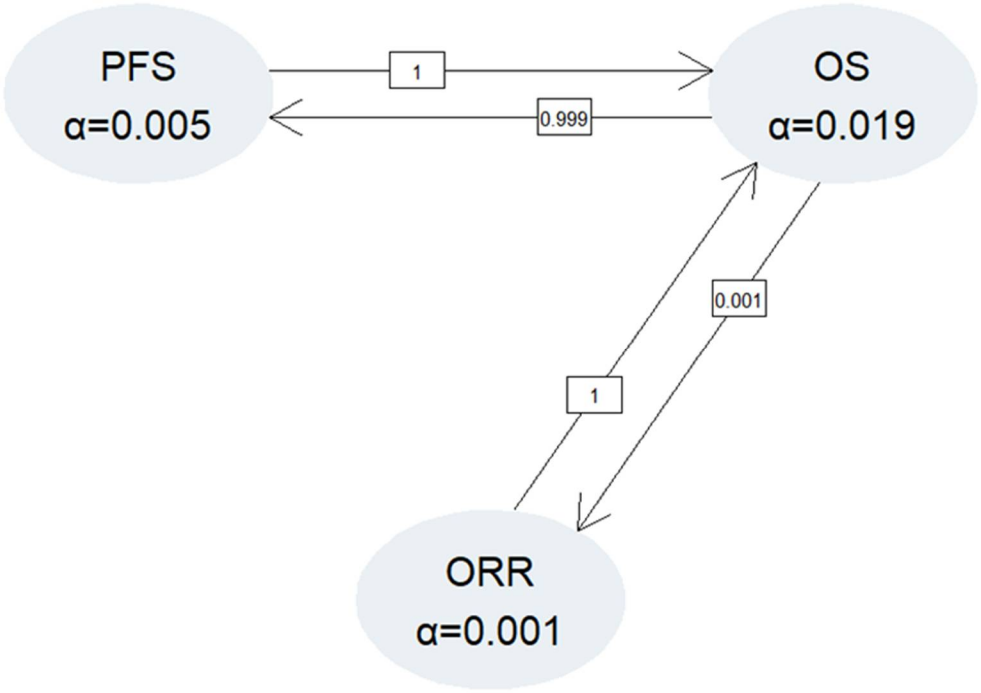
The DMC will be responsible for periodic interim safety reviews, as specified in the DMC charter. Interim safety analyses will also be performed at the time of interim efficacy analyses.

9.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W., et al 2011] to control multiplicity for multiple hypotheses as well as IAs. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. Figure 3 shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are shown in the boxes on the lines connecting hypotheses.

Initial α assigned to OS, PFS and ORR will be 0.019, 0.005 and 0.001, respectively. If any hypothesis is rejected, α will be reallocated to the other hypotheses.

Figure 3 Multiplicity Diagram for Type I Error Control (One-Sided)



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9.9 Sample Size and Power Calculations

The study will randomize approximately 736 participants in a 1:1 ratio to the belzutifan and everolimus arms. PFS and OS are primary endpoints for the study, with ORR as the key secondary endpoint.

Based on all randomized participants, the power of the ORR testing at the allocated α=0.001 is approximately 99.9% to detect a 15-percentage point difference between an underlying 5% response rate in the control arm and a 20% response rate in the experimental arm.

For the PFS endpoint, based on an expected number of 626 events at the final analysis and one interim analysis at 90% of the final target number of events, the study has approximately 96.9% power to demonstrate an HR of 0.7 at an overall α level of 0.005 (1 sided), 99.3% power at an α level of 0.024 (1-sided), and 99.3% power at an α level of 0.025 (1-sided).

For the OS endpoint, based on a target number of 483 events at the final analysis and 2 interim analyses at approximately 62% and 85% of the final target number of events, the study has approximately 85.4% power to detect an HR of 0.75 at an overall α level of 0.019 (1-sided), 85.8% power at an α level of 0.020 (1-sided), 87.4% power at an α level of 0.024 (1-sided), and 87.7% power at an α level of 0.025 (1-sided).

