2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme LLC, Rahway, NJ, USA (hereafter called the Sponsor or MSD)

COMPOUND NAME: Belzutifan (MK-6482)

PROTOCOL TITLE: Phase 2 Study of MK-6482 in Participants With Advanced Renal Cell Carcinoma

STUDY IDENTIFIERS:

IND: 132,120	EudraCT: 2020-001907-18	WHO: Not applicable	NCT: 04489771
JRCT: Not applicable	UTN: Not applicable	EU CT: Not applicable	

STUDY PHASE: Phase 2

INDICATION: Renal cell carcinoma

STUDY CENTERS: This study is being conducted at 48 centers in 9 countries.

STUDY STATUS:

This study is ongoing; this report is based on the data cutoff date of 10-FEB-2023 with a median follow-up duration of 17.2 months.

First Participant, First Visit	Data Cutoff	Database Lock Date
13-SEP-2020	10-FEB-2023	16-MAR-2023

METHODOLOGY:

This is an ongoing, open-label, multicenter, Phase 2 study to evaluate the efficacy and safety of belzutifan 200 mg QD and 120 mg QD in participants with advanced ccRCC that has progressed after up to 3 prior systemic regimens. A total of 154 participants were randomized in a 1:1 ratio to receive either 200 mg QD or 120 mg QD of belzutifan (study interventions are shown in the table below). Randomization was stratified by IMDC prognostic scores (0 vs 1 to 2 vs 3 to 6) and number of prior TKI therapies for advanced RCC (0 vs 1 vs 2 to 3). Participants were evaluated radiologically at Week 9, then every 8 weeks for the first 49 weeks, and every 12 weeks thereafter to assess response to treatment. Treatment will continue until documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, or administrative reasons requiring cessation of treatment. Participants who

discontinue study treatment for reasons other than disease progression should continue with imaging assessments. Participants may be permitted to continue treatment beyond disease progression, after Sponsor consultation.

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen
Belzutifan 120 mg	Belzutifan	40 mg tablet	120 mg	Oral	QD
Belzutifan 200 mg	Belzutifan	40 mg tablet	200 mg	Oral	QD

QD=once daily

Part of this study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its standard operating procedures for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate impact on study conduct.

ELIGIBILITY CRITERIA:

This study included male and female participants ≥18 years of age with locally advanced or metastatic ccRCC who had disease progression on or after systemic treatment with an anti-PD-1/L1 monotherapy or in combination with other agents, but had received up to 3 prior systemic regimens, and who had measurable disease per RECIST 1.1, a KPS score ≥70%, and adequate organ function.

OBJECTIVES AND ENDPOINTS:

This study is being conducted in male and female participants with previously treated advanced ccRCC.

Primary Objective	Primary Endpoint
Objective: To compare the 120 mg once daily (QD) dose and 200 mg QD dose of belzutifan with respect to objective response rate (ORR) based on Response Criteria in Solid Tumors (RECIST) 1.1 as assessed by blinded independent central review (BICR). Hypothesis (H1): Belzutifan 200 mg QD is superior to belzutifan 120 mg QD in terms of ORR per RECIST 1.1 by BICR.	Objective response (OR): complete response (CR) or partial response (PR).

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

Exploratory endpoint analyses are not included in this CSR.

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total was 150 participants. As of the data cutoff date for this report enrollment was complete; 154 participants were randomized and included in the ITT population for analysis (78 in the belzutifan 200 mg QD group, 76 in the belzutifan 120 mg QD group).

STATISTICAL AND ANALYSIS METHODS:

Efficacy analyses were conducted using the ITT population, which included all participants randomized to study intervention. The primary hypothesis comparing the 200 mg QD dose of belzutifan to the 120 mg QD dose of belzutifan with respect to ORR was evaluated using the stratified Miettinen and Nurminen method with strata weighted by sample size. PFS and OS were summarized within each dose group using the KM method, and HR was estimated using a stratified Cox regression model. The KM method was used to estimate DOR. The difference in CBR between the 2 belzutifan doses and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size was reported. Sensitivity analyses were also performed to assess ORR, PFS, and DOR based on the investigator's assessment.

Safety analyses were conducted using data from the APaT population, which included all randomized participants who received at least 1 dose of study intervention. Analysis followed a tiered approach; details of the tiered approach are described in the study protocol.

RESULTS:

Participant Disposition:

- Belzutifan 200 mg QD: 78 randomized, 78 treated, 57 (73.1%) discontinued treatment, 21 (26.9%) ongoing on treatment, 28 (35.9%) discontinued study, 50 (64.1%) ongoing in the study.
- Belzutifan 120 mg QD: 76 randomized, 76 treated, 58 (76.3%) discontinued treatment, 18 (23.7%) ongoing on treatment, 25 (32.9%) discontinued study, 51 (67.1%) ongoing in the study.

Demographics and Baseline Characteristics:

Demographics and baseline disease characteristics were generally well balanced for the 2 dose groups (ITT population).

