CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

215383Orig1s006

Trade Name:	**WELIREG**
Generic or Proper Name:	(belzutifan)
Sponsor:	MERCK SHARPE & DOHME
Approval Date:	December 14, 2023

Indication:

WELIREG is a hypoxia-inducible factor inhibitor indicated:

Von Hippel-Lindau (VHL) disease

- for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

Advanced Renal Cell Carcinoma

- for the treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 215383/S-006

SUPPLEMENT APPROVAL

Merck Sharp & Dohme LLC
Attention: Julie M. Forte, MS, MT (ASCP), RAC
Senior Director, Global Regulatory Affairs
126 East Lincoln Ave, P.O. Box 2000
Rahway, NJ 07065

Dear Julie Forte:

Please refer to your supplemental new drug application (sNDA) dated July 17, 2023, received July 17, 2023, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for WELIREG (belzutifan).

This Prior Approval sNDA provides for a new indication: WELIREG for the treatment of adult patients with advanced renal cell carcinoma following a programmed death receptor-1 or programmed death-ligand 1 inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which the FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4561-1 Complete clinical trial LITESPARK-005, “An Open-label, Randomized Phase 3 Study of Belzutifan Versus Everolimus in Participants with Advanced Renal Cell Carcinoma That Has Progressed After Prior PD-1/L1 and VEGF-Targeted Therapies” to provide the final overall survival analyses.

The timetable you submitted on December 5, 2023, states that you will conduct this study according to the following schedule:

Trial Completion:	05/2024
Final Report Submission:	11/2024

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submit clinical protocols to your IND 132120 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to the FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to the FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, email Benjamin Chukwurah, Regulatory Project Manager, at benjamin.chukwurah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Daniel Suzman, MD
Deputy Division Director
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DANIEL L SUZMAN
12/14/2023 02:40:08 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use WELIREG safely and effectively. See full prescribing information for WELIREG.

WELIREG® (belzutifan) tablets, for oral use
Initial U.S. Approval: 2021

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Exposure to WELIREG during pregnancy can cause embryo-fetal harm.**
- **Verify pregnancy status prior to the initiation of WELIREG.**
- **Advise patients of these risks and the need for effective non-hormonal contraception. WELIREG can render some hormonal contraceptives ineffective. (5.3, 7.2, 8.1, 8.3)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Advanced Renal Cell Carcinoma (RCC) (1.2)	12/2023
Dosage and Administration, Dosage Modification for Adverse Reactions (2.2)	12/2023
Warnings and Precautions (5.1, 5.2)	12/2023

----------INDICATIONS AND USAGE----------

WELIREG is a hypoxia-inducible factor inhibitor indicated:

von Hippel-Lindau (VHL) disease

- for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. (1.1)

Advanced Renal Cell Carcinoma (RCC)

- for treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI). (1.2)

----------DOSAGE AND ADMINISTRATION----------

The recommended dosage of WELIREG is 120 mg administered orally once daily with or without food. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 40 mg (3)

----------CONTRAINDICATIONS----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Anemia: Monitor for anemia before initiation of and periodically throughout treatment with WELIREG.(2.2, 5.1)
- Withhold WELIREG until hemoglobin ≥8g/dL, then resume at the same or reduced dose or discontinue. For life threatening anemia, or for anemia requiring urgent intervention, withhold WELIREG until hemoglobin ≥8g/dL and resume at a reduced dose or permanently discontinue WELIREG. (2.2, 5.1)
- Hypoxia: Monitor oxygen saturation before initiation of, and periodically throughout, treatment with WELIREG. For hypoxia at rest, withhold until resolved, resume at reduced dose, or discontinue depending on severity. For life-threatening hypoxia, permanently discontinue WELIREG. (2.2, 5.2)

---------- ADVERSE REACTIONS ----------

VHL disease: Most common (≥25%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin, fatigue, increased creatinine, headache, dizziness, increased glucose, and nausea. (6.1)

Advanced RCC: Most common (≥25%) adverse reactions, including laboratory abnormalities were decreased hemoglobin, fatigue, musculoskeletal pain, increased creatinine, decreased lymphocytes, increased alanine aminotransferase, decreased sodium, increased potassium, and increased aspartate aminotransferase. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

UGT2B17 or CYP2C19 Inhibitors: Monitor for signs and symptoms of anemia and hypoxia and reduce the dosage of WELIREG as recommended. (2.2, 7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

- Lactation: Advise not to breastfeed. 8.2)
- Infertility: May impair fertility in males and females. 8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

- **Exposure to WELIREG during pregnancy can cause embryo-fetal harm.**
- **Verify pregnancy status prior to the initiation of WELIREG.**
- **Advise patients of these risks and the need for effective non-hormonal contraception. WELIREG can render some hormonal contraceptives ineffective *[see Warnings and Precautions (5.3), Drug Interactions (7.2), Use in Specific Populations (8.1, 8.3)]*.**

1 INDICATIONS AND USAGE

1.1 von Hippel-Lindau (VHL) disease

WELIREG is indicated for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

1.2 Advanced Renal Cell Carcinoma (RCC)

WELIREG is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of WELIREG is 120 mg administered orally once daily until disease progression or unacceptable toxicity. WELIREG should be taken at the same time each day and may be taken with or without food.

Advise patients to swallow tablets whole. Do not chew, crush, or split WELIREG prior to swallowing.

If a dose of WELIREG is missed, it can be taken as soon as possible on the same day. Resume the regular daily dose schedule for WELIREG the next day. Do not take extra tablets to make up for the missed dose.

If vomiting occurs any time after taking WELIREG, do not retake the dose. Take the next dose on the next day.

2.2 Dosage Modifications for Adverse Reactions

Dosage modifications for WELIREG for adverse reactions are summarized in Table 1.

The recommended dose reductions are:

- First dose reduction: WELIREG 80 mg orally once daily
- Second dose reduction: WELIREG 40 mg orally once daily
- Third dose reduction: Permanently discontinue

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Anemia *[see Warnings and Precautions (5.1)]*	Hemoglobin <8 g/dL or transfusion indicated	• Withhold until hemoglobin ≥8g/dL. • Resume at the same or reduced dose; or discontinue depending on the severity of anemia.
	Life-threatening or urgent intervention indicated	• Withhold until hemoglobin ≥8g/dL. • Resume at a reduced dose or permanently discontinue.
Hypoxia *[see Warnings and Precautions (5.2)]*	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%)	• Consider withholding until resolved. • Resume at the same dose or at a reduced dose depending on the severity of hypoxia.
	Decreased oxygen saturation at rest (e.g., pulse oximeter	• Withhold until resolved. • Resume at reduced dose or discontinue depending on the severity of hypoxia.

	<88% or PaO_2 ≤55 mm Hg) or urgent intervention indicated	
	Life-threatening or recurrent symptomatic hypoxia	• Permanently discontinue.
Other Adverse Reactions *[see Adverse Reactions (6)]*	Grade 3	• Withhold dosing until resolved to ≤ Grade 2. • Consider resuming at a reduced dose (reduce by 40 mg). • Permanently discontinue upon recurrence of Grade 3.
	Grade 4	• Permanently discontinue.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg, blue, oval shaped, film-coated, debossed with “177” on one side and plain on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anemia

WELIREG can cause severe anemia that can require blood transfusion.

Monitor for anemia before initiation of, and periodically throughout, treatment with WELIREG. Transfuse patients as clinically indicated. For patients with hemoglobin <8g/dL, withhold WELIREG until ≥8g/dL, then resume at the same or reduced dose or permanently discontinue WELIREG, depending on the severity of anemia. For life threatening anemia or when urgent intervention is indicated, withhold WELIREG until hemoglobin ≥8g/dL, then resume at a reduced dose or permanently discontinue WELIREG *[see Dosage and Administration (2.2)]*.

von Hippel-Lindau (VHL) disease

In LITESPARK-004, decreased hemoglobin occurred in 93% of patients and 7% had Grade 3 events *[see Adverse Reactions (6.1)]*. Median time to onset of anemia was 31 days (range: 1 day to 8.4 months).

The safety of erythropoiesis stimulating agents (ESAs) for treatment of anemia in patients with VHL disease treated with WELIREG has not been established. Randomized controlled trials in patients with cancer receiving myelosuppressive chemotherapy with ESAs have shown that ESAs increased the risks of death and serious cardiovascular reactions, and decreased progression-free survival and/or overall survival. See the prescribing information for ESAs for more information.

Advanced Renal Cell Carcinoma (RCC)

In LITESPARK-005, decreased hemoglobin occurred in 88% of patients and 29% had Grade 3 events *[see Adverse Reactions (6.1)]*. Median time to onset of anemia was 29 days (range: 1 day to 16.6 months). Of the patients with anemia, 22% received transfusions only, 20% of patients received ESAs only and 12% received both transfusion and ESAs.

5.2 Hypoxia

WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization *[see Dosage and Administration (2.2)]*.

Monitor oxygen saturation before initiation of, and periodically throughout, treatment with WELIREG. For decreased oxygen saturation with exercise (e.g., pulse oximeter <88% or P_aO_2 ≤55 mm Hg), consider withholding WELIREG until pulse oximetry with exercise is greater than 88%, then resume at the same

dose or at a reduced dose. For decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 ≤55 mm Hg) or urgent intervention indicated, withhold WELIREG until resolved and resume at a reduced dose or discontinue. For life-threatening hypoxia or for recurrent symptomatic hypoxia, permanently discontinue WELIREG *[see Dosage and Administration (2.2)]*.

Advise patients to report signs and symptoms of hypoxia immediately to a healthcare provider.

von Hippel-Lindau (VHL) disease

In LITESPARK- 004, hypoxia occurred in 1.6% of patients *[see Adverse Reactions (6.1)]*.

Advanced Renal Cell Carcinoma (RCC)

In LITESPARK- 005, hypoxia occurred in 15% of patients and 10% had Grade 3 events *[see Adverse Reactions (6.1)]*. Of the patients with hypoxia, 69% were treated with oxygen therapy. Median time to onset of hypoxia was 30.5 days (range: 1 day to 21.1 months).

5.3 Embryo-Fetal Toxicity

Based on findings in animals, WELIREG can cause fetal harm when administered to a pregnant woman. In an animal reproduction study, oral administration of belzutifan to pregnant rats during the period of organogenesis caused embryo-fetal lethality, reduced fetal body weight, and fetal skeletal malformations at maternal exposures ≥0.2 times the human exposures AUC) at the recommended dose of 120 mg daily.

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose, since WELIREG can render some hormonal contraceptives ineffective *[see Drug Interactions (7.1)]*. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling:

- Anemia *[see Warnings and Precautions (5.1)]*
- Hypoxia *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

von Hippel-Lindau (VHL) disease

LITESPARK-004

The safety of WELIREG was evaluated in an open-label clinical trial (LITESPARK-004) in 61 patients with VHL disease who had at least one measurable solid tumor localized to the kidney *[see Clinical Studies (14.1)]*. Patients received WELIREG 120 mg orally once daily. The median duration of exposure to WELIREG was 68 weeks range: 8.4 to 104.7 weeks).

Serious adverse reactions occurred in 15% of patients who received WELIREG, including anemia, hypoxia, anaphylaxis reaction, retinal detachment, and central retinal vein occlusion (1 patient each).

Permanent discontinuation of WELIREG due to adverse reactions occurred in 3.3% of patients. Adverse reactions which resulted in permanent discontinuation of WELIREG were dizziness and opioid overdose (1.6% each).

Dosage interruptions of WELIREG due to an adverse reaction occurred in 39% of patients. Adverse reactions which required dosage interruption in >2% of patients were fatigue, decreased hemoglobin, anemia, nausea, abdominal pain, headache, and influenza-like illness.

Dose reductions of WELIREG due to an adverse reaction occurred in 13% of patients. The most frequently reported adverse reaction which required dose reduction was fatigue (7%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, that occurred in patients who received WELIREG were decreased hemoglobin, fatigue, increased creatinine, headache, dizziness, increased glucose, and nausea.

Table 2 summarizes the adverse reactions reported in patients treated with WELIREG in LITESPARK-004.

Table 2: Adverse Reactions Occurring in ≥10% of Patients Who Received WELIREG in LITESPARK-004

Adverse Reaction	WELIREG (n=61)	
	All Grades* %)	Grade 3-4 %)
General		
Fatigue†	64	5
Nervous system		
Headache†	39	0
Dizziness†	38	0
Gastrointestinal		
Nausea	31	0
Constipation	13	0
Abdominal pain†	13	0
Eye Disorders		
Visual impairment‡	21	3.3
Infections		
Upper respiratory tract infection †	21	0
Respiratory, Thoracic and Mediastinal		
Dyspnea	20	1.6
Musculoskeletal and Connective Tissue		
Arthralgia	18	0
Myalgia	16	0
Vascular		
Hypertension	13	3.3
Metabolism and Nutrition		
Weight increased	12	1.6

*Graded per NCI CTCAE v4.0
† Includes other related terms
‡Includes visual impairment, vision blurred, central retinal vein occlusion and retinal detachment

Table 3 summarizes the laboratory abnormalities in LITESPARK-004.

Table 3: Select Laboratory Abnormalities (≥10% That Worsened from Baseline in Patients Who Received WELIREG in LITESPARK-004

Laboratory Abnormality*	WELIREG (n=61)	
	Grades 1-4 %	Grades 3-4 %
Hematology		
Decreased hemoglobin	93	7
Decreased leukocytes	11	0
Chemistry		
Increased creatinine	64	0
Increased glucose	34	4.9
Increased ALT	20	0
Increased AST	16	0
Decreased calcium (corrected)	10	0
Decreased phosphate	10	1.6

*The denominator used to calculate the rate is based on all patients in the safety analysis population.

Advanced Renal Cell Carcinoma (RCC)

LITESPARK-005

The safety of WELIREG was evaluated in a randomized, active-controlled study (LITESPARK- 005) in 732 patients with advanced RCC that has progressed after prior PD-1 or PD-L1 checkpoint inhibitor and VEGF receptor targeted therapies *[see Clinical Studies (14.2)]*. Patients received 120 mg WELIREG (n=372) or 10 mg everolimus (n=360) by oral administration once daily. The median duration of exposure to WELIREG was 7.6 months (range 0.1 to 28.5 months).

Serious adverse reactions occurred in 38% of patients who received WELIREG. Serious adverse reactions in ≥2% of patients treated with WELIREG were hypoxia (7%), anemia (5%), pneumonia (3.5%), hemorrhage (3%), and pleural effusion (2.2%). Fatal adverse reactions occurred in 3.2% of patients who received WELIREG, including sepsis (0.5%) and hemorrhage (0.5%).

Permanent discontinuation of WELIREG due to adverse reactions occurred in 6% of patients. Adverse reactions which resulted in permanent discontinuation (≥0.5% of WELIREG were hypoxia (1.1%), anemia (0.5%), and hemorrhage (0.5%).

Dosage interruptions of WELIREG due to an adverse reaction occurred in 39% of patients. Adverse reactions which required dosage interruption in ≥2% of patients were anemia (8%), hypoxia (5%), COVID-19 (4.3%), fatigue (3.2%), and hemorrhage (2.2%).

Dose reductions of WELIREG due to an adverse reaction occurred in 13% of patients. Adverse reactions which required dose reduction in ≥1% of patients were hypoxia (5% and anemia 3.2%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, that occurred in patients who received WELIREG were decreased hemoglobin, fatigue, musculoskeletal pain, increased creatinine, decreased lymphocytes, increased alanine aminotransferase, decreased sodium, increased potassium, and increased aspartate aminotransferase.

Table 4 summarizes the adverse reactions in LITESPARK-005.

Table 4: Adverse Reactions ≥10%) in Patients with Advanced RCC Receiving WELIREG in LITESPARK-005

Adverse Reaction	WELIREG (n=372)		Everolimus (n=360)	
	All Grades* %)	Grade 3-4 %)	All Grades* %)	Grade 3-4 %)
Fatigue†	43	3.2	41	6
Edema†	20	0.5	23	0.6

Musculoskeletal and Connective Tissue				
Musculoskeletal Pain†	34	1.1	27	2.2
Gastrointestinal				
Nausea	17	0.5	11	0.3
Constipation	15	0	8	0
Vomiting	11	0.8	8	0.8
Diarrhea†	11	1.3	19	1.4
Abdominal Pain†	10	0.8	8	0.3
Respiratory, Thoracic, and Mediastinal				
Dyspnea†	16	1.6	16	2.5
Hypoxia	15	10	1.4	1.4
Metabolism and Nutrition				
Decreased Appetite	13	1.1	16	0
Nervous Systems				
Headache†	12	0.5	8	0.3
Dizziness†	11	0	1.9	0

* Graded per NCI CTCAE v5.0
† Includes other related terms

Clinically relevant adverse reactions in <10% of patients who received WELIREG in LITESPARK-005 included hemorrhage (9%) [including intracranial/cerebral hemorrhage (0.8%)], rash (8%), hypertension (6%), visual impairment [including vision blurred (4%), visual acuity decreased (1.1%), visual impairment (0.5%), and retinal detachment (0.3%)] (6%) and increased weight (5%).

Table 5 summarizes the laboratory abnormalities in LITESPARK-005.

Table 5: Select Laboratory Abnormalities (≥20%) That Worsened from Baseline In Patients with Advanced RCC who Received WELIREG in LITESPARK-005

Laboratory Test*	WELIREG		Everolimus	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Decreased hemoglobin	88	29	76	17
Decreased lymphocytes	34	8	53	20
Chemistry				
Increased creatinine	34	4.7	43	5.1
Increased alanine aminotransferase	32	2.2	40	1.1
Decreased sodium	31	1.6	36	0.8
Increased potassium	29	2.5	20	2.8
Increased aspartate aminotransferase	27	2.2	38	2
Decreased glucose	22	1.1	19	1.1
Decreased calcium	21	1.1	45	3.1

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available WELIREG (range: 359 to 366 patients), and everolimus (range: 351 to 356 patients).
† Graded per NCI CTCAE v5.0

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on WELIREG

UGT2B17 or CYP2C19 Inhibitors

Coadministration of WELIREG with inhibitors of UGT2B17 or CYP2C19 increases plasma exposure of belzutifan *[see Clinical Pharmacology (12.3, 12.5)]*, which may increase the incidence and severity of adverse reactions of WELIREG. Monitor for anemia and hypoxia and reduce the dosage of WELIREG as recommended *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.2), Adverse Reactions (6)]*.

7.2 Effect of WELIREG on Other Drugs

Sensitive CYP3A4 Substrates

Coadministration of WELIREG with CYP3A4 substrates decreases concentrations of CYP3A substrates *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of these substrates. The magnitude of this decrease may be more pronounced in patients who are dual UGT2B17 and CYP2C19 poor metabolizers *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of WELIREG with sensitive CYP3A4 substrates, for which minimal decrease in concentration may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dosage in accordance with its Prescribing Information.

Hormonal Contraceptives

Coadministration of WELIREG with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding *[see Clinical Pharmacology (12.3), Use in Specific Populations (8.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies, WELIREG can cause fetal harm when administered to a pregnant woman. There are no available data on the use of WELIREG in pregnant women to inform the drug-associated risk. In an animal reproduction study, oral administration of belzutifan to pregnant rats during the period of organogenesis caused embryo-fetal lethality, reduced fetal body weight, and fetal skeletal malformations at maternal exposures ≥0.2 times the human exposure (AUC) at the recommended dose of 120 mg daily (*see Data*). Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data

In a pilot embryo-fetal development study, pregnant rats received oral doses of 6, 60, or 200 mg/kg/day of belzutifan during the period of organogenesis. Belzutifan caused embryo-fetal lethality at doses ≥60 mg/kg/day (approximately 1 time the human exposure at the recommended dose based on AUC). Reduced fetal body weights, fetal rib malformations, and reduced skeletal ossification occurred at doses of 6 and 60 mg/kg/day approximately ≥0.2 times the human exposure at the recommended dose based on AUC).

8.2 Lactation

Risk Summary

There are no data on the presence of belzutifan or its metabolites in human milk or their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a

breastfed child, advise women not to breastfeed during treatment with WELIREG and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

WELIREG can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with WELIREG.

Contraception

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose. WELIREG can render some hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose.

Infertility

Based on findings in animals, WELIREG may impair fertility in males and females of reproductive potential *[see Nonclinical Toxicology (13.1)]*. The reversibility of the effect on fertility is unknown.

8.4 Pediatric Use

Safety and effectiveness of WELIREG have not been established in pediatric patients.

8.5 Geriatric Use

Of the patients who received WELIREG in LITESPARK-004, 3.3% were ≥65 years old *[see Clinical Studies (14.1)]* Clinical trials of WELIREG in patients with VHL did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

Of the 372 patients who received WELIREG for advanced RCC in LITESPARK-005, 62% of patients younger than 65 years, 28% of patients were 65 to 74 years, and 10% were 75 years and over. No overall difference in efficacy was reported between patients who were ≥65 years of age and younger patients. Dose interruptions occurred in 48% of patients ≥65 years of age and in 34% of younger patients. Dose reductions occurred in 18% of patients ≥65 years of age and in 10% of younger patients.

8.6 Renal Impairment

No dosage modification of WELIREG is recommended in patients with mild (eGFR 60-89 mL/min/1.73 m^2 estimated by MDRD) and moderate (eGFR 30-59 mL/min/1.73 m^2) renal impairment *[see Clinical Pharmacology (12.3)]*. WELIREG has not been studied in patients with severe (eGFR 15-29 mL/min/1.73 m^2) renal impairment.

8.7 Hepatic Impairment

No dosage modification of WELIREG is recommended in patients with mild [total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin >1 to 1.5 x ULN and any AST] hepatic impairment. WELIREG has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and any AST) *[see Clinical Pharmacology (12.3)]*.

8.8 Dual UGT2B17 and CYP2C19 Poor Metabolizers

Patients who are dual UGT2B17 and CYP2C19 poor metabolizers have higher belzutifan exposures, which may increase the incidence and severity of adverse reactions of WELIREG. Closely monitor for

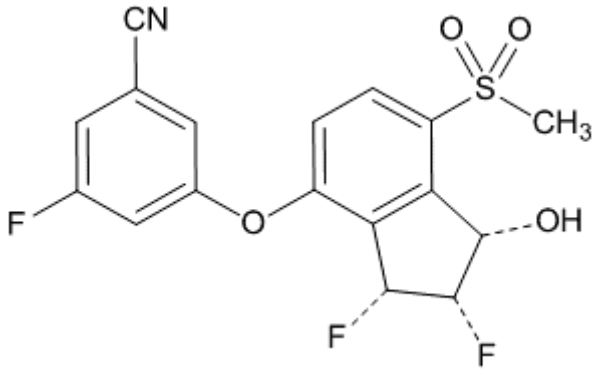
adverse reactions in patients who are dual UGT2B17 and CYP2C19 poor metabolizers *[see Warnings and Precautions (5), Adverse Reactions (6), Clinical Pharmacology (12.5)]*.

10 OVERDOSAGE

There is no specific treatment for WELIREG overdose. In cases of suspected overdose, withhold WELIREG and institute supportive care. Grade 3 hypoxia occurred at dosages of 120 mg twice a day and Grade 4 thrombocytopenia occurred at dosages of 240 mg once daily (approximately 2 times the recommended dosage).

11 DESCRIPTION

Belzutifan is an inhibitor of hypoxia-inducible factor-2α HIF-2α). The chemical name of belzutifan is 3-[[(1S,2S,3R)-2,3-Difluoro-2,3-dihydro-1-hydroxy-7-(methylsulfonyl)-1H-inden-4-yl]oxy]-5-fluorobenzonitrile. The molecular formula is $C_{17}H_{12}F_3NO_4S$ and the molecular weight is 383.34 Daltons. The chemical structure is:



Belzutifan is a white to light brown powder that is soluble in acetonitrile, dimethoxyethane, and acetone, sparingly soluble in ethyl acetate, very slightly soluble in isopropanol and toluene, and insoluble in water.

WELIREG is supplied as blue, film-coated tablets for oral use containing 40 mg of belzutifan together with croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, mannitol, microcrystalline cellulose, and silicon dioxide, as inactive ingredients. In addition, the film-coating contains FD&C Blue #2 aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Belzutifan is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α). HIF-2α is a transcription factor that plays a role in oxygen sensing by regulating genes that promote adaptation to hypoxia. Under normal oxygen levels, HIF-2α is targeted for ubiquitin-proteasomal degradation by VHL protein. Lack of functional VHL protein results in stabilization and accumulation of HIF-2α. Upon stabilization, HIF-2α translocates into the nucleus and interacts with hypoxia-inducible factor 1 beta (HIF-1β) to form a transcriptional complex that induces expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumor growth. Belzutifan binds to HIF-2α, and in conditions of hypoxia or impairment of VHL protein function, belzutifan blocks the HIF-2α-HIF-1β interaction, leading to reduced transcription and expression of HIF-2α target genes. In vivo, belzutifan demonstrated anti-tumor activity in mouse xenograft models of renal cell carcinoma.

12.2 Pharmacodynamics

Reductions in plasma levels of erythropoietin (EPO) were observed to be dose- and exposure-dependent at dosages up to 120 mg once daily. The maximum EPO suppression occurred following 2 weeks of consecutive dosing of WELIREG (mean percent decrease from baseline of approximately 60%). Mean EPO levels gradually returned to baseline values after 12 weeks of treatment.

The incidence of Grade 3 anemia increased with higher belzutifan exposure in patients with baseline hemoglobin levels <12 g/dL *[see Warnings and Precautions (5.1)]*.

Cardiac Electrophysiology

At the recommended dosage, WELIREG does not cause large mean increases (i.e., >20 msec) in the QT interval.

12.3 Pharmacokinetics

The C_{max} and AUC of belzutifan increase proportionally over a dose range of 20 mg to 120 mg WELIREG (0.17 to 1 times the approved recommended dose). The estimated geometric mean steady-state (CV%) C_{max} is 1.5 µg/mL 45%) and $AUC_{0\text{-}24h}$ is 20.4 µg•hr/mL (62%) in patients treated with 120 mg WELIREG. Steady state is reached after approximately 3 days.

Absorption

The median T_{max} occurs at 1 to 2 hours after WELIREG administration.

Effect of Food

A high-fat, high-calorie meal (total calories approximately 1000 kcal, 56 g fat, 55 g carbohydrate, and 31 g protein) delayed T_{max} by approximately 2 hours with no clinically meaningful effect on C_{max}, and AUC of belzutifan.

Distribution

The estimated mean (CV% volume of distribution is 119 L (28% Plasma protein binding of belzutifan is 45%. The blood-to-plasma concentration ratio of belzutifan is 0.88.

Elimination

The estimated mean (CV%) clearance is 6.0 L/hr (58% and the mean elimination half-life is 14 hrs.

Metabolism

Belzutifan is primarily metabolized by UGT2B17 and CYP2C19 and to a lesser extent by CYP3A4 *[see Clinical Pharmacology (12.5)]*.

Excretion

Following oral administration of radiolabeled belzutifan to healthy subjects, approximately 49.6% of the dose was excreted in urine and 51.7% in feces (primarily as inactive metabolites).

Specific Populations

Patients who are poor metabolizers of UGT2B17 and CYP2C19 had higher belzutifan AUC *[see Clinical Pharmacology (12.5)]*.

There were no clinically significant differences in the pharmacokinetics of belzutifan based on age (19 to 90 years), sex, ethnicity (non-Hispanic, Hispanic), race (White, Black, Asian, Native American, Pacific Islander), body weight (42 to 166 kg), mild to moderate renal impairment (eGFR 30-89 mL/min/1.73 m^2 estimated by MDRD), or mild hepatic impairment (total bilirubin ≤ ULN with AST > ULN or total bilirubin > ULN to 1.5 x ULN with any AST). The effect of severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) and moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and any AST) have not been studied.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of Belzutifan on CYP3A Substrates: Coadministration of WELIREG 120 mg once daily with midazolam (a sensitive CYP3A4 substrate) decreased the midazolam AUC by 40% and the C_{max} by 34%. Midazolam AUC is predicted to decrease up to 70% in patients with higher belzutifan concentrations (e.g., dual poor metabolizers) *[see Clinical Pharmacology (12.5)]*.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Belzutifan does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

Belzutifan does not induce CYP1A2 or CYP2B6.

Transporter Systems: Belzutifan is a substrate of P-gp, OATP1B1, and OATP1B3, but is not a substrate of BCRP.

Belzutifan inhibits MATE2K. Belzutifan does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or MATE1.

12.5 Pharmacogenomics

Patients who are UGT2B17, CYP2C19, or dual UGT2B17 and CYP2C19 poor metabolizers are estimated to have 2.5-, 1.3-, or 3.2-fold higher belzutifan steady state $AUC_{0\text{-}24h}$, respectively compared to patients who are UGT2B17 normal (extensive) metabolizers and CYP2C19 non-poor (ultrarapid, rapid, normal, and intermediate) metabolizers *[see Use in Specific Populations (8.7)].*

UGT2B17 poor metabolizers who are homozygous for the UGT2B17*2 allele have no UGT2B17 enzyme activity. CYP2C19 poor metabolizers (such as *2/*2, *3/*3, *2/*3) have significantly reduced or absent CYP2C19 enzyme activity. Approximately 15% of White, 6% of Black or African American, and up to 77% of certain Asian populations are UGT2B17 poor metabolizers. Approximately 2% of White, 5% of Black or African American, and up to 19% of certain Asian populations are CYP2C19 poor metabolizers. Approximately 0.4% of White, 0.3% of Black or African American, and up to 15% of certain Asian populations are dual UGT2B17 and CYP2C19 poor metabolizers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with belzutifan.

Belzutifan was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. Belzutifan was not clastogenic in either an in vitro micronucleus assay or an in vivo rat bone marrow micronucleus assay.

Fertility studies in animals have not been conducted with belzutifan. In repeat-dose toxicity studies up to 3-month duration, belzutifan-related findings included degeneration/atrophy of testes and hypospermia and cellular debris of the epididymis in rats administered ≥2 mg/kg/day (approximately 0.1 times the human exposure at the recommended dose of 120 mg daily). Findings in testes and epididymis were associated with decreased sperm count and motility and abnormal sperm morphology at ≥6 mg/kg/day (approximately 0.2 times the human exposure at the recommended dose of 120 mg daily) and did not reverse by the end of the recovery period. Belzutifan had no adverse effects on female reproductive organs in repeat-dose toxicity studies up to 3-month duration; however, belzutifan caused embryo-fetal lethality (post-implantation loss) in pregnant rats given oral doses ≥60 mg/kg/day (approximately 1 time the human exposure at the recommended dose based on AUC) during the period of organogenesis *[see Use in Specific Population (8.1)].*

14 CLINICAL STUDIES

14.1 von Hippel-Lindau (VHL) disease

The efficacy of WELIREG was evaluated in LITESPARK-004 (NCT03401788), an open-label clinical trial in 61 patients with VHL-associated RCC diagnosed based on a VHL germline alteration and with at least one measurable solid tumor localized to the kidney as defined by response evaluation criteria in solid tumors (RECIST) v1.1. Enrolled patients had other VHL-associated tumors including CNS hemangioblastomas and pNET. CNS hemangioblastomas and pNET in these patients were diagnosed based on the presence of at least one measurable solid tumor in brain/spine or pancreas, respectively, as defined by RECIST v1.1 and identified by IRC. The study excluded patients with metastatic disease. Patients received WELIREG 120 mg once daily until progression of disease or unacceptable toxicity.

The study population characteristics were: median age 41 years [range 19-66 years], 3.3% age 65 or older; 53% male; 90% were White, 3.3% were Black or African-American, 1.6% were Asian, and 1.6% were Native Hawaiian or other Pacific Islander; 82% had an ECOG PS of 0, 16% had an ECOG PS of 1, and 1.6% had an ECOG PS of 2; and 84% had VHL Type I Disease. The median diameter of RCC target lesions per central independent review committee (IRC) was 2.2 cm (range 1-6.1). Median time from initial radiographic diagnosis of VHL-associated RCC tumors that led to enrollment on LITESPARK-004 to the time of treatment with WELIREG was 17.9 months (range 2.8-96.7). Seventy-seven percent of patients had prior surgical procedures for RCC.

The major efficacy endpoint for the treatment of VHL-associated RCC was objective response rate (ORR) measured by radiology assessment using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 as assessed by IRC. Additional efficacy endpoints included duration of response (DoR), and time to response (TTR).

Table 6 summarizes the efficacy results for VHL-associated RCC in LITESPARK-004.

Table 6: Efficacy Results (IRC assessment) for LITESPARK-004 for VHL-Associated RCC

Efficacy Outcome Measure	**WELIREG n=61**
Objective Response Rate, % n (95% CI)	49% (30)* (36, 62)
Complete response	0%
Partial response	49%
Duration of Response	
Median in months (range)	Not reached (2.8+, 22+)
% n with DoR ≥ 12 months	56% (17/30)

* All patients with a response were followed for a minimum of 18 months from the start of treatment.
\+ Denotes ongoing response.

For VHL-associated RCC, median TTR was 8 months (range 2.7, 19).

Table 7 summarizes the efficacy results for VHL-associated pNET or CNS hemangioblastomas in LITESPARK-004.

Table 7. Efficacy Results (IRC assessment) for LITESPARK-004 for VHL-Associated Subgroups with CNS Hemangioblastomas or pNET

Endpoint	**Patients with CNS Hemangioblastomas n=24***	**Patients with pNET n=12***
Objective Response Rate, % n (95% CI)	63%, (15) (41, 81)	83% (10 (52, 98)
Complete response	4% (1)	17% (2)
Partial response	58% (14	67% 8
Duration of Response		
Median in months (range)	Not reached 3.7+, 22+)	Not reached 11+, 19+)
% n with DoR ≥12 months	73% (11/15)	50% (5/10)

* Number of patients with measurable solid lesions, based on IRC assessment.
\+ Denotes ongoing response.

For VHL-associated CNS hemangioblastomas, TTR was 3.1 months (range 2.5, 11). For VHL-associated pNET, median TTR was 8.1 months (range 2.7, 11).
Decreases in size of CNS hemangioblastoma-associated peri-tumoral cysts and syringes were observed.

14.2 Advanced Renal Cell Carcinoma (RCC)

The efficacy of WELIREG was evaluated in LITESPARK-005 (NCT04195750), an open-label, randomized, active-controlled clinical trial in 746 patients with unresectable, locally advanced or metastatic clear cell RCC that progressed following PD-1 or PD-L1 checkpoint inhibitor and VEGF receptor targeted therapies either in sequence or in combination.

Patients could have received up to 3 prior treatment regimens and were required to have measurable disease per RECIST v1.1. Patients were randomized in a 1:1 ratio to receive 120 mg WELIREG or 10 mg everolimus by oral administration once daily. Randomization was stratified by IMDC risk categories (favorable versus intermediate versus poor) and number of prior VEGF receptor targeted therapies (1 versus 2-3). Patients were evaluated radiologically at Week 9 from the date of randomization, then every 8 weeks through Week 49, and every 12 weeks thereafter.

The study population characteristics were: median age 63 years [range 22 to 90 years], 42% age 65 or older; 78% male; 79% White; 12% Asian; 1% Black or African American; 11% Hispanic or Latino; 44% ECOG performance status 0 and 55% ECOG performance status 1. Prior therapies: 13% patients had 1 prior line of therapy, 43% had 2 prior lines of therapy and 43% had 3 prior lines of therapy; 49% received 2 to 3 prior VEGF receptor targeted therapies. Patient distribution by IMDC risk categories was 22% favorable, 66% intermediate, and 12% poor. Common sites of metastasis in patients were 65% lung, 59% lymph nodes, and 49% bone.

The major efficacy endpoints were Progression Free Survival (PFS) measured by BICR using RECIST v1.1 and Overall Survival (OS). Additional efficacy endpoint included objective response rate (ORR) by BICR using RECIST v1.1.

The trial demonstrated a statistically significant improvement in PFS for patients randomized to WELIREG compared with everolimus. Table 8 and Figure 1 summarize the efficacy results for LITESPARK-005.

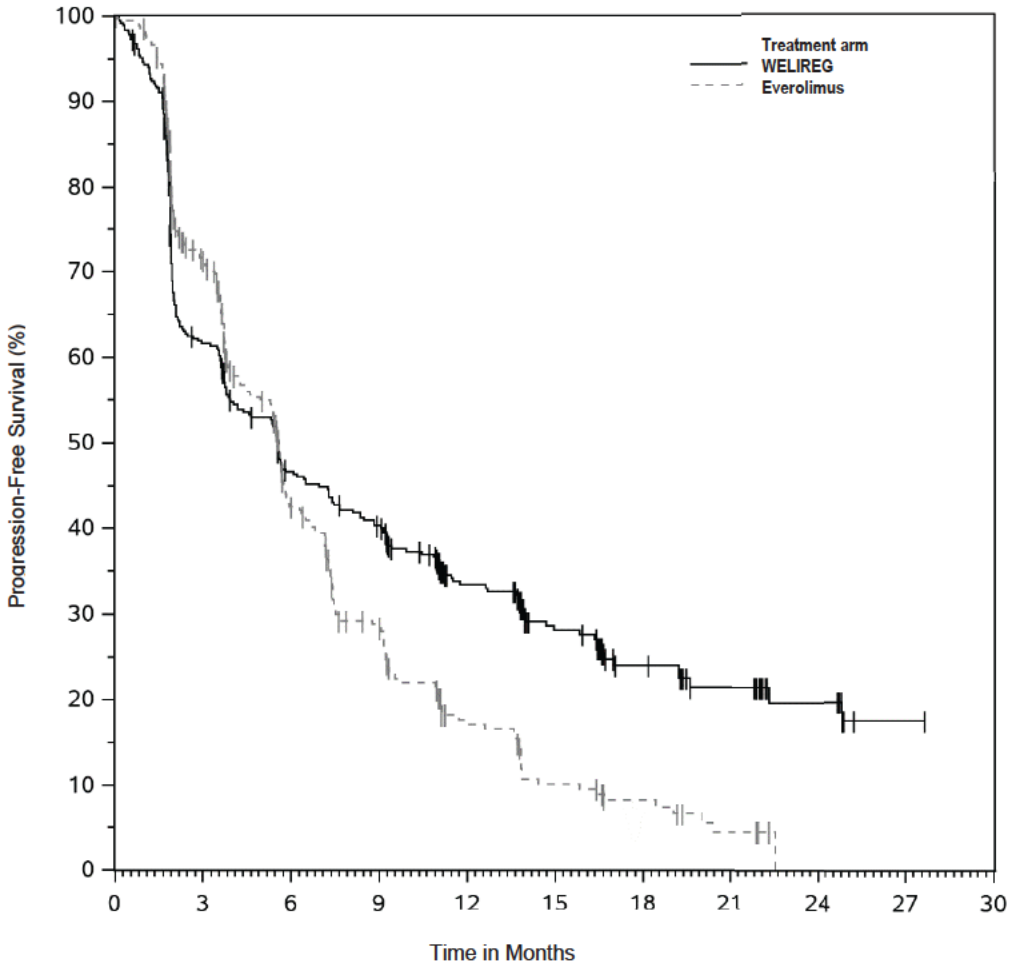
Table 8: Efficacy Results for Advanced RCC (IRC assessment) for LITESPARK-005

Efficacy Outcome Measure	WELIREG n=374	Everolimus n=372
Progression-Free Survival (PFS)		
Number of events, n (%)	257 (69%)	262 (70%)
Progressive disease	234 (63%)	222 (60%)
Death	23 (6%)	40 (11%)
Median in months (95% CI) *	5.6 (3.9, 7.0)	5.6 (4.8, 5.8)
Hazard ratio † (95% CI)	0.75 (0.63, 0.90)	
p-Value ‡	0.0008	
Confirmed Objective Response Rate		
Number of patients with measurable disease at baseline	373	364
ORR % (n) (95% CI)	22% (82) 18, 27	4% (13) (2, 6)
Complete response	3% (10)	0% (0)
Partial response	19% (72)	4% (13)
p-Value§	<0.0001	

* From product-limit (Kaplan-Meier) method for censored data
† Based on the stratified Cox proportional hazard model.
‡ One-sided p-Value based on stratified log-rank test compared with the significance boundary of 0.0021.
§ One-sided p-value based on stratified Miettinen and Nurminen (M&N) method.

Among the 82 patients treated with WELIREG who achieved a confirmed response based on BICR per RECIST 1.1, 25 (30% patients had a duration of response ≥12 months. OS results were immature. At the time of the subsequent pre-specified analysis, 59% of the patients had died in the randomized population.

Figure 1: Kaplan-Meier Curve for Progression-Free Survival in LITESPARK-005



Number at Risk											
WELIREG	374	218	157	134	85	55	32	20	11	1	0
Everolimus	372	226	113	68	31	17	10	4	0	0	0

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

WELIREG tablets are supplied as 40 mg blue, oval shaped, film-coated, debossed with "177" on one side and plain on the other side, available in:

- bottles of 90 tablets with child-resistant closure: NDC 0006-5331-01.

The bottle also contains two desiccant canisters. Do not eat.

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Anemia

Inform patients that WELIREG can cause severe anemia that may require blood transfusions and that red blood cell levels will be monitored routinely during treatment. Advise patients to contact their healthcare provider if the patient experiences any symptoms suggestive of anemia *[see Warnings and Precautions (5.1)]*.

Hypoxia

Inform patients that WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization; and that oxygen levels will be monitored routinely during treatment. Advise patients to contact their healthcare provider if the patient experiences any symptoms suggestive of hypoxia *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.3) and Use in Specific Population (8.1)]*.
- Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose *[see Use in Specific Populations (8.3)]*.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise females not to breastfeed during treatment with WELIREG and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise male and female patients that WELIREG may impair fertility *[see Use in Specific Populations (8.3)]*.

Dosage and Administration

Instruct patients to take their dose of WELIREG at the same time each day (once daily). Advise patients WELIREG can be taken with or without food. Each tablet should be swallowed whole *[see Dosage and Administration (2.1)]*.

Manufactured for: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

For patent information: www.msd.com/research/patent

uspi-mk6482-t-xxxxx

MEDICATION GUIDE
WELIREG™ (Well-ih-reg)
(belzutifan)
tablets

What is the most important information I should know about WELIREG?