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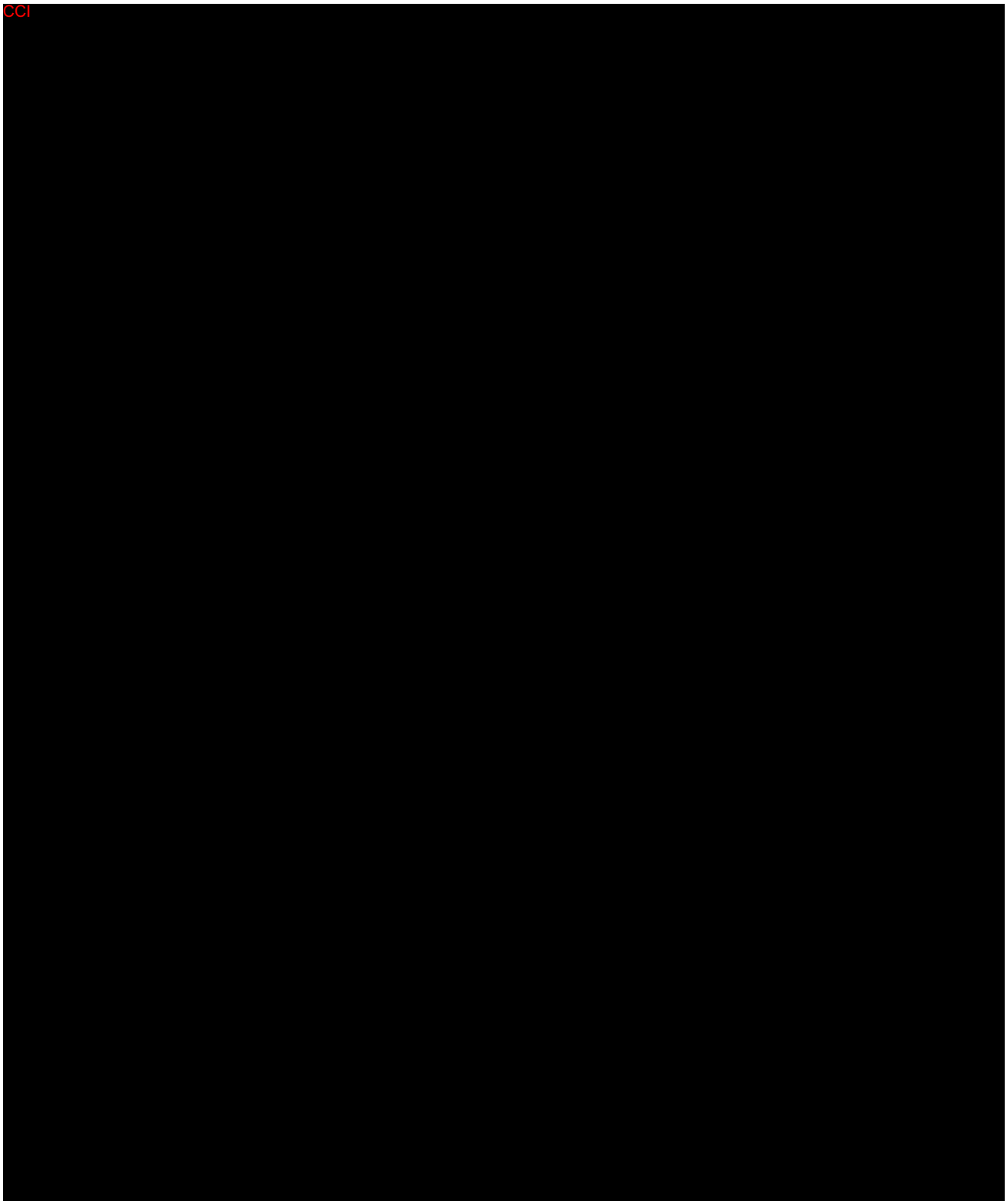

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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 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 (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (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 fraud, scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish 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. 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 (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

The participant must be informed that their 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 their 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee

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.

10.1.4.2 Executive Oversight Committee

The EOC is comprised of members of Sponsor senior management. The EOC will receive and decide on any recommendations made by the DMC regarding the study. Additional details regarding the EOC can be found in the DMC charter.

10.1.4.3 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7), and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the protocol team, meeting facilitation, the minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all DMC members.

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 ICMJE 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 trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 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 (eg, EU CTR: 25 years after the end of the study). 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 14 will be performed by the central laboratory.

If local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.

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

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Pregnancy testing:

- Pregnancy testing requirements for study inclusion are described in Section 5.1.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1. 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
  - Everolimus: at least 8 weeks 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 14 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: • MCV • MCH • % Reticulocytes	• WBC count with differential[a] • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
Chemistry	BUN or urea[b]	Potassium	Aspartate Aminotransferase (AST) / Serum Glutamic-oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Albumin	CO2 or bicarbonate[c]	Chloride	Phosphorous
	Creatinine or CrCl[d]	Sodium	Alanine Aminotransferase (ALT) / Serum Glutamic-pyruvic Transaminase (SGPT)	Total Protein
	Glucose[e]	Calcium	Alkaline phosphatase	Triglycerides and total cholesterol (fasting ≥8 hours)
Routine Urinalysis[f]	• 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	• Serum or urine β-hCG pregnancy test (as needed for WOCBP)[f]. • Serology (HIV, HBsAg and HCV antibody) as required by local health authority or institutional regulations[f]. • Coagulation factors (PT or INR, and aPTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy.			

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. At baseline, the participant should be in the fasted state for glucose measurement.
f. To be performed locally. Urine β-hCG pregnancy test will additionally be performed monthly, at EOT, and at 30 days after last dose of study intervention.

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

Refer to Appendix 7 for country-specific requirements.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

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

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

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

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

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

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

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

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

10.3.4 Additional Events Reported 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 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:
  - Exposure: Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - Time Course: Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - Likely Cause: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - Dechallenge: Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

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

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

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE

TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE IRB/IEC.

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

Follow-up of AE and SAE

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

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

Not applicable for this study, except as described in Section 10.7.6.

10.4.1 Definition of Device Event

Not applicable for this study, except as described in Section 10.7.6.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

WOCBP

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

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

Women in the following categories are not considered WOCBP:

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

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

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

10.5.2 Contraceptive Requirements

Table 15 Highly Effective Contraception Methods

• **Contraceptives allowed during the study**[a]
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen-only contraceptive implant[b,c] ● IUS[c,d] ● Nonhormonal IUD ● Bilateral tubal occlusion
● Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia 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.
Notes: [a] Contraceptive use by men and women should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. [b] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [c] Male condoms must be used in addition to hormonal contraception. [d] IUS is a progestin-releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

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

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens

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

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

7. Retention of Specimens[3, 4]

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

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

8. Data Security[3, 4]

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

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

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

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be

identified by name in any published reports about this study or in any other scientific publication or presentation.