- **Overall Median Age (Range):** 64.0 years (31 to 82 years)
- **Sex:** 123 (79.9%) male, 31 (20.1%) female
- **Ethnicity:** 141 (91.6%) not Hispanic or Latino, 7 (4.5%) Hispanic or Latino, 3 (1.9%) not reported, 3 (1.9%) unknown
- **Race:** 140 (90.9%) White, 6 (3.9%) Black or African American, 5 (3.2%) Asian, 1 (0.6%) Native Hawaiian or Other Pacific Islander, 2 (1.3%) missing
- **IMDC Risk Categories:** 27 (17.5%) favorable; 106 (68.8%) intermediate; 21 (13.6%) poor
- **Number of Prior Lines of Therapy:** 73 (47.4%) 1 line; 60 (39.0%) 2 lines; 21 (13.6%) 3 lines

Efficacy/Pharmacokinetics:

Primary Efficacy Endpoint

- Belzutifan 200 mg QD did not demonstrate superiority to belzutifan 120 mg QD with respect to ORR per RECIST 1.1 by BICR after a median duration of 17.2 months of follow-up.
- ORR was 23.1% (95% CI: 14.3, 34.0) in the belzutifan 200 mg QD group and 23.7% (95% CI: 14.7, 34.8) in the belzutifan 120 mg QD group. The difference in ORR was -0.5% (95% CI: -14.0, 12.9; *p*=0.5312).

Secondary Efficacy Endpoints

- The median DOR among participants with a confirmed response was 16.1 months (range: 2.1+ to 23.5+ months) for the belzutifan 200 mg QD group and not reached (range: 2.1+ to 16.1+ months) for the belzutifan 120 mg QD group. The percentage of responders at each response duration time point (6 months through 15 months) was comparable. The median TTR was 3.6 months (range: 1.7 to 5.5 months) for the belzutifan 200 mg QD group and 3.6 months (range: 1.8 to 16.8 months) for the belzutifan 120 mg QD group.
- The PFS was comparable between the belzutifan 200 mg QD and belzutifan 120 mg QD groups with an HR of 0.94 (95% CI: 0.63, 1.40). The median PFS was 9.1 months (95% CI: 5.5, 12.0) and 7.3 months (95% CI: 5.6, 9.5) in the belzutifan 200 mg QD and belzutifan 120 mg QD groups, respectively.
- CBR by BICR was comparable between the belzutifan 200 mg QD and belzutifan 120 mg QD groups (41.0% [95% CI: 30.0, 52.7] and 47.4% [95% CI: 35.8, 59.2], respectively).
- The OS was comparable between the belzutifan 200 mg QD and belzutifan 120 mg QD groups with an HR of 1.11 (95% CI: 0.65, 1.90). The median OS was not reached in either the belzutifan 200 mg QD group [95% CI: 20.6, NR] or the belzutifan 120 mg QD group (95% CI: 22.0, NR). OS rates, based on KM estimates, were comparable between the 2 dose groups at each time point (6 months through 24 months).

Pharmacokinetics

- C_{max} and C_{trough} values were proportionally higher (~1.6-fold) for the belzutifan 200 mg QD group compared to the belzutifan 120 mg QD group.

Safety:

- The safety results in this study are similar overall between the belzutifan 200 mg QD and belzutifan 120 mg QD groups and generally consistent with the known safety profile for belzutifan.

- After an overall median duration of exposure of 7.5 months (range: 0.1 to 26.0 months), the incidence of participants with AEs and severity of AEs, including AEs leading to death, SAEs, and Grade 3 to 5 AEs, were generally similar (<10% difference) between the 2 dose groups, except for the incidence of participants with an AE leading to any dose modification (combining discontinuations, reductions, and interruptions), which was higher (≥10% difference) in the belzutifan 200 mg QD group (57.7%) compared to the belzutifan 120 mg QD group (46.1%). The incidence of participants with AEs leading to discontinuation of study treatment was 14.1% in the belzutifan 200 mg QD group and 5.3% in the belzutifan 120 mg QD group.
- Overall, the most frequently reported AEs (reported in ≥20% participants in either dose group) were anemia, fatigue, nausea, hypoxia, headache, dyspnea, edema peripheral, and arthralgia.
- Most participants in the belzutifan 200 mg QD and 120 mg QD groups reported Grade 2 (25.6% and 27.6%, respectively) or Grade 3 (61.5% and 63.2%, respectively) AEs. Three (3.8%) participants in the belzutifan 200 mg QD group and 4 (5.3%) participants in the belzutifan 120 mg QD group reported Grade 4 AEs.
- Three (3.8%) deaths resulting from AEs (COVID-19, sepsis, and septic shock) were reported in the belzutifan 200 mg QD group. None of these AEs resulting in death were assessed by the investigator as related to the study treatment. No AEs leading to death were reported in the belzutifan 120 mg QD group.
- SAEs reported in ≥5% participants in the belzutifan 200 mg QD and 120 mg QD groups were hypoxia (9 [11.5%] and 4 [5.3%] participants, respectively) and anemia (4 [5.1%] and 4 [5.3%] participants, respectively).
- The incidence and severity of anemia (an ADR for belzutifan) were generally similar (<10% difference) between the 2 dose groups. Most AEs of anemia were Grade 1 or Grade 2. No Grade 4 or Grade 5 events of anemia were reported. Anemia was manageable with dose modification and/or treatment with ESAs/blood transfusions. More participants with AEs of anemia in the belzutifan 200 mg QD group received ESAs and blood transfusions compared with the belzutifan 120 mg QD group. No participants discontinued belzutifan due to anemia.
- The incidence and severity of hypoxia (an ADR for belzutifan) were generally similar (<10% difference) between the 2 dose groups. Most AEs of hypoxia were Grade 3. No Grade 4 or Grade 5 events of hypoxia were reported. Hypoxia was manageable with dose modification and/or supplemental oxygen. Two (2.6%) participants in each group discontinued belzutifan due to hypoxia.
- The incidence of participants with postbaseline grade shifts in laboratory parameters was generally similar between the 2 dose groups.
- Mean changes from baseline in SBP, DBP, and heart rate were similar between the 2 dose groups. In both dose groups, there was a mean decrease from baseline in oxygen saturation by approximately 2% starting at Week 3 and stabilizing through the end of treatment.