WELIREG may cause serious side effects, including:

- **Low red blood cell counts (anemia).** Low red blood cell counts are common with WELIREG and can be severe. You may need a blood transfusion if your red blood cell counts drop too low. Your healthcare provider will do blood tests to check your red blood cell counts before you start and during treatment with WELIREG. Tell your healthcare provider if you get any symptoms of low red blood cell counts, including tiredness, feeling cold, shortness of breath, chest pain, or fast heartbeat.
- **Low oxygen levels in your body.** WELIREG can cause low oxygen levels in your body that can be severe and may require you to stop treatment with WELIREG, receive oxygen therapy, or be hospitalized. Your healthcare provider will monitor your oxygen levels before you start and during treatment with WELIREG. Tell your healthcare provider or get medical help right away if you get symptoms of low oxygen in your body, including shortness of breath or increased heart rate.
- **Harm to your unborn baby.** Treatment with WELIREG during pregnancy can cause harm to your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider will do a pregnancy test before you start treatment with WELIREG.
  - You should use an effective form of non-hormonal birth control (contraception) during treatment with WELIREG and **for 1 week** after your last dose.
  - Birth control methods that contain hormones (such as birth control pills, injections, or transdermal system patches) may not work as well during treatment with WELIREG.
  - Talk to your healthcare provider about birth control methods that may be right for you during treatment with WELIREG.
  - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with WELIREG.

  Males with female partners who are able to become pregnant:
  - You should use effective birth control (contraception) during treatment with WELIREG and **for 1 week** after your last dose.
  - Tell your healthcare provider right away if your partner becomes pregnant or thinks she is pregnant while you are taking WELIREG.

See **"What are the possible side effects of WELIREG?"** for more information about side effects.

What is WELIREG?

WELIREG is a prescription medicine used to treat adults with:

- von Hippel-Lindau (VHL) disease who need treatment for a type of kidney cancer called renal cell carcinoma (RCC), tumors in the brain and spinal cord called central nervous system hemangioblastomas (CNS), or a type of pancreatic cancer called pancreatic neuroendocrine tumors (pNET), that do not require surgery right away.
- kidney cancer that has spread (advanced RCC) following treatment with a PD-1 or PD-L1 and VEGF cancer medicines.

It is not known if WELIREG is safe and effective in children.

Before taking WELIREG, tell your healthcare provider about all of your medical conditions, including if you:

- have low red blood cell counts (anemia)
- are pregnant or plan to become pregnant. See **"What is the most important information I should know about WELIREG?"**
- are breastfeeding or plan to breastfeed. It is not known if WELIREG passes into your breast milk. **Do not** breastfeed during treatment with WELIREG and for 1 week after your last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. WELIREG and certain other medicines can affect each other and cause serious side effects.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take WELIREG?

- Take WELIREG exactly as your healthcare provider tells you.
- Do not stop taking WELIREG or change your dose without talking to your healthcare provider.

- Take your prescribed dose of WELIREG 1 time a day, at the same time each day.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with WELIREG if you have certain side effects.
- Take WELIREG with or without food.
- Swallow WELIREG tablets whole. **Do not** chew, crush, or split WELIREG tablets.
- If you miss a dose of WELIREG, take it as soon as possible on the same day. Then take your next dose of WELIREG at your regular time the next day. **Do not** take extra tablets to make up for the missed dose.
- If you vomit after taking a dose of WELIREG, **do not** take an extra dose. Take your next dose at your regular time the next day.
- If you take too much WELIREG, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of WELIREG?

WELIREG may cause serious side effects, including:

- See **"What is the most important information I should know about WELIREG?"**

The most common side effects of WELIREG in adults with VHL disease include:

- tiredness
- increased creatinine (kidney function test)
- headache
- dizziness
- increased blood sugar (glucose) levels
- nausea

The most common side effects of WELIREG in adults with advanced RCC include:

- tiredness
- decreased white blood cells
- increased creatinine (kidney function test)
- muscle and joint pain
- increased liver function tests
- decreased blood salts (sodium) levels
- increased blood potassium levels

WELIREG may cause fertility problems in males and females, which may affect your ability to have children. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of WELIREG.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store WELIREG?

- Store WELIREG at room temperature between 68°F to 77°F (20°C to 25°C).
- The WELIREG bottle contains 2 desiccant canisters that help keep your medicine dry. **Do not** eat the desiccant canisters.

Keep WELIREG and all medicines out of the reach of children.

General information about the safe and effective use of WELIREG.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use WELIREG for a condition for which it was not prescribed. Do not give WELIREG to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about WELIREG that is written for health professionals.

What are the ingredients in WELIREG?

Active ingredient: belzutifan

Inactive ingredients: croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, mannitol, microcrystalline cellulose, and silicon dioxide. The film-coating contains FD&C Blue #2 aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured for: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA
For patent information: www.msd.com/research/patent

usmg-mk6482-t-xxxx

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 12/2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215383Orig1s006

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Supplement
Application Number(s)	215383
Priority or Standard	Priority
Submit Date(s)	7/17/2023
Received Date(s)	7/17/2023
PDUFA Goal Date	1/17/2024
Division/Office	CDER/OOD/DO1
Review Completion Date	12/08/2023
Established Name	Belzutifan
(Proposed) Trade Name	WELIREG
Pharmacologic Class	Hypoxia-inducible factor inhibitor
Code name	MK-6482
Applicant	Merck
Formulation(s)	Belzutifan
Dosing Regimen	120 mg once daily
Applicant Proposed Indication(s)/Population(s)	WELIREG is indicated for treatment of adult patients with advanced renal cell carcinoma (RCC) following immune checkpoint and anti-angiogenic therapies.
Recommendation on Regulatory Action	Traditional Approval
Recommended Indication(s)/Population(s) (if applicable)	WELIREG is indicated for treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Benjamin Chukwurah
Pharmacology/Toxicology Reviewer(s)	Tiffany Ricks
Pharmacology/Toxicology Team Leader(s)	Tiffany Ricks
Office of Clinical Pharmacology Reviewer(s)	Guanming Chen
Office of Clinical Pharmacology Team Leader(s)	Hong Zhao
Clinical Reviewer	Jaleh Fallah (Efficacy) & Brian Heiss (Safety)
Clinical Team Leader	Chana Weinstock
Safety Analyst (if applicable)	Ilynn Bulatao
Statistical Reviewer	Hee-Koung Joeng
Statistical Team Leader	Xin (Cindy) Gao
Associate Director for Labeling (ADL)	William Pierce
Cross-Disciplinary Team Leader	Chana Weinstock
Division Director (DHOT)	John Leighton
Division Director (OCP)	Nam Atiqur Rahman
Division Director (OB)	Mallorie Fiero
Division Director (OOD)	Daniel Suzman
Office Director (or designated signatory authority)	Paul Kluetz

Additional Reviewers of Application

OPQ	n/a
Microbiology	n/a
OPDP	Mispa Ajua-Alemanji
OSI	Yang-Min (Max) Ning
OSE/DEPI	n/a
OSE/DMEPA	n/a
OSE/DRISK	n/a
Other	Vishal Bhatnagar (DCOA)

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

AC	advisory committee
ACE	angiotensin-converting enzyme
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AME	absorption, metabolism, and excretion
APaT	all participants as treated
API	active pharmaceutical ingredient
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-inf}}$	area under the curve from time 0 to infinity
AUC_{avg}	average AUC
AUC_{avgeot}	average AUC until end of treatment or data cutoff date
AUC_{ss}	steady-state area under the curve
BICR	blinded independent central review
BLA	biologics license application
BMI	body mass index
BP	blood pressure
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit-Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COA	clinical outcome assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CYP2C19	cytochrome P450 enzyme 2C19
CYP3A4	cytochrome P450 enzyme 3A4
DDI	drug-drug interaction
DMC	data monitoring committee
DMF	drug master file
DOR	duration of response
ECG	electrocardiogram

EOP2	End of Phase 2
eCTD	electronic common technical document
eDMC	external data monitoring committee
EM	extensive metabolizer
EOC	executive oversight committee
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items
EPO	erythropoietin
E-R	exposure-response
ERC	ethics review committee
EuroQol EQ-5D-5L	European Quality of Life Five Dimensions Five Level Questionnaire
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDARA	Food and Drug Administration Reauthorization Act
FDASIA	Food and Drug Administration Safety and Innovation Act
FKSI-DRS	Functional Assessment of Cancer Therapy – Kidney Symptom Index-disease-related symptoms
FMI	final market image
GCP	good clinical practice
GGP	gamma-glutamyltransferase
GLP	good laboratory practice
GM	geometric mean
GMR	geometric mean ratio
GPP	good pharmacovigilance practices
GRMP	good review management practice
HIF-2α	hypoxia-inducible factor 2α
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
ICI	immune checkpoint inhibitor
IEC	Independent Ethics Committee
IM	intermediate metabolizer
IMDC	International Metastatic RCC Database Consortium
IND	Investigational New Drug
IRB	Institutional Review Board
iPSP	initial pediatric study plan
ISS	integrated summary of safety
ITT	intent to treat
KM	Kaplan-Meier

KPS	Karnofsky performance status
LS	least squares
MARRS	Merck Adverse Event Reporting and Review System
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCT	National Clinical Trial
NDA	new drug application
NME	new molecular entity
NOAEL	no-observed-adverse-effect level
NR	not reached
OCE	Oncology Center of Excellence
OCP	Office of Combination Products
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBPK	physiologically based pharmacokinetic
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFS	progression-free survival
PK	pharmacokinetics
PM	poor metabolizer
PMC	postmarketing commitment
PMR	postmarketing requirement
popPK	population pharmacokinetics
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PSUR	Periodic Safety Update report
PT	Preferred Term
QA	quality assurance
QC	quality control
QD	once daily
QoL	quality of life
QTcF	QT interval corrected using Fridericia criteria
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan

sBLA	supplemental biologics license application
SDSP	Study Data Standardization Plan
SGE	special government employee
sNDA	supplemental new drug application
TK	toxicokinetic(s)
T_{max}	time to maximum concentration
UGT2B17	UDP glucuronosyltransferase family 2 member B17
US	United States
VEGF	vascular endothelial growth factor
VHL	Von Hippel-Lindau
VHL-RCC	Von Hippel-Lindau disease–associated renal cell carcinoma

1 Executive Summary

1.1. Product Introduction

Belzutifan (Welireg) is a hypoxia inducible factor (HIF)-2α inhibitor currently FDA-approved for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. The initial approval of belzutifan as a new molecular entity for the above VHL indications occurred in August 2021. There are currently no other FDA-approved HIF-2α inhibitors, and belzutifan has no current indication in the metastatic setting.

The dosing regimen proposed for belzutifan is 120 mg, orally, once daily (three 40 mg tablets), which is the approved dosing regimen for the VHL indications.

The Applicant's proposed indication for the sNDA is:

"WELIREG is indicated for treatment of adult patients with advanced renal cell carcinoma (RCC) following immune checkpoint and anti-angiogenic therapies."

1.2. Conclusions on the Substantial Evidence of Effectiveness

The evidence to support the proposed indication and to provide substantial evidence of effectiveness derives from LITESPARK-005 (NCT04195750, hereafter referred to as Study 005), an open-label, randomized, head-to-head clinical trial in 746 patients with unresectable, locally advanced or metastatic clear cell RCC that progressed following both a PD-1 or PD-L1 checkpoint inhibitor and a VEGF tyrosine kinase inhibitor(VEGF-TKI) either in sequence or in combination. Patients could have received up to 3 prior treatment regimens and were required to have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Patients were randomized (1:1) to receive 120 mg belzutifan or 10 mg everolimus by oral administration once daily. Randomization was stratified by International mRCC Database Consortium (IMDC) risk categories (favorable versus intermediate versus poor) and number of prior VEGF-TKIs(1 versus 2-3). Patients were evaluated radiologically at Week 9 from the date of randomization, then every 8 weeks through Week 49, and every 12 weeks thereafter. The FDA review team considers everolimus to be an acceptable control arm in this setting, and this choice was agreed upon by the FDA in the end-of-phase 2 (EOP2) meeting preliminary responses sent to the Applicant in March 2019.

The primary efficacy outcomes of Study 005 were dual primary endpoints of progression-free survival (PFS) per blinded independent central review (BICR) using RECIST v1.1 and overall survival (OS). Additional efficacy endpoints included objective response rate (ORR) and duration of response (DoR) by BICR using RECIST v1.1.

A statistically significant improvement was demonstrated in PFS per BICR assessment for belzutifan compared with everolimus at interim analysis (IA) 1 (83% information fraction), with a hazard ratio of 0.75 (95% CI: 0.63, 0.90); 1-sided p-value=0.0008. Median PFS was 5.6 months (95% CI: 3.9, 7.0) in the belzutifan arm and 5.6 months (95% CI: 4.8, 5.8) in the everolimus arm.

OS results were immature with 91% of total planned OS events at the subsequent interim analysis (IA2) that occurred during the review cycle, representing 59% of deaths in the randomized population. The median OS at IA2 was 21.4 (95% CI: 18.2, 24.3) months in the belzutifan arm and 18.1 (95% CI: 15.8, 21.7) months in the everolimus arm [HR=0.88 (95% CI: 0.73, 1.07); 1-sided p-value of 0.0994 which did not reach the significance boundary of 0.014].

Confirmed ORR in the belzutifan arm was higher than in the everolimus arm (22.0% [95% CI: 17.9, 26.5] vs 3.6% [95% CI: 1.9, 6.0], respectively) in the patients with measurable disease assessed by BICR per RECIST v1.1 (difference in ORR between arms=18% [14%, 23%)], 1-sided p-value <0.000), which was statistically significant. FDA analysis showed a high concordance between the confirmed ORR per BICR and per investigator assessment.

When considering Study 005 efficacy results, the FDA review team noted that there was no apparent difference in PFS medians between arms, likely due to non-proportional hazards in the Kaplan-Meier (KM) curve, however, late separation in the KM curves persisted and led to an observed benefit in the PFS HR. The FDA was also concerned about observed asymmetric censoring in the PFS curve including 'early dropouts' on the everolimus arm, discordance between BICR and investigator assessments of PFS, and associated censoring due to new anticancer therapy initiated prior to progression, all leading to uncertainty in the estimation of the magnitude of the PFS treatment effect. Sensitivity analysis results with PFS per investigator, calculation of a variety of conservative and worst-case scenarios, and the restricted mean survival time (RMST) analysis results were all consistent with the primary analysis, demonstrating robustness of the improvement in PFS for belzutifan compared to everolimus.

Patient-reported outcomes (PROs) were assessed using three instruments (FKSI-DRS, EORTC QLQ-C30, and EQ-5D-5L) at the timepoints: Week 1, 3, 5, 9, and every 4 weeks after. PRO data were collected with high compliance (e.g. 92% at week 17). Descriptive analyses of these patient-reported symptom and functional outcomes data were supportive of improved tolerability for belzutifan compared to everolimus in Study 005, although the interpretation is limited by the open-label study design and sparse

PRO assessment. Most symptom and functional scales from the EORTC QLQ-C30 demonstrated similar or worsening symptoms for patients treated with everolimus compared to patients treated with belzutifan, notably favoring belzutifan for patient-reported physical functioning and dyspnea. Despite limitations of this PRO analysis as described in the review below, there was an apparent general trend towards improved tolerability of belzutifan compared to the approved therapy everolimus, which contributed to the positive risk/benefit analysis of belzutifan.

A minority of enrolled patients in Study 005 (15%) had received PD-1 or PD-L1 checkpoint inhibitor concurrently with VEGF-TKI and no subsequent line of therapy (i.e. patients with only 1 prior line of therapy) and FDA was concerned about applicability of Study 005 results to the post-approval population, many of whom will receive combination PD-1 or PD-L1 checkpoint inhibitor and VEGF-TKI therapy in the 1st line for advanced RCC. However, exploratory subgroup analyses in this population for PFS and OS demonstrated consistency of results with the overall trial population, providing reassurance regarding applicability of results to these patients.

Another concern related to relatively high rates of erythropoiesis stimulating agents (ESA) use due to anemia observed in the belzutifan arm (32% of patients) given prior reports of increased cancer mortality and/or tumor progression in patients with various solid tumors receiving ESAs, however exploratory analyses demonstrated no apparent adverse effect on OS or PFS in these patients. Therefore, while the prior warning in the USPI cautioning against the use of ESAs for patients with VHL disease was not modified given the different disease setting and availability of single arm trial data only, a similar warning was not added for patients with advanced RCC treated with belzutifan.

The review team considered the safety profile demonstrated for belzutifan in Study 005 to be acceptable for patients with advanced RCC . Twelve (3.2%) patients died from adverse events in the belzutifan arm. Belzutifan was discontinued due to treatment-emergent adverse events TEAEs) in 6% of patients, most commonly ≥0.5%) due to hypoxia, anemia, and hemorrhage. TEAEs leading to dose interruption occurred in 39% of patients most commonly (>2%) due to anemia, hypoxia, COVID-19, fatigue, and hemorrhage. Dose reduction of belzutifan occurred in 13% of patients, most commonly ≥0.5%) due to hypoxia, anemia, fatigue, alanine aminotransferase increased, dyspnea, aspartate aminotransferase increased, and hypertransaminasemia. The most common ≥25%) adverse reactions, including laboratory abnormalities, in the belzutifan arm include decreased hemoglobin, fatigue, musculoskeletal pain, increased creatinine, decreased lymphocytes, increased alanine aminotransferase, decreased sodium, increased potassium, and increased aspartate aminotransferase.

While Belzutifan and everolimus are associated with different toxicity profiles, all-grade TEAEs, Grade 3-5 TEAEs, TESAEs, and dose reductions due to TEAEs were comparable between arms on Study 005. However, drug discontinuations (39% for belzutifan vs 48% for everolimus) and dose interruptions (6% for belzutifan vs. 14% for

everolimus) were lower for patients receiving belzutifan, which is supportive of the improved tolerability for belzutifan compared to everolimus suggested by the PRO analyses.

No new Warnings and Precautions were included in labeling during this review.

The FDA review team considers there to be a positive benefit-risk for belzutifan in this setting and recommends traditional approval of belzutifan for the treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI). This indication statement was slightly modified from the original indication statement proposed by the Applicant to specify which immune checkpoint inhibitor and anti-angiogenic therapies were included as acceptable prior therapies in Study 005 inclusion criteria.

The recommended dose for belzutifan in this setting is 120 mg, orally, once daily.

A postmarketing commitment (PMC) for submission of final OS results was agreed upon by the FDA review team and the Applicant, based on a projected trial completion date of 5/2024 and with planned submission by 11/2024.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Patients with advanced RCC whose disease has progressed despite treatment with a prior PD-1 or PD-L1 checkpoint inhibitor and VEGF-TKI therapy have a serious and life-threatening condition.

The efficacy of belzutifan in advanced RCC was evaluated in LITESPARK-005/ Study 005, an open-label, randomized, controlled trial of 746 patients with advanced clear cell RCC that progressed following both a PD-1 or PD-L1 checkpoint inhibitor and prior VEGF-TKI therapy. Patients were randomized 1:1 to receive either belzutifan (120 mg daily) or everolimus (10 mg daily). Randomization was stratified by IMDC risk category and number of prior VEGF-TKIs. Study 005 demonstrated a statistically significant improvement in PFS for belzutifan vs. everolimus, with a HR of 0.75 ([95% CI: 0.63, 0.90]; 1-sided p-value=0.0008). Median PFS was 5.6 months (95% CI: 3.9, 7.0) for belzutifan vs. 5.6 months (95% CI: 4.8, 5.8) for everolimus. OS results were immature at IA2 with 91% of total planned events (59% of deaths in the randomized population); no OS detriment was observed [HR=0.88 (95% CI: 0.73, 1.07); 1-sided p-value of 0.0994 which did not reach the significance boundary of 0.014]. Patients on the belzutifan arm had higher ORR vs patients on the everolimus arm (22% vs 3.4%,1-sided p-value <0.0001). Descriptive patient-reported tolerability data also favored the belzutifan arm, including less detriment in treatment related symptoms and functioning for patients on the belzutifan arm compared to the everolimus arm after week 5

Belzutifan demonstrated a safety profile on Study 005 that was qualitatively similar to its previously-described safety profile in patients with VHL. Twelve (3.2%) patients died from AEs in the belzutifan arm, and belzutifan was discontinued due to AEs in 6% of patients, most commonly due to hypoxia, anemia, and hemorrhage. AEs leading to dose reduction of belzutifan occurred in 13% of patients. The most common (≥25%) adverse reactions in the belzutifan arm include decreased hemoglobin, fatigue, musculoskeletal pain, increased creatinine, decreased lymphocytes, increased alanine aminotransferase, decreased sodium, increased potassium, and increased aspartate aminotransferase. The different safety profile of belzutifan vs. everolimus complicates a head-to-head comparison, however patients receiving belzutifan vs. everolimus had fewer drug discontinuations and dose interruptions, suggesting a comparatively favorable toxicity profile. Overall, the review team considered the safety profile of belzutifan acceptable for this setting with evidence supporting improved tolerability compared to everolimus.

The review team recommends traditional approval of belzutifan for treatment of adult patients with advanced RCC following a PD-1 or PD-L1 inhibitor and a VEGF-TKI. Submission of the final analysis of OS from Study 005 is a PMC for this application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In the US, the estimated numbers of new cases and deaths from kidney and renal pelvis cancer in 2022 were 79,000 and 13,920, respectively [3], with ~ 1/3 of patients presenting with advanced RCC at diagnosis and 20% - 30% of patients with localized tumors relapsing after nephrectomy [1]. • According to SEER database analysis, the 5-year overall survival of patients with advanced RCC is 15%.	Advanced RCC is a serious and life-threatening condition.
Current Treatment Options	• Available treatment options for patients with advanced RCC after progression on prior PD-1 or PD-L1 checkpoint inhibitor and VEGF-TKI therapy include axitinib, cabozantinib, everolimus, everolimus plus lenvatinib, and tivozanib (specifically indicated for patients with ≥2 lines of prior therapy).	Although treatment options exist, none is curative and none is approved specifically for patients whose disease has progressed after prior PD-1 or PD-L1 checkpoint inhibitor and prior VEGF-TKI therapy. There is an unmet medical need in this setting.
Benefit	• Efficacy was evaluated in LITESPARK-005/ Study 005, an open-label, randomized, head-to-head trial of 746 patients with unresectable locally advanced or metastatic clear cell RCC that progressed following both a PD-1 or PD-L1 checkpoint inhibitor and a VEGF-TKI. Patients were randomized 1:1 to receive 120 mg belzutifan or 10 mg everolimus once daily. Randomization	Compared to everolimus, belzutifan demonstrated a PFS improvement in a head-to head trial, with no OS detriment, a favorable safety profile, and a descriptive improvement in PROs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	was stratified by IMDC risk category and number of prior VEGF-TKIs. • A statistically significant improvement in PFS was demonstrated for belzutifan compared with everolimus, with a hazard ratio of 0.75 [(95% CI: 0.63, 0.90); 1-sided p-value=0.0008]. Median PFS was 5.6 months (95% CI: 3.9, 7.0) in the belzutifan arm and 5.6 months (95% CI: 4.8, 5.8) in the everolimus arm. OS results were immature with 91% of total planned OS events observed (59% of deaths in the randomized population); no OS detriment was observed [HR=0.88 (95% CI: 0.73, 1.07); 1-sided p-value of 0.0994 which did not reach the significance boundary of 0.014]. • Higher ORR and longer DoR, favorable safety results, and descriptive PRO data in the belzutifan arm also supported a favorable benefit-risk profile of belzutifan in this setting.	The review team considered this to represent a clinically meaningful improvement over everolimus.
Risk and Risk Management	• Belzutifan demonstrated a safety profile consistent with its previously-known safety profile with no new safety signals identified. • The most common (≥25%) adverse reactions in the belzutifan arm decreased hemoglobin, fatigue, musculoskeletal pain, increased creatinine, decreased lymphocytes, increased alanine aminotransferase, decreased sodium, increased potassium, and increased aspartate aminotransferase. • Overall percentages of all-grade TEAEs, Grade 3-5 TEAEs, TESAEs, and dose reductions were similar between arms but patients receiving belzutifan had fewer dose interruptions and drug discontinuations due to TEAEs.	The safety profile of belzutifan is acceptable in patients with advanced RCC that has progressed after prior anti-PD-1/L1 and prior VEGF-TKIs. Belzutifan is comparatively less toxic than everolimus. No new Warnings and Precautions were added to labeling based on review of Study 005. No safety PMRs or REMS are required.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Sections 8.1.2, 8.2.6
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that was not submitted in the application, but was considered in this review.			

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:
RCC accounts for 85% of all adult kidney cancers, representing the 11th most common cancer in men and the 16th most common cancer in women worldwide [1] [2]. In 2020, GLOBOCAN reported an estimated 431,288 newly diagnosed cases of RCC and an estimated 179,368 deaths worldwide per year. In the US, the estimated numbers of new cases and deaths from kidney and renal pelvis cancer in 2022 were 79,000 and 13,920, respectively [3]. Approximately 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 [1]. The 5-year survival rate for patients with advanced RCC is approximately 14% [4].

The FDA's Assessment:
FDA has no additional comments.

2.2. Analysis of Current Treatment Options

The Applicant's Position:
ICIs have become standard treatment options for RCC. Initially, anti-PD-1/L1 therapies were approved as subsequent lines of care after initial treatment with a VEGF-targeting agent [5]. Pembrolizumab is now approved in the adjuvant setting (as monotherapy), and anti-PD-1/L1 therapies are approved in the 1L setting in combination with VEGF-targeting agents or with anti-CTLA-4 checkpoint inhibitors [6]. NCCN guidelines recommend the following combination regimens of PD-1/L1 inhibitors and VEGF-targeting agents as 1L treatments, irrespective of IMDC risk category [6] [7]: pembrolizumab plus axitinib (KEYNOTE-426; [8]); nivolumab plus cabozantinib (CheckMate 9ER; [9]); and pembrolizumab plus lenvatinib (CLEAR/KEYNOTE-581) [10]. Additional 1L preferred treatment options for poor and intermediate risk include cabozantinib and the combination of nivolumab and ipilimumab [6].

Although advances have changed the treatment paradigm for RCC patients, there continues to be a need for evidence-based options for the management of pretreated patients, particularly after immunotherapy and antiangiogenic therapies. Current NCCN guidelines [6] identify no preferred regimen for treatment of patients with advanced RCC who have received prior ICI therapy. Axitinib, cabozantinib, lenvatinib and everolimus, and tivozanib were recategorized as Category 2A recommendations since these regimens were approved based on randomized controlled trials in which participants had primarily received VEGF TKIs or non-ICI/non-TKI agents as the 1L standard of

care. Of note, tivozanib is specifically recommended for patients with ≥2 lines of prior therapy.

There have been no Phase 3 clinical studies conducted in participants with advanced RCC following treatment with anti-PD-1/L1 and antiangiogenic therapies, as combination or sequentially. One Phase 3 study (CONTACT-03) was conducted in participants with advanced RCC following treatment with ICIs. CONTACT-03 evaluated the use of cabozantinib in combination with atezolizumab, but it did not meet statistical significance for the hypothesis testing of PFS [11]. Therefore, there remains a high unmet medical need to improve treatment outcomes for patients who received prior PD-1/L1 and VEGF-targeted therapies.

Among patients with advanced RCC who have received prior immune checkpoint and antiangiogenic therapies, there are no notable differences in treatment patterns across the US population by race, ethnicity, sex, and age subgroups.

The FDA's Assessment:
FDA agrees that there is a high unmet medical need for treatment of patients with advanced RCC following treatment with PD-1 and PD-L1 immune checkpoint inhibitors and VEGF-TKI therapies.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
The proposed indication for this application is: WELIREG® is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) following immune checkpoint and antiangiogenic therapies.

Belzutifan was first approved in the US on 13-AUG-2021 under the trade name WELIREG® for the treatment of adult patients with VHL disease who require therapy for associated RCC, CNS hemangioblastomas, or pNET, not requiring immediate surgery, based on the results of the single-arm Phase 2 study MK-6482-004 / LITESPARK-004 (Study 004) in patients with VHL-RCC.

The FDA's Assessment:
FDA agrees with the Applicant's summary of the prior approval for belzutifan in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

[Table 1] summarizes relevant regulatory correspondence with the Agency for belzutifan under IND 132120 for study MK-6482-005 / LITESPARK-005 (hereafter referred to in the text as Study 005).

Table 1: Applicant – Summary of Key Regulatory Communications for Belzutifan

Regulatory Event	Date	Description
Type B (EOP2) Meeting	04-MAR-2019	FDA provided feedback on the development of belzutifan and the design of Study 005 for the indication of belzutifan in advanced RCC following immunotherapy and VEGF-targeted therapy. The Agency agreed with everolimus as the comparator for the Phase 3 Study 005 and recommended to include overall survival (OS) as a dual primary endpoint. The Sponsor cancelled the meeting after receiving FDA's preliminary comments.
Initial Pediatric Study Plan Agreement	12-SEP-2019	FDA agreed with the initial Pediatric Study Plan (iPSP), which included a plan to request a full waiver for RCC.
New Protocol (MK-6482-005)	18-NOV-2019	New protocol and SAP were submitted for Study 005 (005-00).
Protocol Amendment (MK-6482-005)	21-MAY-2020	Protocol amendment for Study 005 (005-02) was submitted in which the preclinical toxicology section was updated to reflect recent nonclinical toxicology findings and inclusion/exclusion criteria were refined.
Protocol Amendment (MK-6482-005)	12-MAR-2021	Protocol amendment for Study 005 (005-04) was submitted to update the contraception appendix.
Protocol Amendment and SDSP (MK-6482-005)	25-JUL-2022	Protocol amendment for Study 005 (005-06) was submitted to update the timing of statistical analyses and reduce the total number of interim analyses in the study. The study data standardization plan (SDSP) for Study 005 was submitted for FDA's review in preparation of the sNDA submission.
Amended SDSP	12-DEC-2022	SDSP amendment submitted for Study 05.
Informal Teleconference	02-FEB-2023	FDA provided feedback on the topline efficacy results from IA1 from Study 005 and the Sponsor's proposed sNDA based on those results. The Agency provided positive feedback on the topline results and requested more mature OS results be provided from IA2 during the sNDA review.
Pre-sNDA Type B Meeting - Preliminary Comments	24-FEB-2023	The FDA provided preliminary comment to the Sponsor's questions proposed in the Type B Pre-sNDA meeting background package to discuss Study 005. The Sponsor cancelled the formal meeting after receiving FDA's preliminary comments.

The FDA's Assessment:

FDA notes agreement with everolimus as a control arm for Study 005 in the preliminary responses to the March 2019 Type B meeting.

In addition to asking for longer OS follow up prior to sNDA submission in the informal

teleconference of February 2023, FDA discouraged the Applicant from submitting a breakthrough therapy designation request based on the topline results, stating that the results did not appear to demonstrate substantial improvement over all available therapies.

As agreed to in the informal Tcon of February 2023, the Applicant provided IA2 results for OS after submission of the sNDA, with the submission of these results on August 21, 2023.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Three participating clinical investigators [Drs. Pooja Ghatalia (Site #1506), Walter Stadler (Site #1539), and Elaine Lam (Site #1540)] in the trial were inspected. The inspections identified no significant regulatory violations in the conduct of this trial by the three investigators. Subjects enrolled and randomized at the investigator sites were found to have met the protocol-specified eligibility criteria and the Applicant's submitted clinical data for these subjects were verifiable with source records reviewed at the sites. There was no evidence of underreporting of adverse events. Overall, the inspection results show that the clinical data generated from these investigator sites are reliable and acceptable for this sNDA.

4.2. Product Quality

See separate OPQ review in DARRTS.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The nonclinical data were reviewed previously under the original NDA and IND and support approval of this sNDA.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position: No cross-reference is made by the Applicant to any other NDA/BLA/DMF.

5.3. Pharmacology

Primary pharmacology
No new data are provided in the current submission.

Secondary Pharmacology
The Applicant's Position:
No new data are provided in the current submission.

Safety Pharmacology
The Applicant's Position:
No new data are provided in the current submission.

5.4. ADME/PK

The Applicant's Position:
There are no new nonclinical PK data. Based on the human ADME study (see Sec. 6.2.1), the most significant metabolites detected in excreta were the glucuronide metabolite M16 (PT3317), which was found in urine and accounted for 32% of the dose, and the oxidative metabolite M9, which was found in feces and accounted for 42% of the dose (see Sec. 6.3.1). This is consistent with in vitro analyses (shared previously) where belzutifan metabolism occurs via UGT2B17 mediated glucuronidation to form PT3317 (M16) and by oxidative metabolism (catalyzed via CYP2C19 and to a lesser extent CYP3A4) to form M9. In this study M16 was detected in plasma at a level that approached that of a major metabolite, with no other major human metabolites detected. M16 is inactive and has been characterized as a major human metabolite in the original NDA submission.

The FDA's Assessment:
The Applicant did not submit new nonclinical PK data. Refer to Clinical Pharmacology Section 6 for clinical ADME assessment.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:
After the approval of the original NDA 215383, additional exploratory and GLP toxicokinetic and toxicity studies in rodents have been conducted to enable the preparation and design of rodent carcinogenicity studies requested by the FDA as postmarketing requirements (FDA approval letter 13-AUG-2021). The following new studies were completed post approval of the original NDA.

A single-dose TK study (TT #21-1023) in 2 strains of rats was conducted to explore whether different forms and formulations of belzutifan could result in increased systemic exposure compared with that achieved with the formulation used in the previous toxicity studies in rats. Based on the results of this study, the (b) (4) form belzutifan in (b) (4) MC (b) (4) HPMCAS (b) (4) /20 mM TRIS pH (b) (4) vehicle was selected for subsequent studies, ie, an Exploratory Four-Week Oral Toxicity and Toxicokinetic Study in Rats (TT #21-1032), a GLP 13-Week Study by Oral Gavage in Wistar Han Rats (TT#22-9011), and an Exploratory Single-Dose Oral Toxicokinetic Study in Mice (TT #21-1033).

The Exploratory Four-Week Oral Toxicity and TK Study in Rats (TT #21-1032) was conducted to determine the potential toxicity and TK profile of belzutifan when administered 100 or 300 mg/kg/day by oral gavage to (b) (4) WI(Han) rats for approximately 4 weeks. No new toxicities were found in this study despite achieving approximately 11-fold higher systemic exposure at the NOAEL (in females) of 300 mg/kg/day (AUC_{0-24} of 400 µg*h/mL) relative to the exposure attained in the original GLP 4-week study in rats at the NOAEL (in females) of 200 mg/kg/day (AUC_{0-24} of 35.3 µg*h/mL). The 13-Week Study by Oral Gavage in Wistar Han Rats (TT #22-9011) was conducted to determine toxicity and TK profile of belzutifan when administered 30, 100, or 300 mg/kg/day by oral gavage to (b) (4) WI(Han) rats for approximately 13 weeks. No new findings of toxicological relevan o humans were found in this study.

The Exploratory Single-Dose Oral Toxicokinetic Study in Mice (TT #21-1033) was conducted to determine the TK profile of belzutifan following a single oral administration at 60, 200, and 600 mg/kg to Crl:CD1(ICR) mice. The results of this study indicate that administration of belzutifan to mice at all dose levels was well tolerated. A 28-Day Study by Oral Gavage in CByB6F1/Tg rasH2 Hemizygous Mice (TT #22-9012) was conducted to determine toxicity and TK profile of belzutifan (b) (4) formulated in (b) (4) MC (b) (4) HPMCAS (b) (4) 20 mM TRIS pH (b) (4)) when administered at 30, 60, 150, or 600 mg/kg/day by oral g ge to CByB6F1/Tg rasH2 hemizygous mice for 28 days. Administration of belzutifan to CByB6F1/Tg rasH2 hemizygous mice at all dose levels was well tolerated with no new toxicities found in this study.

The potential toxicity and TK profile of belzutifan with a new impurity profile was assessed in a 13-week impurity qualification study conducted in Sprague-Dawley rats (TT #22-9010). No new toxicities were found in this study.

The FDA's assessment:
FDA agrees with the Applicant's conclusions.

5.5.2. Genetic Toxicology

No new data are provided in the current submission.

5.5.3. Carcinogenicity

No new data are provided in the current submission.

5.5.4. Reproductive and Developmental Toxicology

No new data are provided in the current submission.

5.5.5. Other Toxicology Studies

No new data are provided in the current submission.

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Tiffany Ricks
Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:
In this efficacy supplement submission, the applicant seeks approval of belzutifan (WELIREG) for the treatment of patients with advanced renal cell carcinoma (RCC). The efficacy and safety data to support this indication are from the randomized, Phase 3 study of belzutifan versus everolimus. The results of the study demonstrated clinically meaningful improvement of progression-free survival (PFS) over everolimus with no new safety findings. The recommended dosage for this new indication is the same as for the approved indications (i.e., 120 mg once daily, with or without food).

Exposure-response (E-R) analyses showed a positive relationship between belzutifan exposure (AUC) and efficacy endpoints of PFS and OS. E-R analyses for safety did not show significant safety concerns associated with higher belzutifan exposures.

This submission also included results from four dedicated clinical pharmacology studies. Study MK-6482-008 showed that excretion of belzutifan was 51.7% via feces and 49.6% in urine. Study MK-6482-014 showed that food had no clinically meaningful effect on the exposure to belzutifan. Study MK-6482-009 suggested that belzutifan is a weak CYP3A4 inducer, but PBPK modeling predicted that belzutifan is a moderate inducer of CYP3A4 in patients with higher belzutifan plasma concentrations (e.g., those who are dual UGT2B17/CYP2C19 poor metabolizers [PM]). Study MK-6482-019 demonstrated that (b) (4) content up to (b) (4) drug substance in tablets did not have a clinically meaningful effect on the PK of belzutifan.

The Office of Clinical Pharmacology has reviewed this supplemental NDA and found that it is approvable from a clinical pharmacology standpoint, provided that the applicant

and the FDA reach an agreement regarding the labeling language.

Review issue	Recommendations and comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness in patients with advanced RCC comes from the pivotal Phase 3 Study MK-6482-005. The proposed dosing regimen is supported by the clinically significant improvement in PFS and OS, and E-R analyses for safety and efficacy.
General dosing instructions	WELIREG 120 mg administered orally once daily with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Closely monitor for adverse reactions in patients who are dual UGT2B17 and CYP2C19 PM. • Coadministration of WELIREG with CYP3A4 substrates decreases concentrations of CYP3A4 substrates. Avoid coadministration of WELIREG with sensitive CYP3A4 substrates.
Labeling	The review team provided modifications to Clinical Pharmacology Section of the proposed labeling based on the results provided in the current sNDA.
Bridge between the to-be marketed and clinical trial formulations	The to-be-marketed formulation (FMI) of belzutifan was studied in MK-6482-019 and MK-6482-014, which demonstrated either [(b) (4)] content up to [(b) (4)] drug substance in tablets or taking with food did not have a clinically meaningful effect on the PK of belzutifan. Thus, the belzutifan FMI formulation can be administered without regard to food.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The updated clinical pharmacology assessment for this submission includes data from the 4 dedicated studies (listed below). In addition, the popPK and E-R analysis for safety and efficacy have been updated with data in participants with advanced RCC from Study 005.

Study	Study Description
MK-6482-008	ADME study
MK-6482-014	Definitive food effect study with the FMI tablet formulation
MK-6482-009	DDI study to evaluate the impact of multiple-dose belzutifan administration on midazolam PK
MK-6482-019	Study to compare the bioavailability profiles of belzutifan FMI tablets containing (b) (4) API to that of tablets containing (b) (4) API

Key findings from the ADME study (Study 008) are: 1) Belzutifan was eliminated primarily as oxidative (M9) and glucuronide (M16) metabolites, consistent with earlier assessments that elimination of belzutifan is catalyzed primarily by UGT2B17 and CYP2C19 with a lesser contribution by CYP3A4. Excretion was roughly equal via feces (51.7%) and urine (49.6%). 2) Approximately 6% of the administered oral belzutifan dose was recovered as parent drug in urine, indicating that renal clearance is a minor elimination pathway. 3) Trace levels of belzutifan were detected in the feces, indicating nearly complete absorption. 4) Belzutifan accounted for the majority of circulating drug-related material in plasma (73% across the first 48 hours).

The definitive food effect study (Study 014) supports the current dosing and administration recommendations that belzutifan can be administered without regard to food.

In the midazolam DDI study (Study 009), multiple-dose administration of belzutifan 120 mg QD resulted in an approximately 40% decrease in midazolam AUC and an approximately 34% decrease in C_{max}, an effect consistent with a weak CYP3A4 inducer. Based on PBPK modeling, midazolam AUC is predicted to decrease up to 70% in patients who have higher belzutifan plasma exposures.

In the bioavailability study (Study 019), (b) (4) content in the API up to (b) (4) did not impact oral bioavailability of the FMI.

The FDA's Assessment:

In the updated clinical pharmacology assessment, the applicant submitted results from the following four studies.

Study	Study Description
MK-6482-008 ADME	A single-dose, open-label study to investigate the absorption, metabolism, and excretion of [^{14}C] belzutifan in 6 healthy subjects (one subject was a CYP2C19 poor metabolizer [PM]).
MK-6482-014 Food effect	An open-label, randomized, 2-period crossover study to assess the effect of food on the pharmacokinetics of the MK-6482 final market image (FMI) tablet formulation in healthy subjects

MK-6482-009 DDI	An open-label, nonrandomized, fixed-sequence, single-site study to Evaluate the Effect of Multiple Doses of MK-6482 on the pharmacokinetics of midazolam in healthy subjects
MK-6482-019 % AP	An open-label, single-dose, 3-period, randomized, crossover study to compare the bioavailability profiles of belzutifan FMI tablets containing (b) (4) API to that of tablets containing (b) (4) API

The pharmacokinetics of belzutifan have been characterized in patients with VHL disease-associated RCC, patients with advanced RCC, and healthy subjects. In the current submission, the pop-PK analysis for belzutifan was updated with PK data from Studies MK-6482-014 and MK-6482-005.

Per the approved labeling, the C_{max} and AUC of belzutifan increased proportionally over a dose range of 20 mg to 120 mg WELIREG (0.17 to 1 times the approved recommended dose). Steady state is reached after approximately 3 days. Based on the updated pop-PK analysis, the estimated geometric mean (CV%) C_{max} at steady-state is 1.5 µg/mL (45%) and AUC_{0-24h} is 20.4 µg•hr/mL (62%) in patients treated with 120 mg WELIREG once daily.