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

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

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

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

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

12. Questions

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

13. References

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 Germany

Section 1.3 Schedule of Activities

Study Period	Screening		Treatment Period						EOT	Notes
Week	**Screening[a] (Visit 1)**		**1**	**4**	**8**	**12**	**16**	**20+[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 prior to treatment allocation, unless otherwise noted.
b. Following Week 20, visits are to occur approximately every 4 weeks (~28 days) until documented PD, death, withdrawal of consent, or the end of the study, whichever occurs first.

Section 5.1 Inclusion Criteria

10. The participant provides written informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the main study without participating in FBR.

Section 5.2 Exclusion Criteria

27. 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 prior to the first dose of study intervention randomization. An exception is HIV and hepatitis testing which may be done up to 42 days prior to the first dose of study intervention randomization.

Appendix 2 Clinical Laboratory Tests

Other Screening Tests: Serology (HIV RNA)

10.7.2 United Kingdom

Section 1.3 Schedule of Activities

Study Period	Screening		Treatment Period						EOT	Notes
Week	**Screening[a] (Visit 1)**		**1**	**4**	**8**	**12**	**16**	**20+[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 prior to treatment allocation, unless otherwise noted.
b. Following Week 20, visits are to occur approximately every 4 weeks (~28 days) until documented PD, death, withdrawal of consent, or the end of the study, whichever occurs first.

Section 5.2 Exclusion Criteria

27. Participant has a known history of human immunodeficiency virus (HIV) infection. Testing for HIV is required at screening.

Section 6.5.1 Prohibited Concomitant Medications

- Live vaccines while participating in the study, and within 90 days of the last dose of study intervention.

  Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, intranasal seasonal influenza, rabies, BCG, and typhoid (oral).

  Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

Section 8.11.1 Screening

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

Appendix 2 Clinical Laboratory Tests

Other Screening Tests: Serology (HIV antibody).

10.7.3 Ireland

Section 1.3 Schedule of Activities

Study Period	Screening		Treatment Period						EOT	Notes
Week	**Screening[a] (Visit 1)**		**1**	**4**	**8**	**12**	**16**	**20+[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 prior to treatment allocation, unless otherwise noted.
b. Following Week 20, visits are to occur approximately every 4 weeks (~28 days) until documented PD, death, withdrawal of consent, or the end of the study, whichever occurs first.

Section 5.2 Exclusion Criteria

27. Participant has a known history of human immunodeficiency virus (HIV) infection. Testing for HIV is required at screening.

Section 6.5.1 Prohibited Concomitant Medications

- Live vaccines while participating in the study, and within 90 days of the last dose of study intervention.

  Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, intranasal seasonal influenza, rabies, BCG, and typhoid (oral).

  Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and, once confirmed, are allowed.

Section 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 that the investigator considers to be clinically significant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

Section 8.11.1 Screening

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

Appendix 2 Clinical Laboratory Tests

Other Screening Tests: Serology (HIV antibody).

10.7.4 Norway

Section 1.3 Schedule of Activities

Study Period	**Screening**	**Treatment Period**					**EOT**	**Posttreatment**				**Notes**
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**56 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	
Urine or serum β-hCG - WOCBP only	X	X		X	X	Q4W	X	X	**X***			Female participants of childbearing potential will have a serum or highly sensitive urine pregnancy test within 1 day prior to randomization. If more than 1 day has elapsed between the screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed within 24 hours of first dose and must be negative in order for the participant to start receiving study medication. Pregnancy tests will be conducted locally.

Study Period	Screening	Treatment Period					EOT	Posttreatment				Notes
Visit:	**Screening[a]**	**Wk 1 Day 1[a]**	**Wk 3 Day 1**	**Wk 5 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**	**±5**	**At time of DC**	**30 Days After Last Dose (+7 days)**	**56 Days After Last Dose (+7 days)**	**Q8W or Q12W (±7 days)**	**Q12W (±7 days)**	

*Pregnancy testing at 56 days post EOT is only required for WOCBP on the everolimus treatment arm.

a. Week 1 Day 1 denotes the first dose of study treatment, which should be on the date of randomization, but can be within 3 days following 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, contact, medical record review, etc. Participant status information includes survival status and subsequent antineoplastic therapies for RCC.

10.7.5 Czech Republic

Section 1.3 Schedule of Activities

Study Period	Screening	Treatment Period						EOT	Notes
Week	**Screening[a] (Visit 1)**	**1**	**4**	**8**	**12**	**16**	**20+[b]**	**DC**	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7+**		
Scheduling Window (Days):	**–28 to –1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of DC**	
Safety Procedures									
HIV testing	X								Testing is required.
HBV testing	X								Testing is required.
HBC testing	X								Testing is required.

a. All screening procedures should be performed within 28 days prior to treatment allocation, unless otherwise noted.
b. Following Week 20, visits are to occur approximately every 4 weeks (~28 days) until documented PD, death, withdrawal of consent, or the end of the study, whichever occurs first.

Section 5.2 Exclusion Criteria

27. Has a known history of HIV infection.

Note: Testing for HIV at screening will be performed up to 28 days prior to randomization.

28. 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 will be performed up to 28 days prior to randomization.

Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 16 will be performed by the central laboratory.

- If local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 16 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential[a] Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN or urea[b]	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Albumin	CO_2 or bicarbonate	Chloride	Phosphorous
	Creatinine or CrCl[c]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose[d]	Calcium	Alkaline phosphatase	Triglycerides and total cholesterol (fasting ≥ 8 hours)
Routine Urinalysis[e]	• 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	• Serum or urine β-hCG pregnancy test (as needed for WOCBP)[e]. • Serology (HIV, HBsAg and HCV antibody)[e]. • Coagulation factors (PT or INR, and aPTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy.			

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. GFR (measured or calculated) or CrCl can be used in place of creatinine.
d. At baseline, the participant should be in the fasted state for glucose measurement.
e. To be performed locally.

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

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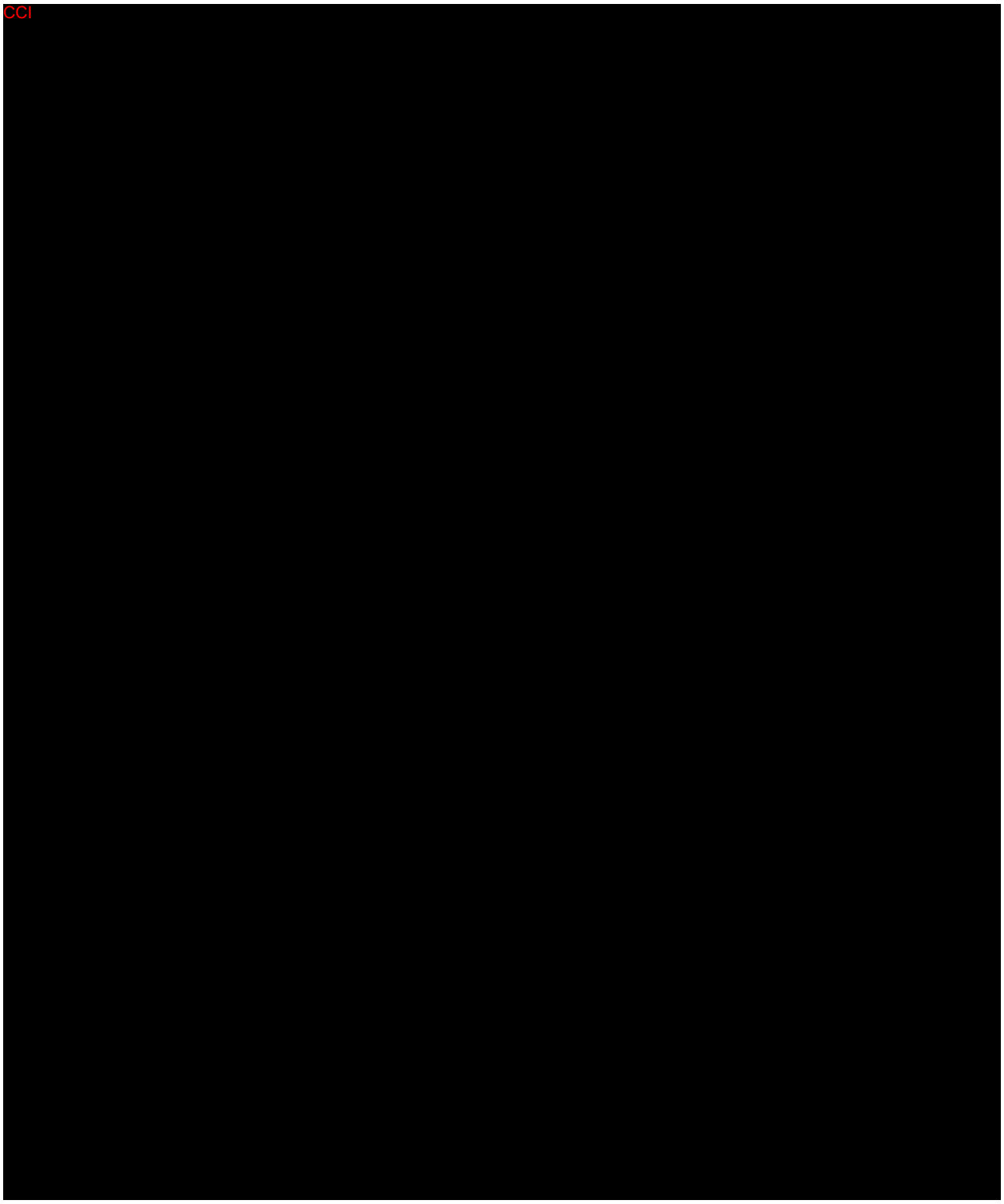