- Body weight increase from baseline was noted in both dose groups over time. The mean percent increase from baseline in body weight at 25 weeks and 53 weeks was 4.35% (SD: 5.89) and 7.92% (SD: 7.95), respectively, in the belzutifan 200 mg QD group and 2.28% (SD: 6.39) and 6.09% (SD: 8.18), respectively, in the belzutifan 120 mg QD group.

Adverse Event Summary
(APaT Population)

	Belzutifan 200 mg QD		Belzutifan 120 mg QD		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	78		76		154	
with one or more adverse events	77	(98.7)	75	(98.7)	152	(98.7)
with no adverse event	1	(1.3)	1	(1.3)	2	(1.3)
with drug-related[a] adverse events	72	(92.3)	70	(92.1)	142	(92.2)
with toxicity grade 3-5 adverse events	54	(69.2)	52	(68.4)	106	(68.8)
with toxicity grade 3-5 drug-related adverse events	36	(46.2)	35	(46.1)	71	(46.1)
with serious adverse events	33	(42.3)	33	(43.4)	66	(42.9)
with serious drug-related adverse events	17	(21.8)	13	(17.1)	30	(19.5)
who died	3	(3.8)	0	(0.0)	3	(1.9)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
with any dose modification[b] due to an adverse event	45	(57.7)	35	(46.1)	80	(51.9)
with any dose interruption due to an adverse event	27	(34.6)	22	(28.9)	49	(31.8)
with any dose reduction due to an adverse event	25	(32.1)	19	(25.0)	44	(28.6)
discontinued drug due to an adverse event	11	(14.1)	4	(5.3)	15	(9.7)
discontinued drug due to a drug-related adverse event	7	(9.0)	2	(2.6)	9	(5.8)
discontinued drug due to a serious adverse event	8	(10.3)	3	(3.9)	11	(7.1)
discontinued drug due to a serious drug-related adverse event	4	(5.1)	1	(1.3)	5	(3.2)

[a] Determined by the investigator to be related to the drug.

[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Grades are based on NCI CTCAE 5.0.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA Version: 25.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 10FEB2023

Source: [P013V01MK6482: adam-adsl; adae]

CONCLUSIONS:

Efficacy/Pharmacokinetics

Based on the results from this study, the following efficacy conclusion can be made regarding belzutifan for the treatment of individuals with advanced RCC who have received up to 3 prior systemic regimens:

- Belzutifan 200 mg administered once daily is not superior to belzutifan 120 mg administered once daily as assessed by ORR per RECIST 1.1 by BICR.

The following key results were also observed in the treatment of pretreated participants with advanced RCC:

- No clinically meaningful differences were noted in DOR, PFS, CBR, or OS between belzutifan administered orally at doses of 200 mg QD or 120 mg QD.
- Belzutifan PK at 200 mg QD and 120 mg QD was dose proportional.

Safety

Based on the results from this study, the following safety conclusions can be made:

- Safety profiles of the 200 mg QD and 120 mg QD belzutifan doses are generally similar and are consistent with the known safety profile of belzutifan.
- The belzutifan 200 mg QD dose is associated with a higher rate of overall dose modifications and drug discontinuation, and a higher rate of intervention for the treatment of anemia.

LIST OF ABBREVIATIONS:

Abbreviation/Term	Definition
ADR	adverse drug reaction
APaT	All-Participants-as-Treated
ccRCC	clear cell renal cell carcinoma
CI	confidence interval
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ESA	erythropoiesis-stimulating agent
HR	hazard ratio
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
ITT	intent-to-treat
KM	Kaplan-Meier
KPS	Karnofsky performance status
MedDRA	medical dictionary for regulatory agencies
NCI	National Cancer Institute
NR	not reached
PD-1/L1	programmed cell-death 1/programmed cell-death ligand 1
RCC	renal cell carcinoma
SAE	serious adverse event
SD	standard deviation
TKI	tyrosine-kinase inhibitor
TTR	time to response

PUBLICATIONS: As of the date of this report, there are no publications based on this study.

REPORT DATE: 31-JUL-2023

REVISED REPORT DATE: Not applicable.