Effect of varying % (b) (4) API

Study MK-6482-019 evaluated and compared the PK profile of belzutifan administered as the FMI product ((b) (4) API content) to that of tablets containing different levels of (b) (4) API content (b) (4) in 18 healthy subjects. The geometric me GMR) for AUC_{0-24h}, AUC_{inf}, and C_{max} were all within the acceptance range of 80 to 125%, and median T_{max} was comparable for all three levels of (b) (4) API content, suggesting there were no clinically meaningful differences in drug products containing up to (b) (4) content.

Effect of Food

Study MK-6482-014 investigated the effect of food on the PK of a single dose of WELIREG 120 mg (FMI) in a randomized, single-dose, 2-period, 2-sequence, open-label, crossover study in 14 healthy subjects. Taking WELIREG with a high-fat, high-calorie meal (total calories approximately 1000 kcal, 56 g fat, 55 g carbohydrate, and 31 g protein) delayed T_{max} by 2 hours and decreased C_{max} by 24% with no change in AUC compared to that under fasted conditions. Food does not have a clinically meaningful effect on the PK of belzutifan; thus, WELIREG can be administered with or without food.

Metabolism

Belzutifan is primarily metabolized by UGT2B17 and CYP2C19 and to a lesser extent by CYP3A4. Belzutifan is a weak inducer of CYP3A4 and is predicted to be a moderate inducer at higher belzutifan exposures.

Study MK-6482-009 investigated the potential effect of multiple doses of belzutifan on midazolam exposure in an open-label, nonrandomized, fixed-sequence study in 14 healthy women subjects. Results of the study suggested that belzutifan may be classified as a weak CYP3A4 inducer as multiple dose administration of belzutifan did not substantially change the exposures of a single oral 2-mg dose of midazolam. However, PBPK modeling suggested that belzutifan is a moderate CYP3A4 inducer. Therefore, the applicant does not propose changing the approved labeling regarding the dosing recommendation of sensitive CYP3A4 substrates.

Excretion

In Study MK-6482-008, following a single dose administration of [^{14}C] belzutifan to 6 healthy subjects, belzutifan was the major drug-related component found in plasma, accounting for 73% of the radioactivity in $AUC_{0\text{-}48h}$. Elimination of belzutifan occurred primarily via metabolism, with metabolites eliminated in both urine and feces. The glucuronic acid metabolite M16 was the predominant drug-related radioactive component in the urine, accounting for 32% of the dose. In feces, the hydroxylated metabolite M9 was the major component, accounting for 42% of the dose. Excretion was roughly equal via feces (51.7%) and urine (49.6%), primarily as inactive metabolites.

The applicant is currently conducting two special population studies include assessment of the impact of moderate hepatic impairment (MK-6482-020) and renal impairment (MK-6482-021) on belzutifan PK.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:
Previously, pooled PK data from the Phase 1 studies (MK-6482-001, -002, -006, and -007), as well as the pivotal Phase 2 study in patients with VHL-RCC (Study 004), were used as the foundation of the popPK analysis with 239 participants. The updated analysis dataset for the present supplemental application included an additional 14 healthy participants from Study 014 and 381 patients with advanced RCC in Study 005. A total of 379 participants were available for the efficacy, safety, and biomarker exploratory E-R analyses.

The Applicant's Position:
The effects of key intrinsic factors including age, sex, metabolizer phenotype (UGT2B17 and CYP2C19 phenotypes), body weight/BMI, race, ethnicity, disease status/cancer type (healthy volunteers, patients with VHL-RCC, advanced RCC, or other advanced non-RCC solid tumors), renal impairment, and hepatic impairment on PK were evaluated using a nonlinear mixed effects model. No additional covariates have been identified in this model update. Based on univariate impact analyses of covariates on belzutifan exposures (AUC), the individual effects of the majority of evaluated intrinsic

factors are within approximately 0.8- and 1.25-fold of the typical subject. In reference to a UGT2B17 EM/CYP2C19 non-PM subject, the subjects with CYP2C19 PM phenotype, UGT2B17 IM phenotype, UGT2B17 PM phenotype, and UGT2B17/CYP2C19 dual PM phenotype are projected to have 1.3×, 1.4×, 2.5×, and 3.2× the exposures (AUC_{ss}), respectively. No dose adjustment is proposed for these specific enzyme phenotypes.

The 120-mg dose of belzutifan is recommended for patients with advanced RCC and is supported by both efficacy and safety results from Study 005 and an overall favorable risk-benefit profile. E-R analyses for efficacy and safety further support the dose recommendation (Sec. 6.3.2).

The FDA's Assessment:

The proposed dosing regimen of WELIREG for patients with advanced RCC is 120 mg once daily with or without food supported by pop-PK analysis and E-R analyses for safety and efficacy. Comparable results were found between the updated pop-PK model and the previous model. No new intrinsic factors (age, body weight, CYP2C19 and UGT2B17 phenotypes) or extrinsic factors (food intake and formulation) were identified for dose adjustment. The updated E-R analyses included all patients from Study MK-6482-005 for evaluation on efficacy, safety, and pharmacodynamic markers to support dose justification. E-R analyses showed a positive relationship between belzutifan exposure (AUC) and efficacy endpoints of PFS. E-R analyses for safety did not reveal significant safety concerns associated with higher belzutifan exposures.

Both UGT2B17 phenotype and CYP2C19 phenotype were identified as significant covariates in the pop-PK analysis. Patients who are poor metabolizers (PM) of UGT2B17, CYP2C19, or dual UGT2B17 and CYP2C19 are estimated to have 2.5-, 1.3-, or 3.2-fold higher belzutifan steady state $AUC_{0\text{-}24h}$, respectively compared to patients who are UGT2B17 normal (extensive) metabolizers and CYP2C19 non-poor (ultrarapid, rapid, normal, and intermediate) metabolizers. However, no dosage adjustment is recommended for those who are dual UGT2B17/CYP2C19 PM based on the following reasons: 1) similar to the findings in the previous NDA review, increase in exposure of belzutifan is predicted to have a modest increase in the incidence of Grade 3+ anemia similar to previous NDA review; 2) the current management strategy is adequate for anemia monitoring along with potential dose interruptions and reductions. The applicant does not propose modifications to the approved labeling regarding coadministration belzutifan with UGT2B17 and CYP2C19 inhibitors, monitor for signs and symptoms of anemia and hypoxia and reduce the dosage of WELIREG as recommended.

No dose adjustment is recommended for patients with mild or moderate renal impairment or mild hepatic impairment. This is acceptable as mild to moderate renal impairment (as evaluated by eGFR as a continuous covariate) or mild hepatic impairment were not identified as a significant covariate in the pop-PK analysis.

The applicant is currently conducting two specific population studies include assessment of the impact of moderate hepatic impairment (MK-6482-020) and end-stage renal disease (MK-6482-021) on belzutifan PK.

6.2.2.2. Therapeutic Individualization

Data:
See Sec. 6.2.1 and 6.3.1.

The Applicant's Position:
No dose adjustments are recommended for any special populations.

The FDA's Assessment:
Refer to the FDA's assessment listed in Section 6.2.2.1.

6.2.2.3. Outstanding Issues

The Applicant's Position:
A clinical DDI study is currently planned to evaluate the impact of a strong inducer rifampin on belzutifan PK (MK-6482-017 [Study 017]). In this study, rifampin is being used as a prototypic inducer of CYP2C19. Two ongoing special population studies include assessment of the impact of moderate hepatic impairment (MK-6482-020) and renal impairment (MK-6482-021) on belzutifan PK.

The FDA's Assessment:
No new PMR is identified for this sNDA. FDA agrees with that the planned DDI study and ongoing organ impairment studies are necessary to provide appropriate dosage recommendation/adjustment regarding DDI and organ impairment.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:
An overview of the AME properties, PK, and DDI potential of belzutifan are summarized below:

Absorption: A high-fat, high-calorie meal delayed T_{max} by approximately 2 hours, but had no effect on belzutifan AUC. There was a decrease of C_{max} by 24% following consumption of a high-fat, high-calorie meal, but this was not clinically meaningful. Therefore, belzutifan can be taken without regard to food.

Metabolism: The following key results were observed in MK-6482-008: 1) Mass balance was achieved with 101% of the administered radioactivity recovered in urine and feces following a single oral [^{14}C]belzutifan dose to healthy adult participants over the 288-hour collection period. 2) Elimination of belzutifan occurred primarily via metabolism, with metabolites eliminated in both urine and feces. Excretion was roughly equal via feces (51.7%) and urine (49.6%). 3) Approximately 6% of the

administered oral belzutifan dose was recovered as parent drug in urine. 4) Trace levels of belzutifan were detected in the feces, indicating nearly complete absorption. 5) Belzutifan accounted for the majority of circulating drug-related material in plasma (73% across the first 48 hours). 6) The glucuronide metabolite M16, which is inactive, circulates in plasma at a level approaching that of a major metabolite and has been characterized as such, and no other major human metabolites are identified.

Clinical Pharmacokinetics: Based on the updated popPK model analysis, the steady-state GM for C_{max} and AUC_{ss} for 120 mg in all participants in the popPK analysis are predicted to be 1.5 µg/mL (3.9 µM) and 20.4 µg•hr/mL (53.2 µM•hr), respectively. Steady state is reached after approximately 3 days.

Intrinsic Factors: Based on updated popPK model, no additional intrinsic factors have been identified.

Extrinsic Factors: Based on an in vitro risk assessment, belzutifan has the potential to induce CYP3A4. The results from the midazolam DDI study (Study 009) were provided to the Agency during the review of the original NDA. The GMR (90% CI) for the plasma $AUC_{0\text{-}inf}$ and C_{max} for midazolam (midazolam + belzutifan/midazolam alone) were 0.60 (0.53, 0.69) and 0.66 (0.55, 0.78), respectively, an effect consistent with a weak CYP3A4 inducer. To further quantify this risk, a PBPK model was built to project the impact of repeat dosing of 120 mg QD belzutifan on midazolam exposures in subjects with higher belzutifan exposures. These projections suggest that belzutifan may be a moderate CYP3A4 inducer in patients with higher belzutifan plasma concentrations.

No other DDI studies have been conducted for this submission.

The FDA's Assessment:

The updated information in the proposed labeling is summarized in the table below,

Formulation development	Fit-for-purpose (FFP) formulation was initially developed and used in the FIH dose escalation (MK-6482-001) and switched to final market formulation (FMF) in Study MK-6482-004 for initial approval for VHL-RCC indication. Results from the two newly conducted Phase 1 studies (MK-6482-014 and MK-6482-019) with the FMI formulation showed that no clinically meaningful food effect was on the PK of belzutifan. The pivotal study of belzutifan versus everolimus in patients with advanced RCC (MK-6482-005) initially used FMF formulation then switched to FMI formulation.
Absorption	
Absolute bioavailability	The absolute bioavailability of belzutifan has not been characterized. Formulations with up to (b) (4) content had no impact on oral bioavailability.

Food effect	High-fat meal did not have a clinically meaningful effect on the PK profile of belzutifan. The belzutifan FMI tablets can be administered without regard to food.
Distribution	
Volume of distribution	The estimated mean (CV%) volume of distribution after a 120 mg oral dose of belzutifan is 119 L (28%)
Clinical pharmacokinetics	Based on pop-PK analysis he C_{max} and AUC of belzutifan increase proportionally over a dose range of 20 mg to 120 mg WELIREG. The estimated geometric mean steady-state (CV%) C_{max} is 1.5 µg/mL (45%) and AUC_{0-24h} is 20.4 µg•hr/mL (62%) in patients treated with 120 mg WELIREG. Steady state is reached after approximately 3 days.
Metabolism	
DDI potential	Study MK-6482-009 found that belzutifan is a weak CYP3A4 inducer. However, PBPK modeling results predicted that belzutifan may be a moderate CYP3A4 inducer in patients with higher belzutifan plasma concentrations (e.g., those who are dual UGT2B17/CYP2C19 PM).
Excretion	
Primary excretion pathway	Following oral administration of radiolabeled belzutifan to healthy subjects, elimination occurred primarily via metabolism, with approximately 49.6% of the dose excreted in urine and 51.7% in feces (primarily as inactive metabolites).

FDA agrees with the use of pop-PK analysis to model the impact of UGT2B17 and CYP2C19 phenotype on belzutifan exposure. Refer to Information Request dated April 2021, FDA recommended comparison of dual UGT2B17/CYP2C19 PMs to a reference group of UGT2B17 normal metabolizers (NMs)/CYP2C19 non-PMs in the presentation of change of exposure. In the updated pop-PK analysis by the applicant, patients who are UGT2B17, CYP2C19, or dual UGT2B17 and CYP2C19 poor metabolizers are estimated to have 2.5-, 1.3-, or 3.2-fold higher belzutifan steady state AUC_{0-24h}, respectively compared to patients who are UGT2B17 normal (extensive) metabolizers and CYP2C19 non-poor (ultrarapid, rapid, normal, and intermediate) metabolizers. No dose adjustment is proposed for these specific enzyme phenotypes. Below are tables showing results of UGT2B17 and CYP2C19 phenotype on belzutifan exposure based on the entire population in the pop-PK analysis.

Effect of UGT2B17 and UGT2B17 Phenotypes on Belzutifan Exposure in the All Participants in the Pop-PK Population

PK Exposures	Compared to UGT2B17 IM		Compared to UGT2B17 EM	
	Covariate Group	Fold-change	Covariate Group	Fold-change
AUCss (µg·h/mL)	CYP2C19 PM	1.26	CYP2C19 PM	1.27
	UGT2B17 EM	0.716	UGT2B17 IM	1.40
	UGT2B17 PM	1.78	UGT2B17 PM	2.49
	UGT2B17 PM & CYP2C19 PM	2.25	UGT2B17 PM & CYP2C19 PM	3.15

Abbreviations: AUC=area under the plasma concentration-time curve for a 24-hour dosing interval, Cmax=maximum plasma concentration, Cmin=minimum plasma concentration; EM=extensive metabolizer phenotype, IM=intermediate metabolizer phenotype, PK=pharmacokinetic; PM=poor metabolizer phenotype, SS=steady state.

Effect of UGT2B17 and CYP2C19 Phenotypes on Belzutifan Exposure and PK Model Parameters

Phenotype	N	Geometric Mean (%CV)				
		AUCss (µg·h/mL)	Cmax,ss (ng/mL)	Cmin,ss (ng/mL)	Clearance (L/h)	Half-life (h)
UGT2B17 EM	131	15.8 (47.0%)	1260 (34.3%)	303 (76.0%)	9.03 (40.0%)	10.8 (34.6%)
UGT2B17 IM	175	22.3 (40.3%)	1540 (31.0%)	527 (59.6%)	6.34 (43.0%)	15.1 (33.8%)
UGT2B17 PM	51	44.6 (30.8%)	2550 (27.1%)	1330 (38.3%)	3.34 (32.3%)	25.6 (27.2%)
CYP2C19 PM	22	39.2 (59.7%)	2440 (47.1%)	1090 (76.2%)	4.52 (55.3%)	20.9 (51.0%)
UGT2B17 PM and CYP2C19 PM	11	57.4 (33.1%)	3290 (30.1%)	1730 (40.9%)	2.64 (38.5%)	27.8 (39.4%)

Findings from midazolam interaction study (Study MK-6482-009) that evaluated the CYP3A4 induction potential of belzutifan suggested that belzutifan is a weak inducer of CYP3A4. Coadministration of belzutifan 120 mg QD with midazolam decreased the midazolam AUC by 40% and the C_{max} by 34%. Results of the study supported that multiple dose administration of belzutifan does not substantially affect the exposures of a single oral 2-mg dose of midazolam. However, based on PBPK modeling, belzutifan 120 mg QD in the Japanese population (high prevalence of dual UGT2B17/CYP2C19 PM) would result in approximately 2-fold increase in belzutifan exposure (AUC) and correspondingly decrease the midazolam AUC_{inf} by 50% and C_{max} by 40%. Under the latter situation, belzutifan is predicted to be a moderate inducer (midazolam AUC is predicted to decrease up to 70%) in patients with higher belzutifan concentrations. This evidence supports the current labeling that avoid coadministration of WELIREG with sensitive CYP3A4 substrates.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Exploratory E-R analyses for efficacy and safety were performed with the Study 005 population in advanced RCC.

The Applicant's Position:

The exploratory E-R relationships for efficacy, safety and biomarker/pharmacodynamic markers provide supportive evidence of effectiveness for the belzutifan 120 mg QD dose as described further below.

The FDA's Assessment:

FDA agrees with the applicant's position. The currently approved dosage of belzutifan is 120 mg QD for patients with VHL-RCC. The recommended clinical dosage of 120 mg QD is supported by efficacy and safety data from the pivotal Phase 3 Study MK-6482-005 in patients with advanced RCC. E-R analysis for efficacy is considered exploratory due to immature data for efficacy endpoints including OS and DOR. There was a positive relationship between exposure and efficacy endpoints (PFS, OS). The relationship between belzutifan exposure and efficacy endpoints (ORR, DOR) is not significant. The results of this exploratory analysis should be interpreted with caution.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:
See Sec. 6.2.2.

The Applicant's Position:
Based on the totality of data, the 120-mg QD dose of belzutifan for patients with advanced RCC is supported by efficacy and safety results from Study 005, E-R relationships for efficacy, safety and biomarker markers, and an overall favorable risk-benefit profile.
For PFS, OS, and DOR, KM plots to assess time to event were generated and stratified by belzutifan exposure quartiles. Nominal p-values are provided to assess the associations for exposure-response and are not multiplicity adjusted. Descriptive statistics of these endpoints stratified by quartiles were tabulated as well. The exposure metric for PFS was performed with the AUC_{avg} until progression or censoring. The exposure metric for OS and DOR was the AUC_{avgeot} until the end of treatment.

The probability of ORR response (ie, the proportion of patients with a CR or PR) versus belzutifan exposure was plotted, with probabilities calculated across sets of patients binned by exposure quartiles. The exposure metric for ORR was the AUC_{avgeot}. Quantitative methods for the evaluation of E-R relationships included a logistic regression analysis.

PFS
The time at which 50% of the 379 patients in the E-R PFS analyses had progressed or died was 24.1 weeks, with wide CIs across exposure quartiles. In the KM curves by exposure quartile, Q1 and Q2 exposures overlapped but separated from Q3 and Q4 exposure curves, with nominal Cox regression p-value <0.05. This observation appears to suggest a positive association between exposure and time to progression or death at the time of IA1.

OS
At IA1, 167 (44%) of the 379 patients in the E-R OS analyses had an event. The median time to event was 97.1 weeks. The KM curves by exposure quartiles showed the Q1 to Q3 exposures overlapped, with the Q4 exposure curve separated. Given the immaturity of OS data at IA1, interpretation of results is premature.

ORR
Among the 367 participants from Study 005 with RCC tumors in the E-R efficacy analysis dataset, 83 (23%) participants were responders. A logistic regression has been applied to the individual data with nominal p-value >0.05 across the observed range. No clear trend is observed between ORR and exposure.

DOR
There were 83 ORR responders with DOR available. The median DOR time could not be quantified, and no trend with exposure was observed in the KM plot.

Safety (anemia and hypoxia)

In general, E-R analyses for safety do not show significant safety concerns associated with higher belzutifan exposures. Positive associations were observed for ≥Grade 3 and all grades of anemia in patients with advanced RCC. Consistent with the original NDA submission for the indication of VHL-RCC, a strong relationship between lower baseline hemoglobin and incidence of anemia was observed. Based on limited data, no clear E-R relationship for hypoxia was detected in patients with advanced RCC.

Biomarkers (EPO and hemoglobin)

EPO levels decreased on treatment with belzutifan, and the mean percentage change from baseline at Week 3 was -61.0%. The relationship of exposure dependent decrease in EPO seemed to plateau at higher exposures, consistent with previous findings.

Based on prior experience, hemoglobin decreases from the start of belzutifan and is at nadir by Week 13. Therefore, it was selected as the endpoint for E-R analysis for hemoglobin. Hemoglobin levels decreased on treatment with belzutifan, the mean change from baseline at Week 13 was –2.74 g/dL. A trend of larger absolute change from baseline hemoglobin at Week 13 with higher exposure was not observed.

The FDA's Assessment:
Yes, the proposed dosing regimen is appropriate for the general patient population with advanced RCC. In Study MK-6482-005, belzutifan demonstrated a statistically significant and clinically meaningful improvement in PFS compared with everolimus. Results for the immature OS favored belzutifan over everolimus. There was a positive relationship between exposure and efficacy endpoints (PFS, OS). The relationship between belzutifan exposure and efficacy endpoints (ORR, DOR) is not significant. The results of this exploratory analysis should be interpreted with caution.

Regarding the EPO levels following administration of belzutifan, the mean (Stdev) and median (range) EPO at Week 3 expressed as percentage change from baseline were

stratified by exposure quartile for AUCwk3 (table shown below). Larger percent change from baseline of EPO levels with higher exposure of belzutifan was also observed, which is consistent with the previous results.

EPO Percentage Change From Baseline at Week 3 Stratified by AUCwk3Quartiles

	Quartiles				
	Q1 (N = 78)	Q2 (N = 78)	Q3 (N = 77)	Q4 (N = 78)	Total (N = 311)
AUCwk3 (µg.h/mL) Median (Range)	10.5 (5.63; 12.9)	16.3 (12.9; 19.4)	23.5 (19.4; 28.2)	36.9 (28.3; 129)	19.4 (5.63; 129)
Mean (Stdev) EPO Week 3 (cfb%)	-55.6 (24.6)	-53.3 (43.6)	-61.2 (25.3)	-68.1 (20.7)	-61.0 (30.2)
Median (Range) EPO Week 3 (cfb%)	-60.7 (-92.3; 54.3)	-64.5 (-91.2; 234)	-67.4 (-94.8; 63.2)	-74.1 (-96.4; 8.50)	-66.6 (-96.4; 234)

Regarding the risk of anemia, there was a significant relationship between belzutifan exposure and anemia ≥ grade 3 in patients with advanced RCC. Lower baseline Hgb was associated with a greater risk of anemia. There was no clear E-R relationship between belzutifan exposure and hypoxia.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position:
Based on updated popPK analysis, no alternative doing regimen or management strategy is required for subpopulations in patients with advanced RCC.

The FDA's Assessment:
FDA agrees with the applicant's position.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:
A high-fat meal, when administered with belzutifan as the FMI tablet, did not have a clinically meaningful impact on belzutifan PK, and belzutifan can be administered without regard to food.

Multiple-dose administration of belzutifan resulted in a decrease in midazolam plasma concentrations, consistent with the effect of a weak CYP3A4 inducer. To further quantify this risk, a PBPK model was built to project the impact of repeat dosing of 120 mg QD belzutifan on midazolam exposures in participants with higher belzutifan exposures. These projections suggest that belzutifan may be a moderate CYP3A4 inducer in patients with higher belzutifan plasma concentrations.

The FDA's Assessment:

FDA agrees with applicant's position on food effect. Table 2.7.1:3 below shows that GMRs of C_{max}, AUC_{last}, AUC_{inf} were within the acceptance range (80 to 125%) between the fed and fasted conditions following administration of a single dose 120 mg belzutifan as the FMI formulation. Therefore, food intake did not have a clinically meaningful effect on belzutifan exposure with the FMI formulation.

Table 2.7.1: 3
The Effect of Food on the Pharmacokinetics of Belzutifan Administered as the FMI Formulation

		AUC0-last	AUC0-inf	Cmax
Comparison	N	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
Fed / Fasted	14	1.00 (0.94, 1.07)	1.00 (0.94, 1.07)	0.76 (0.64, 0.91)

Table 2.7.1:4 below demonstrates that [redacted] (b) (4) content up to [redacted] (b) (4) drug substance does not have a clinically meaningful effect on the PK of belzutifan.

Table 2.7.1: 4
Comparison of Pharmacokinetics of a Single 120-mg Belzutifan Oral Dose With FMI Formulations Containing [redacted] (b) (4) Drug Substance

		AUC0-24	AUC0-inf	Cmax
Comparison	N	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
F-A / FMI	17	0.98 (0.93, 1.03)	1.03 (0.96, 1.10)	0.98 (0.85, 1.12)
F-B / FMI	17	0.95 (0.91, 1.00)	1.01 (0.96, 1.05)	0.95 (0.84, 1.08)
F-A=Formulation A ([redacted] (b) (4) content); F-B=Formulation B ([redacted] (b) (4) content); FMI=final market image.				

Table 2.7.2 below shows that coadministration of belzutifan 120 mg QD with midazolam decreased the midazolam AUC_{inf} by 40% and C_{max} by 34%, suggesting belzutifan is a weak inducer of CYP3A4. Based on PBPK modeling, midazolam AUC is predicted to decrease up to 70% in patients who have higher belzutifan plasma exposures. FDA agrees with the applicant's position that belzutifan may be a moderate CYP3A4 inducer in patients with higher belzutifan plasma concentrations. Higher exposure of belzutifan is expected among patients who are dual UGT2B17/CYP2C19 PM based on pop-PK results. Remaining the recommendation on avoiding sensitive CYP3A4 substrates when co-administered with belzutifan is appropriate.

Appendix 2.7.2-rce2: 2
Tabular Summary of Pharmacokinetic Parameter Values

PN	Design / Population Subgroups (if applicable)	Dose	Day/ Period	N	Analyte	GM (GCV%)						
						Cmax (ng/mL)	Tmax[a]	AUC0-inf (ng/mL•hr)	AUC0-last (ng/mL•hr)	t½ (hr)	CL/F (L/hr)	Vz/F (L)
Healthy Subject PK and Initial Tolerability Studies												
008	Open-label, nonrandomized, no treatment control study	120 mg [^{14}C]belzutifan	Day 1	6	belzutifan	1620 (16.7)	0.75 (0.50 - 1.00)	15500 (49.7)	15200 (50.8)	10.6 (39.6)	7.97 (50.0)	121 (17.5)
Extrinsic Factor PK Study Reports												
009	Open-label, nonrandomized, fixed-sequence, no treatment control study	Period 1: SD midazolam 2 mg Period 2: belzutifan 120 mg qd × 7 days; SD midazolam 2 mg	Day 2	14	belzutifan	1400 (24.1)	2.00 (1.00 – 4.08)	---	---	---	---	---
			Day 8	13	belzutifan	2020 (30.6)	2.00 (1.00 – 4.05)	---	---	---	---	---
			Period 1	14	midazolam	11400 (37.8)	0.50 (0.25 – 2.00)	27700 (43.2)	---	5.12 (47.7)	72.1 (43.2)	533 (33.5)
			Period 2	13	midazolam	7470 (29.3)	0.50 (0.25 – 1.00)	16800 (33.7)	---	4.63 (48.6)	119 (33.7)	797 (32.7)

AUC=area under the plasma concentration-time curve; AUC0-inf=AUC from time 0 to infinity; AUC0-last=AUC from time 0 to last measurable concentration; CL/F=apparent clearance; Cmax=maximum concentration; GCV=geometric coefficient of variation; GMR=geometric mean ratio; N=number of participants; PK=pharmacokinetic; PN=protocol number; SD=single dose; t1/2=half-life; Tmax=time of maximum concentration; Vz/F=volume of distribution
[a] Median (Minimum-Maximum)

The reviewers verified and confirmed the analyses. Belzutifan and the glucuronide metabolite (PT3317) were measured using a validated LC-MS/MS method.

X X

Primary Reviewer Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Study 005, the pivotal Phase 3 study for this application, is shown in [Table 2].

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Table 2: Applicant – Clinical Trial Relevant to this sNDA

Controlled Studies to Support Efficacy and Safety	
Trial Identity/ NCT no.	MK-6482-005 / NCT04195750
Trial Design	Phase 3, multicenter, randomized, open-label study
Regimen/ Schedule/ Route	belzutifan 120 mg once daily/oral; everolimus 10 mg once daily/oral
Study Endpoints	**Primary:** PFS (per RECIST 1.1 by BICR) and OS **Secondary:** ORR and DOR per RECIST 1.1 by BICR, safety, EORTC QLQ-C30, FKSI-DRS, EQ-5D-5L
Treatment Duration/ Follow-up	Treatment continued until meeting the protocol-defined discontinued criteria. All participants underwent long-term follow-up for OS until death, withdrawal of consent, or the end of study.
No. of Patients Enrolled	ITT: 746; APaT: 732
Study Population	Male and female participants with advanced clear cell RCC
No. of Centers	147 study sites in 23 countries

APaT=all participants as treated; BICR=blinded independent central review; DOR=duration of response; EORTC=European Organization for Research and Treatment of Cancer; FKSI-DRS=Functional Assessment of Cancer Therapy – Kidney Symptom Index-disease-related symptoms; ITT=intent to treat; NCT=national clinical trial; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QLQ-C30=Quality of Life Questionnaire Core 30 items; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; RCC=renal cell carcinoma.

The Applicant's Position:
[Table 2] presents details of Study 005, which supports the safety and efficacy in the proposed indication.

The FDA's Assessment:
This sNDA was submitted based on the results of Study 005 (also known as LITESPARK-005 and MK-6482-005). FDA agrees with the summary of the trial information provided in Table 2.

8 Statistical and Clinical Evaluation

8.1.1. **Review of Relevant** Individual Trials Used to Support Efficacy

8.1.2. **MK-6482-005**

Trial Design

The Applicant's Description:

Study 005 is an ongoing 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.

The study procedures below are a summary of complete details found in the study protocol.

Trial Location: A total of 746 participants were randomized to receive either belzutifan or everolimus across 147 sites in 23 countries. Participating countries were Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hong Kong, Hungary, Italy, Japan, Norway, Russia, South Korea, Spain, Sweden, Taiwan, Turkey, Ukraine, United Kingdom, and United States.

Dose Selection: Participants were randomized to receive either belzutifan 120 mg administered orally once daily or everolimus 10 mg administered orally once daily. Belzutifan 120 mg was identified as the optimal dose based on previous clinical study experience in study MK-6482-001 / LITESPARK-001 (Study 001), an ongoing Phase 1 study to assess the tolerability, safety, PK, and PD properties of belzutifan in participants with various advanced solid tumors, including RCC. This is the approved dose for belzutifan based on results from Study 004, an ongoing Phase 2 study to evaluate belzutifan for the treatment of VHL-RCC. The dose selected for everolimus in Study 005 is the current approved dose.

Assignment to treatment: Participants were randomized in a 1:1 ratio and stratified by IMDC prognostic scores (0 versus 1 to 2 versus 3 to 6) and number of prior VEGF-targeted therapies for advanced RCC (1 versus 2 to3).

Blinding: This is an open-label study; however, analyses or summaries generated by randomized treatment assignment, or actual treatment received, were limited and documented. An independent radiologist(s) performed central imaging review without knowledge of treatment assignments.

Concomitant medications: Participants were prohibited from receiving antineoplastic systemic chemotherapy or biological therapy not specified in this protocol, investigational agents other than belzutifan, radiation therapy for disease control except as palliative treatment for symptomatic lesions or to the brain, live vaccines, systemic glucocorticoids other than to modulate symptoms from an AE, strong CYP3A4 inhibitors, P-gp inhibitors for participants receiving belzutifan, and ACE inhibitors for participants receiving everolimus.

Treatment compliance: Drug accountability data were collected, and any deviation was reported.

Dose modification: Toxicity management guidelines for belzutifan, including treatment reduction, interruption, or discontinuation, were managed per protocol, and for participants receiving everolimus was managed per the current everolimus label.

Dose discontinuation: Participants could 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 have occurred. In addition, a participant could be discontinued from study intervention by the investigator or the Sponsor if study intervention was inappropriate, the study plan was violated, or for administrative and/or

other safety reasons.

Administrative structure: A central imaging vendor used RECIST 1.1 to assess applicable primary and secondary endpoints. The study was developed in collaboration with a Scientific Advisory Committee. An eDMC monitored interim data from the study and made recommendations to the EOC regarding steps to ensure participant safety and data integrity.

Study procedures: Schedule of Assessments for the study is available in the protocol (Sec. 1.3).

Subject completion, discontinuation, or withdrawal: Participants could withdraw consent at any time for any reason. Participants who withdrew from the study were encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. With Sponsor approval, treatment could continue beyond BICR-verified progression. A participant must be discontinued from the trial if the participant met any of the criteria for discontinuation. Participants who discontinued from the trial were not replaced.

The FDA's Assessment:

Study 005 Design:
FDA agrees with the Applicant's description of the study design as above. As mentioned, Study 005 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 anti-PD-1/L1 and VEGF-targeted therapies.

Patients were randomized 1:1 to receive either belzutifan or everolimus. Randomization was stratified by IMDC prognostic scores (0 vs 1-2 vs 3-6) and number of prior VEGF-targeted therapies for advanced RCC (1 vs 2-3), but not the number of prior lines of therapy. Primary endpoints were PFS by BICR and OS. Patients were evaluated radiologically at Week 9 Day 1 then every 8 weeks thereafter for the first 49 weeks and then every 12 weeks thereafter.

Treatment continued until disease progression radiographically documented per RECIST 1.1, unacceptable adverse events (AEs), intercurrent illness that prevented further administration of treatment, investigator's decision to discontinue the participant, or administrative reasons requiring cessation of treatment. Patients who discontinued treatment for reasons other than radiographic disease progression had post-treatment follow-up imaging for disease status until disease progression was documented radiographically per RECIST 1.1, initiation of a new anticancer treatment, withdrawal of consent, pregnancy, death, lost to follow-up, or end of study.

Choice of control arm in Study 005:
In the EOP2 meeting preliminary responses in March 2019, FDA agreed with

everolimus as the treatment regimen in the control arm for Study 005.

Available treatment options for the proposed indication 2L+ mRCC, with ≥1 prior anti-VEGF and ICI) are axitinib, cabozantinib, tivozanib, everolimus, and everolimus plus lenvatinib, and current NCCN guidelines identify no preferred regimen for treatment of patients with mRCC and ≥1 prior anti-VEGF and ICI. Thus, while everolimus may have lower activity than a further VEGF-TKI in this setting (although this has not been evaluated in a randomized trial following both a PD-1 or PD-L1 and prior VEGF-TKI), FDA considered everolimus an acceptable choice of comparator in Study 005 at the time of study design and still considers this an acceptable control arm at the time of sNDA review, as it continues to reflect a standard of care option for patients in this setting.

Concomitant anti-neoplastic drugs in LITESPARK-005
The use of non-protocol specified anticancer therapies was not allowed during the Therapeutic phase in LITEPARK-005. In the Post-Treatment phase, patients received non-study anticancer therapies as determined by the treating investigator. Per the study data entry guidelines, all the non-study anti-cancer therapies were reported on the Oncologic Drugs and Biologics Follow Up (ODBF) CRF. In addition, if a patient received non-study related oncologic treatment for the cancer under study within 14 days of (or concurrent with) the onset of a SAE or an event of clinical interest, the oncologic treatment had to be recorded on both the ODBF and the Concomitant Medication CRF.

Eligibility Criteria

The Applicant's Description:
The eligibility criteria reflect the advanced or metastatic clear cell RCC population in the US.

Key Inclusion Criteria: Male or female ≥18 years of age; diagnosis of unresectable, locally advanced or metastatic clear cell RCC; measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology; 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; received no more than 3 prior systemic regimens for locally advanced or metastatic RCC; demonstrated radiographic disease progression for the most recently received regimen; hemoglobin ≥10 g/dL; and KPS score of at least 70% assessed within 10 days prior to randomization.

Key Exclusion Criteria: Hypoxia as defined by pulse oximeter reading <92% at rest, or required intermittent supplemental oxygen, or required chronic supplemental oxygen; known additional malignancy that was progressing or had required active treatment within the past 3 years; known CNS metastases and/or carcinomatous meningitis;

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; poorly controlled hypertension defined as systolic BP ≥150 mm Hg and/or diastolic BP ≥90 mm Hg; moderate to severe hepatic impairment (Child-Pugh B or C); received prior treatment with belzutifan or another HIF-2α inhibitor, everolimus, or any other specific or selective TORC1/PI3K/AKT inhibitor (e.g., temsirolimus) in the advanced disease setting, radiotherapy within 2 weeks prior to randomization, or major surgery within 3 weeks prior to randomization.

The inclusion criteria specified that to be eligible for enrollment, patients were required to have systemic treatment for locally advanced or metastatic RCC with a PD-1/L1 checkpoint inhibitor (at least 2 doses of a PD-1/L1 checkpoint inhibitor) and a VEGF-targeted therapy (including tyrosine kinase inhibitors or monoclonal antibodies) as monotherapy, or in combination, with no more than 3 prior systemic regimens for locally advanced or metastatic RCC.

This was slightly different from the Applicant's proposed indication, which was "for treatment of patients with advanced renal cell carcinoma (RCC) following immune checkpoint and anti-angiogenic therapies" (underlined here for emphasis). Only two patients enrolled who had received a non-VEGF-TKI (bevacizumab) as their only prior anti-angiogenic therapy, which the review team did not consider a sufficient number to allow the indication to include patients who had not received a prior VEGF-TKI, particularly given that bevacizumab does not have an indication for RCC in the US. Therefore, the FDA review team revised the indication to specify the prior therapies as a PD-1/PD-L1 inhibitor and a VEGF-TKI, consistent with the enrolled population.

Study Endpoints

The Applicant's Description: The study endpoints are detailed in [Table 3].

Table 3: Applicant – Study Endpoints

Primary Endpoints (comparing belzutifan to everolimus)	
PFS	The time from randomization to the first documented disease progression (per RECIST 1.1 by BICR) or death due to any cause, whichever occurs first
OS	The time from randomization to the date of death due to any cause
Secondary Endpoints (comparing belzutifan to everolimus)	
ORR	the proportion of participants who had CR or PR per RECIST 1.1 by BICR
DOR	the time from the first documented evidence of CR or PR per RECIST 1.1 by BICR until either disease progression or death due to any cause, whichever occurs first
Safety	AEs and study intervention discontinuations due to AEs
QoL	PRO scores, including change from baseline in EORTC QLQ-

	C30 and FKSI-DRS, and health utility scores from EQ-5D-5L

AE=adverse event; BICR=blinded independent central review; CR=complete response; DOR=duration of response; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; EQ-5D-5L= European Quality of Life Five Dimensions Five Level Questionnaire; FKSI-DRS= Functional Assessment of Cancer Therapy – Kidney Symptom Index-disease-related symptoms; OS=overall survival; PFS=progression-free survival; PR=partial response; QoL=quality of life; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1.

The FDA's Assessment:
FDA agrees with the Applicant's description of study endpoints.

One of the key inclusion criteria was patients with measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Though PFS, one of the primary endpoints, and ORR, a key secondary endpoint, were assessed by BICR, not every patient had measurable disease at baseline per BICR assessment. There were 9 patients who did not have measurable disease at baseline per BICR assessment. This is unlikely to have compromised overall interpretation of study results in an appreciable way due to very small numbers of patients to whom this applied, including only 1 in the treatment arm; this issue will be discussed further in the baseline characteristics section below.

Statistical Analysis Plan and Amendments

The Applicant's Description:
[Table 4] summarizes the analysis strategy for the endpoints described in [Table 3].

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Table 4: Applicant – Summary of Analysis Strategy for Key Efficacy Endpoints in MK-6482-005

Analysis Populations	Efficacy: ITT (all randomized participants); Safety: APaT (all randomized participants who received at least 1 dose of study treatment)	
Statistical Methods for Key Efficacy Analyses	The primary hypotheses comparing belzutifan to everolimus with respect to PFS and OS was evaluated using a stratified log-rank test. The HR was estimated using a stratified Cox regression model. Event rates over time were estimated within each treatment group using the KM method. The stratified Miettinen and Nurminen method with strata weighted by sample size was used for analysis of ORR.	
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs were provided for between-treatment differences in the percentage of participants with events, these analyses were performed using the Miettinen and Nurminen method.	
Interim and Final Analyses	IA1	• Timing: planned to be performed after ~563 PFS events had occurred AND ~7 months after last participant randomized. NOTE: IA1 could take place if the PFS events accrued slower than expected when participants had been followed up for ~7 months and ~525 PFS events had occurred. • Primary purpose: efficacy analyses for PFS, OS, and ORR.
	IA2	• Timing: to be performed after ~410 OS events have occurred AND at least 17 months after last participant randomized. • Primary purpose: efficacy analyses for OS and PFS (final analysis).
	FA	• Timing: to be performed after ~483 OS events have occurred AND ~27 months after last participant randomized. • 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 Mauer and Bretz, if one hypothesis is rejected, the alpha will be shifted to other hypotheses [Maurer, W. 2013].	
Sample Size and Power	The planned sample size was approximately 736 participants. Approximately 483 deaths are expected at the final OS analysis. With 483 deaths, the study has ~85% power for detecting an HR of 0.75 at an initially assigned 0.019 (1-sided) significance level. Approximately ~626 events were expected at the final PFS analysis (ie, the second IA of the study). With 626 PFS events, the study has ~97% power for detecting an 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.	
APaT=all participants as treated; CI=confidence intervals; FA=final analysis; HR=hazard ratio; IA=interim analysis; ITT=intention-to-treat; KM=Kaplan-Meier; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.		

Source: Protocol 6482-005-06

The FDA's Assessment:

The Applicant used the graphical method that allowed for the possibility of re-evaluating

the RECIST-based endpoints (PFS and ORR) after evaluating OS. During the conduct of the trial, FDA communicated to the Applicant that FDA was concerned that there may be a potential for inflating Type I error depending on the approach (Hung, Wang and O'Neill,2007). However, as OS at IA1 was not statistically significant, the re-evaluation of the endpoints (PFS and ORR) was not conducted and this was thus no longer of concern.

Per protocol and SAP, the definition of primary PFS by BICR accounted for initiation of subsequent anti-cancer therapy, i.e., any patient who experienced an event (disease progression or death) immediately after >=2 missed disease assessments were censored at the last disease assessment prior to the missed visit. In addition, any patient who initiated new anticancer therapy was censored at the last disease assessment prior to the initiation of new anticancer therapy. Patients who did not start new anticancer therapy and who did not experience an event were censored at the last disease assessment. If a patient assessment. If a patient met multiple criteria for censoring, the censoring criterion that occurred earliest was applied.
As discussed in the previous paragraph and for the topics of concomitant anti-neoplastic drugs, all non-study anticancer therapy were collected on ODBF form and were accounted for in the primary PFS analysis. Similarly, for the key secondary endpoint of ORR by BICR per RECIST 1.1, only the tumor assessment prior to initiation of subsequent anticancer therapy are used in the endpoint assessment. Therefore, there is no need for additional sensitivity analyses for any anticancer therapies captured on the Concomitant Medication CRF.