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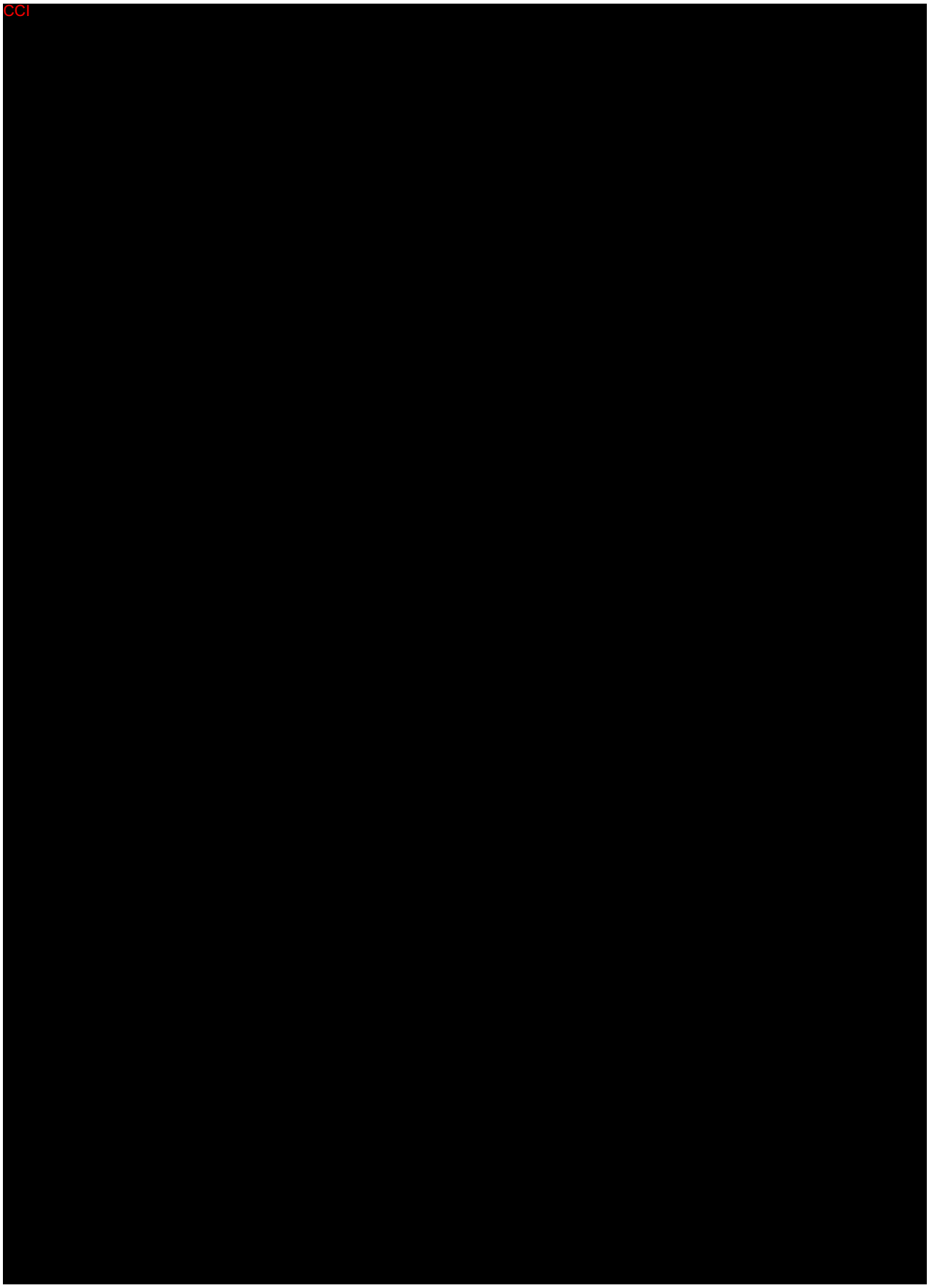

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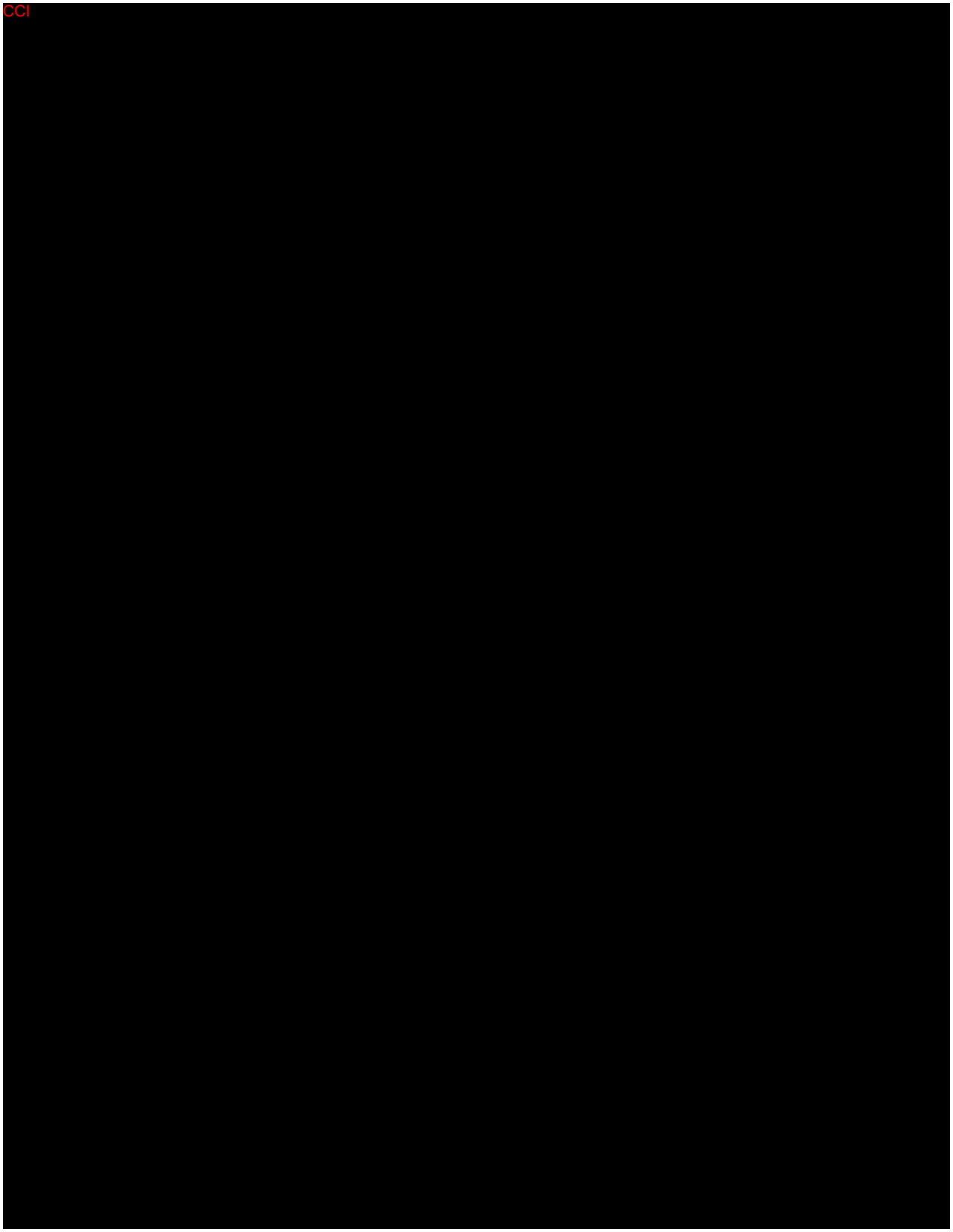
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10.7.6.3 Use of Erythropoiesis-stimulating Agents

Background and Overview

ESAs are not approved in Japan for chemotherapy-induced anemia and the Sponsor considers that ESA use for belzutifan-induced anemia is off-label use in Japan. CCI

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Study Interventions Administered

In addition to the study intervention described in Table 2, the study intervention to be used in this study specific for Japan is outlined in Table 18.

Table 18 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Belzutifan	Experi-mental	M-darbe	Combination Product	Sterile Solution	180 µg prefilled syringe	360 µg	SC	Refer to ESA dose for belzutifan-induced anemia	Test Product	IMP	Central

Abbreviations: EEA = European economic area; IMP = Investigational Medicinal Product; M-darbe = darbepoetin alfa; NIMP/AxMP = Noninvestigational/Auxiliary Medicinal Product; SC = subcutaneously.

According to hemoglobin level, dosage levels is to be reduced as outlined in the ESA dose for belzutifan-induced anemia.

The participants who are assigned to the belzutifan arm will be administered M-darbe according to hemoglobin level.

M-darbe will be provided as a single-dose prefilled syringe, which is defined as a combination product (syringe device and M-darbe).

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

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[redacted]

Evaluation of M-darbe for Belzutifan-induced Anemia in Japanese Participants

All Japanese participants, including the participants in the safety run-in cohort, who receive at least 1 dose of belzutifan and receive at least 1 dose of M-darbe after experiencing belzutifan-induced anemia (hemoglobin <10.0 g/dL), will be evaluated to assess the effectiveness of M-darbe in the treatment of belzutifan-induced anemia. The following endpoints will be evaluated and reported for Japanese participants:

- Percentage of participants with change from baseline in hemoglobin ≥2.0 g/dL

Percentage of participants with change from baseline in hemoglobin ≥2.0 g/dL will be calculated. Baseline measurement is defined as the last value measured between start date of the AE of anemia and before the first M-darbe administration for each participant. The postbaseline measurements are defined as the values measured after the start date of receiving M-darbe, and before the earliest date of 12 weeks after receiving M-darbe, the date of discontinuation of belzutifan, and the start date of blood transfusion. Change from baseline in hemoglobin will be calculated as the maximum value of postbaseline measurements minus the value of baseline measurement.

- Percentage of avoidance of a blood transfusion

Percentage of avoidance of a blood transfusion will be calculated and is defined as the percentage of participants who did not receive a blood transfusion.

- The percentage of participants whose minimum value of post-baseline measurements of hemoglobin ≥7.0 g/dL
- The percentage of participants whose minimum value of post-baseline measurements of hemoglobin ≥8.0 g/dL

In addition, AEs will also be summarized for all participants included in this evaluation of M-darbe.

AE Monitoring and Reporting Related to M-darbe

Based on Sections 1.3 and 8.4, AE monitoring of administration of M-darbe, which is considered as an IMP in Japan, will also be performed. Treatment with M-darbe is considered as study intervention, and therefore, the time period for collecting AE, SAE, and other reportable safety event information will be as described in Section 8.4.1.

Concomitant Therapy

Based on Section 6.5, all concomitant medications received within 28 days before randomization and up to 30 days after the last dose of study intervention, defined by the last dose of belzutifan, everolimus, or M-darbe should be recorded. Concomitant medications administered >30 days after the last dose of study intervention defined by the last dose of belzutifan, everolimus, or M-darbe should be recorded for SAEs as defined in Section 8.4.

Serious Syringe Device Events (Incidents)

M-darbe will be provided as a single-dose prefilled syringe, which is defined as a combination product (syringe device and M-darbe). A syringe device corresponds to a medical device, and serious syringe device events (incidents) must be reported to the Sponsor.