Protocol Amendments

The Applicant's Description:
The original protocol was finalized on 30-SEP-2019 and amended 7 times [Table 5].

Table 5: Applicant - Protocol Amendments for MK-6482-005

Document (Date of Issue)	Overall Rationale
Amendment 7 (13-JUL-2022)	Japan-specific amendment: Amendment 6 updates added to the Japan-specific study protocol.
Amendment 6 (13-JUL-2022)	To update the timing of statistical analyses and reduce the total number of interim analyses in the study.
Amendment 5 (16-FEB-2021)	Japan-specific amendment: Amendment 4 updates added to the Japan-specific study protocol.
Amendment 4 (16-FEB-2021)	To update contraception appendix to align with program wide requirements.
Amendment 3 (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.

Document (Date of Issue)	Overall Rationale
Amendment 2 (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.
Amendment 1 (18-DEC-2019)	To add a safety run-in component for Japan to ensure the correct dose of belzutifan is used in that participant population.

The FDA's Assessment:
In general, FDA agrees with the description of protocol amendment listed above.

The protocol version 6 updated the timing of statistical analysis due to longer-than-planned accrual. The key changes in Amendment 6 are summarized below:

- reduced the number of IAs from 3 to 2
- reduced the target/expected PFS event number from 634 to 626; and changed corresponding power from 97.1 % to 96.6%
- changed the timing of the ORR analysis at IA1 instead of IA2
- changed the accrual duration from 18 to 22

8.1.3. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:
Study 005 was conducted in conformance with the ethical principles originating from the Declaration of Helsinki, GCP requirements, and applicable country and/or local statutes and regulations regarding IEC review, informed consent, and the protection of human participants in biomedical research. The protocol and any amendments, information provided to participants, and any recruitment materials were reviewed and approved by the IECs (also referred to as an IRB, ERC, or any other ethics committee). Informed consent was obtained from all participants prior to performing any study-related procedures or assessments.

The FDA's Assessment:
FDA has no additional comments.

Financial Disclosure

The Applicant's Position:
Disclosure of financial interests of the investigators who conducted Study 005 has been

collected and submitted by the Applicant.

The FDA's Assessment:
FDA has no additional comment.

Patient Disposition

The Applicant's Position:
A total of 746 participants were randomly assigned in a 1:1 ratio to receive either belzutifan or everolimus. A total of 732 participants received at least 1 dose of study intervention. The median duration of follow-up was 13.5 months (range: 0.2 to 31.8 months) and was similar between the 2 treatment groups. As of the data cutoff for IA1, treatment with study intervention was ongoing for 117 (31.5%) participants receiving belzutifan and 35 (9.7%) participants receiving everolimus. A total of 204 (54.5%) participants in the belzutifan group and 182 (48.9%) participants in the everolimus group continued to be followed in the study.

Nine participants were enrolled in the Japan Safety Run-in Phase. These participants were not randomized to treatment in the study; all received belzutifan.

The FDA's Assessment:
Having measurable disease per investigator assessment was an eligibility criterion and 18 patients who did not have measurable disease per investigator assessment were excluded at screening. Of 746 patients who were enrolled, 374 and 372 patients were assigned to belzutifan and everolimus, respectively. FDA agrees with the additional details on patient disposition provided by the Applicant.

As specified in the protocol and SAP, patients who were randomized but not administered study medication were included in the intention-to treat (ITT) population for the primary efficacy analyses. FDA notes the imbalance of 12 patients randomized into the everolimus arm who were not administered study medication compared to only 2 patients in the belzutifan arm who were randomized but who were not administered study medication.

The disposition status for these 14 patients who were randomized but not treated is summarized in **Table 6**.

Table 6: Disposition Status for Not-treated Patients

	Belzutifan N=374	Everolimus N=372
Number of patients who were randomized but not treated	2 (0.5%)	12 (3.2%)
Discontinued	2	10
Death	1	8

Withdrawal by subjects	1	2
Participant ongoing	0	2

DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023

Additional analyses related to impact of early discontinuation and censoring of patients on the everolimus arm in particular are presented below in the FDA Assessment of "Efficacy Results – Primary Endpoints (Including Sensitivity Analyses)" in the section discussing PFS, and in Table 15 below.

Protocol Violations/Deviations

The Applicant's Position:
Protocol deviations were classified as per the ICH E3 classification of protocol deviations as important (those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant's rights, safety, or well-being) or not important. Important protocol deviations were further classified as either clinically important (deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety) or not clinically important.

Important protocol deviations were reported for 242 participants in the main Phase 3 part of the study; none of the important protocol deviations were considered clinically important. No participant's data were excluded from analysis due to an important protocol deviation. No protocol deviations were classified as a serious GCP compliance issue.

The FDA's Assessment:
FDA agrees with the summary of protocol deviations. The majority of important protocol deviations were related to Safety Reporting (Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the
protocol), which occurred in 108 (28.9%) patients in belzutifan arm and 92 (24.7%) patients in everolimus arm. Deviations in Trial Procedures occurred in 25 (6.7%) of patients in the belzutifan arm and 6 (1.6%) in the everolimus arm. Trial Procedures with deviation included the following:
1. Meeting criteria for dose interruption, reduction or discontinuation and not taking the appropriate action.
2. Participant misses two consecutive imaging time points as outlined in Protocol.
3. Participant misses two consecutive hemoglobin assessments.
4. Participant restarts study intervention without Site/Sponsor Communication after an interruption of study intervention for >28 consecutive days.
5. Pulse oximetry not performed per protocol in a participant receiving MK-6482.
6. Re-escalation to the next higher dose level is performed without Site/Sponsor Communication.

Of note, 1 patient was enrolled despite lack of measurable disease per investigator assessment (patient had measurable disease per BICR assessment).

FDA agrees with the Applicant's assertion that none of the protocol deviations were considered clinically important or compromised interpretation of study results.

Table of Demographic Characteristics

Data:
Overall, most participants in the ITT population were male [Table 6]. Most participants were White, and most were not Hispanic or Latino. The overall median age was 63.0 years (range: 22 to 90 years), with most participants in both treatment groups in the <65 years of age category. Half of the participants (50.0%) were enrolled at sites in Western Europe, and the rest were enrolled in North America (22.0%) and Rest of World (28.0%).

Table 7: Applicant - Participant Characteristics (ITT Population)

	Belzutifan		Everolimus		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	374		372		746	
Sex						
Male	297	(79.4)	284	(76.3)	581	(77.9)
Female	77	(20.6)	88	(23.7)	165	(22.1)
Age (Years)						
< 65	232	(62.0)	201	(54.0)	433	(58.0)
>= 65	142	(38.0)	171	(46.0)	313	(42.0)
Mean	61.6		63.1		62.4	
SD	10.2		9.7		10.0	
Median	62.0		63.0		63.0	
Range	22 to 90		33 to 87		22 to 90	
Race						
American Indian Or Alaska Native	3	(0.8)	2	(0.5)	5	(0.7)
Asian	43	(11.5)	47	(12.6)	90	(12.1)
Black Or African American	4	(1.1)	4	(1.1)	8	(1.1)
Multiple	6	(1.6)	11	(3.0)	17	(2.3)
American Indian Or Alaska Native Asian	1	(0.3)	0	(0.0)	1	(0.1)
American Indian Or Alaska Native Black Or African American	1	(0.3)	1	(0.3)	2	(0.3)
American Indian Or Alaska Native White	1	(0.3)	7	(1.9)	8	(1.1)
Black Or African American White	2	(0.5)	3	(0.8)	5	(0.7)

	Belzutifan		Everolimus		Total	
	n	(%)	n	(%)	n	(%)
White Asian	1	(0.3)	0	(0.0)	1	(0.1)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(0.3)	1	(0.1)
White	297	(79.4)	291	(78.2)	588	(78.8)
Missing	21	(5.6)	16	(4.3)	37	(5.0)
Ethnicity						
Hispanic Or Latino	42	(11.2)	37	(9.9)	79	(10.6)
Not Hispanic Or Latino	299	(79.9)	303	(81.5)	602	(80.7)
Not Reported	26	(7.0)	21	(5.6)	47	(6.3)
Unknown	5	(1.3)	8	(2.2)	13	(1.7)
Missing	2	(0.5)	3	(0.8)	5	(0.7)
Geographic Region of Enrolling Site						
North America	75	(20.1)	89	(23.9)	164	(22.0)
Western Europe	191	(51.1)	182	(48.9)	373	(50.0)
Rest of the World	108	(28.9)	101	(27.2)	209	(28.0)

Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl]
Note: Data for race and ethnicity were not routinely provided in France.

The Applicant's Position:
The baseline demographic characteristics of participants were well balanced between the 2 treatment groups.

The FDA's Assessment:
Overall, the baseline characteristics were well-balanced between the treatment arms.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:
Most participants had a baseline KPS score of 90/100, most were in the IMDC intermediate or poor risk categories, and most had a baseline ECOG PS of 0 or 1. The most common metastatic sites were lung, lymph nodes, and bone. Most participants had received 2 (43.3%) or 3 (42.8%) prior lines of systemic oncologic therapy before study entry. As required for this study, all participants had received prior PD-1/L1 and VEGF/VEGF receptor-targeted therapies alone or in combination.
The Applicant's Position:
Baseline characteristics were representative of a patient population with advanced RCC.

The races and ethnicities represented in this study are shown in [Table 6]. The study population also included participants who identified as multiple races. Diversity in

clinical trials has been and continues to be a priority for the Applicant, as an integral component of the Applicant's broader Diversity and Inclusion strategy and commitments, and in recognition of the clinical value of continued focus on the diversity of our studies.

The FDA's Assessment:
A total of 2 patients in LITESPARK-005 (both in the belzutifan arm) received prior bevacizumab only without any other prior VEGF-TKI drug.

Half of the patients in Study 005 had only 1 prior VEGF-TKI. Additionally, less than 15% of the patients in each arm had 1 prior line of therapy, meaning that they received the combination of a PD-1 or PD-L1 checkpoint inhibitor plus VEGF-TKI in the first line of therapy, and were thus eligible per Study 005 enrollment criteria. As the treatment strategy of use of a combination of PD-1 or PD-L1 checkpoint inhibitor plus a VEGF-TKI as first-line therapy becomes more widely accepted as standard of care, the FDA review team anticipates that patients progressing on that combination may represent a large portion of those who may be prescribed belzutifan post-approval (i.e. only 1 prior line of therapy, comprising a combination of a PD-1 or PD-L1 checkpoint inhibitor plus VEGF-TKI). Efficacy in this subset of 1 prior line of therapy will be reviewed in subgroup analyses presented below.

As previously noted, 18 patients were excluded at the time of screening due to having no measurable disease per investigator assessment at baseline; one randomized patient (SUBJID (b) (6) in the everolimus arm) did not have measurable disease per investigator assessment but had measurable disease per BICR assessment at baseline; an additional 9 randomized patients (1 in the belzutifan arm and 8 in the everolimus arm) had measurable disease per investigator assessment but did not have measurable disease per BICR baseline assessment. Although the proposed indication is regardless of having measurable disease, (despite this being a component of eligibility criteria for Study 005), at this stage of advanced RCC it is exceedingly rare for a patient not to have measurable disease, as evidenced by the actual low observed numbers of patients for whom this occurred on Study 005 during either screening or BICR baseline imaging evaluation (~1-2%). Thus, this potential difference between eligible and approved patient population appears to affect only a minor potential number of patients and is thus not expected to be a major issue in terms of applicability of trial results.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:
Study intervention was dispensed to participants for oral administration, and a count of the number of tablets returned at a visit was used to assess compliance. Median

treatment compliance was similar in both treatment groups (99.6% in the belzutifan group and 98.4% in the everolimus group), with >90% of participants in each treatment group having compliance >80%.

Prior nononcologic medications reported for ≥10% of participants in either group were levothyroxine sodium, amlodipine, paracetamol, omeprazole, and acetylsalicylic acid. The most frequently reported concomitant nononcologic medications (incidence ≥50% in either group) were in the categories of ophthalmological, stomatological preparations, analgesics, corticosteroids/dermatological preparations, corticosteroids for systemic use, otologicals, drugs for acid-related disorders, nasal preparations, antidiarrheals/intestinal anti-inflammatory/anti-infective agents, and vasoprotectives. Higher medication use (≥10% difference) in the belzutifan group compared with the everolimus group was reported in the category of anti-anemic preparations only (39.5% and 26.4%, respectively).

Rescue medications and supportive care were allowed in the study as deemed necessary by the treating investigator as per protocol.

The Applicant's Position:
Participants were compliant with the study intervention.

Overall, the prior and concomitant medications administered were comparable between treatment groups, representative of those commonly prescribed for the target population, and not considered to have impacted the study results.

The FDA's Assessment:
FDA has no additional comment. The use of erythropoiesis stimulating agents (ESAs) for treatment of anemia in Study 005 will be discussed further in the discussion of efficacy results and in the safety section of this review.

Efficacy Results – Primary Endpoints (Including Sensitivity Analyses)

Data:
The efficacy results presented are from IA1 for Study 005, with a database cutoff date of 01-NOV-2022, and with a median of 13.5 months of follow-up. Results are presented for the dual primary endpoints of PFS [Table 7] [Figure 1] and OS [Table 8] [Figure 2].

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Table 8: Applicant - Analysis of Progression-free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (ITT Population)

	Belzutifan (N=374)	Everolimus (N=372)
Number of Events (%)	257 (68.7)	262 (70.4)
Death	23 (6.1)	40 (10.8)
Documented progression	234 (62.6)	222 (59.7)
Number of Censored (%)	117 (31.3)	110 (29.6)
Last assessment prior to 2 or more consecutive missed assessments	1 (0.3)	4 (1.1)
Last assessment showing no progression	91 (24.3)	23 (6.2)
Last radiologic assessment prior to new anti-cancer therapy showing no progression	21 (5.6)	68 (18.3)
Randomization	4 (1.1)	15 (4.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	5.6 (3.9, 7.0)	5.6 (4.8, 5.8)
[Q1, Q3]	[1.9, 16.7]	[2.1, 9.2]
Person-months	2718.2	1953.8
Event Rate / 100 Person-months	9.5	13.4
vs Everolimus		
Hazard Ratio (95% CI)[b]	0.75 (0.63, 0.90)	
p-value[c]	0.00077	
Rate at month 6 (%) (95% CI)	46.6 (41.3, 51.7)	42.5 (36.8, 48.0)
Rate at month 9 (%) (95% CI)	40.4 (35.2, 45.4)	28.4 (23.2, 33.8)
Rate at month 12 (%) (95% CI)	33.4 (28.4, 38.5)	17.1 (12.7, 22.1)
Rate at month 18 (%) (95% CI)	24.0 (19.0, 29.4)	8.3 (4.9, 12.7)
Rate at month 24 (%) (95% CI)	19.7 (14.1, 26.0)	0.0 (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and Number of prior VEGF/VEGF receptor targeted therapies for advanced RCC (1 vs. 2-3).

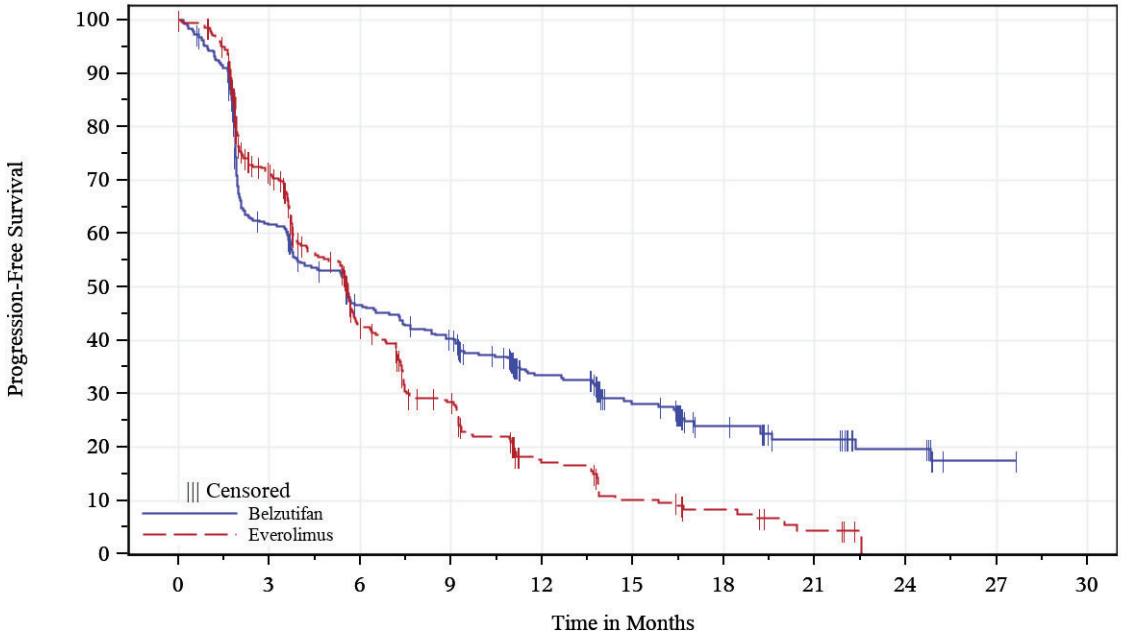
[c] One-sided p-value based on log-rank test stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and Number of prior VEGF/VEGF receptor targeted therapies for advanced RCC (1 vs. 2-3).

NR = Not reached.

Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adtte]

Figure 1: Applicant - Kaplan-Meier Plot of Progression-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (ITT Population)



At Risk

Belzutifan	374	218	157	134	85	55	32	20	11	1	0
Everolimus	372	226	113	68	31	17	10	4	0	0	0

Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adtte]

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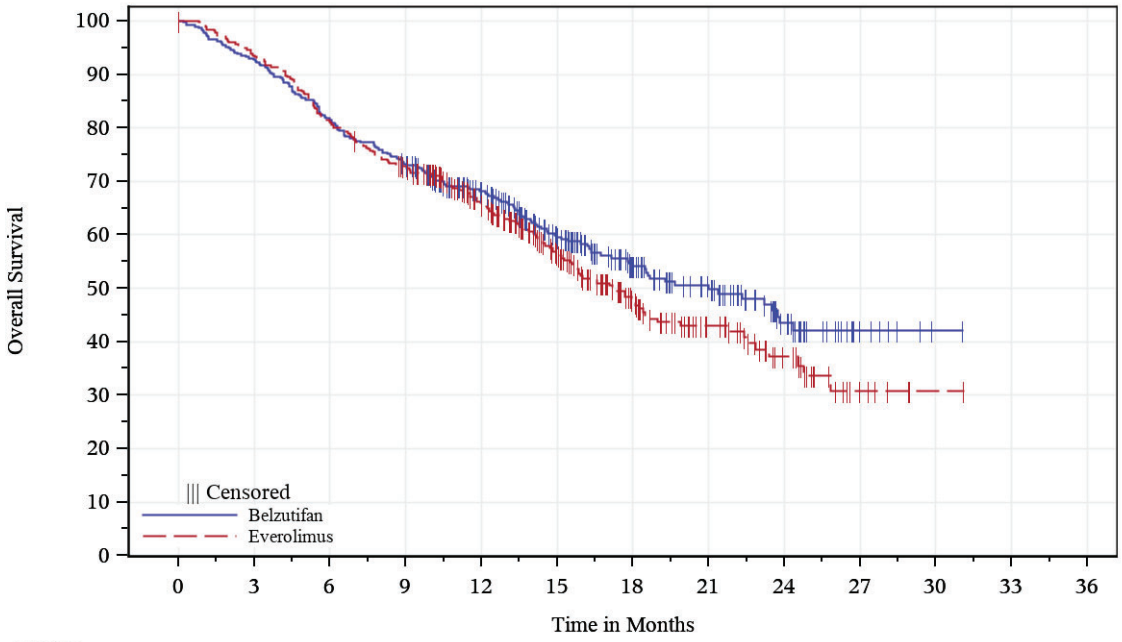
Table 9: Applicant – Analysis of Overall Survival (ITT Population)

	Belzutifan (N=374)	Everolimus (N=372)
Number of Events (%)	169 (45.2)	186 (50.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	21.0 (17.2, 24.3)	17.2 (15.3, 19.0)
[Q1, Q3]	[8.4, NR]	[7.8, NR]
Person-months	5077.9	4852.4
Event Rate / 100 Person-months	3.3	3.8
vs Everolimus		
Hazard Ratio (95% CI)[b]	0.87 (0.71, 1.07)	
p-value[c]	0.09583	
Rate at month 6 (%) (95% CI)	81.6 (77.2, 85.1)	81.1 (76.8, 84.8)
Rate at month 12 (%) (95% CI)	68.2 (63.2, 72.7)	65.6 (60.4, 70.3)
Rate at month 18 (%) (95% CI)	54.1 (48.4, 59.5)	47.9 (42.0, 53.5)
Rate at month 24 (%) (95% CI)	43.5 (36.3, 50.4)	37.2 (30.1, 44.2)
Rate at month 30 (%) (95% CI)	42.1 (34.6, 49.3)	30.8 (22.1, 39.9)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and Number of prior VEGF/VEGF receptor targeted therapies for advanced RCC (1 vs. 2-3).
[c] One-sided p-value based on log-rank test stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and Number of prior VEGF/VEGF receptor targeted therapies for advanced RCC (1 vs. 2-3).
NR = Not reached.
Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adtte]

Figure 2: Applicant –Kaplan-Meier Plot of Overall Survival (ITT Population)



At Risk

Belzutifan	374	347	305	273	218	155	103	67	34	7	1	0	0
Everolimus	372	347	301	266	207	143	85	48	24	6	1	0	0

Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adtte]

The Applicant's Position:

PFS

Belzutifan demonstrated a statistically significant improvement in PFS compared with everolimus, as assessed by BICR per RECIST 1.1. The PFS HR was 0.75 (95% CI: 0.63, 0.90; 1-sided *p*=0.00077); the p-value crossed the prespecified boundary for statistical significance of 0.0021 and represents a 25% reduction in the risk of disease progression or death with belzutifan compared with everolimus [Table 7]. The median PFS was similar in the belzutifan group (5.6 months; 95% CI: 3.9, 7.0) and in the everolimus group (5.6 months; 95% CI: 4.8, 5.8). PFS rates were higher in the belzutifan group compared with the everolimus group at 6, 9, and 12 months. At 12 months, the PFS rate was almost 2-fold higher for the belzutifan group compared with

the everolimus group (33.4% vs 17.1%) [Table 7].There was a separation of the KM curves for PFS at approximately 6 months in favor of belzutifan, and the curves continued to separate over time [Figure 1].

The improvement in PFS for belzutifan compared with everolimus in protocol-specified subgroups of IMDC risk category, geographic region, age category, sex, race, number of prior VEGF/VEGF receptor-targeted therapies, and number of prior lines of therapy was consistent with the overall ITT population.

The treatment effect of belzutifan on PFS based on BICR per RECIST 1.1 was consistent with the primary analysis when applying sensitivity analysis 1 (HR 0.75; 95% CI: 0.63, 0.88; 1-sided; *p*=0.00027) and sensitivity analysis 2 (HR 0.68; 95% CI: 0.58, 0.80; *p*<0.00001). Analysis of PFS based on investigator assessment per RECIST 1.1 (PFS HR: 0.68; 95% CI: 0.58, 0.81; *p*<0.00001) was consistent with analysis by BICR, with concordance of PD assessment between the BICR and the investigator assessments of 90% and 78% for the belzutifan and everolimus groups, respectively.

OS

The dual primary endpoint of OS favored belzutifan over everolimus; however, statistical significance was not reached at IA1. The OS HR was 0.87 (95% CI: 0.71, 1.07; 1-sided *p*=0.09583) [Table 8]; the p-value did not cross the statistical hypothesis testing p-value boundary of 0.0045 at IA1. The median OS was longer in the belzutifan group (21.0 months; 95% CI: 17.2, 24.3) than in the everolimus group (17.2 months; 95% CI: 15.3, 19.0). The OS rates, based on KM estimates, were numerically higher in the belzutifan group compared with the everolimus group at 12 and 18 months [Table 8]. The corresponding KM curves for OS separated at around Month 12 and remained separated throughout the evaluation period in favor of belzutifan [Figure 2].

The FDA's Assessment: The FDA has the following additional comments about the analysis of primary endpoints:

- **Interim PFS Analysis**

PFS by BICR was tested at the pre-specified IA1 with 83% information fraction and was found to be statistically significant in the ITT population with a HR of 0.75 (95% CI: 0.63, 0.90). As mentioned by the Applicant, the KM curves crossed at around 6 months with the curve of the everolimus arm above the curve of the belzutifan arm prior to the ~6 month mark. Additionally, the estimated medians of PFS were the same in both the belzutifan arm and in the everolimus arm, at 5.6 months each. Both of these factors make it challenging to fully interpret and contextualize the PFS benefit observed in Study 005, which appears modest, albeit over an active control which is considered a clinically acceptable treatment option in this setting. The overall risk/benefit assessment of belzutifan over everolimus, and how PFS results are interpreted in this context, will be more fully discussed in the Integrated Summary of Efficacy below.

Sensitivity Analysis of PFS per Investigator Assessment

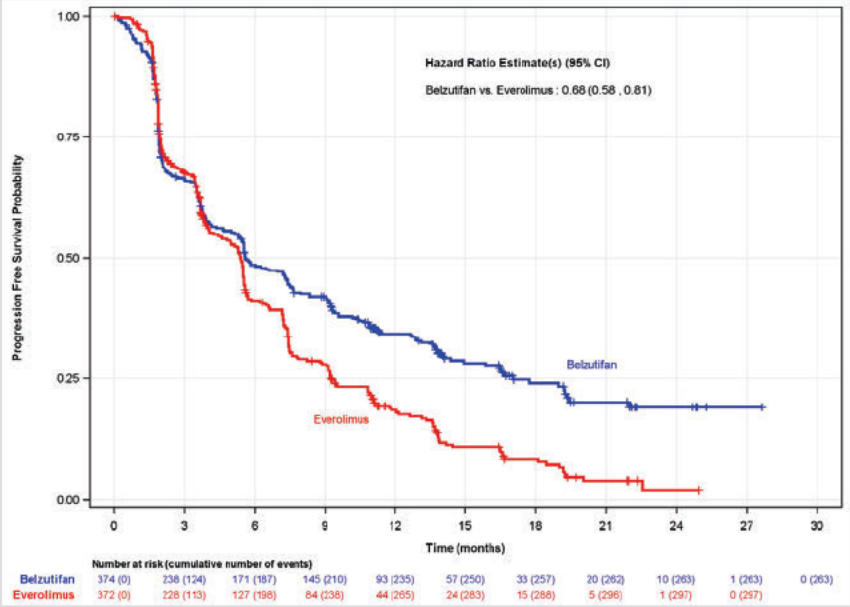
FDA performed a sensitivity analysis of PFS per investigator assessment, with results summarized in Table 10 and Figure 3. The event rate was greater in both arms per investigator assessment compared with PFS per BICR assessment, while the difference in event rate observed when comparing BICR vs. investigator assessments was more pronounced in the everolimus arm. The HR of the PFS per investigator assessment was slightly smaller than the HR of PFS per BICR assessment; medians were the same per investigator and BICR assessments. The investigator-assessed KM curves overlapped between the arms until ~6 months, and separated thereafter, similar to the separation of the KM curves that only occurred after ~6 months in the BICR-assessed KM curves.

Table 10. Analysis of PFS Assessed by Investigator in ITT Population

	Belzutifan N=374	Everolimus N=372
Number of events (%)	263 (70.3%)	297 (79.8%)
Median, months (95% CI)	5.6 (5.2, 7.4)	5.4 (4.1, 5.6)
Hazard Ratio (95% CI)	0.68 (0.58, 0.81)	

DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023

Figure 3: Kaplan-Meier Plot of PFS Assessed by Investigator in ITT Population



DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023

Censoring Reasons for PFS by BICR

The types of PFS events and reasons for censoring per BICR by time (whether they occurred within the initial 6 weeks or later), are summarized in Table 10. FDA notes some degree of imbalance in the censoring reasons between the two treatment arms. The major reason for censoring was due to ongoing study treatment without observed progression by DCO (November 1, 2022) in the belzutifan arm and was due to initiation of new anti-cancer therapy without disease progression per BICR in the everolimus arm.

In addition, a slight imbalance between the two treatment arms was observed between the number of patients censored at randomization [4 patients (1.1%) in the belzutifan arm and 15 (4.0%) in the everolimus arm], and censoring within 6 weeks from randomization. The imbalances were potentially due to 10 censored patients who were not administered study medication in the everolimus arm only (i.e. patients with "early dropout" in the everolimus arm, not unexpected in this open-label trial with a control arm that may not represent the treatment of choice for some investigators in this setting where other options exist). Sensitivity analyses exploring the impact of this early censoring on interpretation of PFS results will be discussed later in this review in Table 15.

Table 11: Reasons of Censoring and Event for PFS Assessed by BICR in ITT Population

	Belzutifan N=374	Everolimus N=372	Belzutifan N=374	Everolimus N=372	Belzutifan N=374	Everolimus N=372
	Early Event/Censoring (≤6 weeks)		Other (>6 weeks)		Total	
Number of events (%)	**30 (8%)**	**15 (4%)**	**227 (60.7%)**	**247 (66.4%)**	**257 (68.7%)**	**262 (70.4%)**
Death	8	5	15	35	23	40
Not treated	0	0	2	2	2	2
Documented progression	22	10	212	212	234	222
Number of censored (%)	**6 (1.6%)**	**17 (4.6%)**	**111 (29.7%)**	**93 (25%)**	**117 (31.3%)**	**110 (29.6%)**
Randomization	4	15	0	0	4	15
Not treated	0	10	0	0	0	10
Last radiologic assessment prior to new anti-cancer therapy showing no progression	2	2	19	66	21	68
Last assessment prior to 2 or more consecutive missed assessments	0	0	1	4	1	4
Last assessment showing no progression	0	0	91	23	91	23

DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023

Discordance Between PFS per BICR Assessment and Investigator Assessment

FDA performed an analysis to investigate the concordance and discordance rate of PFS per BICR assessment or per INV assessment, and summarized the results in Table 12. The overall concordance rate between BICR-assessed PFS and INV-assessed PFS was 89.8% (95% CI: 86.3%, 92.7%) for the belzutifan arm and 82.5% (95% CI: 78.3%, 86.2%) for the everolimus arm.

Table 12: Concordance and Discordance Rate of PFS per BICR or Investigator Assessment in ITT Population

Investigator Assessment	BICR Assessment			
	Belzutifan N=374		Everolimus N=372	
	Event	Censor	Event	Censor
Event	241 (64.4%)	22 (5.9%)	247 (66.4%)	50 (13.4%)
Censor	16 (4.3%)	95 (25.4%)	15 (4.0%)	60 (16.1%)

DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023

Per the table above, FDA noted that 22 (5.9%) events per investigator assessment in the belzutifan arm vs. 50 (13.4%) events per investigator assessment in the everolimus arm were censored per BICR assessment, indicating a potential imbalanced censoring between the two arms and potential investigator assessment bias which may be due to the open label study design, and increasing the uncertainty in the overall PFS results of Study 005.

Therefore, FDA performed an analysis of early discordance rate (EDR) and late discordance rate (LDR) to further evaluate the risk of this potential investigator assessment bias. FDA first summarized the PD and non-PD occurrences in Table 13 to determine the EDR and LDR.

Table 13: PD vs. non-PD of PFS per BICR Assessment

Investigator Assessment	BICR Assessment			
	Belzutifan N=374		Everolimus N=372	
	PD	Non-PD	PD	Non-PD
PD	215[a]	24[b]	201[a]	58[b]
Non-PD	19[c]	116	21[c]	92

a1: number of agreements on timing and occurrence of PD (143 in Belzutifan vs. 127 in Everolimus)
a2: number of times INV declares PD later than BICR (52 in Belzutifan vs. 53 in Everolimus)
a3: number of times INV declares PD earlier than BICR (20 in Belzutifan vs. 21 in Everolimus)
b1: number of time INV declares PD later than censored BICR, excluded for EDR and LDR calculation (1

in Belzutifan vs. 2 in Everolimus)
b2: number of time INV declares PD on or earlier than censored BICR (23 in Belzutifan vs. 56 in Everolimus)
c1: number of time BICR declares PD later than censored INV, excluded for EDR and LDR calculation (1 in Belzutifan vs. 1 in Everolimus)
c2: number of time BICR declares PD on or earlier than censored INV, excluded for EDR and LDR calculation (1 in Belzutifan vs. 1 in Everolimus)
a=a1+a2+a3; b=b1+b2; and c=c1+c2
EDR=(a3+b2)/(a+b2); and LDR=(a2+c2)/(a2+a3+b2+c2)
DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023

EDR is the frequency that the investigator declares recurrence earlier than BICR and LDR is the frequency that the investigator declares recurrence later than BICR. A negative differential discordance for the EDR and/or a positive differential discordance for the LDR between the experimental arm and the control arm beyond a threshold would suggest a possible bias in the investigator assessment favoring the belzutifan arm. Threshold values ranging from 0.075 to 0.1 were recommended based on simulation studies in Amit et al. 2011.

According to Table 13, FDA calculated the EDR and LDR. In summary, the EDR was 0.18 for the belzutifan arm and 0.30 for the everolimus arm with a difference of -0.12. The LDR was 0.62 for the belzutifan arm and 0.49 for the everolimus arm with a difference of 0.13. The difference for EDR and LDR was greater than the recommended threshold of 0.1, indicating that some degree of potential investigator assessment bias might exist in Study 005, which as mentioned may be due to the open-label study design with a control arm that might not be favored by some investigators as a treatment option in this setting when others exist.

Sensitivity Analyses of PFS to Investigate the Impact of Potential Investigator Bias

As the results of EDR and LDR indicated some degree of potential investigator assessment bias, FDA conducted sensitivity analyses to evaluate the impact of this finding, and summarized results in Table 14.

Of note, 99.6% confidence intervals instead of 95% confidence interval was used for the sensitivity analyses of hazard ratio due to the nature of the interim analysis of PFS with 1-sided alpha of 0.0021 (2-sided 0.0042) for the efficacy boundary.

Table 14: Sensitivity of PFS Analysis to Investigate the Potential Impact of Investigator Assessment Bias

Issues and Scenario		HR (99.6% CI)
Primary Analysis		0.75 (0.58, 0.97)
Patients assessed as events per	1. Assuming patients were event free until death or the next (scheduled) assessment time after the event per INV,	0.77 (0.59, 0.99)

investigator assessment but censored per BICR assessment	whichever occurred first (22 patients in the belzutifan arm and 50 patients in in the everolimus arm)	
	2. Assuming 22 patients in the belzutifan arm were considered to have events at the next (scheduled) assessment time after the event per INV or death, whichever occurred first	0.80 (0.62, 1.03)

DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023

Based on these two scenarios, the sensitivity analyses of PFS showed similar results with the primary PFS analysis supporting the robustness of the improvement in PFS for the belzutifan arm. The second sensitivity analysis is an extreme case where only patients in the belzutifan arm who were censored per BICR due to investigator assessment were assumed to have a true BICR event at the next scheduled assessment time (shortened PFS survival time), while all such patients remained as censored per BICR in the everolimus arm. The upper bound of the HR confidence interval was slightly above 1 based for the second scenario. However, this is considered an extreme scenario, which is unlikely to occur.

Imbalanced Early Dropout and Censoring

FDA noted a slightly greater percentage of patients with early dropout (Table 11) who were therefore censored in the PFS analysis in the belzutifan arm compared to the everolimus arm. FDA thus performed sensitivity analyses to evaluate the impact of these patients with "early drop-out" on the PFS analysis.

FDA's analysis focused on three concerns:
(a) Among 14 patients who were not administered study medication after randomization, there were 10 patients in the everolimus arm who were censored at randomization.
(b) There were 19 patients (4 patients in the belzutifan arm and 15 patients in the everolimus arm) who were censored at randomization.
(c) There were 23 patients (6 patients in belzutifan arm and 17 patients in in everolimus arm) censored within 6 weeks from randomization.

The results of the sensitivity analyses are summarized in Table 15. For the concern described in (a), the second sensitivity analysis was a tipping point analysis which quantified the increase or decrease in the risk of event in patients with asymmetric censorings. The results showed that the 10 patients would need to have at least 95% lower risk of progression compared to other patients in the everolimus arm in order for the 99.6% confidence interval to include 1, which is considered extreme and is unlikely to occur. The third sensitivity analysis could be considered a worst case analysis, as it assumed these patients were event-free until the observed death time or DCO, whichever occurs earlier. In this case, though PFS lost statistical significance, the upper bound of the hazard ratio was only 1.01.

Table 15: Sensitivity Analyses of PFS Assessed by BICR in ITT Population

Issue and Scenario		HR (99.6%CI)
Primary Analysis		0.75 (0.58, 0.97)
(a) for the 10 censored patients in the everolimus arm, who were not administered study medication	1. Sampling PFS time from the top 20% best PFS times observed (based on KM approach)	0.78 (0.60, 1.00)
	2. Assuming the risk of events was 95% lower than other patients in the everolimus arm	0.78 (0.60, 1.00)
	3. Assuming the 10 patients PFS were event free until DCO date (November 1, 2022) or death, whichever occurred first	0.78 (0.6 0, 1.01)
(b) for the patients censored at randomization	4. Sampling PFS time from the top 20% best PFS times observed (based on the KM approach) in both arms (4 patients in the belzutifan arm and 15 patients in in the everolimus arm)	0.78 (0.61, 1.01)
	5. Assuming risk of events for the patients was 95% lower than other patients in the everolimus arm	0.78 (0.60, 1.00)
	6. Assuming the patients in the everolimus arm were PFS event free until DCO date (November 1, 2022) or death, whichever occurred first	0.78 (0.61, 1.01)
(c) for the patients censored within 6 weeks from randomization	7. Sampling PFS time from the top 20% best PFS times observed (based on KM approach) in both arms	0.76 (0.59, 0.97)
	8. Assuming the risk of an event for patients was 90% lower than other patients in the everolimus arm	0.78 (0.60, 1.00)
	9. Assuming the patients in the everolimus arm were PFS event free until DCO date (November 1, 2022) or death, whichever occurred first	0.79 (0.61, 1.01)

DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023

Overall, these sensitivity analyses showed that the PFS effect in terms of the HR remained close to the estimated treatment effect in the primary analysis of the ITT population, indicating robustness of the PFS estimates.

Imbalanced Censoring Due to Initiation of New Anti-cancer Therapy

FDA observed that there were 89 patients (21 patients in the belzutifan arm and 68 patients in the everolimus arm) censored for PFS per BICR due to initiation of new anti-cancer therapy before the occurrence of PFS event. FDA performed sensitivity analyses and the results are summarized in Table 16.

Table 16: Sensitivity Analyses of PFS Assessed by BICR in ITT Population

Issue and Scenario	HR (99.6%CI)
Primary Analysis	0.75 (0.58, 0.97)
New anticancer therapy in the belzutifan arm is considered an event at the start date of new anticancer therapy (21 patients in the belzutifan arm)	0.81 (0.63, 1.05)

DCO Date: November 1, 2022

Source: FDA review based on datasets submitted on July 17, 2023

The sensitivity analysis of PFS showed similar results with the primary PFS analysis. The scenario assumed that only patients in the belzutifan arm who were censored per BICR due to initiating new anti-cancer therapy would all have had a true BICR event at the start date of anticancer therapy (shortened PFS survival time), while all such patients in the everolimus arm remained censored. Although the upper bound of the HR confidence interval was 1.05 for this sensitivity analysis, it is considered an extreme case and unlikely to occur.

Exploratory Analysis to Investigate Non-Proportional Hazards for PFS per BICR

FDA observed that the KM curves of PFS per BICR assessment overlapped before 6 months and started to slightly separate thereafter. This indicated that the assumption of proportional hazards for the Cox PH model was not met in Study 005 and makes interpretation of the treatment benefit in terms of PFS more challenging. Therefore, FDA performed exploratory analyses using restricted mean survival time (RMST) to further quantify the treatment benefit in PFS.

Table 17 and Figure 4 provide the FDA's restricted mean survival time (RMST) analysis of PFS per BICR in the ITT population.

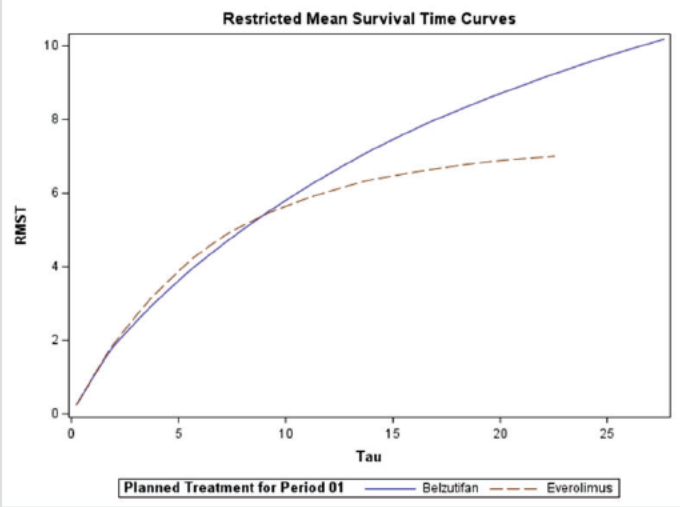
The choice of the timing in the RMST analysis is 22.5 months for the ITT population, which is
the smallest value among the largest observed times across the two treatment arms. This choice of time is generally recommended by the literature. The mean difference of the RMST of PFS between the two treatment arms as calculated by the FDA was 2.2 months. However, the choice of timing of the RMST analysis is subjective and the RMST results could potentially change if a different time was chosen.

Table 17: RMST Analysis of PFS Assessed by BICR in ITT Population at 22.5 months

	Belzutifan N=374	Everolimus N=372
Mean (SE), months	9.2 (0.5)	7.0 (0.3)
RMST difference (SE), months	2.2 (0.6)	

DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023

Figure 4: RMST Plot of PFS by BICR in ITT Population



DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023

- **Interim OS Analyses**

FDA agrees with the Applicant's above presentation of the 1st interim OS analysis, other than a slight correction to the sentence which states that, "The median OS was longer in the belzutifan group (21.0 months; 95% CI: 17.2, 24.3) than in the everolimus group (17.2 months; 95% CI: 15.3, 19.0)." Per the FDA's calculations, the median OS in the belzutifan group was (21.0 months; 95% CI: **17.1**, 24.3).

During the course of the sNDA review, OS reached the pre-specified planned number of events (91% information fraction, DCO Date: June 13, 2023) at the 2nd interim analysis (IA2). The Applicant performed the analysis and formally tested OS with the interim data. The results and data were submitted to the FDA for review.

With 91% information fraction (441 deaths) and a longer follow up time of 16.8 months after the last patient enrolled (data cutoff June 13, 2023), the 2nd interim analysis of OS did not reach statistical significance. FDA generally agrees with the Sponsor's topline results for OS except for the slight difference in the stated 95% confidence interval of the median OS, "(15.8, 21.8)" in the everolimus arm. The hazard ratio was 0.88 (95% CI: 0.73, 1.07) with medians of 21.4 (95%CI: 18.2, 24.3) months in the belzutifan arm and 18.1 (95%CI: 15.8, 21.7) months in the everolimus arm.

KM curves for OS overlapped heavily until ~12-15 months, and then began to slightly separate.

Note that the results of OS at IA2 remained consistent with the results of OS at IA1. However, the interpretation of OS results remains challenging due to the heavy

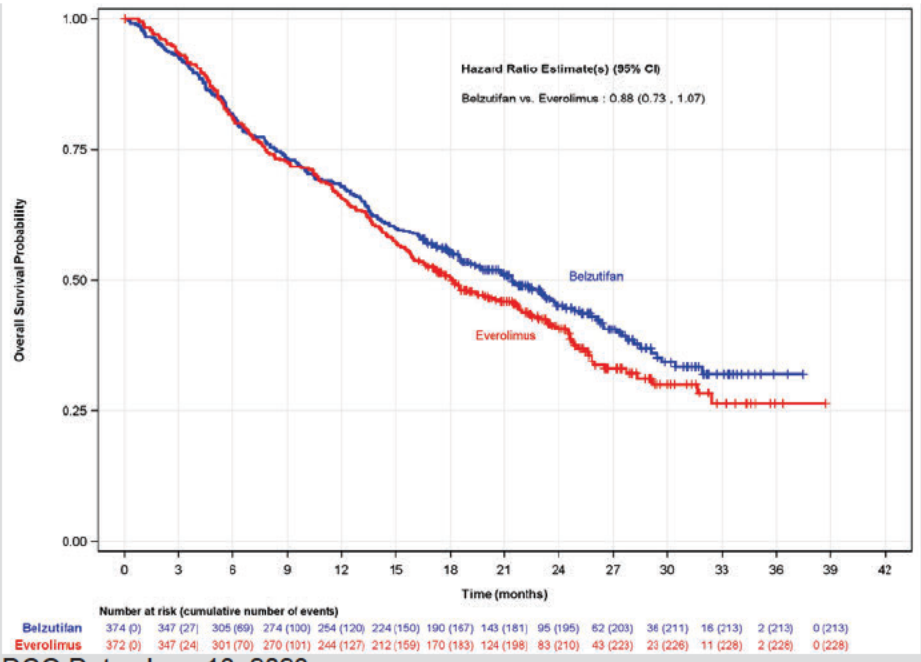
censoring from ~15-18 months. No OS detriment effect was observed in either OS IA1 or IA2. The FDA did not include numeric data on OS results in Section 14 of product labeling, other than to state that OS results were immature with 59% of deaths in the randomized population (91% of total planned events).

Table 18: Analysis of OS at IA2 in ITT Population

	Belzutifan N=374	Everolimus N=372
Number of events (%)	213 (57.0%)	228 (61.3%)
Median, months (95% CI)	21.4 (18.2, 24.3)	18.1 (15.8, 21.7)
Hazard Ratio (95% CI)	0.88 (0.73, 1.07)	
1-sided p-value	0.0994	

DCO Date: June 13, 2023
Source: FDA review based on datasets submitted on October 13, 2023

Figure 5: Kaplan-Meier Plot of OS at IA2 in ITT



DCO Date: June 13, 2023
Source: FDA review based on datasets submitted on October 13, 2023

As neither OS IA1 nor IA2 reached statistical significance, the study is continuing to follow patients' OS information. The final OS analysis is planned to occur after observing 483 deaths, which is projected to occur in Q2 2024. Submission of final OS results for Study 005 will occur as a PMC.

- **Low Representation of Patients in 2nd Line Setting**

In Study 005 there was overall low representation of patients in the 2nd line setting (n=98), which was less than 15% of the patients in each treatment arm. The FDA review team was concerned that despite a low percentage of overall patients in Study 005 in this subgroup, who presumably received PD-1 or PD-L1 checkpoint inhibitor therapy in combination with a VEGF-TKI, this might represent a large percentage of patients prescribed belzutifan in the real-world setting after sNDA approval, as combination PD-1 or PD-L1 checkpoint inhibitor + VEGF-TKI therapy increasingly becomes used as the standard of care frontline regimen for mRCC. However, subgroup analyses of PFS and OS by number of prior lines of therapy (1 vs 2 vs 3) indicated favorable results for belzutifan that were consistent across the subgroup of those with only 1 prior line of therapy: PFS HR = 0.57 (95% CI: 0.35 to 0.93) and OS HR=0.69 (95% CI: 0.34, 1.40) at IA1. Thus, despite the small sample size, FDA determined that there was likely consistent effect of belzutifan in this subgroup, supporting an indication that includes these patients..

- **Subgroup Analysis by The Status of ESA Use**

In LITESPARK-005, the median hemoglobin (Hb) level which led to the first ESA use was above 8, which was slightly higher than the median Hb level which led to the first blood transfusion. ESA use varied by geographic region and its use in North America (4.6%) was much less than the rate of ESA use in all patients as treated (21%). The FDA review team was concerned that use of ESA to treat anemia, a common adverse reaction for belzutifan (see safety section on anemia for further details), might have compromised efficacy in those patients treated with ESAs, as randomized controlled trials in patients with cancer receiving myelosuppressive chemotherapy with ESAs have shown that ESAs increased the risks of death and serious cardiovascular reactions, and decreased PFS and/or OS. While a Warning providing caution for ESA use to treat belzutifan-induced anemia was added to Section 5 of product labeling for belzutifan during the initial approval for VHL, the trial supporting that approval was a relatively small single-arm design and there was insufficient data available to fully characterize whether ESA use did indeed contribute to tumor progression and/or other adverse outcomes in that setting.

FDA therefore performed a subgroup analysis of PFS and OS by ESA use for patients treated on Study 005, who were allowed to receive ESAs at the discretion of the investigator, per protocol*. Reassuringly in this exploratory post-hoc analysis, the subgroup of patients on the belzutifan arm who received ESA had better outcomes vs. those patients on the belzutifan arm who did not receive ESAs. While it is possible that this result may be related to an association between longer PFS and longer exposure to the toxicities of the drug and thus patients with prolonged PFS were thus more likely to receive ESAs, these exploratory findings are generally reassuring that ESA use did not demonstrate an obvious detrimental effect in patients treated for belzutifan-induced anemia.

*** Dose Modification Section of protocol for Study 005:**

"*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 2 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 in order 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 MK-6482 treatment, EPO replacement is an effective management strategy for participants who may develop and subsequently require intervention for MK-6482-induced anemia."

The FDA notes that the mechanism of action of ESAs in belzutifan-induced anemia may differ from that in the treatment of anemia in other malignancies and thus the findings of adverse outcomes in those settings may not be applicable to the current indication.

Table 19: PFS and OS analyses by the status of ESA use in LITESPARK-005.

Treatment arm		With ESA (N = 163)	Without ESA (N = 63)	HR (95% CI)
Belzutifan	**Median PFS** (months)	12.7	3.8	**0.48** (0.35, 0.65)
	Median OS (months)	NR	17.8	**0.54** (0.37, 0.80)
Everolimus	**Median PFS** (months)	7.5	5.6	**0.73** (0.38, 1.43)
	Median OS (months)	NR	17.7	**0.66** (0.25, 1.79)

DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023 and September 29, 2023 and September 29, 2023

ESA Use in Study 004
To further assess the potential impact of ESA use on disease progression or death, the FDA review team sent an IR to the Applicant and asked for a descriptive report of the outcomes of patients with and without ESA use on Study 004 (VHL disease setting) with further follow-up from the initial approval data:

Table 20: Efficacy Outcomes in Study 004, by the status of ESA Use

Patients in LITESPARK-004	Received ESA	Did not receive ESA
Number of patients	15	46

Median duration of follow up (range)	50.1 (48.2 - 57.8)	49.7 (4.2 - 58.1)
Number (%) of patients who eventually had disease progression[#]	1 (6.7%)	11 (23.9%)
Median time to disease progression	NE (NE, NE)	49.8 (49.8, NE)
Number (%) of patients who developed metastasis	1 (6.7%)	0
Number (%) of patients with secondary malignancies[*]	1 (6.7%)	1 (2.2%)
Number (%) of death	0	2 (4.3%)

Disease progression includes BICR PD or death (same as PFS analysis).
* Second malignancy in ESA group: vulval cancer.
Second malignancy in No ESA subgroup: non-small cell lung cancer. "Lobular breast carcinoma in situ" was also reported under the SOC of neoplasm, malignant and unspecified (incl cysts and polyps); it was not a second malignancy as it was not considered malignant in nature by the investigator based on the biopsy "classic type, and atypical lobular hyperplasia of the breast".
Data cutoff date: 01APR2023

Based on these results and considering the exploratory analysis in small number of patients, ESA use did not appear to show possible detrimental effect on the examined efficacy outcomes by comparing the 2 subgroups in Study 004.

Based on the subgroup analyses of Study 004 and 005 by the status of ESA use, which did not show any obvious detrimental effect from ESA use, the review team made the following change in the label:

Removed:

(b) (4)

Replaced with:
The safety of erythropoiesis stimulating agents (ESAs) for treatment of anemia in patients with VHL disease treated with WELIREG has not been established.

See also the safety section discussion on anemia.

- **Additional Subgroup Analyses**

Table 17 summarizes FDA's subgroup analyses for PFS at IA1 and OS at IA2. The subgroup analysis results were generally consistent with the primary PFS analysis and OS interim analysis in the ITT population. In particular, results were consistent for the subgroup of patients with 1 prior line of therapy, as discussed previously.

The results of some subgroup analyses should be interpreted with caution given small sample sizes in the subgroups.

Table 21: Subgroup Analyses in ITT Population

	PFS per BICR Assessment at IA1			OS at IA2		
	Belzutifan #Events/N (%)	Everolimus #Events/N (%)	HR (95% CI)	Belzutifan #Events/N (%)	Everolimus #Events/N (%)	HR (95% CI)
AGE						
< 65	161/232 (69.4%)	139/201 (69.2%)	0.82 (0.65, 1.03)	138/232 (59.5%)	122/201 (60.7%)	0.95 (0.74, 1.21)
>= 65	96/142 (67.6%)	123/171 (71.9%)	0.68 (0.52, 0.90)	75/142 (52.8%)	106/171 (62.0%)	0.79 (0.59, 1.06)
Sex						
Female	49/77 (63.6%)	60/88 (68.2%)	0.68 (0.46, 1.00)	46/77 (59.7%)	52/88 (59.1%)	0.98 (0.65, 1.46)
Male	208/297 (70%)	202/284 (71.1%)	0.78 (0.64, 0.95)	167/297 (56.2%)	176/284 (62.0%)	0.85 (0.69, 1.06)
Race						
White	212/297 (71.4%)	207/291 (71.1%)	0.76 (0.62, 0.92)	180/297 (60.6%)	187/291 (64.3%)	0.88 (0.72, 1.08)
All Others	30/56 (53.6%)	44/65 (67.7%)	0.63 (0.39, 1.01)	22/56 (39.3%)	33/65 (50.8%)	0.72 (0.42, 1.24)
Missing	15/21 (71.4%)	11/16 (68.8%)	1.30 (0.60, 2.85)	11/21 (52.4%)	8/16 (50%)	1.14 (0.46, 2.83)
Geographic Region						
North America	50/75 (66.7%)	59/89 (66.3%)	0.70 (0.48, 1.03)	42/75 (56%)	55/89 (61.8%)	0.82 (0.55, 1.23)
Western Europe	139/191 (72.8%)	126/182 (69.2%)	0.89 (0.70, 1.13)	115/191 (60.2%)	117/182 (64.3%)	0.92 (0.71, 1.19)
Rest of the World	68/108 (63%)	77/101 (76.2%)	0.61 (0.43, 0.85)	56/108 (51.9%)	56/101 (55.4%)	0.87 (0.6, 1.26)
IMDC Risk Category						
Favorable	45/79 (57%)	51/83 (61.4%)	0.79 (0.53, 1.19)	30/79 (38.0%)	39/83 (47.0%)	0.75 (0.47, 1.21)
Intermediate	177/249 (71.1%)	177/244 (72.5%)	0.75 (0.61, 0.93)	148/249 (59.4%)	152/244 (62.3%)	0.92 (0.73, 1.15)
Poor	35/46 (76.1%)	34/45 (75.6%)	0.67 (0.41, 1.09)	35/46 (76.1%)	37/45 (82.2%)	0.78 (0.49, 1.25)
IMDC Risk Category2						
Favorable	45/79 (57%)	51/83 (61.4%)	0.79 (0.53, 1.19)	30/79 (38.0%)	39/83 (47%)	0.75 (0.47, 1.21)
Intermediate or Poor	212/295 (71.9%)	211/289 (73%)	0.74 (0.61, 0.90)	183/295 (62.0%)	189/289 (65.4%)	0.90 (0.73, 1.1)
Number of Prior VEGF/VEGF						
1	130/187 69.5%)	132/190 (69.5%)	0.79 (0.61, 1.01)	106/187 (56.7%)	117/190 (61.6%)	0.87 (0.67, 1.13)
2-3	127/187 (67.9%)	130/182 (71.4%)	0.73 (0.57, 0.94)	107/187 (57.2%)	111/182 (61.0%)	0.89 (0.68, 1.16)
Number of Prior Line of Therapy						

	PFS per BICR Assessment at IA1			OS at IA2		
	Belzutifan #Events/N (%)	Everolimus #Events/N (%)	HR (95% CI)	Belzutifan #Events/N (%)	Everolimus #Events/N (%)	HR (95% CI)
1	30/46 (65.2%)	38/52 (73.1%)	0.57 (0.35, 0.93)	20/46 (43.5%)	25/52 (48.1%)	0.83 (0.46, 1.5)
2	106/157 (67.5%)	117/166 (70.5%)	0.83 (0.64, 1.09)	93/157 (59.2%)	108/166 (65.1%)	0.84 (0.63, 1.1)
3	119/169 (70.4%)	103/150 (68.7%)	0.76 (0.58, 1.00)	98/169 (58.0%)	92/150 (61.3%)	0.94 (0.71, 1.25)
4	2/2 (100%)	4/4 (100%)	4.22 (0.37,47.51)	2/2 (100%)	3/4 (75%)	0.71 (0.11, 4.45)

DCO Date: November 1, 2022 for PFS and June 13, 2023 for OS
Source: FDA review based on datasets submitted on July 17, 2023 and October 13, 2023

Data Quality and Integrity

APPEARS THIS WAY ON ORIGINAL

The Applicant's Position:
Quality and integrity of study data were assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures.
The clinical study program was conducted in accordance with GCP guidelines. The Sponsor's QA function independently assessed quality through a comprehensive, risk-based audit program to ensure adherence with applicable GCP and GPP regulations, and applicable company policies and procedures. Part of this study was conducted during the COVID-19 pandemic. Contingency measures were implemented to manage study conduct during the pandemic. There were no changes in the planned conduct of the study or planned analyses due to the COVID-19 pandemic and no data integrity concerns were reported.

The FDA's Assessment:
FDA has no additional comment.

Efficacy Results – Secondary and other relevant endpoints

Data:
Results are presented for the secondary efficacy endpoints of ORR [Table 9] (key secondary efficacy endpoint) and DOR [Table 10].

Table 22: Applicant – Analysis of Objective Response (Confirmed) Based on BICR per RECIST 1.1 (ITT Population)

Treatment	N	Number of Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Everolimus	
				Estimate (95% CI)[a]	p-Value[b]
Belzutifan	374	82	21.9 (17.8, 26.5)	18.4 (14.0, 23.2)	<0.00001
Everolimus	372	13	3.5 (1.9, 5.9)		

Responses are based on BICR per RECIST 1.1.
[a] Based on Miettinen & Nurminen method stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and Number of prior VEGF/VEGF receptor targeted therapies for advanced RCC (1 vs. 2-3).
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adrs]

Table 23: Applicant – Summary of Time to Response and Duration of Response Based on BICR per RECIST 1.1 in Participants with a Confirmed Response (ITT Population)

	Belzutifan (N=374)	Everolimus (N=372)
Number of participants with response[a]	82	13
Time to Response (months)		
Mean (SD)	4.7 (3.3)	3.5 (1.2)
Median (Range)	3.7 (1.7-16.6)	3.7 (1.8-5.4)
Response Duration[b] (months)		
Median (Range)	NR (1.7+ - 23.2+)	17.2 (3.8 - 18.0+)
Number (%[b]) of Participants with Extended Response Duration:		
≥6 months	65 (93.1)	10 (76.9)
≥9 months	42 (81.7)	6 (68.4)
≥12 months	25 (74.2)	6 (68.4)
≥15 months	17 (71.1)	2 (51.3)
≥18 months	9 (61.9)	0 (NR)
≥21 months	5 (61.9)	0 (NR)

[a] Includes participants with confirmed complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adtte]

The Applicant's Position:

ORR

Confirmed ORR per RECIST 1.1 by BICR, a key secondary endpoint, was higher in the belzutifan group (21.9%; 95% CI: 17.8, 26.5) compared with the everolimus group (3.5%; 95% CI: 1.9, 5.9), with an estimated difference in percentage for belzutifan versus everolimus of 18.4% (95% CI: 14.0, 23.2; 1-sided $p<0.00001$) [Table 9]. The p-value crossed the prespecified boundary for statistical significance of 0.001. Results were consistent with the ITT population across protocol-specified subgroups.

DOR

Confirmed responses were more durable in the belzutifan group compared with the everolimus group. Among participants with confirmed response (82 responders [21.9%] in the belzutifan group and 13 responders [3.5%] in the everolimus group), the median DOR based on BICR per RECIST 1.1 was not reached (range: 1.7+ to 23.2+ months) for the belzutifan group and was 17.2 months (range: 3.8 to 18.0+ months) for the

everolimus group [Table 10]. The percentage of responders was higher in the belzutifan group compared with the everolimus group at each response duration time point (6 months through 21 months) based on KM estimates [Table 10]. The median time to response was 3.7 months (range: 1.7 to 16.6 months) in the belzutifan group and 3.7 months (range: 1.8 to 5.4 months) in the everolimus group. Differences were noted in the range of time to responses, indicating that while early responses occurred in both treatment groups, late responses occurred predominantly in the belzutifan group.

The FDA's Assessment: The FDA does not agree with the Applicant's analysis of the confirmed ORR and DoR per BICR assessment. The confirmed ORR by BICR should be evaluated based on all patients with measurable disease at baseline; the Applicant's analyses above were based on all randomized patients, including those without measurable disease.

Table 20 summarizes FDA analyses of confirmed ORR assessed by BICR based on randomized patients with measurable disease at baseline. The ORR by BICR was statistically significant between the two treatment arms.

Table 24: Confirmed Objective Response Rate and Duration of Response per BICR Assessment in Participants with Measurable Disease at Baseline

	Belzutifan N=374	Everolimus N=372
Number of Participants with Measurable Disease at baseline	373	364
Confirmed ORR: n, % (95%CI)	82 22.0 (17.9, 26.5)	13 3.6 (1.9, 6.0)
Difference %, (95%CI)	18.4 (14.0, 23.2)	
One sided p-value	< 0.0001	
Median DOR (Range), months	NR (1.7+, 23.2+)	17.2 (3.8, 18.0+)

DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023 and September 29, 2023 and September 29, 2023

Concordance and discordance of confirmed ORR between BICR assessment and Investigator assessment

The concordance and discordance of ORR assessment between BICR and investigator were examined and summarized in Table 24. The concordance was 89.8% (95% CI: 86.3%, 92.7%) for the belzutifan arm and 96.5% (CI: 94.1%, 98.1%) for the everolimus arm. The results showed good concordance between BICR and investigator assessment of ORR in the ITT population.

Table 25: Concordance and Discordance of Confirmed ORR per BICR Assessment in ITT Population

Investigator Assessment	BICR Assessment			
	Belzutifan N=374		**Everolimus** N=372	
	Response[a]	Non-response[b]	Response[a]	Non-response[b]
Response[a]	60 (16.0%)	16 (4.3%)	6 (1.6%)	6 (1.6%)
Non-response[b]	22 (5.9%)	276 (73.8%)	7 (1.9%)	353 (94.9%)

[a]: either confirmed CR or PR per RECIST 1.1
[b]: one of confirmed NE, PD, SD per RECIST 1.1 or missing
DCO Date: November 1, 2022
Source: FDA review based on datasets submitted on July 17, 2023

The Applicant proposed [redacted] However, FDA was concerned [redacted]

With these considerations, the FDA review team removed the proposed [redacted] but retained a statement in the text that commented on the fact that 25/82 (30%) patients who achieved a confirmed response had DoR ≥12 months, [redacted]

In addition, the Applicant proposed [redacted] However, this was not an issue in Study 005 [redacted] Therefore, the FDA review team considered [redacted] to be less relevant [redacted] and removed these from section 14 of the label.

Dose/Dose Response

The Applicant's Position: Not Applicable.

The FDA's Assessment:
Not applicable.

Durability of Response

The Applicant's Position: This topic is discussed above in Secondary and other relevant endpoints.

The FDA's Assessment:
Longer DoR and improvement in the PFS HR in the belzutifan arm provide supportive evidence for superior treatment effect of belzutifan compared to everolimus.

Persistence of Effect

The Applicant's Position: This topic is discussed above in Secondary and other relevant endpoints.

The FDA's Assessment:
FDA has no additional comment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
Data:
PRO assessments in this study included FKSI-DRS, EORTC QLQ-C30, and EQ-5D-5L. For PRO analyses, no adjustments for multiple testing were applied; therefore, all p-values and CIs are nominal and descriptive. A decrease in FKSI-DRS score denotes deterioration. Decreases in EORTC QLQ-C30 scores denote deterioration with the exception of the EORTC symptoms scales, for which an increase in score denotes worsening.

KM estimates of time to deterioration for the FKSI-DRS and EORTC QLQ-C30 Global Health Status/QoL are shown in [Figure 3] and [Figure 4], respectively.

The completion and compliance rates for the FKSI-DRS, EORTC QLQ-C30, and EQ-5D-5L from baseline through Week 17 were high in both treatment groups (>90% compliance rates at Week 17 in both groups).

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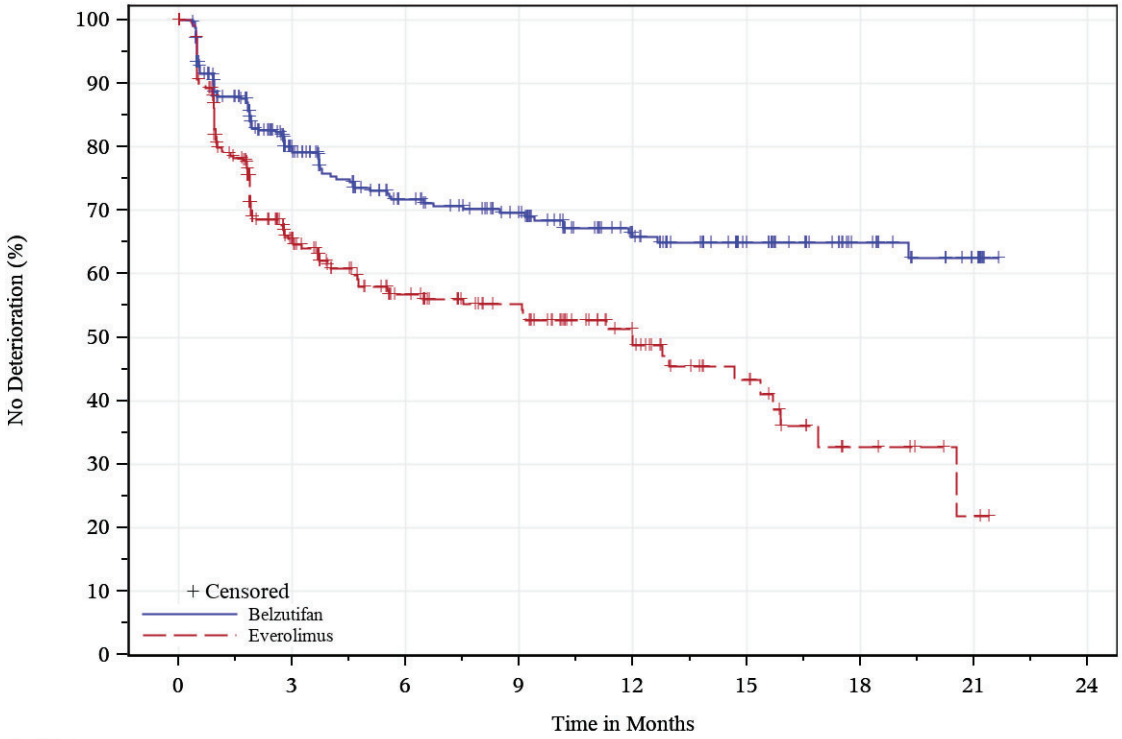
Figure 6: Applicant –Kaplan-Meier Estimates of Time to True Deterioration for FKSI-DRS (PRO FAS Population with Baseline)



At Risk

Belzutifan	356	196	147	126	88	57	32	16	0
Everolimus	336	139	85	64	36	21	7	2	0

Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adprotte]

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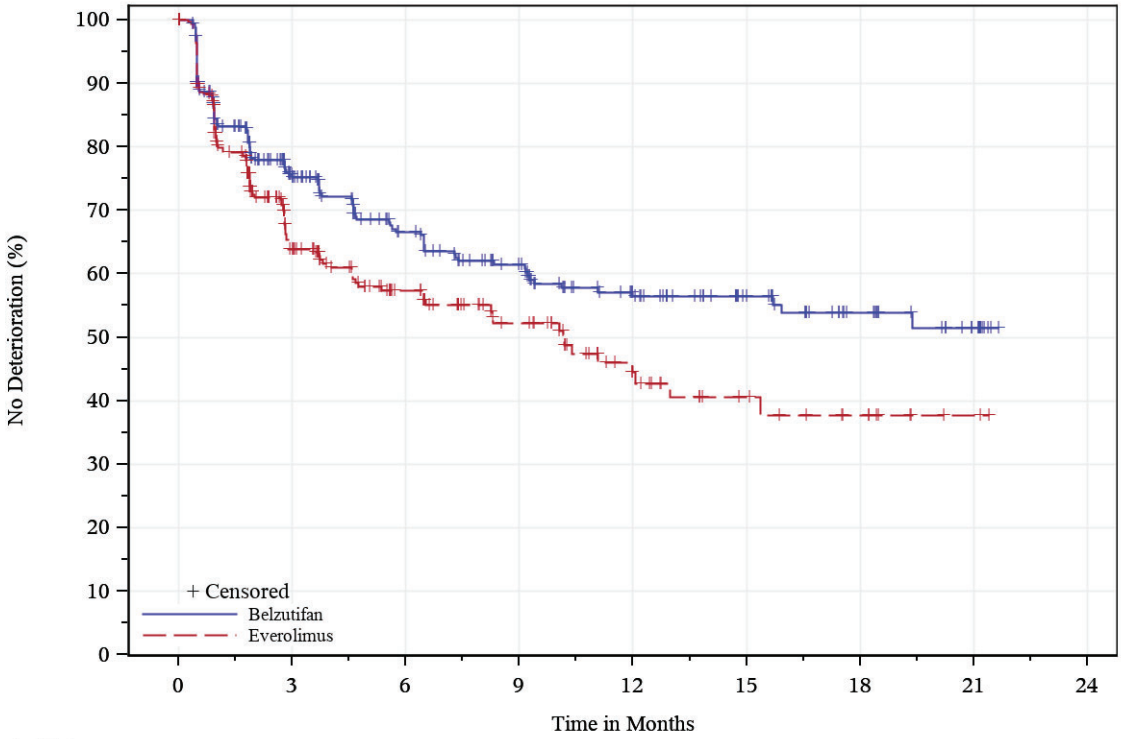
Figure 7: Applicant –Kaplan-Meier Estimates of Time to True Deterioration for EORTC QLQ-C30 Global Health Status/QoL (PRO FAS Population with Baseline)



At Risk

Belzutifan	355	187	134	107	75	51	30	16	0
Everolimus	335	130	80	52	26	15	9	2	0

Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adprotte]

The Applicant's Position:

FKSI-DRS, EORTC QLQ-C30 global health status/QoL scale, and EORTC QLQ-C30 role and physical functioning scales showed a higher percentage of participants with improvement or stable assessments over time in the belzutifan group compared with the everolimus group as follows:

- The LS mean decrease from baseline to Week 17 for FKSI-DRS was greater in the everolimus group compared with the belzutifan group (difference between treatment groups of 1.54 [95% CI: 0.81, 2.28; nominal p<0.0001]). No clinically relevant empirical mean change from baseline to Week 17 was observed in either treatment group. The proportion of participants with improved/stable HRQoL scores on the FKSI-DRS was 74.3% (95% CI: 69.5, 78.6) in the belzutifan group compared with

64.0% (95% CI: 58.8, 69.0) in the everolimus group. The percentage of participants with confirmed deterioration in the FKSI-DRS was 26.7% in the belzutifan group and 40.5% in the everolimus group. The median time to confirmed deterioration in the FKSI-DRS was longer in the belzutifan group (NR; 95% CI: NR, NR) compared with the everolimus group (11.99 months; 95% CI: 6.44, 15.70), with an HR of 0.53 (95% CI: 0.41, 0.69; nominal $p<0.0001$) [Figure 3].

- The LS mean change from baseline to Week 17 for EORTC QLQ-C30 global health status/QoL was 0.38 in the belzutifan group compared with -6.13 in the everolimus group at Week 17. The difference between treatment groups in LS means was 6.52 (95% CI: 3.39, 9.64; nominal $p<0.0001$). No clinically relevant empirical mean change from baseline in EORTC QLQ-C30 global health status/QoL or in physical and role functioning scores was observed in either treatment group. The proportion of participants with improved/stable HRQoL scores was 75.6% (95% CI: 70.9, 79.9) in the belzutifan group compared with 66.6% (95% CI: 61.4, 71.5) in the everolimus group for EORTC QLQ-C30 global health status/QoL. Results were similar for physical and role functioning. The percentage of participants who reported deterioration in EORTC QLQ-C30 global health status/QoL score was 16.5% (95% CI: 12.9, 20.7) in the belzutifan group and 22.2% (95% CI: 18.0, 26.9) in the everolimus group. The percentage of participants with confirmed deterioration in EORTC QLQ-C30 global health status/QoL was 33.8% the belzutifan group and 39.1% in the everolimus group. The median time to confirmed deterioration in EORTC QLQ-C30 global health status/QoL was longer in the belzutifan group (NR; 95% CI: 11.99, NR) compared with the everolimus group (10.15 months; 95% CI: 6.47, 12.98), with an HR of 0.74 (95% CI: 0.58, 0.95; nominal $p=0.0179$) [Figure 4].
- The LS mean changes (reductions in both groups) from baseline to Week 17 for EQ-5D-5L VAS scores were -0.18 in the belzutifan group and -3.95 in the everolimus group. The difference between treatment groups in LS means was 3.77 (95% CI: 1.21, 6.34; nominal $p=0.0040$).

The FDA's Assessment:

Patient-reported outcomes were assessed for patients on Study 005 using three instruments (FKSI-DRS, EORTC QLQ-C30, and EQ-5D-5L) at the timepoints: Week 1, 3, 5, 9, every 4 weeks after.

PRO data were collected with high compliance, meaning a high proportion of the patients who were eligible for PRO assessment responded (e.g., week 17 = 92% compliance rate). The Applicant selected a change from baseline to week 17 timepoint as a primary PRO endpoint of interest, however all PRO endpoints were considered exploratory as they were not prespecified or multiplicity adjusted.

Therefore, the focus of FDA's PRO analysis was assessment of treatment-related symptoms and tolerability, and not the comparative improvement in disease related

symptoms, especially considering the open label study design. Furthermore, the FDA examined patient-reported outcomes examining mean change from baseline at specific timepoints and overall instead of time to deterioration as the sponsor provides above.

At week 17, compared to baseline, patients experienced a worsening in all functional scales in the EORTC QLQ-C30. Although there were overlapping confidence intervals between arms, the overall descriptive trend is that everolimus impacted functioning more negatively than belzutifan at week 17 relative to baseline. Focusing on the EORTC QLQ-C30 physical function subscale at all PRO assessment timepoints up to and including week 25, the mean change scores from baseline were stable over time and similar for both arms. However, the scores showed greater worsening in the everolimus arm compared to the belzutifan arm after week 5 (see Section 19.6 in the Appendix).

Most symptom scales from the EORTC QLQ-C30 also demonstrated similar or worsening symptoms for patients treated with everolimus compared to patients treated with belzutifan (see Section 19.6 in the Appendix). Notably, dyspnea and appetite loss were markedly different between arms, favoring belzutifan. Despite hypoxia being an adverse event of concern for belzutifan, patients did not appear to report increased dyspnea on the belzutifan arm compared to the everolimus arm (see Figure 8 below). Patients in the everolimus arm were more likely to report any dyspnea, “quite a bit”, and “very much” dyspnea, particularly at the week 9, 13, and 17 assessment timepoints. More frequent assessment of treatment related AEs such as dyspnea would have provided additional detail of within cycle patient experiences. A similar result was seen from FKSI-DRS item B1 (dyspnea), which provided additional confidence that dyspnea does not appear to increase on the belzutifan arm compared to everolimus arm.

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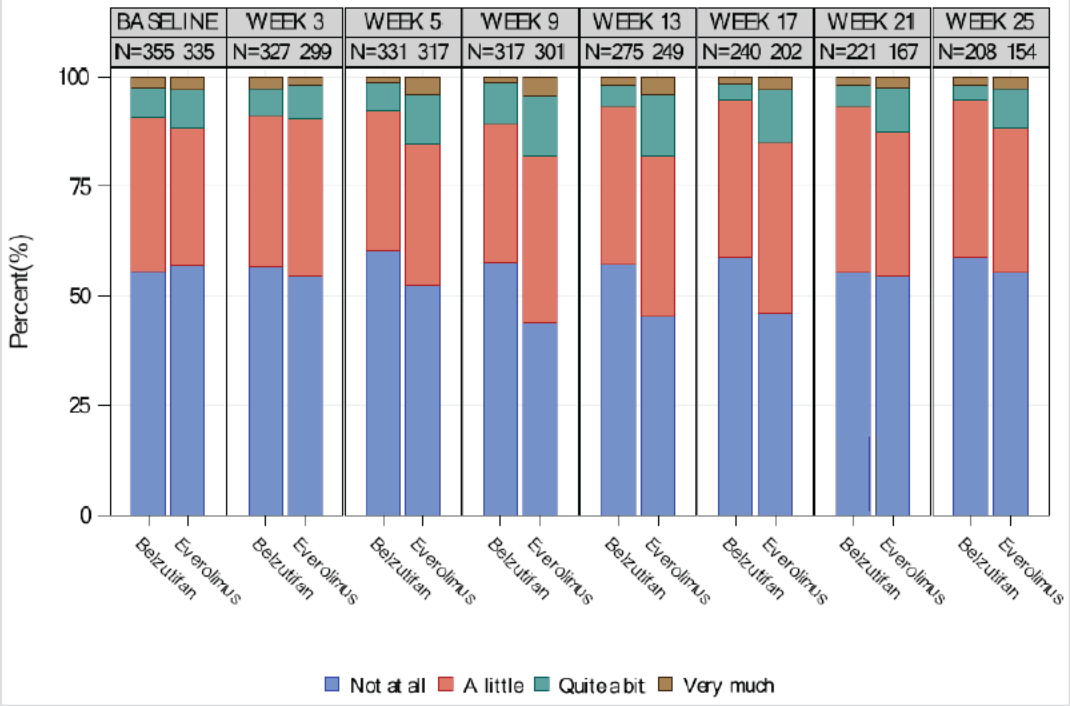
Figure 8: Distribution of Categorical Responses for QLQ-C30 – Dyspnea



From the Applicant's IR Response dated December 5, 2023 (SDN 447)

As mentioned above, strengths of the submitted patient-reported outcomes were sustained high compliance rates and measurement of important treatment-related symptoms such as dyspnea. Limitations to interpretation of these PRO results are the open-label design of the trial, sparse assessment of symptoms, and lack of multiplicity adjusted PRO endpoints.

Overall, exploratory analysis of PRO data appeared to support belzutifan being more tolerable than everolimus in this trial. In the setting of marginal improvement in efficacy in terms of PFS, and no statistically significant OS improvement, tolerability of therapy becomes an important component of the overall risk/benefit assessment of belzutifan in the proposed indication, thus the PRO analysis showing relative tolerability in a descriptive manner was considered a crucial part of FDA's review and assessment.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position: Not Applicable.

The FDA's Assessment:
Not applicable.

8.1.4. Integrated Review of Effectiveness

The FDA's Assessment:

This sNDA was submitted based on the results of Study 005, an open-label, head-to-head, randomized trial of belzutifan versus everolimus in patients with unresectable, locally advanced or metastatic clear cell RCC that had progressed following a PD-1 or PD-L1 checkpoint inhibitor and a VEGF-TKI either in sequence or in combination. The primary endpoints were PFS by BICR assessment and OS.

A statistically significant improvement in PFS per BICR assessment was demonstrated for belzutifan compared with everolimus, with a hazard ratio of 0.75 (95% CI: 0.63, 0.90); 1-sided p-value=0.0008. Median PFS was 5.6 months (95% CI: 3.9, 7.0) in the belzutifan arm and 5.6 months (95% CI: 4.8, 5.8) in the everolimus arm. The Kaplan-Meier curves of PFS per BICR crossed at around 6 months and started to separate thereafter. Sensitivity analysis of PFS per investigator assessment showed consistent results with primary PFS per BICR analysis and similar median PFS estimates of 5.6 months in both arms. Kaplan-Meier curves of PFS per BICR assessment and Kaplan Meier curves of PFS per investigator assessment both indicated the presence of non-proportional hazards.

Through the analysis of concordance and discordance of PFS assessed by BICR or investigator, the FDA review team identified the issue of investigator assessment bias, which may be due to the open-label study design. Additionally, an imbalanced dropout and censoring between the two treatment arms were noted by the review team. The FDA review team therefore performed sensitivity analyses to evaluate the robustness of the primary PFS results. Overall, the sensitivity analyses, including a tipping point analysis and a worst-case analysis, generated hazard ratios similar to the primary PFS analysis results, supporting the robustness of the efficacy findings.

OS results were immature with 91% of total planned OS events (59% deaths in the randomized population) at IA2. The OS at IA2 did not reach statistical significance [HR=0.88 (95% CI: 0.73, 1.07), and 1-sided p-value of 0.0994 which did not reach the significance boundary of 0.014] with medians of 21.4 (95% CI: 18.2, 24.3) months in belzutifan arm and 18.1 (95% CI: 15.8, 21.7) months in the everolimus arm

A statistically significance improvement in confirmed ORR was also observed in the belzutifan arm compared to the everolimus arm (22% [95% CI: 17.9, 26.5] vs 3.6% [95% CI: 1.9, 6.0], respectively), and PROs were improved with belzutifan compared to everolimus.

Despite a modest improvement in PFS and no demonstrated OS benefit (albeit with a HR for OS trending favorably and with sufficient maturity to make a detriment extremely unlikely at the final OS analysis), the FDA review team noted that Study 005 represents a head-to-head trial of active therapies (rather than an add-on design), thus any PFS

benefit demonstrated against everolimus is likely additive to that of everolimus in this setting vs. placebo.

8.1.5. Assessment of Efficacy Across Trials

Primary Endpoints

The Applicant's Position: Not applicable for this submission.

The FDA's Assessment:
Not applicable.

Secondary and Other Endpoints

The Applicant's Position: Not applicable for this submission.

The FDA's Assessment:
Not applicable.

Subpopulations

The Applicant's Position: Not applicable for this submission.

The FDA's Assessment:
Not applicable.

Additional Efficacy Considerations

The FDA's Assessment:
FDA has no additional comment.

8.1.6. Integrated Assessment of Effectiveness

The Applicant's Position: Not applicable for this submission.

The FDA's Assessment:
See the Integrated Review of effectiveness in section 8.1.3.

8.2. Review of Safety

The Applicant's Position:
Belzutifan 120 mg administered orally once daily to participants with advanced RCC was well tolerated and had a manageable safety profile, consistent with its overall established safety profile before availability of Study 005 results. The incidence of participants who reported AEs, including AEs leading to death, SAEs, and Grade 3 to 5

AEs were similar between the 2 treatment groups [Table 13] (Sec. 8.2.4). The incidence of participants with AEs leading to treatment discontinuation was 5.6% in the belzutifan group and 14.4% in the everolimus group. The incidence of participants with dose modification was 47.8% in the belzutifan group and 62.5% in the everolimus group [Table 13].

The incidence of participants with AEs of anemia was 82.3% in the belzutifan group and 55.8% in the everolimus group. The incidence of participants with AEs of hypoxia was 14.5% in the belzutifan group and 1.4% in the everolimus group. Most anemia AEs in the belzutifan group were Grade 2 and were manageable with dose modification, and/or treatment with ESAs/blood transfusions, and approximately half of all anemia events were resolved or resolving. Most hypoxia events were Grade 3 and were manageable with dose modification and/or supplemental oxygen; most were resolved. Few participants discontinued belzutifan because of anemia or hypoxia.