Instructions for medical device use are provided in the Pharmacy Manual.

Definition of Serious Syringe Device Events (Incidents)

A serious syringe device event (incident) is any malfunction or deterioration in the characteristics and/or performance of the device, as well as any inadequacy in the labeling or the instructions for use that, directly or indirectly, led to the death of a participant or user, or of other persons, or to a serious deterioration in their state of health.

A serious deterioration in the state of health can include:

1. Life-threatening illness;
2. Permanent impairment of a body function or permanent damage to a body structure;
3. A condition necessitating medical or surgical intervention to prevent 1 or 2;
4. A condition that requires hospitalization or significant prolongation of existing hospitalization; or
5. Fetal distress, fetal death, or any congenital abnormalities or birth defects.

Definition of Malfunction Which may Lead to Serious Adverse Events - Any malfunction of a medical device which might have led to the death of a participant and/or the associated person or to a serious deterioration in his/her state of health. “Which might have led to” means that there is the possibility that death or a serious deterioration might have occurred in a participant and/or the associated person, although these cases have not actually occurred.

Monitoring, Reporting, and Follow-up of Serious Syringe Device Events (Incidents)

For the time period beginning when the consent form is signed through the duration of the participant’s study participation, any serious syringe device event (incident), including follow-up to an incident and death due to any cause, that occurs to any participant must be reported within 24 hours to the Sponsor both by paper reporting for the event (incident) and electronic reporting for SAEs. Malfunction which may lead to SAEs will be reported to the Sponsor within 5 calendar days of learning of the information via a paper reporting form.

Any serious syringe device event (incident) that occurs in study personnel must be reported within 24 hours to the Sponsor both by paper reporting for the event (incident) and spontaneous reporting to the Sponsor.

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

Additionally, any serious syringe device event (incident) considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified above must be reported immediately to the Sponsor.

All participants involved with serious syringe device events (incidents) must be followed up for outcome.

10.7.7 South Korea

Section 5.1 Inclusion Criterion 11

Table 19 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
Renal	
Serum creatinine or estimated CrCl using the Cockcroft-Gault equation, or based on a 24-hour urine test[a] (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥51 mL/min for participants with creatinine levels >1.5 x 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
Fasting serum triglycerides and total cholesterol	≤2.5 x ULN AND total cholesterol ≤300 mg/dL (≤7.75 mmol/L). Lipid-lowering medication is allowed
Fasting glucose	A fasting glucose ≤125 mg/dL (≤6.9 mmol/L) is required.

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. Estimated creatinine clearance using Cockcroft-Gault:

$$\frac{(140\text{-age [years]} \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} \quad (\times F)^*$$

*where F = 0.85 for females and F = 1 for males

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.

10.8 Appendix 8: Belzutifan ECI Guidance

10.8.1 Belzutifan ECI Criteria

Anemia: Any ≥ Grade 3 anemia/decreased hemoglobin event	
Anemia	Decreased hemoglobin
Hypoxia: Any ≥ Grade 3 hypoxia	
Hypoxia	
Any ≥Grade 3 SAE/AE deemed related to belzutifan by the investigator, including laboratory abnormalities.	
≥ Grade 3 belzutifan-related clinical AEs	≥ Grade 3 belzutifan-related laboratory AEs
Common Terminology Criteria for Adverse Events (CTCAE) Version 5 will be used.	

10.8.2 Anemia/Decreased Hemoglobin ECI Reporting

The following AE terms are considered ECIs and should be reported to the Sponsor within 5 calendar days of learning of the event if the event is non-serious or within 24 hours if the event is an SAE:

- ≥Grade 3 anemia
- ≥Grade 3 decreased hemoglobin

Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 mL of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.

CTCAE Version 5 definition of Anemia Grades:

- Grade 1: Hemoglobin <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L
- Grade 2: Hemoglobin <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80 g/L
- Grade 3: Hemoglobin <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death

10.8.3 Anemia Management

Decreased EPO is the potential etiology of anemia with belzutifan treatment. EPO replacement is an effective management strategy for participants who may develop and subsequently require intervention for belzutifan-induced anemia. Transfusion can also be used to manage anemia in patients receiving belzutifan.

Grade 3 events (report as ECI):

- Dose Modification not required

Grade 4 events (report as ECI):

- First episode: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by 1 level
- Second episode: Permanently discontinue belzutifan

All attempts should be made to rule out other causes of anemia. Relevant diagnostic studies may include peripheral blood smear, reticulocyte count, LDH, haptoglobin, Coomb's test, blood levels of vitamin B12, folate, iron studies, etc.

While dose interruption is not required, the investigator may elect to hold belzutifan for participants who develop anemia Grade 1-3. If belzutifan is held for anemia Grade 1-3, the participant can be re-challenged with belzutifan at the same dose.

10.8.4 Hypoxia ECI Reporting

The following AE terms are considered ECIs and should be reported to the Sponsor within 5 calendar days of learning of the event if the event is non-serious or within 24 hours if the event is an SAE:

- ≥ Grade 3 hypoxia

Definition: A disorder characterized by a decrease in the level of oxygen in the body.