Body weight increase over time was noted in the belzutifan group. Based on Study 005 IA1 results, and with consideration of all available safety data, the Sponsor determined that weight increased is an ADR for belzutifan.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. In section 6.1 of product labeling for belzutifan, dose modifications as presented above for belzutifan are divided into dosage interruptions (39%) and dosage reductions (13%). The preferred term "anemia" term (b) (4) (b) (4) the laboratory value of 'decreased hemoglobin' which occurred at a greater incidence than "anemia" is presented instead (overall incidence of88% in the belzutifan arm and 76% in the everolimus arm).

8.2.1. Safety Review Approach

The Applicant's Position:
Safety results are presented from Study 005 IA1 [Table 11]. Additional safety tables that support the safety results provided for the submission are in the ISS.

Table 26: Applicant – Summary of Clinical Safety Datasets

Dataset	Population	Nomenclature in Tables	Nomenclature in Text
MK-6482-005 belzutifan	N=372: Safety data from participants who received belzutifan.	MK-6482-005 Data for Belzutifan 120 mg QD	Belzutifan Treatment Group
MK-6482-005 everolimus	N=360: Safety data from participants who received everolimus.	MK-6482-005 Data for Everolimus 10 mg QD	Everolimus Treatment Group

The FDA's Assessment:
The FDA agrees with the Applicant that the results from the interim analysis 1 of Study 005 were the primary source of safety data. The data cutoff for the original submission

was November 01, 2022, and June 13, 2023, for the Safety Update.

The Applicant defined treatment-emergent as adverse events on and after the treatment start date and before the treatment end date +30 days for a non-serious adverse event, or +90 days for a serious adverse event.

For FDA review, the following preferred terms (PT) were pooled as grouped terms (GT):

- Acute Kidney Injury (GT): renal failure, acute kidney injury, oliguria, renal impairment, azotemia, and nephropathy toxic
- Abdominal Pain (GT): abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort, epigastric discomfort, and gastrointestinal pain
- Anemia (GT): anemia and hemoglobin decreased
- Arrhythmia (GT): ventricular extrasystoles, atrial fibrillation, supraventricular tachycardia, electrocardiogram qt prolonged, ventricular arrhythmia, atrioventricular block first degree, sinus tachycardia, atrial flutter, atrioventricular block, bundle branch block left, and sinus bradycardia
- Cough (GT): cough, upper-airway cough syndrome, and productive cough
- COVID-19 (GT): COVID-19 and COVID-19 pneumonia
- Diarrhea (GT): diarrhea, colitis, and enterocolitis
- Dizziness (GT): vertigo and dizziness
- Dyspnea (GT): dyspnea and dyspnea exertional
- Edema (GT): edema peripheral, face edema, generalized edema, edema, periorbital edema, eyelid edema, localized edema, edema genital, eye edema, and swelling
- Fatigue (GT): asthenia, and fatigue
- Headache (GT): headache and migraine
- Hemorrhage (GT): hematuria, intra-abdominal hemorrhage, epistaxis, small intestinal hemorrhage, rectal hemorrhage, gastrointestinal hemorrhage, pulmonary hemorrhage, hemoptysis, muscle hemorrhage, hemorrhage intracranial, cerebral hemorrhage, gingival bleeding, hemorrhage urinary tract, upper gastrointestinal hemorrhage, eyelid bleeding, vitreous hemorrhage, anal hemorrhage, and pericardial hemorrhage
- Hypertension (GT): hypertension and blood pressure increased
- Hypotension (GT): hypotension, orthostatic hypotension, and blood pressure decreased
- Hypothyroidism (GT): hypothyroidism, and blood thyroid stimulating hormone increased
- Musculoskeletal pain (GT): musculoskeletal chest pain, back pain, bone pain, pain in extremity, spinal pain, arthralgia, myalgia, musculoskeletal pain, non-cardiac chest pain, neck pain, arthritis, musculoskeletal discomfort, and musculoskeletal stiffness
- Neuropathy Peripheral (GT): hyperesthesia, neuropathy peripheral,

hypoesthesia, paranesthesia, neuralgia, peripheral sensory neuropathy, and peripheral motor neuropathy
- Pneumonia (GT): lower respiratory tract infection, pneumonia, pneumonia aspiration, atypical pneumonia, and pneumonia bacterial
- Pneumonitis (GT): pneumonitis, interstitial lung disease, and acute interstitial pneumonitis
- Pyrexia (GT): pyrexia, body temperature increased, hyperpyrexia, and hyperthermia
- Rash (GT): palmar-plantar erythrodysesthesia syndrome, rash, rash maculo-papular, dermatitis acneiform, eczema, drug eruption, rash pruritic, rash pustular, rash papular, rash erythematous, dermatitis, skin exfoliation, exfoliative rash, nodular rash, and pemphigoid
- Stomatitis (GT): stomatitis, aphthous ulcer, oral mucosal erythema, cheilitis, mucosal inflammation, glossitis, and mouth ulceration
- Urinary Tract Infection (GT): urinary tract infection, pyelonephritis acute, and cystitis
- Visual Impairment (GT): visual impairment, vision blurred, visual acuity reduced, and retinal detachment

Unless otherwise indicated, the use of each of the above grouped terms in this document includes all preferred terms listed in the grouping.

8.2.2. Review of the Safety Database

Overall Exposure

Data:
As of the data cutoff of 01-NOV-2022, the median duration of exposure was 7.6 months (range: 0.1 to 28.5 months) in the belzutifan group and 3.9 months (range: 0 to 24.9 months) in the everolimus group [Table 12]. Among participants treated with belzutifan, 71 (19.1%) participants had at least 1 dose reduction. A total of 67 (18.0%) and 16 (4.3%) participants had belzutifan dose reductions to 80 mg and 40 mg, respectively. AEs that led to discontinuation of study intervention, dose reduction, or dose interruption are summarized in Sec. 8.2.4.

Table 27: Applicant – Summary of Summary of Drug Exposure (APaT Population)

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	Belzutifan (N=372)	Everolimus (N=360)
Duration on Therapy[a] (months)		
n	372	360
Mean (SD)	8.9 (7.3)	6.3 (5.6)
Median	7.6	3.9
Range	0.1 to 28.5	0.0 to 24.9
Total Dose Administered (mg)[b]		
n	372	360
Mean (SD)	30342.7 (25821.4)	1616.0 (1510.8)
Median	23960.0	1005.0
Range	280.0 to 101640.0	10.0 to 7010.0
Average Daily Dose Administered (mg)[c]		
n	372	360
Mean (SD)	115.4 (12.0)	9.2 (1.5)
Median	120.0	10.0
Range	44.2 to 126.4	3.0 to 10.0

[a]Duration on Therapy is calculated as the time between first dose date and last dose date in each treatment arm.
[b]Total Dose Administered for a participant is the total doses that the participant took.
[c]Average Daily Dose Administered for a participant is calculated by the Total Dose Administered divided by the total number of days when the participant took non-zero doses.
Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adexsum]

The Applicant's Position:
The median duration of exposure was 7.6 months (range: 0.1 to 28.5 months) in the belzutifan group and 3.9 months (range: 0 to 24.9 months) in the everolimus group. More participants in the belzutifan group had durations of exposure of ≥3, ≥6, ≥9, ≥12, ≥18, and ≥24 months than in the everolimus group.

The FDA's Assessment:
The FDA agrees with the Applicant's position on duration of exposure to randomized treatments.

Relevant characteristics of the safety population:

Data:
See [Table 6] in Sec. 8.1.2.

The Applicant's Position:
Characteristics of the safety population were similar to the ITT population.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. For interpretation of the safety results, the FDA reviewer highlights that the belzutifan arm had a higher percentage of patients under the age of 65 years at 62% compared to 53% in the everolimus arm.

Adequacy of the safety database:

The Applicant's Position:
The safety database is of an adequate size, considering exposure to the appropriate dose, duration of treatment, patient demographics, and disease characteristics that are relevant to a US target population.

The FDA's Assessment:
The FDA agrees with the Applicant's position that the size of the safety database and exposure to belzutifan is adequate to characterize the safety profile of belzutifan.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
Data quality assurance included QA and QC oversight activities implemented at the investigation site and centrally by the Sponsor in accordance with ICH GCP 5.1. The Applicant conducted periodic, independent audits to ensure the accuracy and integrity of the clinical study data. There were no issues with data integrity or analysis that precluded the inclusion of data in the safety analysis. The sNDA submission contains all required components. The overall quality and integrity of the application is sufficient for substantive review to be completed.

The FDA's Assessment:
No issues regarding integrity and/or quality of the submitted data were identified.

Categorization of Adverse Events

The Applicant's Position: Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence, severity, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs were monitored throughout Study 005 and graded in severity according to the guidelines outlined in the NCI CTCAE Version 5.0. AEs were coded using MedDRA (Version 25.1).

The FDA's Assessment:
The FDA agrees with the Applicant's position; however, FDA used grouped terms for

certain adverse events (e.g., fatigue, musculoskeletal pain, hemorrhage) as outlined in Section 8.2.1 of this review.

Routine Clinical Tests

The Applicant's Position: Participants underwent routine evaluation for safety events, including laboratory testing, vital sign measurements, oxygen saturation, as measured by pulse oximetry, physical examinations, and AE monitoring.

The FDA's Assessment:
The FDA agrees with the Applicant's description of clinical and laboratory monitoring for patients on Study 005.

8.2.4. Safety Results

Table 28: Applicant – Overall Summary of Adverse Events (ApaT Population)

	Belzutifan		Everolimus	
	n	(%)	n	(%)
Participants in population	372		360	
with one or more adverse events	368	(98.9)	357	(99.2)
with no adverse event	4	(1.1)	3	(0.8)
with drug-related[a] adverse events	329	(88.4)	320	(88.9)
with toxicity grade 3-5 adverse events	214	(57.5)	221	(61.4)
with toxicity grade 3-5 drug-related adverse events	137	(36.8)	139	(38.6)
with serious adverse events	143	(38.4)	134	(37.2)
with serious drug-related adverse events	50	(13.4)	45	(12.5)
who died	12	(3.2)	18	(5.0)
who died due to a drug-related adverse event	1	(0.3)	2	(0.6)
with any dose modification[b] due to an adverse event	178	(47.8)	225	(62.5)
with any dose interruption due to an adverse event	145	(39.0)	173	(48.1)
with any dose reduction due to an adverse event	49	(13.2)	51	(14.2)
discontinued any drug due to an adverse event	21	(5.6)	52	(14.4)
discontinued any drug due to a serious adverse event	14	(3.8)	29	(8.1)

[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 25.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adae]

The FDA's Assessment:
The FDA agrees with the overview of treatment-emergent adverse events (TEAEs). Nearly every patient experienced a TEAE.

All-grade TEAEs, Grade 3-4 TEAEs, treatment-emergent serious adverse events (TESAEs), and dose reduction due to TEAEs were similar between the belzutifan and everolimus arms. Grade 5 TEAEs, drug interruption due to TEAEs, and drug discontinuation due to TEAEs were higher in the everolimus arm compared to the belzutifan arm.

Table 29: Study 005 Safety Summary

Safety Overview	Belzutifan N=372; n (%)	Everolimus N=360; n (%)
All-Grade TEAEs	368 (99)	357 (99)
Grade 3-4 TEAEs	202 (54)	203 (56)
Grade 3-5 TEAEs	214 (58)	221 (61)
Grade 5 (Deaths due to TEAEs)	12 (3.2)	18 (5)
Serious TEAEs (TESAEs)	143 (38)	134 (37)
Drug interrupted due to AEs	145 (39)	173 (48)
Drug dose reduced due to AEs	49 (13)	51 (14)
Drug discontinued due to AEs	21 (6)	52 (14)

Source: ADSL, ADAE; Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AETOXGR, AESER, AEACN

Deaths

Data:
The incidence of participants with AEs leading to death was similar between the 2 treatment groups (12 [3.2%] participants in the belzutifan group and 18 [5.0%] in the everolimus group) [Table 14].

Table 30: Applicant – Subjects with Adverse Events Resulting in Death (Incidence >0% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (ApaT Population)

	Belzutifan		Everolimus	
	n	(%)	n	(%)
Participants in population	372		360	
with one or more adverse events	12	(3.2)	18	(5.0)
with no adverse events	360	(96.8)	342	(95.0)

Cardiac disorders	**2**	**(0.5)**	**0**	**(0.0)**
Myocardial infarction	1	(0.3)	0	(0.0)
Pericardial haemorrhage	1	(0.3)	0	(0.0)
Gastrointestinal disorders	**1**	**(0.3)**	**2**	**(0.6)**
Intra-abdominal haemorrhage	0	(0.0)	1	(0.3)
Pancreatitis acute	0	(0.0)	1	(0.3)
Upper gastrointestinal haemorrhage	1	(0.3)	0	(0.0)
General disorders and administration site conditions	**3**	**(0.8)**	**0**	**(0.0)**
Death	2	(0.5)	0	(0.0)
Multiple organ dysfunction syndrome	1	(0.3)	0	(0.0)
Infections and infestations	**3**	**(0.8)**	**10**	**(2.8)**
Abdominal sepsis	1	(0.3)	0	(0.0)
COVID-19	0	(0.0)	2	(0.6)
COVID-19 pneumonia	0	(0.0)	4	(1.1)
Pneumonia	1	(0.3)	3	(0.8)
Sepsis	1	(0.3)	1	(0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(0.3)**	**0**	**(0.0)**
Gastric cancer	1	(0.3)	0	(0.0)
Nervous system disorders	**1**	**(0.3)**	**0**	**(0.0)**
Seizure	1	(0.3)	0	(0.0)
Psychiatric disorders	**0**	**(0.0)**	**1**	**(0.3)**
Assisted suicide	0	(0.0)	1	(0.3)
Renal and urinary disorders	**0**	**(0.0)**	**1**	**(0.3)**
Acute kidney injury	0	(0.0)	1	(0.3)

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Participants With Adverse Events Resulting in Death
(Incidence > 0% in One or More Treatment Groups)
(ApaT Population)

	Belzutifan		Everolimus	
	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.3)**	**4**	**(1.1)**
Hypoxia	1	(0.3)	0	(0.0)
Pleural effusion	0	(0.0)	1	(0.3)
Pulmonary embolism	0	(0.0)	2	(0.6)
Respiratory failure	0	(0.0)	1	(0.3)

Every participant is counted a single time for each applicable row and column.
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 25.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adae]

The Applicant's Position:
The incidence of participants with fatal AEs was similar in the belzutifan and everolimus groups.

The FDA's Assessment:
FDA agrees with the Applicant's assessment that there were 12 (3.2%) deaths due to TEAEs on the belzutifan arm compared to 18 (5%) deaths due to TEAEs in the everolimus arm. Product labeling for belzutifan, per the table below, includes deaths related to sepsis and hemorrhage which each affected 2 patients (0.5%) each.

Table 31: Deaths due to AEs

Deaths	Belzutifan N=372; n (%)	Everolimus N=360; n (%)
Death due to AEs	**12 (3.2)**	**18 (5)**
Sepsis[1]	2 (0.5)	1 (0.3)
Hemorrhage (GT)[2]	2 (0.5)	1 (0.3)
Death	2 (0.5)	0 (0)
Pneumonia	1 (0.3)	3 (0.8)
Gastric Cancer	1 (0.3)	0 (0)
Hypoxia	1 (0.3)	0 (0)
Multiple Organ Dysfunction Syndrome	1 (0.3)	0 (0)
Myocardial Infarction	1 (0.3)	0 (0)
Seizure	1 (0.3)	0 (0)
COVID-19 (GT)	0 (0)	6 (1.7)

Pulmonary Embolism	0 (0)	2 (0.6)
Acute Kidney Injury	0 (0)	1 (0.3)
Assisted Suicide	0 (0)	1 (0.3)
Pancreatitis Acute	0 (0)	1 (0.3)
Pleural Effusion	0 (0)	1 (0.3)
Respiratory Failure	0 (0)	1 (0.3)

Source: ADSL, ADAE; Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEBODSYS, AEDECOD, AEOUT, AESDTH, AETOXGR
[1] Sepsis here includes the PT terms sepsis and abdominal sepsis.
[2] Hemorrhage here includes PT terms pericardial hemorrhage, upper gastrointestinal hemorrhage, and intra-abdominal hemorrhage.

The narratives for each of the patients treated with belzutifan are summarized below.

Patient (SUJID) Preferred Term	**Narrative**
(b) (6) Upper Gastrointestinal Hemorrhage	73-year-old White man with a history of DVT on acenocoumarol and TIA who presented to the ED on Day 5 with hypotension and melena. Diagnosed with upper GI hemorrhage. Patient went into refractory shock without response to resuscitation and died on Day 5. Last dose of belzutifan was on Day 4.
(b) (6) Death	68-year-old White man with a history of hypertension, type 2 diabetes mellitus, chronic kidney disease, and atrial fibrillation died at home on Day 109. The primary reported cause of death was unknown. The last dose of belzutifan was given on Day 26 after being discontinued for hypoxia.
(b) (6) Gastric Cancer	79-year-old White man was diagnosed with concomitant Grade 3 gastric cancer on Day 335 and eventually died of gastric cancer on Day 410. The last dose of belzutifan was Day 320.
(b) (6) Death	62-year-old White woman with a history of hypertension, atrial fibrillation, peripheral edema, and pleural effusion died at home on Day 50. The primary reported cause of death was unknown. The patient was hospitalized on Day 24 for dyspnea after a new episode of atrial fibrillation with Grade 3 cardiac failure. The patient was treated and the cardiac failure resolved, leading to discharge on Day 27. The last does of belzutifan was given on Day 28.
(b) (6) Hypoxia	57-year-old White woman with a history of pleural effusion (tumor locations in lungs and pleura), dyspnea, and anemia experienced Grade 5 hypoxia on Day 255 associated with worsening pleural effusion. Last dose of belzutifan was Day 245.
(b) (6) Sepsis	63-year-old White man was admitted to the hospital on Day 133 with fever, hypotension, and hypoxia and was found to have blood cultures positive for *Streptococcus agalactiae* and *Staphylococcus*

	aureus. He was diagnosed with Grade 3 sepsis. Belzutifan was discontinued (last dose) on Day 132. While hospitalized, the patient developed Grade 3 pneumonia and Grade 1 COVID-19. Sepsis worsened to Grade 4 on Day 155. On Day 158, the patient was transferred to palliative care and died on Day 161.
(b) (6) Multiple Organ Dysfunction Syndrome	48-year-old Asian man, who on Day 12 had Grade 1 pyrexia and Day 15 had Grade 2 platelet count, Grade 2 increased AST, and Grade 1 ALT leading to belzutifan interruption, was hospitalized after being found unconscious at home on Day 20. The participant was diagnosed with multiple organ dysfunction syndrome, DIC, and hepatic failure (all Grade 4), and sepsis and hypocalcemia (both Grade 3). He was diagnosed with a Grade 2 brain abscess on Day 43. On Day 45, the patient's vital signs gradually deteriorated and later that day, the patient died. Last dose of belzutifan was Day 14.
(b) (6) Pneumonia	66-year-old Asian man discontinued belzutifan for progressive disease, with the last dose was given on Day 228. He presented to the ED on Day 296 with lower back pain and was found to have Grade 3 pneumonia, leading to admission. The pneumonia worsened despite treatment, and the patient died on Day 348.
(b) (6) Myocardial Infarction	73-year-old White man with a history of hypertension, polymyalgia rheumatica, and pneumonitis was unable to sleep due to Grade 2 dyspepsia on Day 9. He took magnesium carbonate, with the pain resolving in a hour. Later the same day, in the morning, the patient was found dead; the primary reported cause of death was MI. The last dose of belzutifan was given on Day 8.
(b) (6) Pericardial Hemorrhage	72-year-old White man with a history of atrial fibrillation, diabetes mellitus, coronary artery disease, and anemia had two holds of belzutifan, with the first for anemia and the second for increased hepatic enzymes. The last hold was on Day 111 but resumed on Day 169 (although by Day 176, the patient's relative reported that he had stopping taking the drug). On Day 126, the patient had a chest x-ray which showed an enlarged cardiac silhouette. On Day 168, the patient had chest discomfort which evolved to chest pain radiating to the left arm with pleuritic chest pain. Troponins were WNL, CTA showed no abnormalities, except for minimal pericardial effusion. Chest pain resolved, and the patient was sent home. On Day 177, the patient died at home. According to the death certificate, the primary reported cause of death was pericardial hemorrhage (reported as acute on chronic hemorrhagic pericarditis).
(b) (6) Seizure	56-year-old White man went to the ED in an acute confusional state on Day 265 and had a tonic-clonic seizure with clinical evidence of increased intracranial pressure. Despite treatment, the patient died. The primary reported cause of death was seizure. According to the

	study site notes, the underlying cause was known brain metastasis; however, it does not appear that imaging tests were performed. Last dose of belzutifan was on Day 264.
(b) (6) Abdominal Sepsis	54-year-old multi-racial man with history of vena cava thrombosis and pelvic venous thrombosis on rivaroxaban was hospitalized on Day 22 due to generalized edema and hypoalbuminemia. He was found to have Grade 3 abdominal sepsis on the same day. On Day 27, the patient had Grade 2 hypoxia and dyspnea (worsened to Grade 3 dyspnea by Day 28). The patient started palliative care on Day 30 and subsequently died on Day 34; the primary reported cause of death was abdominal sepsis. Last dose of belzutifan was on Day 26.

Serious Adverse Events

Data:
The overall incidence of participants who reported SAEs in Study 005 was similar between the 2 treatment groups (38.4% in the belzutifan group and 37.2% in the everolimus group) [Table 13]. The most frequently reported SAEs (≥3% incidence) in the belzutifan group were hypoxia (7.3%), anemia (5.4%), and pneumonia (3.2%). The most frequently reported SAEs (≥3% incidence) in the everolimus group were pneumonitis (4.2%), pneumonia (4.4%), and COVID-19 pneumonia (3.1%).

The Applicant's Position:
The overall incidence of participants who reported SAEs in Study 005 was similar between the 2 treatment groups.

The FDA's Assessment:
TESAEs were similar between the two arms, occurring in 38% of patients on the belzutifan arm and 37% of patient on the everolimus arm. Using FDA grouped terms, the following table was generated representing TEAEs occurring in >2% of patients in either treatment arm in Study 005.

Table 32: Treatment-Emergent Serious Adverse Events in >2% of Patients in Both Arms in Study 005

TESAEs	Belzutifan N=372; n (%)	Everolimus N=360; n (%)
Patients with TESAEs	**143 (38)**	**134 (37)**
Hypoxia	27 (7)	1 (0.3)
Anemia	20 (5)	7 (1.9)
Pneumonia (GT)	13 (3.5)	19 (5)

TESAEs	Belzutifan N=372; n (%)	Everolimus N=360; n (%)
Patients with TESAEs	**143 (38)**	**134 (37)**
Hemorrhage (GT)	11 (3.0)	3 (0.8)
Pleural Effusion	8 (2.2)	10 (2.8)
Pneumonitis (GT)	1 (0.3)	20 (6)
COVID-19 (GT)	7 (1.9)	19 (5)

Source: ADSL, ADAE; Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGR, AEACN, AEBODSYS, AESER

Hypoxia (7%), anemia (5%), and hemorrhage (3%) occurred at higher incidences in the belzutifan arm compared to the everolimus arm. Consistent with its known safety profile, everolimus led to higher incidences of pneumonitis compared to belzutifan. The everolimus arm also had two other pulmonary-related related treatment-emergent SAEs, pneumonia and COVID-19, that occurred at a higher rate compared to belzutifan.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:
The incidence of participants with AEs leading to treatment discontinuation in Study 005 was 5.6% in the belzutifan group and 14.4% in the everolimus group. The most frequently reported (>0.5% incidence) AEs leading to discontinuation were hypoxia (1.1%) and anemia (0.5%) in the belzutifan group and pneumonitis (4.2%), fatigue (0.8%), interstitial lung disease (0.8%), anemia (0.6%), blood creatinine increased (0.6%), and pneumonia (0.6%) in the everolimus group.

The Applicant's Position:
The incidence of participants with AEs resulting in treatment discontinuation in Study 005 was lower in the belzutifan group than in the everolimus group.

The FDA's Assessment:
The FDA agrees the Applicant's assessment. Per FDA analysis, TEAEs leading to treatment discontinuation were 6% for belzutifan and 14% for everolimus. The most common (≥0.5%) TEAEs leading to treatment discontinuation in the belzutifan arm were hypoxia (1.1%), anemia (0.5%), and hemorrhage (0.5%). The most common TEAEs leading to treatment discontinuation with everolimus were pneumonitis (5%) and fatigue (1.1%).

Table 33: Discontinuations due to TEAEs Occurring in ≥0.5% of Patients in Either Arm in Study 005

	Belzutifan N = 372; n (%)	Everolimus N = 360; n (%)
Overall discontinuations due to AEs	**21 (6)**	**52 (14)**
Hypoxia	4 (1.1)	0 (0)
Anemia	2 (0.5)	2 (0.6)
Hemorrhage (GT)	2 (0.5)	1 (0.3)
Pneumonitis (GT)	0 (0)	19 (5)
Fatigue (GT)	1 (0.3)	4 (1.1)
Pneumonia (GT)	1 (0.3)	2 (0.6)
Arrhythmia (GT)	0 (0)	2 (0.6)
Blood Creatinine Increased	0 (0)	2 (0.6)
COVID-19 (GT)	0 (0)	2 (0.6)
Rash (GT)	0 (0)	2 (0.6)

Source: ADSL, ADAE. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, ATOXGR, AEACN, AESER

Dose Reduction/Interruption Due to Adverse Effects

Data:
The incidence of participants with AEs leading to dose reduction was similar between the treatment groups (13.2% in the belzutifan group and 14.2% in the everolimus group). The most frequently reported (≥1.0% incidence) AEs leading to dose reduction were hypoxia (5.1%) and anemia (3.2%) in the belzutifan group and stomatitis (2.8%), anemia (1.4%), pneumonitis (1.4%), and hyperglycemia (1.1%) in the everolimus group.

The Incidence of participants with AEs leading to dose interruption was 39.0% for the belzutifan group and 48.1% for the everolimus group. The most frequently reported (≥5% incidence) AEs leading to dose interruption were anemia (8.1%) and hypoxia (5.4%) in the belzutifan group and stomatitis (7.8%) in the everolimus group.

The Applicant's Position:
The incidence of participants with AEs resulting in dose reduction in Study 005 was similar in the belzutifan group and the everolimus group. The overall incidence of participants with AEs resulting in treatment interruption was lower for the belzutifan group than the everolimus group.

The FDA's Assessment:
The percentage of patients with dose reductions due to TEAEs was similar between the belzutifan arm (13%) and the everolimus arm (14%). The two most common TEAEs

leading to dose reduction in the belzutifan arm were hypoxia (5%) and anemia (3.2%). The most common TEAEs leading to dose reduction with everolimus were stomatitis (2.8%), pneumonitis (1.4%), and anemia (1.4%).

Table 34: Dose Reductions due to TEAEs in ≥0.5% of Patients in Either Arm in Study 005

	Belzutifan N = 372; n (%)	Everolimus N = 360; n (%)
Dose reductions due to TEAEs	**49 (13)**	**51 (14)**
Hypoxia	19 (5)	0 (0)
Anemia	12 (3.2)	5 (1.4)
Fatigue (GT)	3 (0.8)	4 (1.1)
Alanine Aminotransferase Increased	3 (0.8)	1 (0.3)
Dyspnea (GT)	2 (0.5)	2 (0.6)
Aspartate Aminotransferase Increased	2 (0.5)	0 (0)
Hypertransaminasemia	2 (0.5)	0 (0)
Stomatitis (GT)	0 (0)	10 (2.8)
Pneumonitis (GT)	1 (0.3)	5 (1.4)
Hyperglycaemia	0 (0)	4 (1.1)
Blood Creatinine Increased	0 (0)	3 (0.8)
Edema (GT)	0 (0)	3 (0.8)
General Physical Health Deterioration	1 (0.3)	2 (0.6)
Pneumonia (GT)	1 (0.3)	2 (0.6)
Acute Kidney Injury (GT)	0 (0)	2 (0.6)
Blood Triglycerides Increased	0 (0)	2 (0.6)
Decreased Appetite	0 (0)	2 (0.6)
Hypertriglyceridemia	0 (0)	2 (0.6)
Pruritus	0 (0)	2 (0.6)

Source: ADSL, ADAE. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, ATOXGR, AEACN, AESER

Dose interruptions due to TEAEs were lower for patients treated with belzutifan (39%) compared to patients treated with everolimus (48%). Consistent with dose reductions due to TEAEs, the most common (>5%) TEAEs leading to dose interruption were anemia (8%) and hypoxia (5%). Additional TEAEs leading to dose interruption occurring in >1.5% of patients treated with belzutifan include COVID-19, fatigue (GT), hemorrhage (GT), pneumonia (GT), diarrhea (GT), pleural effusion, and dizziness (GT). The most

common (5%) TEAEs leading to dose interruption for everolimus were stomatitis (9%) and rash (6%).

Table 35: Interruptions due to TEAEs in >1% of Patients in Both Arms of Study 005

	Belzutifan N = 372; n (%)	Everolimus N = 360; n (%)
Overall interruptions due to TEAEs	**145 (39)**	**173 (48)**
Anemia	30 (8)	6 (1.7)
Hypoxia	20 (5)	1 (0.3)
Covid-19 (GT)	16 (4.3)	15 (4.2)
Fatigue (GT)	12 (3.2)	14 (3.9)
Hemorrhage (GT)	8 (2.2)	3 (0.8)
Pneumonia (GT)	7 (1.9)	10 (2.8)
Diarrhea (GT)	6 (1.6)	9 (2.5)
Pleural Effusion	6 (1.6)	3 (0.8)
Dizziness (GT)	6 (1.6)	1 (0.3)
Pyrexia (GT)	5 (1.3)	8 (2.2)
Aspartate Aminotransferase Increased	5 (1.3)	5 (1.4)
Dyspnea (GT)	5 (1.3)	5 (1.4)
Nausea	5 (1.3)	0 (0)
Abdominal Pain (GT)	4 (1.1)	1 (0.3)
Stomatitis (GT)	0 (0)	32 (9)
Rash (GT)	3 (0.8)	20 (6)
Pneumonitis (GT)	1 (0.3)	17 (4.7)
Cough (GT)	1 (0.3)	8 (2.2)
Hypertriglyceridemia	0 (0)	7 (1.9)
Decreased Appetite	0 (0)	6 (1.7)
Platelet Count Decreased	3 (0.8)	5 (1.4)
Acute Kidney Injury (GT)	2 (0.5)	5 (1.4)
Vomiting	3 (0.8)	4 (1.1)
Neutropenia	1 (0.3)	4 (1.1)
Edema (GT)	1 (0.3)	4 (1.1)
Blood Triglycerides Increased	0 (0)	4 (1.1)
Hyperglycemia	0 (0)	4 (1.1)
Pruritus	0 (0)	4 (1.1)

Significant Adverse Events

Data:
The overall incidence of participants with Grade 3 to 5 AEs was similar between the treatment groups (57.5% in the belzutifan group and 61.4% in the everolimus group). The most common (≥5% incidence) Grade 3 to 5 AEs were anemia and hypoxia in the belzutifan treatment group and anemia, hyperglycemia, and hypertriglyceridemia in the everolimus group [Table 15].

Table 36: Applicant–Participants With Grade 3-5 Adverse Events by Decreasing Frequency of Preferred Term (Incidence ≥5% in One or More Treatment Groups) (aPaT Population)

	Belzutifan		Everolimus	
	n	(%)	n	(%)
Participants in population	372		360	
with one or more adverse events	214	(57.5)	221	(61.4)
with no adverse events	158	(42.5)	139	(38.6)
Anaemia	109	(29.3)	59	(16.4)
Hypoxia	37	(9.9)	5	(1.4)
Hyperglycaemia	2	(0.5)	20	(5.6)
Hypertriglyceridaemia	0	(0.0)	18	(5.0)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
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 25.1 preferred terms“"Neoplasm progressio"",“"Malignant neoplasm progressio"" and“"Disease progressio"" not related to the drug are excluded.
Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adae]

The Applicant's Position:
The incidence of Grade 3 to 5 AEs was similar in the belzutifan group and the everolimus group.

The FDA's Assessment:
The FDA conducted an analysis of Grade 3-5 TEAEs occurring in Study 005 using FDA standard grouped terms, resulting in the table below:

Table 37: Grade 3-5 TEAEs Occurring in ≥5% of Patients in Either Arm of Study 005

Grade 3-5 TEAEs	Belzutifan N=372; n (%)	Everolimus N=360; n (%)
Grade 3-5 TEAEs	214 (58)	221 (61)

Anemia	109 (29)	59 (16)
Hypoxia	37 (10)	5 (1.4)
Pneumonia (GT)	15 (4)	19 (5)
Fatigue (GT)	12 (3.2)	22 (6)
COVID-19 (GT)	8 (2.2)	22 (6)
Hyperglycemia	2 (0.5)	20 (6)
Hypertriglyceridemia	0 (0)	18 (5)

Source: ADSL, ADAE. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, ATOXGR, AEACN

For the belzutifan arm, anemia and hypoxia were the two Grade 3-5 TEAEs that occurred in ≥5% of patients. For the everolimus arm, anemia, pneumonia (GT), fatigue (GT), COVID-19 (GT), hyperglycemia, and hypertriglyceridemia were the Grade 3-5 TEAEs that occurred in ≥5% of patients. Overall, the incidence of Grade 3-5 TEAEs were similar between arms.

Treatment Emergent Adverse Events and Adverse Reactions

Table 38: Applicant – Subjects with Adverse Events (Incidence ≥10% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (aPaT Population)

	Belzutifan		Everolimus	
	n	(%)	n	(%)
Participants in population	372		360	
with one or more adverse events	368	(98.9)	357	(99.2)
with no adverse events	4	(1.1)	3	(0.8)
Anaemia	304	(81.7)	198	(55.0)
Fatigue	113	(30.4)	91	(25.3)
Nausea	62	(16.7)	41	(11.4)
Oedema peripheral	57	(15.3)	60	(16.7)
Constipation	55	(14.8)	28	(7.8)
Hypoxia	54	(14.5)	5	(1.4)
Dyspnoea	52	(14.0)	49	(13.6)
Arthralgia	50	(13.4)	24	(6.7)
Asthenia	50	(13.4)	60	(16.7)
Decreased appetite	49	(13.2)	56	(15.6)
Headache	44	(11.8)	27	(7.5)
Back pain	43	(11.6)	30	(8.3)
Vomiting	42	(11.3)	30	(8.3)
Alanine aminotransferase increased	40	(10.8)	32	(8.9)
Aspartate aminotransferase increased	40	(10.8)	32	(8.9)
Diarrhoea	40	(10.8)	69	(19.2)
Blood creatinine increased	29	(7.8)	43	(11.9)
Cough	27	(7.3)	74	(20.6)
Pruritus	27	(7.3)	57	(15.8)

Pyrexia	19	(5.1)	46	(12.8)
Rash	16	(4.3)	68	(18.9)
Hypertriglyceridaemia	14	(3.8)	53	(14.7)
Stomatitis	13	(3.5)	136	(37.8)
Hyperglycaemia	9	(2.4)	54	(15.0)

Participants With Adverse Events by Decreasing Incidence
(Incidence ≥ 10% in One or More Treatment Groups)
(aPaT Population)

	Belzutifan		Everolimus	
	n	(%)	n	(%)
Pneumonitis	3	(0.8)	51	(14.2)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
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 25.1 preferred terms“"Neoplasm progressio"","“"Malignant neoplasm progressio"" and“"Disease progressio"" not related to the drug are excluded.
Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adae]

Table 39: Applicant Participants With Adverse Events of Anemia, Hypoxia, and Dyspnea (Incidence > 0% in One or More Treatment Groups) (aPaT Population)

	Belzutifan		Everolimus	
	n	(%)	n	(%)
Participants in population	372		360	
with one or more adverse events	321	(86.3)	221	(61.4)
with no adverse events	51	(13.7)	139	(38.6)
Anemia	**306**	**(82.3)**	**201**	**(55.8)**
Anaemia	304	(81.7)	198	(55.0)
Haemoglobin decreased	2	(0.5)	4	(1.1)
Dyspnea	**52**	**(14.0)**	**49**	**(13.6)**
Dyspnoea	52	(14.0)	49	(13.6)
Hypoxia	**54**	**(14.5)**	**5**	**(1.4)**
Hypoxia	54	(14.5)	5	(1.4)

Every participant is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 01NOV2022

Source: [P005V01MK6482: adam-adsl; adae]

The Applicant's Position:

The most frequently reported AEs ≥20%) in the belzutifan group included anemia and fatigue; the most frequently reported AEs in the everolimus group included anemia,

stomatitis, fatigue, and cough [Table 16].

The incidences of participants with AEs of anemia, hypoxia, and dyspnea are presented in [Table 17]. Most anemia events in both groups were Grade 2; 29.3% participants in the belzutifan group and 16.4% participants in the everolimus group reported ≥Grade 3 anemia. Grade 4 AEs of anemia were reported for 3 (0.8%) participants in the belzutifan group and 1 (0.3%) participant in the everolimus group. There were no Grade 5 anemia events in either group. Approximately half of all anemia events were resolved or resolving in both treatment groups (resolved: 88/306 [28.8%] belzutifan, 88/201 [43.8%] everolimus; resolving: 58/306 [19.0%] belzutifan, 23/201 [11.4%] everolimus). Most anemia AEs were manageable with dose modification and/or treatment with ESAs/blood transfusions. Two participants in each group discontinued because of an AE of anemia.

Most hypoxia events in both groups were Grade 3 (9.7% for belzutifan, 1.1% for everolimus). Hypoxia events were manageable with dose modification and/or supplemental oxygen, and most were resolved in both treatment groups (43/54 [79.6%] in the belzutifan group and 3/5 [60%] in the everolimus group). Four participants in the belzutifan group and 0 in the everolimus group discontinued because of an AE of hypoxia.

Most AEs of dyspnea were Grade 1 or 2 in the belzutifan group. Five (1.3%) and 1 (0.3%) participants in the belzutifan group had Grade 3 and Grade 4 dyspnea, respectively, compared with 9 (2.5%) and 0 (0.0%) participants, respectively, in the everolimus group. Most dyspnea AEs in the belzutifan group were resolved (25/52 [48.1%]) or resolving (4/52 [7.7%]). Most dyspnea AEs in the everolimus group were not resolved (29/49 [59.2%]). One participant in the belzutifan group and 0 participants in the everolimus group discontinued because of AE dyspnea.

The FDA's Assessment:
To examine TEAEs reported on Study 005, FDA conducted an analysis of all-grade TEAEs using the FDA standard grouped terms. The table reflecting these results is presented below:

Table 40: Any Grade TEAEs in ≥10% of Patients in Both Arms of Study 005

	Belzutifan N=372		Everolimus N=360	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Patients with TEAEs	368 (99)	202 (54)	357 (99)	203 (56)
Anemia	306 (82)	109 (29)	201 (56)	59 (16)
Fatigue (GT)	160 (43)	12 (3.2)	147 (41)	22 (6)
Musculoskeletal Pain (GT)	125 (34)	4 (1.1)	97 (27)	8 (2.2)
Edema (GT)	73 (20)	2 (0.5)	82 (23)	2 (0.6)

Nausea	62 (17)	2 (0.5)	41 (11)	1 (0.3)
Dyspnea (GT)	59 (16)	6 (1.6)	57 (16)	9 (2.5)
Constipation	55 (15)	0 (0)	28 (8)	0 (0)
Hypoxia	54 (15)	36 (10)	5 (1.4)	5 (1.4)
Decreased Appetite	49 (13)	4 (1.1)	56 (16)	0 (0)
Headache (GT)	45 (12)	2 (0.5)	27 (8)	1 (0.3)
Vomiting	42 (11)	3 (0.8)	30 (8)	3 (0.8)
Diarrhea (GT)	41 (11)	5 (1.3)	69 (19)	5 (1.4)
Dizziness (GT)	41 (11)	0 (0)	7 (1.9)	0 (0)
Alanine Aminotransferase Increased	40 (11)	4 (1.1)	32 (9)	0 (0)
Aspartate Aminotransferase Increased	40 (11)	3 (0.8)	32 (9)	1 (0.3)
Abdominal Pain (GT)	38 (10)	3 (0.8)	29 (8)	1 (0.3)
Stomatitis (GT)	13 (3.5)	0 (0)	152 (42)	13 (3.6)
Rash (GT)	31 (8)	0 (0)	128 (36)	11 (3.1)
Cough (GT)	28 (8)	0 (0)	79 (22)	0 (0)
Pneumonitis (GT)	4 (1.1)	1 (0.3)	66 (18)	17 (4.7)
Pruritus	27 (7)	0 (0)	57 (16)	5 (1.4)
Hyperglycemia	9 (2.4)	2 (0.5)	54 (15)	20 (6)
Hypertriglyceridemia	14 (3.8)	0 (0)	53 (15)	18 (5)
Pyrexia (GT)	20 (5)	3 (0.8)	48 (13)	0 (0)
Blood Creatinine Increased	29 (8)	0 (0)	43 (12)	1 (0.3)
COVID-19 (GT)	34 (9)	8 (2.2)	41 (11)	17 (4.7)
Hemorrhage (GT)	35 (9)	10 (2.7)	39 (11)	2 (0.6)
Pneumonia (GT)	21 (6)	14 (3.8)	38 (11)	16 (4.4)

Source: ADSL, ADAE. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, ATOXGR, AEACN

The most common TEAE for both belzutifan and everolimus was anemia, although anemia occurred at a higher frequency with belzutifan compared to everolimus (See Anemia section below). Hypoxia was another notable adverse event that occurred at a higher frequency with belzutifan compared to everolimus (see Hypoxia section below). Other TEAEs that occurred at a higher frequency (≥3%) with belzutifan included musculoskeletal pain, nausea, constipation, headache, vomiting, and dizziness. Fatigue, dyspnea, alanine aminotransferase increased, aspartate aminotransferase increased, abdominal pain, COVID-19, and hemorrhage occurred at similar rates (<3% difference) between the two drugs.

Additional TEAEs that occurred in fewer than 10% of patients on the belzutifan arm that were deemed clinically relevant and were included in Section 6 of the label as “clinically

relevant adverse reactions in <10% of patients who received WELIREG." These TEAEs included hemorrhage (9%) [including intracranial/cerebral hemorrhage (0.8%)], rash (8%), hypertension (6%), visual impairment [including vision blurred (4%), visual acuity decreased (1.1%), visual impairment (0.5%), and retinal detachment (0.3%)] (6%), and increased weight (5%).

As expected from its known safety profile, patients treated with everolimus had a higher frequency of stomatitis, rash, cough, pneumonitis, hyperglycemia, hypertriglyceridemia, pyrexia, and blood creatinine increased. Overall, the frequency of TEAEs for both drugs was similar to their known safety profiles.

Specific safety concerns that were reviewed in greater depth for this sNDA include anemia, hypoxia, and hemorrhage, each of which are discussed below. Concerns related to increased weight are discussed in the vital signs section.

- **Anemia**

Any-grade anemia was higher in the belzutifan arm at 306 (82%) patients compared to 201 (56%) patients in the everolimus arm. As mentioned above, these numbers represent the preferred term for anemia, (b) (4) slightly higher percentages of patients with the laboratory adverse reaction of 'decreased hemoglobin' are presented per arm, affecting 88% and 76% of patients on the belzutifan and everolimus arms respectively, including 29% and 17% with grades 3-4.

To better assess the impact of anemia, an IR was sent requesting that the Applicant provide a summary of the number and percentage of patients in each arm requiring red cell transfusions during treatment on Study 005. The Applicant provided Table 42 detailing blood transfusions on the trial. Of the patients who experienced anemia, 103 (33.7%) patients on the belzutifan arm received a blood transfusion compared to 58 (28.9%) on the everolimus arm. The mean number of red cell units transfused was 3.6 (95% CI: 3.0, 4.2) in the belzutifan arm compared to 3.5 (95% CI: 2.6, 4.4) in the everolimus arm. The median number of red cell units transfused was 2 per arm, with a range of 1 to 14 for the belzutifan arm and a range of 1 to 18 for the everolimus arm.

Overall, despite the reported higher rate of anemia with belzutifan, the number of red cell units transfused was only slightly higher with belzutifan compared to everolimus. Despite this, anemia remains a TEAE of concern. Anemia was previously listed in the Warnings and Precautions in the belzutifan label, and this section was updated with the data from Study 005. The following was added to the belzutifan Warnings and Precautions in Section 5.1 (Anemia):

- Decreased hemoglobin occurred in 88% of patients and 29% had Grade 3 events.
- Median time to onset of anemia was 29 days (range: 1 day to 16.6 months).
- Of the patients with anemia, 22% received transfusions only, 20% of patients

received ESAs only, and 12% received both transfusions and ESAs.

- Clinicians are recommended to transfuse for anemia as clinically indicated.
- For patients with hemoglobin <8 g/dL, belzutifan should be held until hemoglobin is ≥8 g/dL. At hemoglobin of ≥8 g/dL, belzutifan can be resumed at the same or reduced dose or the clinician can discontinue belzutifan, depending on the severity of the anemia.
- For life-threatening anemia or when urgent intervention is indicated, belzutifan should be held until the hemoglobin is ≥8 g/dL, then resumed at a reduced dose or permanently discontinued.

Table 41: Summary of Units of Red Cells Transfused for Anemia in Study 005

	Belzutifan	Everolimus
	n (%)	n (%)
Participants in population	372	360
Participants with one or more events of anemia	306	201
Participants with Red Cell Transfusions (a)	103 (33.7)	58 (28.9)
Number of Units of Red Cells Transfused		
Mean (95% CI)	3.6 (3.0, 4.2)	3.5 (2.6, 4.4)
Median (Range)	2 (1 to 14)	2 (1 to 18)
Units of Red Cells Transfused (cumulative) (a)		
1	25 (8.2)	9 (4.5)
2	32 (10.5)	24 (11.9)
3	4 (1.3)	5 (2.5)
4	10 (3.3)	6 (3)
5	5 (1.6)	2 (1)
6	4 (1.3)	1 (0.5)
7	6 (2)	2 (1)
8	3 (1)	1 (0.5)
9	4 (1.3)	1 (0.5)
10	3 (1)	2 (1)
>10	3 (1)	2 (1)

(a) Includes blood transfusions in participants with anemia.
Database Cutoff Date: 01NOV2022.

Source: [P005V01MK6482: adam-adsl; adae; adcm]

From the Applicant's IR Response dated September 11, 2023 (SDN 416).

In terms of the anemia section of the Warnings and Precautions for belzutifan, cautionary language around ESA use that previously appeared in the section describing the VHL indication was revised somewhat to remove the statement: (b) (4)

(b) (4)

(b) (4) This was replaced with a statement that the safety of ESAs for treatment of anemia in patients with VHL disease treated with WELIREG has not been established. This softening of language was primarily due to data submitted by the Applicant in response to an FDA IR regarding further follow-up of VHL patients treated with ESAs, in which no obvious ill-effects were seen in terms of development of advanced disease or disease acceleration in these patients. Summary of the data provided by the Applicant in response to the FDA's IR is presented in the efficacy section, in Table 21. Efficacy Outcomes in Study 004, by the status of ESA Use).

As no apparent OS nor PFS detriment was observed based on ESA use in patients with advanced RCC treated with belzutifan, nor was there evidence of any detriment in the LITESPARK-004 in patients with VHL, no cautionary language around ESA use was added to the anemia Warning and Precautions language describing use of belzutifan in patients with advanced RCC. As the risk/benefit regarding ESA use is different in patients with VHL and the data for the safety of ESAs was more limited in this setting, the warning was retained but modified for this indication as described above.

- **Hypoxia**

Any-grade hypoxia was reported at a higher incidence in the belzutifan arm (54 [14.5%] patients) compared to the everolimus arm (5 [1.4%) patients). To better assess the impact of hypoxia, an IR was sent requesting that the Applicant provide a summary of the supplemental oxygen usage for patients who experienced hypoxia during treatment on Study 005. The Applicant provided the table below and the data in the subsequent sentences. Of the 54 patients treated with belzutifan who experienced hypoxia, 37 (68.5%) received supplemental oxygen. However, data was unavailable for 9 of these patients. The median number of liters of oxygen per administration for those patients with data available was 2.4 (range: 1 to 10). The mean and median durations of supplemental oxygen use were 31.8 (95% CI: 1.8, 61.9) days and 8 (range: 1 to 388) days, respectively.

There were too few patients with hypoxia treated with supplementary oxygen on the everolimus arm for a meaningful interpretation of hypoxia with everolimus. This was consistent with the known safety profile of everolimus which does not include hypoxia as an adverse event of particular concern.

Hypoxia was previously included in the belzutifan label's Warnings and Precautions, and the section was updated for the current label. The following was added to Section 5.2 (Hypoxia):

- Hypoxia occurred in 15% of patients and 10% had Grade 3 hypoxia.
- Of the patients with hypoxia, 69% were treated with oxygen therapy.
- Median time to onset of hypoxia was 30.5 days (range: 1 day to 21.1 months)

Table 42: Summar of Supplementar Ox en Usa e for H poxia

	Belzutifan	Everolimus
	n (%)	n (%)
Participants in population	372	360
Participants with one or more events of hypoxia	54	5
Treated with Oxygen Therapy (%)	37 (68.5)	4 (80)
Liters of Oxygen per administration(a) Median (Range)	2.4 (1 to 10)	2 (1 to 2)
Duration (days) of oxygen use per participant (b)		
Mean (95% CI)	31.8 (1.8, 61.9)	10 (NA, NA)
Median (Range)	8 (1 to 388)	10 (10 to 10)

(a):Average L / administration per patient; data with values <=15 in unit L are included in the calculation.
(b): Sum of all days on oxygen treatment. Includes records with non-missing start / stop dates. If multiple records with same start date and different stop dates, maximum duration used within a start date.
NA='Not Available'
Database Cutoff Date: 01NOV2022.

Source: [P005V01MK6482: adam-adsl; adae; adcm]

From the Applicant's IR Response dated September 11, 2023 (SDN 416).

- **Hemorrhage**

In November 2022, the DO1 clinical team identified hemorrhage as a newly identified safety signal (NISS) for belzutifan after receiving post-marketing safety reports of CNS hemorrhage:

- 2 reports of intracranial hemorrhage in the Applicant's periodic safety reports of Study 004 (both patients were on anticoagulation at the time of hemorrhage), and
- 1 case of spinal hemorrhage reported by Clinical Cancer Research Editorial Board from a pre-publication Letter to the Editor (Trinh et al. PMID: 36722140).

All 3 cases incidents occurred in patients with VHL-associated CNS hemangioblastoma who received belzutifan.

Despite the small number of patients and presence of potential confounding factors such as use of anticoagulation, due to the seriousness and potentially fatal consequences of CNS hemorrhage, DO1 clinical team initiated a NISS report. Additionally, DO1 sent an IR to the Applicant and asked:

1. for further evaluation of safety results for potential association of belzutifan with increased risk of hemorrhage;
2. that mitigation strategies to reduce the risk of hemorrhage be added to the protocol for ongoing clinical trials of belzutifan; and
3. information on the safety reports of CNS hemorrhage be added to the investigator brochure.

According to the NISS evaluation of hemorrhagic events with belzutifan performed by department of pharmacovigilance (DPV) II, there was insufficient evidence to establish a

causal association between the use of belzutifan and hemorrhagic events. This was consistent with the Applicant's conclusions. According to the DPV II report, the review team was unable to determine to what extent, if any, the exposure to belzutifan could have contributed to hemorrhage because of the presence of confounding factors or missing clinical data in all cases (n = 13). The DPV II team identified 6 cases that reported belzutifan administered as monotherapy, and all of them were confounded by concomitant anticoagulant or antiplatelet therapies and/or comorbidities; two of these cases also reported belzutifan use for unapproved indications. The remaining seven cases reported belzutifan in combination with other antineoplastic therapies that are labeled for hemorrhage.

Although the data did not support a drug-event causal association, based on belzutifan activating angiogenic growth factors, the potential for anti-VEGF therapies and belzutifan to affect platelet function remained of concern. Additionally, the reported adverse events of CNS hemorrhage were serious and potentially life-threatening. Thus, DPV II continued routine pharmacovigilance monitoring for hemorrhagic events with belzutifan with plan to continue the pharmacovigilance monitoring for at least 2 years.

DO1 agreed with DPVII's conclusion that there is currently not sufficient data for an association between belzutifan and increased risk of hemorrhage. Additionally, DO1 agreed with continued pharmacovigilance monitoring for hemorrhagic events with belzutifan. Based on these evaluations, the FDA review team concluded that no changes in the FDA labeling for belzutifan was indicated at that time.

In review of Study 005, the FDA review team revisited the issue of hemorrhage with belzutifan and noted that 9% of patients receiving belzutifan had hemorrhage events, including 11 TESAEs of hemorrhage including 2 fatal events. However, despite the prior NISS evaluation, after review of the Study 005 events, the FDA review team concluded that there was not adequate basis in terms of causality or frequency for adding hemorrhage as a Warning and Precaution to the belzutifan label. However, hemorrhage was added to Section 6 of the belzutifan label describing Study 005, in the paragraph of "clinically relevant adverse reactions in <10% of patients who received WELIREG." The label notes that hemorrhage occurred in 9% of patients and included intracranial/cerebral hemorrhage occurring in 0.8% of patients.

Laboratory Findings

The Applicant's Position:

In both groups, most participants with laboratory toxicity grade shifts from baseline had shifts from Grade 0 to Grade 1. Among participants with both baseline and postbaseline measurements, the most frequently reported worsening in grade for a given laboratory test value (incidence ≥40%) for the belzutifan group was hemoglobin decreased (anemia) (87.7%). The most frequently reported worsening in grade for a given

laboratory test value (incidence ≥40%) in the everolimus group included triglycerides increased (77.6%), hemoglobin decreased (75.6%), lymphocytes decreased (53.0%), cholesterol increased (52.3%), calcium decreased (44.5%), and creatinine increased (43.4%). Among participants with both baseline and postbaseline measurements, the incidence of participants with postbaseline Grade 3 or 4 laboratory abnormalities was comparable between the groups. Grade 3 to 4 laboratory abnormalities for which there was a ≥10% difference were anemia, which was higher in the belzutifan group (28.8% versus 17.1%), and triglycerides increased (1.9% versus 14.4%) and lymphocytes decreased (7.5% versus 19.7%), which were higher in the everolimus group.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of laboratory abnormalities as above. Laboratory abnormalities were calculated by the FDA and generally were ~1% lower in incidence than the Applicant calculated values. It was decided that the laboratory abnormalities provided by the Applicant, which were slightly higher than the FDA calculated values, were not clinically meaningfully different and slight discrepancies in numbers were likely related to differences in the denominator of evaluable patients for each laboratory value. (b) (4) (b) (4) The full table of laboratory abnormalities calculated by the Applicant is below:

Table 43: Laboratory Abnormalities That Worsened from Baseline In >20% Patients who Received Belzutifan in Study 005

Laboratory Test*	Belzutifan		Everolimus	
	All Grades† n (%)	Grades 3-4 n (%)	All Grades† n (%)	Grades 3-4 n (%)
Decreased hemoglobin	320 (88)	105 (29)	269 (76)	61 (17)
Increased triglycerides	141 (39)	7 (1.9)	274 (78)	51 (14)
Decreased lymphocytes	123 (34)	27 (8)	186 (53)	69 (20)
Increased creatinine	123 (34)	17 (4.7)	154 (43)	18 (5)
Increased alanine aminotransferase	117 (32)	8 (2.2)	141 (40)	4 (1.1)
Decreased sodium	112 (31)	6 (1.6)	129 (36)	3 (0.8)
Increased potassium	107 (30)	9 (2.5)	71 (20)	10 (2.8)
Increased activated partial thromboplastin time	98 (28)	2 (0.6)	110 (31)	2 (0.6)
Increased alkaline phosphate	102 (28)	9 (2.5)	127 (36)	1 (0.3)
Increased aspartate aminotransferase	99 (27)	8 (2.2)	132 (38)	7 (2.0)
Increased cholesterol	19 (26)	0 (0)	46 (52)	4 (4.5)
Decreased calcium	78 (22)	4 (1.1)	158 (45)	11 (3.1)

Decreased glucose	79 (22)	4 (1.1)	66 (19)	4 (1.1)

*Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available WEIREG (range: 353 to 366 patients), and everolimus (range: 351 to 356 patients).
†Graded per NCI CTCAE v5.0

The most common (≥30%) all-grade laboratory abnormalities with belzutifan included decreased hemoglobin, increased triglycerides, decreased lymphocytes, increased creatinine, increased alanine aminotransferase, decreased sodium, and increased potassium.

The most common (≥2.5%) Grade 3-4 laboratory abnormalities with belzutifan included decreased hemoglobin, decreased lymphocytes, increased creatinine, increased potassium, and increased alkaline phosphatase. Decreased hemoglobin is a lab abnormality of concern and has been addressed previously. Despite decreased lymphocytes, there does not appear to be an increase in clinically significant infections in patients treated with belzutifan. Similarly, despite increased creatinine and increased potassium, there do not appear to be any clinically meaningful increases in renal function or arrhythmias. Increased alkaline phosphate is less of a concern as it generally has a low clinical meaningfulness.

(b) (4) hypertriglyceridemia, elevated cholesterol, elevated aPTT, and elevated alkaline phosphatase were excluded from the table even though their incidence was ≥20%. Hypertriglyceridemia and elevated cholesterol were excluded as they both had low Grade 3-4 incidence, and these adverse events occurred at a lower frequency on the belzutifan arm compared to the everolimus arm, so do not appear to be a toxicity concern. Elevated aPTT and elevated alkaline phosphatase were excluded because of low Grade 3-4 incidence and low clinical meaningfulness.

Overall laboratory abnormalities were generally similar to the profiles reported previously for belzutifan and everolimus.

Vital Signs

In the belzutifan group, there was a decrease from baseline in oxygen saturation, which decreased through Week 3 and stabilized thereafter.

In addition, based on physical examination results, In the belzutifan group, there was a body weight increase from baseline over time observed in the belzutifan group. Mean percent change from baseline in body weight was 5.78% (SD 8.81%) at Week 37 and 6.46% (SD 8.87%) at Week 53. In the everolimus group, there was a decrease in weight over time. Mean percent change from baseline was -2.04% at Week 13; -1.83% at Week 25; -2.57% at Week 37; and -3.43% at Week 53.

The Applicant's Position:

Based on Study 005 IA1 results, and with consideration of all available data, the Sponsor determined that weight increased is an ADR for belzutifan. The initial decrease from baseline in oxygen saturation stabilized after Week 3. There were no other clinically meaningful findings in the vital sign measurements between the treatment groups.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. There was a minor decrease (median of ~1%) in oxygen saturation in patients treated with belzutifan that was not seen with everolimus. The oxygen saturation decrease observed at Week 3 was persistent but stable throughout treatment with belzutifan.

Regarding the TEAE of weight increased, an IR was sent to the Applicant querying whether there was an association between the TEAE and adverse events of swelling. The Applicant responded that there does not appear to be a consistent association between the TEAE of weight increased and adverse events of edema, heart failure, or other swelling/fluid retention. Of the 19 (5%) of patients in the belzutifan arm with the PT of weight increased, 9 reported no TEAEs of peripheral edema, heart failure, or other swelling. Six of the 19 reported the TEAE of peripheral edema. Of the 6 patients, 3 patients had the onset of the peripheral edema TEAE prior to the TEAE of weight increased, 2 patients had the two TEAEs occur in close temporal relationship, and 1 patient had the TEAE of peripheral edema after the TEAE of weight gain. Two of the 19 patients with weight increased reported the TEAE of heart failure, with one patient reporting the TEAE of weight increased prior to the onset of the TEAE of heart failure and the other patient reporting the two TEAEs in close temporal relationship. The remaining 2 of the 19 patients experienced TEAEs of other swelling/fluid retention, with one patient reporting face edema prior to the TEAE of weight increased and one patient reporting the TEAE of edema genital at the same time as weight increased.

Overall, there was not a consistent association between the TEAE of weight increased and edema-related TEAEs. Weight increased was included in the label in Section 6 as a clinically relevant adverse reaction in <10% of patients who received belzutifan.

Electrocardiograms (ECGs)

The Applicant's Position:
Observations related to shifts from baseline in QTcF are discussed below.

The FDA's Assessment:
See below.

QT

The Applicant's Position: The mean shifts from baseline in QTcF at each postbaseline visit up to 30 days after the last dose of study intervention were similar between the treatment groups. The highest percentage of participants in both groups experienced a shift from <450 to ≥450 – <480 msec, which occurred at similar rates in each group (32 participants [8.7%] in the belzutifan group and 41 participants [11.5%] in the everolimus group). Four participants in the belzutifan group had postbaseline QTcF >500 msec. None of the 4 participants reported arrhythmia AEs.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Five patients treated with belzutifan had ECGs with QTcFs >500 msec, 4 of the patients started with a baseline of QTcF of <450 msec and one with a baseline QTcF of >500 msec. None of these 5 patients experienced an arrhythmia TEAE.

Immunogenicity

The Applicant's Position:
No new information concerning immunogenicity is provided.

The FDA's Assessment:
The FDA has no additional comments.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Applicant Submission-Specific Safety Issues

The Applicant's Position:
No submission-specific safety issues are identified by the Applicant.

The FDA's Assessment:
The FDA has no additional comments. For evaluation of anemia, hypoxia, and hemorrhage, see applicable sections above under "Treatment Emergent Adverse Events."

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position: Results from the patient-reported outcomes analyses are in Sec. 8.1.2 Efficacy Results – Secondary or exploratory COA (PRO) endpoints.

The FDA's Assessment:
See section 8.1.2.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position: In Study 005, AE summaries by the subgroups of age, sex, and baseline ECOG PS (0, 1) were similar to the overall study population for the 2 treatment groups.

The FDA's Assessment:

- **Age**

Of the 372 patients who received belzutifan in Study 005, 62% of patients younger than 65 years, 28% of patients were 65 to 74 years, and 10% were 75 years and over.

Table 44: Safety Subgroup Analysis of Study 005 by Age <65 Years and ≥65 Years

	<65 Years		≥65 Years	
	Belzutifan N = 231 n (%)	Everolimus N = 192 n (%)	Belzutifan N = 141 n (%)	Everolimus N = 168 n (%)
All-Grade TEAEs	227 (98)	191 (99)	141 (100)	166 (99)
Grade 3-4 TEAEs	121 (52)	105 (55)	81 (57)	98 (58)
Grade 5 TEAEs	6 (2.6)	8 (4.2)	6 (4.3)	10 (6)
Serious TEAEs (SAEs)	89 (39)	61 (32)	54 (38)	73 (43)
Interrupted due to AEs	78 (34)	19 (10)	67 (48)	97 (58)
Dose reduced due to AEs	23 (10)	191 (99)	26 (18)	32 (19)
Discontinued due to AEs	11 (4.8)	17 (9)	10 (7)	35 (21)

Source: ADSL, ADAE. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, ATOXGR, AESER, AEDECOD, AEACN, AGEGR1

The safety profile for belzutifan was similar between the age groups; however, dose interruptions and dose reductions occurred at ≥5% difference between <65 years and ≥65 years and both were included in the labeling in Section 8.5 (Geriatric Use):

- Dose interruptions occurred in 48% of patients ≥65 years of age and in 34% of younger patients.
- Dose reductions occurred in 18% of patients ≥65 years of age and in 10% of younger patients.

- **Sex**

There are too few enrolled women to conclusively draw meaningful conclusions about

safety in women compared to men. However, the safety profile of belzutifan appeared fairly similar in women compared to men.

Table 45: Safety Subgroup Analysis of Study 005 by Sex

	Male Patients		Female Patients	
	Belzutifan N = 295 n (%)	Everolimus N = 276 n (%)	Belzutifan N = 77 n (%)	Everolimus N = 84 n (%)
All-Grade TEAEs	291 (99)	273 (99)	77 (100)	84 (100)
Grade 3-4 TEAEs	155 (53)	157 (57)	47 (61)	46 (55)
Grade 5 TEAEs	10 (3.4)	13 (4.7)	2 (2.6)	5 (6)
Serious TEAEs (SAEs)	113 (38)	104 (38)	30 (39)	30 (36)
Interrupted due to AEs	111 (38)	129 (47)	34 (44)	44 (52)
Dose reduced due to AEs	34 (12)	41 (15)	15 (19)	10 (12)
Discontinued due to AEs	15 (5)	37 (13)	6 (8)	15 (18)

Source: ADSL, ADAE. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, ATOXGR, AESER, AEDECOD, AEACN, SEX

- **Race**

There were too few Black, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Multi-racial patients to drawn meaningful conclusions on the impact of race on the safety profile of belzutifan in advanced mRCC (see below for numbers of patients in each of these groups).

Race	Belzutifan N = 372 n (%)	Everolimus N=360 n (%)
Black	4 (1.1)	4 (1.1)
American Indian or Alaska Native	3 (0.8)	2 (0.6)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (0.3)
Multiple	6 (1.6)	11 (3.1)

There were too few Asian patients to draw meaningful conclusions about safety compared to White patients. However, the safety profile of Asian patients appeared fairly similar to White patients.

Table 46: Safety Subgroup Analysis of Study 005 by White vs Asian Patients

	Asian		White	
	Belzutifan N = 42	Everolimus N = 45	Belzutifan N = 296	Everolimus N = 281

	n (%)	n (%)	n (%)	n (%)
All-Grade TEAEs	42 (100)	45 (100)	293 (99)	278 (99)
Grade 3-4 TEAEs	21 (50)	22 (49)	165 (56)	160 (57)
Grade 5 TEAEs	2 (4.8)	0 (0)	9 (3.0)	14 (5)
Serious TEAEs (TESAEs)	15 (36)	17 (38)	115 (39)	100 (36)
Interrupted due to TEAEs	18 (43)	21 (47)	119 (40)	135 (48)
Dose reduced due to TEAEs	10 (24)	11 (24)	35 (12)	32 (11)
Discontinued due to TEAEs	1 (2.4)	6 (13)	18 (6)	39 (14)

Source: ADSL, ADAE. Variables used: USUBJID, TRT01A, SAFFL, RACE, TRTEMFL, ATOXGR, AESER, AEDECOD, A

- **Ethnicity**

There were too few Hispanic or Latino patients to drawn meaningful conclusions about safety compared with Not Hispanic or Latino patients. However, the belzutifan safety profile for Hispanic or Latino patients appeared fairly similar to Not Hispanic or Latino patients.

Table 47: Safety Subgroup Analysis of Study 005 by Ethnicity

	Not Hispanic or Latino		Hispanic or Latino	
	Belzutifan N = 297 N (%)	Everolimus N = 293 N (%)	Belzutifan N = 42 N (%)	Everolimus N = 36 N (%)
All-Grade TEAEs	296 (100)	291 (99)	40 (95)	35 (97)
Grade 3-4 TEAEs	163 (55)	163 (56)	26 (62)	22 (61)
Grade 5 TEAEs	9 (3.0)	10 (3.4)	2 (4.8)	6 (17)
Serious TEAEs (SAEs)	112 (38)	107 (37)	19 (45)	15 (42)
Interrupted due to TEAEs	125 (42)	137 (47)	12 (29)	19 (53)
Dose reduced due to TEAEs	38 (13)	37 (13)	8 (19)	9 (25)
Discontinued due to TEAEs	16 (5)	40 (14)	3 (7)	9 (25)

Source: ADSL, ADAE. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, ATOXGR, AESER, AEDECOD, AEACN, E

- **ECOG Performance Status**

There were too few patients with an ECOG performance status (PS) of 2 enrolled on Study 005 to draw meaningful conclusions regarding their outcomes. Patients with ECOG PS 1 or 2 treated with belzutifan appear to have a similar safety profiles

corresponding to patients with the same ECOG PS treated with everolimus. Overall, dose modifications appeared to occur a lower frequency in patients treated with belzutifan compared to those treated with everolimus.

Table 48: Safety Subgroup Analysis of Study 005 by ECOG Performance Status

	Belzutifan						Everolimus					
	0		1		2		0		1		2	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	161		206		5		158		196		6	
with one or more adverse events	160	(99.4)	203	(98.5)	5	(100.0)	155	(98.1)	196	(100.0)	6	(100.0)
with no adverse event	1	(0.6)	3	(1.5)	0	(0.0)	3	(1.9)	0	(0.0)	0	(0.0)
with drug-related[a] adverse events	138	(85.7)	186	(90.3)	5	(100.0)	142	(89.9)	173	(88.3)	5	(83.3)
with toxicity grade 3-5 adverse events	73	(45.3)	138	(67.0)	3	(60.0)	77	(48.7)	140	(71.4)	4	(66.7)
with toxicity grade 3-5 drug-related adverse events	45	(28.0)	90	(43.7)	2	(40.0)	52	(32.9)	84	(42.9)	3	(50.0)
with serious adverse events	51	(31.7)	89	(43.2)	3	(60.0)	45	(28.5)	85	(43.4)	4	(66.7)
with serious drug-related adverse events	20	(12.4)	29	(14.1)	1	(20.0)	17	(10.8)	27	(13.8)	1	(16.7)
who died	5	(3.1)	7	(3.4)	0	(0.0)	6	(3.8)	12	(6.1)	0	(0.0)
who died due to a drug-related adverse event	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.5)	0	(0.0)
with any dose modification[b] due to an adverse event	66	(41.0)	109	(52.9)	3	(60.0)	92	(58.2)	130	(66.3)	3	(50.0)
with any dose interruption due to an adverse event	51	(31.7)	92	(44.7)	2	(40.0)	70	(44.3)	100	(51.0)	3	(50.0)
with any dose reduction due to an adverse event	19	(11.8)	29	(14.1)	1	(20.0)	22	(13.9)	29	(14.8)	0	(0.0)
discontinued any drug due to an adverse event	5	(3.1)	16	(7.8)	0	(0.0)	14	(8.9)	38	(19.4)	0	(0.0)

Source: Belzutifan CSR (dated July 10th, 2023), Table 14.3-7

Considering the safety subgroups overall, there does not appear to be any substantial safety differences between the two arms of the trial within the belzutifan treatment arm subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position: Not applicable.

The FDA's Assessment:
The FDA has no additional comments.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position: Not applicable.

The FDA's Assessment:
The FDA has no additional comments.

Human Reproduction and Pregnancy
The Applicant's Position: There were no pregnancy exposures to study intervention during Study 005; therefore, no new information concerning human reproduction and pregnancy is provided in this supplement.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Issues related to embryo-fetal toxicity already appear in the belzutifan label as both a boxed warning and as a Warning and Precaution in section 5, primarily due to the young patient population, potential for prolonged exposure to belzutifan in the VHL setting, and potential drug interactions with belzutifan that can render some hormonal contraceptives ineffective. No update was deemed necessary during this review.

Pediatrics and Assessment of Effects on Growth
The Applicant's Position: Belzutifan has not been assessed in pediatric patients.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
The Applicant's Position: There was 1 report of belzutifan overdose (defined as >240 mg daily) in Study 005, which was reported as a PT of Grade 3 increased liver function test (Grade 3 GGT increase). The event resolved. Potential for drug abuse or dependence belzutifan has not been characterized. Based on the mechanism of action, belzutifan is unlikely to show abuse potential. Withdrawal or rebound effects were not evaluated after discontinuing belzutifan.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. The details of the 1 report of belzutifan overdose were as follows:

- A 51-year-old (b) (6) taking belzutifan (b) (6) on Day 597 by taking 3600 mg of belzutifa d 3000 mg of "control tablets" per the narrative. (b) (6) was subsequently taken to the ED, where (b) (6) was found conscious and agitated. (b) (6) vitals were stable, but (b) (6) LFTs were found to be increased at Grade 3. On the same day, (b) (6) underwent gastric lavage and was admitted to the ICU. Additional treatments included acetysteine and activated charcoal. The patient was discharged on Day 599. Belzutifan was discontinued due to physician's decision. LFTs eventually resolved.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
The Applicant's Position: The safety profile of belzutifan postmarketing approval was summarized in the PSUR covering 13-AUG-2022 through 12-FEB-2023. There are no records of any belzutifan registration being revoked or withdrawn for safety reasons in any country.

The FDA's Assessment:

In the PSUR, the updated safety profile was similar to the initial safety profile. Grade 3-5 TEAEs were similar (see Table 50). TESAEs were higher in the belzutifan arm (42.2%) compared to everolimus arm (38.1%). Grade 5 TEAEs were lower for belzutifan (3.5%) compared to everolimus (5.3%). TEAEs leading to dose interruptions and discontinuations were lower in the belzutifan group. Notable, there were fewer discontinuations in the belzutifan arm (5.9%) compared to the everolimus arm (14.7%). Dose reductions were similar between the two arms.

There were 2 new deaths due to TEAEs in the belzutifan group in the PSUR:

- A 64-year-old White man (b) (6) died (b) (6) on Day 505. Last dose of belzutifan was on Day 505. The Investigator assessed (b) (6) as unrelated.
- A 59-year-old White man with a history of diabetes mellitus, brachiocephalic vein thrombosis, edema, anemia, and increased transaminases was reported to have increased creatinine and BUN throughout the trial. On Day 543, the patient reported to the ED with a 2-day history of persistent abdominal pain and Grade 3 asthenia. Laboratory tests on Day 544 showed a further increase in creatinine levels and an abdominal CT showed the left kidney had increased volume with inhomogeneous appearance and left upper polar hyperdense cocooning with exophytic development of 4.5 cm in diameter, suggestive of injury. The patient was admitted for Grade 3 acute kidney injury (AKI). After treatment, the patient was discharged on Day 547, after improved electrolytes and stabilization of creatinine, to follow up as an outpatient. On Day 560, the patient was readmitted for complications of renal failure and died on Day 565. Last dose of belzutifan was Day 540. The primary reported cause of death was acute renal failure due to progression of renal disease (Grade 5 AKI). The Investigator did not consider AKI related to belzutifan.

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Table 49: PSUR Summary of Safety for Study 005

	Belzutifan		Everolimus	
	n	(%)	n	(%)
Participants in population	372		360	
with one or more adverse events	369	(99.2)	357	(99.2)
with no adverse event	3	(0.8)	3	(0.8)
with drug-related[a] adverse events	331	(89.0)	322	(89.4)
with toxicity grade 3-5 adverse events	230	(61.8)	225	(62.5)
with toxicity grade 3-5 drug-related adverse events	144	(38.7)	142	(39.4)
with serious adverse events	157	(42.2)	137	(38.1)
with serious drug-related adverse events	49	(13.2)	47	(13.1)
who died	13	(3.5)	19	(5.3)
who died due to a drug-related adverse event	1	(0.3)	2	(0.6)
with any dose modification[b] due to an adverse event	191	(51.3)	225	(62.5)
with any dose interruption due to an adverse event	162	(43.5)	173	(48.1)
with any dose reduction due to an adverse event	52	(14.0)	53	(14.7)
discontinued any drug due to an adverse event	22	(5.9)	53	(14.7)
discontinued any drug due to a serious adverse event	16	(4.3)	30	(8.3)

[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 26.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 13JUN2023

Source: [P005V01MK6482: adam-adsl; adae]

Source: 90-Day Safety Update (10-13-2023), Table 2.7.4

In addition, at the initial belzutifan approval, a PMR was issued to more fully characterize belzutifan-associated anemia and requirements for red cell transfusion and erythropoiesis stimulating agents. The PMR previously issued was PMR 4132-3: "Conduct an analysis from Study MK-6482-004 to further characterize and determine the incidence and severity of anemia, hypoxia, second primary malignancies and other serious adverse events in patients receiving belzutifan. Include incidence rates, time to onset, outcomes, red cell transfusion and the use of erythropoiesis stimulating agents for anemia and steps taken to mitigate these risks in the reports. Provide interim reports annually for 3 years."

The Applicant has provided two interim reports thus far and is expected to provide another interim report in May 2024. Study MK-6482-004 (Study 004) is expected to be completed in June 2026, and the final report for the PMR is expected in December 2026. Fulfilling this PMR should allow for a more robust determination of the relationship between belzutifan-related anemia and the need for red cell transfusion and/or erythropoiesis stimulating agents.

Expectations on Safety in the Postmarket Setting
The Applicant's Position: Postmarket data from the safety reporting database is routinely reviewed for belzutifan. The MARRS database contains all data from postmarket sources, including health care providers, consumers, and scientific literature as well as competent authorities worldwide. There are no specific safety concerns associated with subpopulations not adequately represented in the clinical safety database. Belzutifan administration in the postmarket setting is expected to be similar to administration in Study 005.

The FDA's Assessment:
The FDA agrees with the Applicant's position on expectations for safety in the postmarketing setting.

8.2.11. Integrated Assessment of Safety

The Applicant's Position: The results from Study 005 show that that the benefit/risk profile of belzutifan for the treatment of patients with advanced RCC is positive. The safety profile of belzutifan was manageable and consistent with its known safety profile. ADRs of anemia and hypoxia were manageable. Few participants discontinued belzutifan because of anemia (2 participants in each group) or hypoxia (4 in the belzutifan group and 0 in the everolimus group). The Sponsor has determined that weight increased is an additional ADR for belzutifan.

The FDA's Assessment:
The FDA review team considered the safety profile of belzutifan to be acceptable for the proposed indication.

Twelve (3.2%) patients died from adverse events in the belzutifan arm. Belzutifan was discontinued due to treatment-emergent adverse events (TEAEs) in 6% of patients, most commonly (≥0.5%) due to hypoxia, anemia, and hemorrhage. The most common (≥25%) adverse reactions in the belzutifan arm include decreased hemoglobin, fatigue, musculoskeletal pain, increased creatinine, decreased lymphocytes, increased alanine aminotransferase, decreased sodium, increased potassium, and increased aspartate aminotransferase.

In terms of comparative safety between belzutifan and everolimus, the toxicity profile of each drug differs which complicates direct comparisons between arms. However, when comparing standard metrics of toxicity on Study 005, all-grade TEAEs, Grade 3-5 TEAEs, TESAEs, and dose reductions due to TEAEs were comparable between arms; drug discontinuations and interruptions due to TEAEs were lower on the belzutifan arm compared to the everolimus arm. This suggests a somewhat more favorable toxicity profile for belzutifan, although the specific observed toxicities differed between arms. For example, in the belzutifan arm, anemia and hypoxia were the two Grade 3-5 TEAEs

that occurred in ≥5% of patients. For the everolimus arm, anemia, pneumonia, fatigue, COVID-19, hyperglycemia, and hypertriglyceridemia were the Grade 3-5 TEAEs that occurred in ≥5% of patients. Dose reductions were most commonly (>1%) due to hypoxia and anemia for belzutifan compared to stomatitis, anemia, pneumonitis, fatigue, and hyperglycemia for everolimus.

Specific safety issues investigated in detail during FDA review of Study 005 were anemia, hypoxia, and hemorrhage. Weight increase was also investigated as a concern.

Decreased hemoglobin affected 88% and 76% of patients on the belzutifan and everolimus arms respectively, including 29% and 17% with grades 3-4. The number of red blood cell units transfused for the treatment of anemia was assessed per arm and was only mildly higher with belzutifan compared to everolimus. Despite this, anemia remains a TEAE of concern, and the existing anemia section of Warnings and Precautions was updated with Study 005 data although cautionary language around ESA use was not added, based on review of both Study 005 and LITESPARK-004 data. In addition, this section was updated to modify the language about the use of ESAs for anemia in VHL patients from (b) (4) to "the safety of ESAs has not been established."

Any-grade hypoxia was higher in the belzutifan arm (15%, 69% of whom required supplemental oxygen) compared to the everolimus arm (1.4%); the hypoxia section of the Warnings and Precautions in the belzutifan label was updated with data from Study 005. Despite the incidence of clinician-reported hypoxia for patients treated with belzutifan, review of PRO results suggested that patients did report increased dyspnea on the belzutifan arm compared to the everolimus arm.

Any-grade hemorrhage, a NISS identified in November 2022, was noted in 9% of patients receiving belzutifan. This including 11 TESAEs of hemorrhage including 2 fatal events. However, despite the prior NISS evaluation, after review of the Study 005 events, the FDA review team concluded that there was not adequate basis for adding hemorrhage as a Warning and Precaution to the belzutifan label. Hemorrhage was added to Section 6 of the belzutifan label as a clinically relevant adverse reaction in <10% of patients who received belzutifan.

Any-grade weight increase occurred in 5% of patients treated on the belzutifan arm, which did not appear to be associated with fluid overload/edema. Weight increase was included in the label in Section 6 as a clinically relevant adverse reaction in <10% of patients who received belzutifan.

Exploratory analyses of PROs, which were considered interpretable given a high completion rate, though limited by sparse sampling and the open-label design, supported improved tolerability for belzutifan compared to everolimus, including for the symptoms of dyspnea and appetite loss.

The review team does not recommend any postmarketing requirements (PMRs) related to safety or risk evaluation and mitigation strategies (REMS) at this time.

Overall, belzutifan has an acceptable safety profile for the indicated patient population, with patient-reported outcomes suggestive of improved tolerability compared to everolimus.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

Study 005 (LITESPARK-005) demonstrated a statistically significant improvement in PFS per BICR assessment in the ITT population. The dual primary endpoint of OS did not demonstrate a statistically significant difference at IA1 and IA2; however, the point estimate of the OS HR favored belzutifan and did not show a trend towards OS detriment for the ITT population. The OS results were generally consistent between IA1 and IA2. The key secondary endpoint of confirmed ORR supported these findings.

The FDA was concerned that the same median PFS (5.6 months) was estimated in both arms and there was observed asymmetric censoring in PFS, leading to uncertainty in the estimation of the magnitude of the PFS treatment effect. Particularly, the FDA noted the interpretation of the treatment benefit in PFS was challenging due to the following statistical issues, with analyses to address each issue presented below:

- *Investigator assessment bias.* Through the analysis of concordance and discordance of PFS per investigator and BICR assessment, the FDA determined that some degree of potential investigator assessment bias might exist in Study 005, which may be due to the open-label study design with a control arm that might not be favored by some investigators as a treatment option in this setting, when other treatment options exist. The FDA performed sensitivity analyses by assuming these patients either event free in both treatment arms or progressed in the belzutifan arm only at the next assessment time. The sensitivity analyses showed HRs that were reassuringly close to the primary PFS analysis.

- *Potential informative censoring due to initiation of new anticancer therapy prior to progression*. One impact of the investigator assessment bias is that after the investigator assessed progression, patients might initiate new anticancer therapy prior to the BICR assessed progression, leading to potentially informative censoring in the analysis of PFS per BICR assessment. The FDA identified 21 vs. 68 patients in the belzutifan arm and everolimus arm respectively who initiated new anticancer therapy prior to progression assessed per BICR assessment. The FDA performed

sensitivity analyses by assuming these patients in the belzutifan arm progressed at the start date of new anti-cancer therapy. The results of the sensitivity analyses were similar to the primary PFS results.

- *Imbalanced dropout and censoring.* Although only affecting a small number of patients overall, the FDA noted a slightly greater percentage of patients with early dropout, (therefore censored in the PFS analysis), in the belzutifan arm compared to the everolimus arm. Therefore, FDA performed sensitivity analyses to evaluate the impact of early dropout on the PFS analysis. FDA's analysis accounted for the patients who were not administered study medication, the patients who were censored at randomization, and the patients censored withing 6 weeks from randomization. The sensitivity analyses, including tipping point sensitivity analyses and worst-case sensitivity analysis, showed that the primary PFS results were robust.

- *Presence of non-proportional hazards.* The FDA observed that the KM curves of PFS per BICR assessment overlapped before 6 months and started to slightly separate thereafter. This indicated that the assumption of proportional hazards for the Cox PH model was not met in Study 005 and makes interpretation of the treatment benefit in terms of PFS more challenging due to the issue of non-proportional hazard. Therefore, FDA performed exploratory analyses using restricted mean survival time (RMST) to further quantify the treatment benefit in PFS. The mean difference of the RMST of PFS between the two treatment arms was 2.2 months.

In summary, FDA performed a variety of conservative and worst-case scenarios sensitivity analyses and the RMST sensitivity analysis to evaluate the impact of these issues on the primary PFS results, and ultimately determined that the PFS HR estimate was close to the primary analysis PFS findings, indicating robustness of the primary PFS analysis results.