CTCAE Version 5 definition of Hypoxia Grades:

- Grade 1: Not Applicable
- Grade 2: Decreased oxygen saturation with exercise (eg, pulse oximeter <88%); intermittent supplemental oxygen
- Grade 3: Decreased oxygen saturation at rest (eg, pulse oximeter <88% or PaO2 <=55 mm Hg)
- Grade 4: Life-threatening airway compromise; urgent intervention indicated (eg, tracheotomy or intubation)
- Grade 5: Death

[National Cancer Institute 2017]

10.8.5 Hypoxia Management

Grade 3 events (report as ECI):

- Consult pulmonology
- Provide supplemental oxygen
- Consider appropriate clinical work-up including chest x-ray/CT and ECG to evaluate for potential concomitant/underlying etiologies
- First and second episodes: Hold belzutifan. Once toxicity has resolved to ≤Grade 2 or baseline, dose reduce belzutifan by 1 level (Grade 3 hypoxia [asymptomatic], belzutifan may be continued at the discretion of the investigator)
- Third episode: Permanently discontinue belzutifan

Grade 4 events (report as ECI):

- Consult pulmonology
- Provide supplemental oxygen and endotracheal intubation if indicated
- Consider appropriate clinical work-up including chest x-ray/CT and ECG to evaluate for potential concomitant/underlying etiologies
- Permanently discontinue belzutifan

All attempts should be made to characterize the etiology of the events associated with hypoxia such as heart disease, pulmonary infection, pulmonary metastasis, chronic obstructive pulmonary disease, interstitial lung disease, pulmonary embolism, acute respiratory distress syndrome, chronic liver disease, etc.

10.9 Appendix 9: Abbreviations

Abbreviation	Definition
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AEOSI	Adverse events of special interest
ALP	Alkaline phosphatase
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
BCG	*Bacillus* Calmette–Guérin
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
β-hCG	β-human chorionic gonadotropin
BICR	Blinded independent central review
BID	Twice daily
BUN	Blood urea nitrogen
Ca	Calcium
CBC	Complete blood count
ccRCC	Clear cell renal cell carcinoma
CI	Confidence interval
Cl	Chloride
cLDA	Constrained longitudinal data analysis
CL/F	Clearance
C_{max}	Maximum concentration
CNS	Central nervous system
CO_2	Carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CrCl	Creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	CCI
CTFG	Clinical Trial Facilitation Group
C_{trough}	Trough concentration
CV	Variability
CYP	Cytochrome P450
D	De-escalate to the next lower dose;
DBP	Diastolic blood pressure
DC	Discontinuation
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
DU	Current dose is unacceptably toxic
E	Escalate to the next higher dose
ECG	Electrocardiogram

Abbreviation	Definition
ECI	Event of clinical interest
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data collection
ELISA	Enzyme-linked immunosorbent assay
EOC	Executive Oversight Committee
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire 30
EOT	End-of-treatment
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agents
ESMO	European Society for medical Oncology
EuroQoL EQ-5D-5L	European Quality of Life (EuroQoL)-5 dimensions-5 levels
Exp	Experimental
FA	Final analysis
FAS	Full Analysis Set
FBR	Future biomedical research
FDAAA	Food and Drug Administration Amendments Act
FFPE	Formalin-fixed, paraffin embedded
FKSI-DRS	Functional Assessment of Cancer Therapy – Kidney Symptom Index-disease-related symptoms
FSH	Follicle-stimulating hormone
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
HA	Health authority
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HIF-1β	Hypoxia-inducible factor 1β
HIF-2α	Hypoxia-inducible factor 2α
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
IA	Interim analysis
IB	Investigator's Brochure
IC_{50}	Half-maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
iCRO	Imaging contract research organization
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

Abbreviation	Definition
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous(ly)
IVD	In vitro diagnostic
K	Potassium
KPS	Karnofsky performance status
LAM	Lactational amenorrhea method
LLN	Lower limit of normal
M-darbe	NESP; darbepoetin alfa
Mg	Magnesium
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
Na	Sodium
NCCN	The National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	Non-investigational Medicinal Product
OR	Objective response
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PAS	Per-ARNT-Sim
PD-1	Programmed cell death 1
PD-L1	Programmed cell death 1 ligand 1
pEFD	Preliminary embryo-fetal toxicity
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PO4	Phosphate
PR	Partial response
pRBC	Packed red blood cells
PRO	Patient-reported outcome
PT	Prothrombin time
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
Q16W	Every 16 weeks
Q24W	Every 24 weeks
QD	Once daily
QoL	Quality of life
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
S	Stay at the current dose
SAC	Scientific Advisory Committee
SAE	Serious adverse event

Abbreviation	Definition
SBP	Systolic blood pressure
SC	Subcutaneously
SD	Stable disease
SIM	Site Imaging Manual
SLC2A1	Solute carrier family 2 member 1
SoA	Schedule of activities
SOC	System organ class
sSAP	Supplemental Statistical Analysis Plan
SUSAR	Suspected unexpected serious adverse reaction
TB	*Bacillus* tuberculosis
TK	Toxicokinetic
TKI	Tyrosine kinase inhibitor
t_{max}	Time to maximum concentration
TTD	Time to deterioration
UGT	Uridine 5'-diphospho-glucuronosyltrasnferase
ULN	Upper limit of normal
VAS	Visual Analog Scale
VEGF	Vascular endothelial growth factor
VEGF-A	Vascular endothelial growth factor-A
VHL	Von Hippel Lindau
VZ/F	Apparent volume of distribution
WBC	White blood cell
Wk	Week
WOCBP	Woman/women of childbearing potential

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