The interpretation of OS results remains challenging due to large portion of censoring from approximately 15-18 months, potentially caused by immaturity of the interim data. Final OS results will be submitted as a PMC.

8.4. **Conclusions and Recommendations**

<u>The FDA's Assessment:</u>

The review team recommends traditional approval for belzutifan 120 mg once daily for the treatment of adult patients with advanced RCC following a PD-1 or PD-L1 inhibitor and a VEGFR-TKI. This recommendation is based on the results from Study 005. The primary endpoints were PFS by BICR assessment and OS. A statistically significant

improvement in PFS was demonstrated in patients randomized to receive belzutifan compared with those randomized to receive everolimus. Based on a relatively mature information fraction at the second interim analysis, there was no indication of a potential OS detriment. The ORR and DoR also favored the belzutifan arm.

The FDA review team considered the observed PFS improvement with belzutifan compared to an active control in a head-to head trial, no OS detriment, internal consistency across primary and secondary endpoints, and favorable safety and tolerability profile compared to everolimus to be clinically meaningful.

This indication statement was slightly modified from the original indication statement proposed by the Applicant to specify the required prior therapies.

The recommended dose for belzutifan in this setting is 120 mg orally, once daily.

One PMC to submit the final OS analysis was agreed upon by the FDA and the Applicant.

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

An advisory committee meeting was not convened for this application.

10 Pediatrics

The Applicant's Position:
Study 005 did not enroll any pediatric patients. The Applicant has submitted a full waiver from the requirements of PREA, as amended by FDARA for the RCC indication.

The FDA's Assessment:
Agreed iPSP plan under IND 132120 was issued on 12-Sept-19. The Applicant submitted a request for full waiver of pediatric studies in the proposed indication on the basis that the necessary studies are impossible or highly impractical to conduct. FDA agreed and granted full waiver for pediatric studies for the proposed indication.

11 Labeling Recommendations

The Applicant's Position:
The Applicant has provided proposed labeling separately.

The FDA's Assessment:

Table 50: Summary of the changes in the proposed label.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 1 Indications and usages	The Applicant added the following indication for advanced RCC: "**Advanced Renal Cell Carcinoma (RCC)** • for treatment of adult patients with advanced renal cell carcinoma (RCC) following immune checkpoint and anti-angiogenic therapies."	FDA revised the indication to the following "for treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI)".
Section 2	The Applicant proposed (b) (4) (b) (4) (b) (4) The Applicant proposed resuming at the same or reduced dose; or discontinue depending on the severity of anemia.	FDA (b) (4) (b) (4) set a single cutoff value of hemoglobin <8 g/dL. Resuming at the same or reduced dose; or discontinue depending on the severity of anemia was accepted.
Section 5	Section 5.1 Anemia and Section 5.2 Hypoxia were both updated with data from LITESPARK-005.	(b) (4) (b) (4) Other changes Removed: (b) (4)

		[redacted] Replaced with: The safety of erythropoiesis stimulating agents (ESAs) for treatment of anemia in patients with VHL disease treated with WELIREG has not been established.
Section 6	Added section of LITESPARK-005 general safety data, adverse reactions table, and laboratory abnormalities.	The LITESPARK-005 safety section was accepted with revisions to the adverse reactions to reflect FDA grouped terms. [redacted] was removed [redacted] may be misleading. [redacted] was deleted as it was superseded by the data from LITESPARK-005.
Section 8.5	Updated with data from LITESPARK-005.	Revised to include the differences in dose interruptions and dose reductions in the two age subgroups (<65 years vs ≥65 years).
Section 14 Clinical Studies	Added section of LITESPARK-005 (NCT04195750) including the general study description, patient demographics and baseline characteristics, study results for the PFS endpoint along with Table 8 for a summary of the efficacy results in LITESPARK 005 and Figures 1 Kaplan-Meier Curves of PFS in EMBARK, and study results for selected secondary endpoints.	Removed [redacted] that Applicant proposed [redacted] FDA added a statement in the text for the percentage of patients with an ongoing response at 12 months in the belzutifan arm. Removed [redacted] as this was not relevant [redacted] and is generally not included in the label [redacted]

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS was required for this application.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
One PMC was issued for this approval:

Complete clinical trial LITESPARK-005, "*An Open-label, Randomized Phase 3 Study of Belzutifan Versus Everolimus in Participants with Advanced Renal Cell Carcinoma That Has Progressed After Prior PD-1/L1 and VEGF-Targeted Therapies*" to provide the final overall survival analyses.

Trial Completion: 05/2024
Final Report Submission: 11/2024

According to the Applicant, the timeline outlined above aligns with the expected planned availability date for LITESPARK-005 final OS topline results (~July 2024) previously submitted to the FDA (Sequence No. 0141) in response to the FDA Information Request received on September 11, 2023. Per protocol, the final OS analysis for LITESPARK-005 requires approximately 483 events and a minimum of ~27 months follow-up after last patient randomized (January 19, 2022). Based on current projection, it is expected that the final OS analysis will be triggered by minimum follow-up time, with expected data cutoff date for analyses approximately May 2024 and final report submission in November 2024.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	__ Yes _x_ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _x_ No

▫	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _x_ No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1. References

The Applicant's References:

[1] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: kidney cancer; version 4.2022. Plymouth Meeting (PA): National Comprehensive Cancer Network (NCCN); 2022. 76p.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 May/Jun;71(3):209-49.

[3] American Cancer Society. About kidney cancer. Atlanta (GA): American Cancer Society (ACS); 2022. 11 p.

[4] SEER*Stat [Internet]. Bethesda (MD): National Cancer Institute (NCI). 2021. Cancer stat facts: kidney and renal pelvis cancer; [about 16 screens]. Available from: https://seer.cancer.gov/statfacts/html/kidrp.html.

[5] Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5;373(19):1803-13.

[6] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: kidney cancer; version 4.2023. Plymouth Meeting (PA): National Comprehensive Cancer Network (NCCN); 2023. 81 p.

[7] Powles T, Albiges L, Bex A, Grunwald V, Porta C, Procopio G, et al. ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma. Ann Oncol. 2021;32(12):1511-9.

[8] Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019 Mar 21;380(12):1116-27.

[9] Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2021 Mar 4;384(9):829-41.

[10] Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med. 2021 Apr 8;384(14):1289-300.

[11] Pal SK, Albiges L, Tomczak P, Suarez C, Voss MH, de Velasco G, et al. Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial. The Lancet. In press 2023.

19.2. Financial Disclosure

The Applicant's Position:
Disclosure of financial interests of the investigators who conducted Study 005 is described in this submission, including statements of due diligence (FDA forms 3454) in cases where the Sponsor was unable to obtain a signed form from the investigator. Disclosure of financial interests and/or arrangements, including statements of due diligence for the investigators who conducted Study 005, are described in FDA forms 3454, 3455 and Module 1.3.4.

The FDA's Assessment:
FDA has no additional comments.

Covered Clinical Study (Name and/or Number):* MK-6482-005

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1248		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: MSD		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4		
Is an attachment provided with the	Yes ☒	No ☐ (Request explanation

reason:		from Applicant)

*The table above should be filled by the Applicant and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

Data:
No new nonclinical pharmacology is included in this submission.
No new data are provided in the current submission for genetic toxicology, carcinogenicity, reproductive and developmental toxicity, or other toxicology studies.

The Applicant's Position:
See Sec. 5.5.1 for new exploratory TK and toxicity studies completed since the original NDA submission for the indication of VHL-RCC.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:
In general, the population PK model adequately characterizes belzutifan PK, and the model predicted exposure metrics of AUCavg, AUCavgeot, AUCwk3, AUCwk13 are adequate for use in E-R analyses.

Physiologically and mechanistically relevant clinical covariates were reevaluated in the model with additional data. No new intrinsic factors were identified for dose adjustment. The recommended dosage for belzutifan in patients with advanced RCC is supported by the population PK analysis results as well as other analyses results (ie., clinical efficacy, safety, and ER analyses).

19.4.1.2. PPK Assessment Summary

The Applicant's Position:
Full details of the popPK analysis were provided in the original NDA submission for the indication of VHL-RCC. Additional available data have been described in Sec. 6.

The FDA's Assessment:
The Applicant's population PK analysis is acceptable. Overall, the final population PK model is adequate to characterize the PK profile of belzutifan as indicated in the

Applicant's goodness-of-fit plots and VPC plots. The FDA reviewer was able to repeat and verify the Applicant's analysis with no significant discordance identified. The reviewer agrees with the Applicant's conclusion regarding the effect of covariates on belzutifan exposure. FDA accepted the labeling language in 12.3 related to PK parameters and effect of covariates (age, sex, ethnicity, race, body weight, UGT2B17 phenotype, CYP2C19 phenotype, renal impairment and hepatic impairment) except that the mean (CV%) volume of distribution is 119 L (28%) instead of (b) (4) (originally proposed by sponsor).

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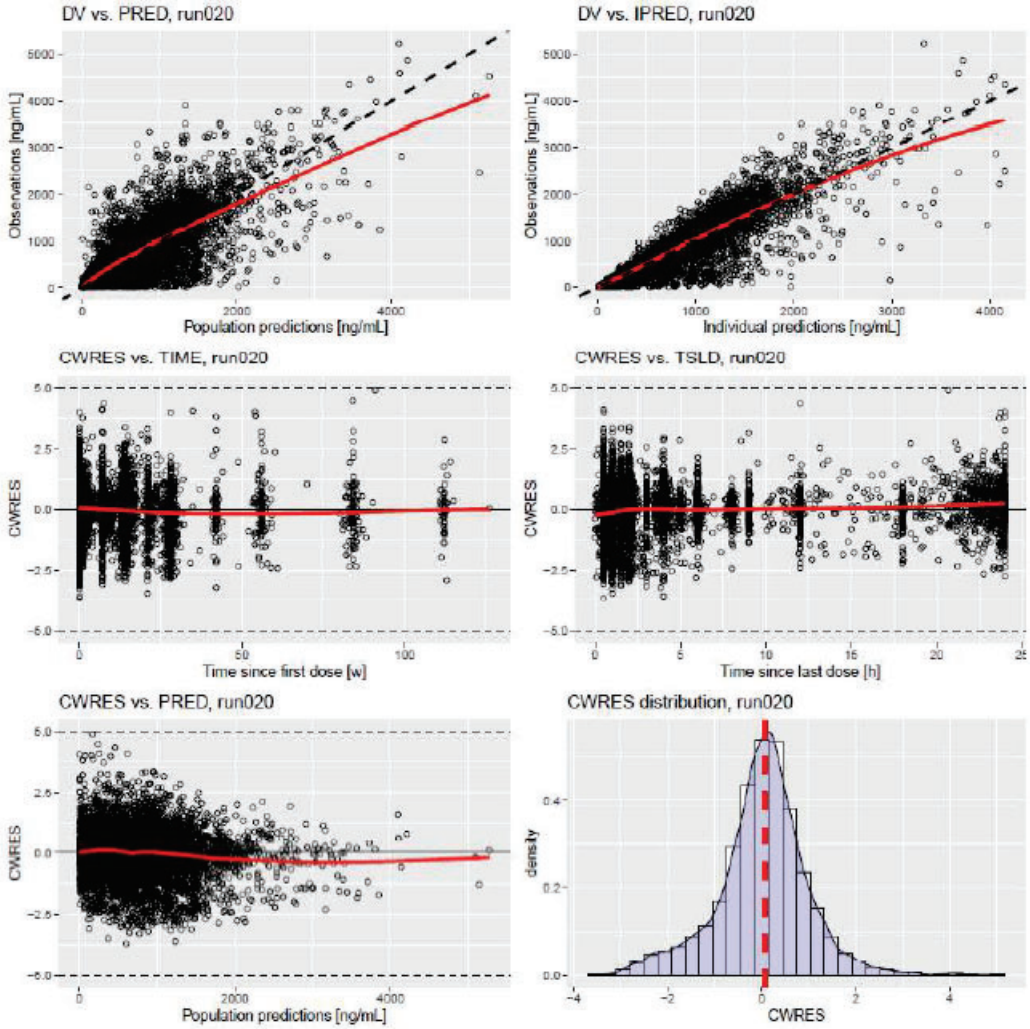
Table 51: Parameter Estimates (RSE) and Median (95% CI) for Final Population Pharmacokinetic Model

Parameter	Estimate	RSE (%)	Asymptotic 95% CI	Shrinkage (%)
Fixed Effects				
CL/F (L/h)	5.79	2.70	5.48; 6.10	--
V2/F (L)	87.9	3.50	81.8; 94.0	--
Q/F (L/h)	5.17	26.7	2.47; 7.88	--
V3/F (L)	33.1	9.50	26.9; 39.3	--
KA (/h)	2.44	6.10	2.15; 2.73	--
Lag time (h)	0.165	1.20	0.161; 0.169	--
Fed status effect on KA	-0.871	10.9	-1.06; -0.685	--
Body weight exponent on CL/F and Q/F	0.638	11.4	0.496; 0.780	--
Body weight exponent on V2/F and V3/F	1.03	4.90	0.932; 1.13	--
UGT2B17 extensive metabolizer effect on CL/F	0.404	13.6	0.297; 0.511	--
UGT2B17 poor metabolizer effect on CL/F	-0.370	8.50	-0.432; -0.308	--
CYP2C19 poor metabolizer effect on CL/F	-0.211	25.2	-0.315; -0.107	--
UGT2B17 poor metabolizer effect on F	0.129	17.1	0.0857; 0.172	--
FMF effect on KA	-0.444	16.0	-0.584; -0.304	--
Age exponent on V2/F	-0.164	31.6	-0.266; -0.0623	--
Age exponent on CL/F	-0.367	22.3	-0.528; -0.206	--
Random Effects				
IIV on CL/F	0.165	7.90	0.139; 0.191	7.50
IIV on V2/F	0.015	49.3	0.00051; 0.0295	43.1
IIV on V3/F	0.162	72.2	-0.0670; 0.391	55.7
IIV on KA	1.28	16.5	0.866; 1.69	19.2
Residual Error				
RES HV	0.266	4.90	0.240; 0.292	--
RES PAT	0.326	2.30	0.312; 0.340	--
EPS	1 FIX	0	--	7.00

Source: pirana_sum_run020.html, parameters020.xlsx
Abbreviations: CI=confidence interval; CL/F=apparent clearance; CYP=Cytochrome P450; EPS=ε (random error); F=bioavailability; FMF=final market formulation; HV=healthy volunteer; IIV=inter-individual variability; KA=absorption rate constant; PAT=patient; Q/F=apparent inter-compartmental clearance; RES=proportional residual error; RSE=relative standard error; UGT=Uridine 5'-diphospho-glucuronosyltransferase; V2/F=apparent central volume of distribution; V3/F=apparent peripheral volume of distribution.

Source: Table 9 in the Population PK report 08bqrv.

Figure 9: Goodness-of-Fit Plots for Final Population Pharmacokinetic Model



Source: MK6482-005014-pk-gof-plots-run020.pdf, 2022-08-03-mk6482-005-ppk-gof.r
Abbreviations: CWRES=conditional weighted residuals; DV=dependent variable (MK-6482 concentration); GOF=goodness-of-fit; IPRED=individual predictions; PRED=population predictions
Notes: Dots are individual data points and red lines are linear regression lines. In the two plots in the upper row, dashed black lines are lines of identity, while in the two plots in the lower row, dashed lines show the boundaries of the CWRES ± 5 interval.
Source: Figure 4 in the Population PK report 08bqrv.

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Table 52: Derived Population PK parameters

	Study 005		All Studies	
Parameter	**Geometric mean**	**Geometric %CV**	**Geometric mean**	**Geometric %CV**
CL/F (L/h)	5.93	57.1	6.00	58.6
Vc/F (L)	**86.5**	**24.6**	**86.8**	**27.3**
Vd/F (L)	**119**	**24.6**	**119**	**28.2**
Vp/F (L)	**32.7**	**36.0**	**32.3**	**32.2**
KA (1/h)	1.15	110	1.35	118
AUCss (ug*h/mL)	20.7	60.4	18.5	66.6
t1/2 alpha (h)	2.80	11.1	2.79	13.8
t1/2 beta (h)	15.8	39.9	15.7	38.9
t1/2 eff (h)	13.9	47.8	13.8	46.6
t1/2 abs (h)	0.605	110	0.515	118
Time to SS (days)	3.29	39.9	3.27	38.9

Source: Derived_parameters-fda.docx, 2023-04-03-mk6482-005-pk-exposures.r

Abbreviations: AUCss=area under the plasma concentration-time curve for one dosing interval at steady state based on Dose*F/(CL/F); CL/F=apparent clearance; CV=coefficient of variation; F= bioavailability; GM=geometric mean; KA=absorption rate constant; SS=steady state; t1/2 abs=absorption half-life; t1/2 alpha=initial elimination half-life; t1/2 beta=terminal elimination half-life; t1/2 eff=effective elimination half-life; Vc/F=apparent central volume of distribution; Vd/F=apparent total volume of distribution; Vp/F=apparent peripheral volume of distribution.

Note: Time to SS was determined as 5 times the t1/2 beta.

Source: Table 11 in clinical-information-amendment-01nov2023.

Table 53: Model-predicted PK Exposures for Patients with Advanced RCC in Study 005 and for All Subjects after 120 mg QD

PK Exposures	Study 005		All Studies	
	Geometric Mean (%CV)	**Arithmetic Mean (Stdev)**	**Geometric Mean (%CV)**	**Arithmetic Mean (Stdev)**
AUC Dose 1 (µg·h/mL)	13.4 (39.5%)	14.4 (5.52)	13.4 (41.9%)	14.5 (5.90)
AUC_{ss} (µg·h/mL)	20.6 (60.3%)	24.3 (15.4)	20.4 (61.8%)	24.2 (15.6)
Cmin Dose 1 (ng/mL)	269 (74.9%)	328 (204)	264 (78.6%)	327 (210)
Cmin,ss (ng/mL)	424 (105.4%)	602 (545)	413 (107.3%)	591 (545)
Cmax Dose 1 (ng/mL)	1040 (35.2%)	1100 (349)	1060 (36.3%)	1130 (377)
Cmax,ss (ng/mL)	1500 (43.6%)	1640 (751)	1520 (44.6%)	1660 (772)
Tmax Dose 1 (h)	2.38 (64.0%)	2.93 (2.57)	2.15 (67.9%)	2.68 (2.35)
Tmax at SS (h)	2.21 (54.4%)	2.54 (1.51)	2.01 (59.4%)	2.35 (1.48)

Source: Simulated_exposures.docx, 2023-04-03-mk6482-005-pk-exposures.r

Abbreviations: AUC=area under the plasma concentration-time curve for a 24-hour dosing interval, Cmax=maximum plasma concentration, Cmin=minimum plasma concentration; CV=coefficient of variation; PK=pharmacokinetic; QD=once daily; RCC=renal cell carcinoma; SS=steady state; Stdev =standard deviation; Tmax=time to maximum plasma concentration.

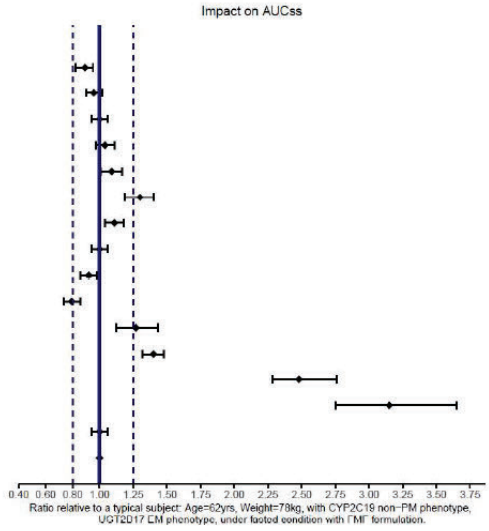
Note: Parameters were derived by simulation of 24-hour PK profiles following 120 mg QD administration at first dose and SS.

Source: Table 14 in the Population PK report 08bqrv.

Figure 10: Univariate Impact of Covariates on $AUC_{0\text{-}24h,ss}$ (A), $C_{max,ss}$ (B) and $C_{min,ss}$ (C) of Belzutifan (Study 005) Compared to a Typical Subject who is a UGT2B17 Extensive Metabolizer

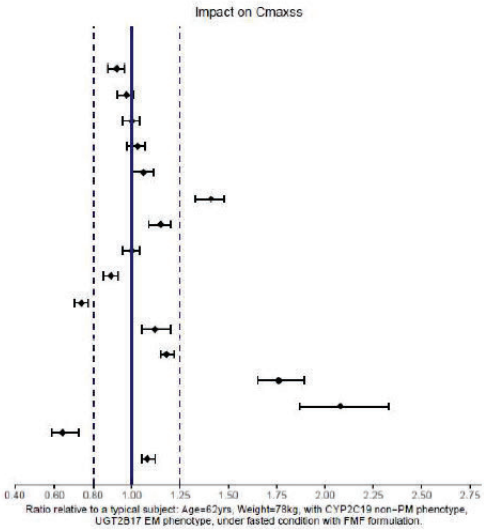
A

Covariate	Percentile	Value	Ratio [90% CI]
Age (years)	5th	45	0.892 [0.823, 0.949]
	25th	55	0.957 [0.899, 1.02]
	50th	62	1 [0.941, 1.06]
	75th	69	1.04 [0.973, 1.11]
	95th	78	1.09 [1.01, 1.17]
Weight (kg)	5th	52	1.3 [1.19, 1.4]
	25th	66	1.11 [1.04, 1.18]
	50th	78	1 [0.941, 1.06]
	75th	89	0.92 [0.859, 0.98]
	95th	112	0.794 [0.734, 0.857]
CYP2C19 phenotype		PM	1.27 [1.12, 1.43]
UGT2B17 phenotype		IM	1.4 [1.32, 1.48]
		PM	2.48 [2.28, 2.76]
UGT2B17 & CYP2C19		PM & PM	3.15 [2.75, 3.65]
Food status		Fed	1 [0.941, 1.06]
Formulation		Formulation A (FFP)	1 [1, 1]



B

Covariate	Percentile	Value	Ratio [90% CI]
Age (years)	5th	45	0.923 [0.875, 0.96]
	25th	55	0.972 [0.924, 1.01]
	50th	62	1 [0.951, 1.04]
	75th	69	1.03 [0.975, 1.07]
	95th	78	1.06 [1, 1.11]
Weight (kg)	5th	52	1.41 [1.33, 1.48]
	25th	66	1.15 [1.09, 1.2]
	50th	78	1 [0.951, 1.04]
	75th	89	0.893 [0.851, 0.93]
	95th	112	0.74 [0.704, 0.774]
CYP2C19 phenotype		PM	1.12 [1.05, 1.2]
UGT2B17 phenotype		IM	1.18 [1.15, 1.22]
		PM	1.76 [1.65, 1.89]
UGT2B17 & CYP2C19		PM & PM	2.08 [1.87, 2.33]
Food status		Fed	0.642 [0.585, 0.725]
Formulation		Formulation A (FFP)	1.08 [1.05, 1.12]



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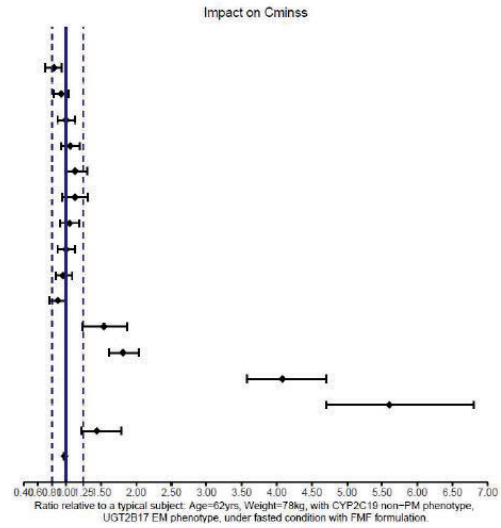


Source: MK6482-005014-pk-forestplot-EM-005-020.pdf, 2023-04-04-mk6482-005-forest.r
Abbreviation: AUCss=area under the plasma concentration-time curve at steady state; CI=confidence interval; CYP=Cytochrome P450; EM=extensive metabolizer; FFP=fit-for-purpose; FMF=final market formulation; IM=intermediate metabolizer; PM=poor metabolizer; UGT=Uridine 5'-diphospho-glucuronosyltransferase.
Note: First and second dashed vertical lines correspond to ratios of 0.8 and 1.25, respectively. The solid vertical line corresponds to a ratio of 1 and represents the typical subject. Points and whiskers represent the median and 90% CI, respectively.

Source: Figure 11 in the Population PK report 08bqrv.

19.4.1.3. PPK Review Issues

No substantive issue.

19.4.1.4. Reviewer's Independent Analysis

Reviewer's independent analysis was not performed.

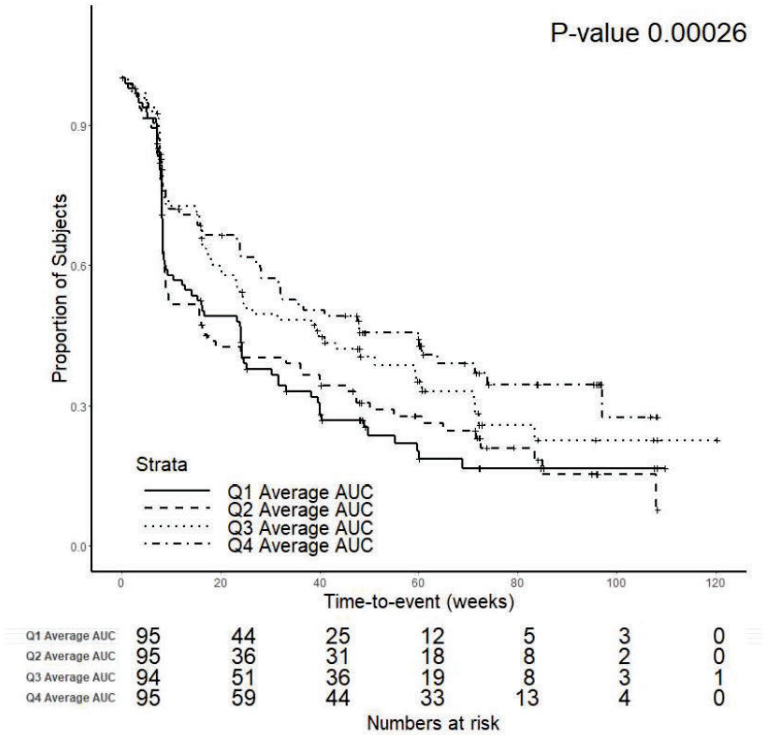
19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

E-R analysis for efficacy is considered exploratory due to immature data for efficacy endpoints including OS and DOR. There was a positive relationship between exposure and efficacy endpoints (PFS, OS). The relationship between belzutifan exposure and efficacy endpoints (ORR, DOR) is not significant. The results of this exploratory analysis should be interpreted with caution.

Figure 11: Kaplan-Meier Curves by AUCavg Quartile for PFS



Source: KM-PFS-AUCss-Study5.png, ER-analysis-31-May-2023.html, ER-analysis-31-May-2023.Rmd
Note: + symbols represent censoring of patients due to study discontinuation or other reasons.
Abbreviations: AUC=area under the plasma concentration-time curve; Average AUC (AUCavg) =steady state AUC based on average dose intensity up to the event; PFS=progression-free survival; Q=quartile

Source: Figure 4 in the ER report 08bvhj.

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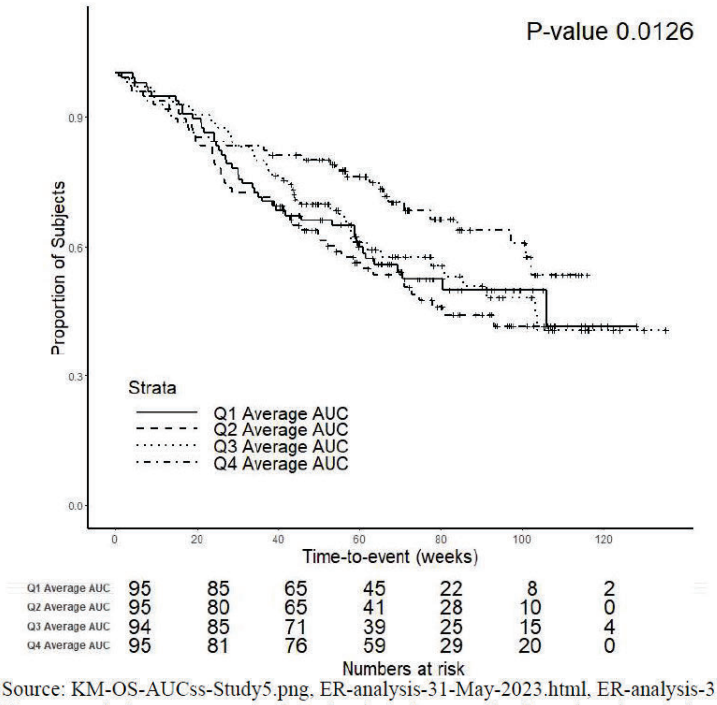
Figure 12: Kaplan-Meier Curves by AUCavg Quartile for OS



Source: KM-OS-AUCss-Study5.png, ER-analysis-31-May-2023.html, ER-analysis-31-May-2023.Rmd
Note: + symbols represent censoring of patients due to study discontinuation or other reasons.
Abbreviations: AUCavgeot=average area under the concentration-time curve until end of treatment; AUC=area under the concentration-time curve; Q=quartile

Source: Figure 5 in the ER report 08bvhj.

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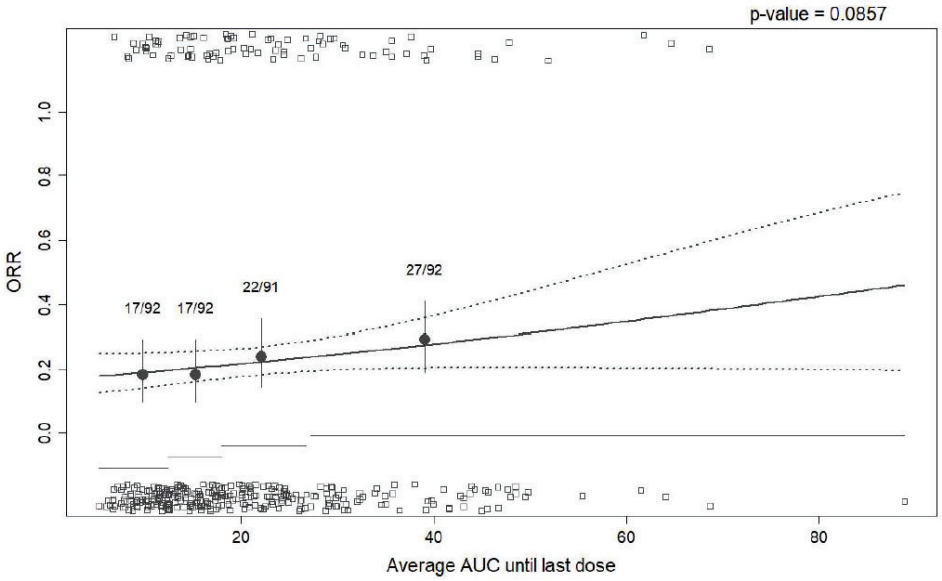
Figure 13: Relationship of ORR vs. AUCavgeot, with ORR Grouped by AUCavgeot Quartiles and a Linear Logistic Regression Fit



Source: QuantilePlot-NOSTRT-ORR-AUCORR-eff.png, ER-analysis-31-May-2023.html, ER-analysis-31-May-2023.Rmd

Note: Open squares represent individual values, represent patients with event (at the top) and patients with no event (at the bottom). Observations were jittered for improved visualization. Numbers depict n/N for each exposure quartile, with n being the number of patients with an event and N being the total number of patients. Solid dots and vertical lines represent incidence and 95% CI of observations at mean exposure within quartile; the solid line represents the logistic regression fit of the form logit(prob[event]) AUC × slope + intercept; dashed lines represent 95% CI; and horizontal lines represent width of exposure quartiles.

Abbreviations: AUC=area under the plasma concentration-time curve; AUCavgeot=steady state AUC based on average dose intensity until end of treatment; CI=confidence interval; ORR=overall response rate, defined as complete response or partial response; RCC=renal cell carcinoma

Source: Figure 6 in the ER report 08bvhj.

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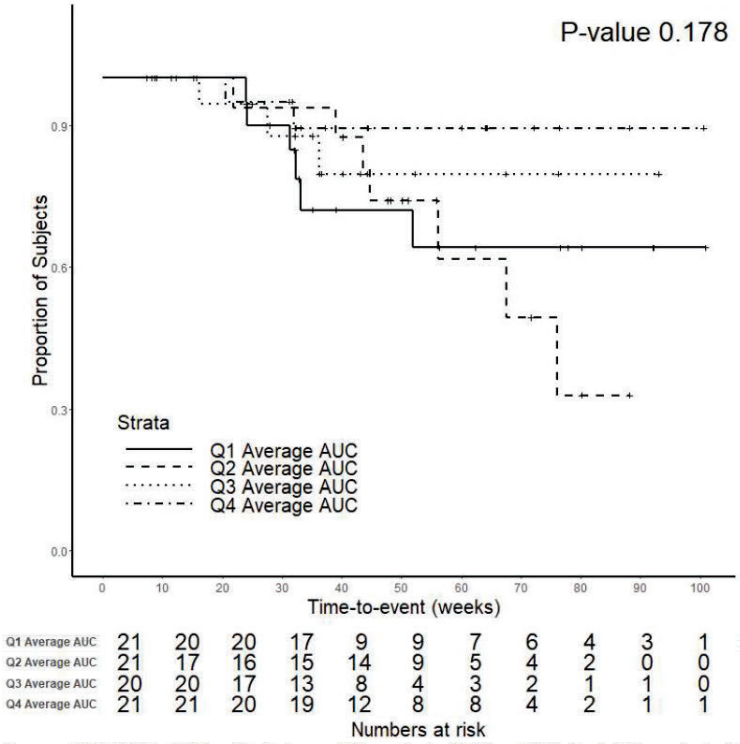
Figure 14: Kaplan-Meier Curves for DOR Stratified by AUCavgeot Quartile



Source: KM-DOR-AUCss-Study5.png, ER-analysis-31-May-2023.html, ER-analysis-31-May-2023.Rmd
Note: + symbols represent censoring of patients due to study discontinuation or other reasons.
Abbreviations: AUCavgeot=average area under the concentration-time curve until end of treatment; AUC=area under the concentration-time curve; Q=quartile

Source: Figure 9 in the ER report 08bvhj.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

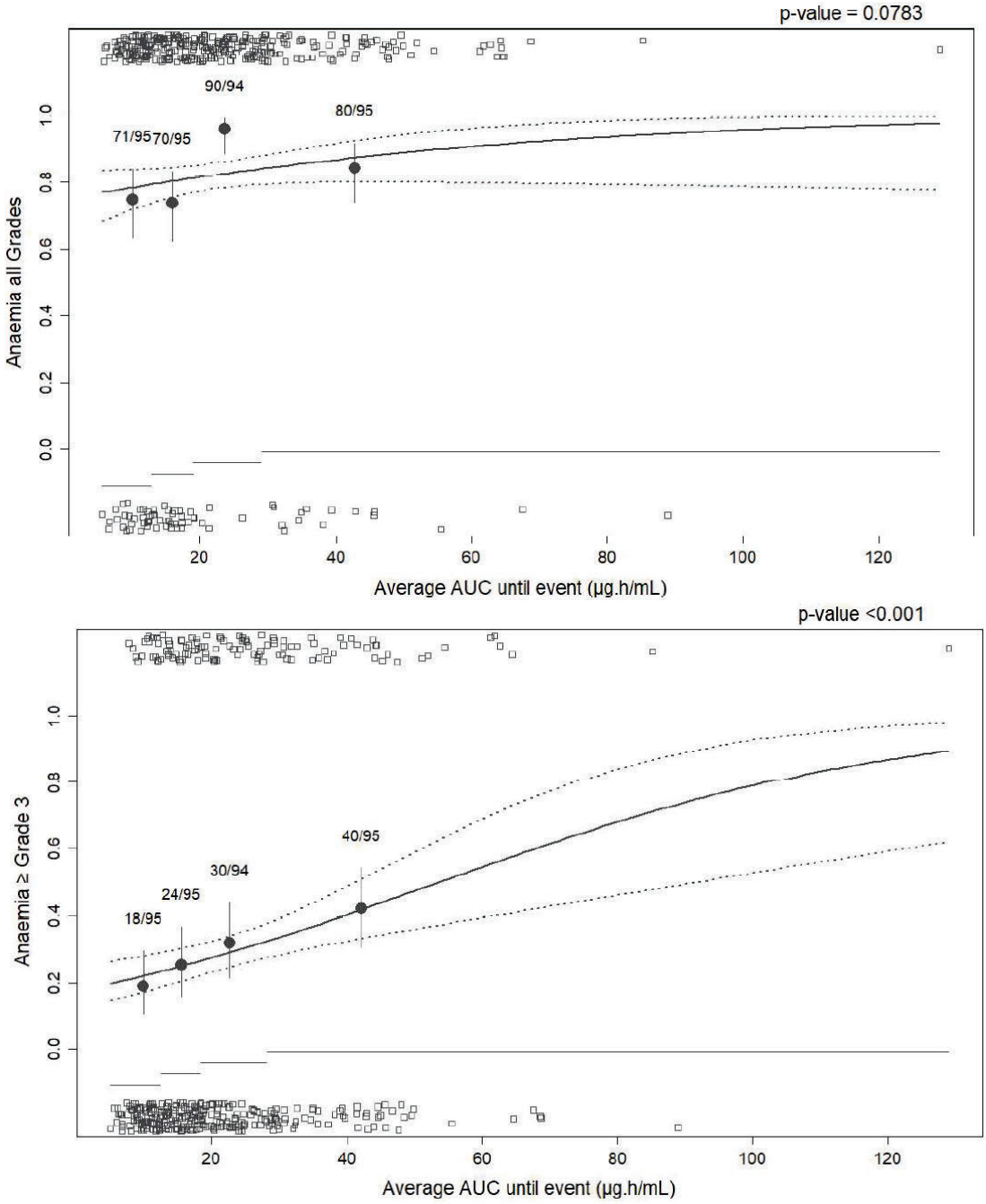
E-R for efficacy has been applied to Study 005, and the results are described in Sec. 6.3.2.

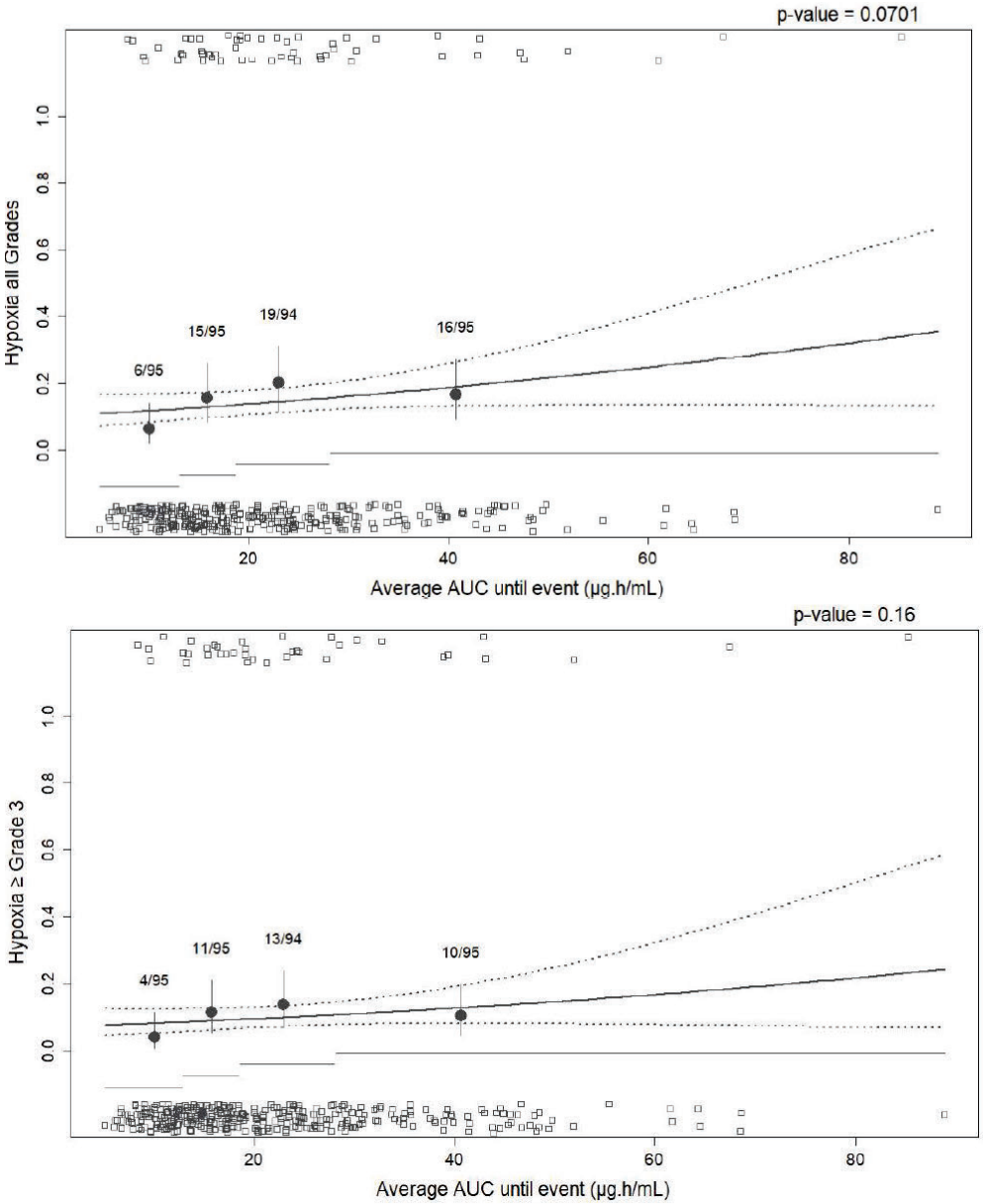
19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:

There was a significant relationship between belzutifan exposure and anemia ≥ grade 3 in patients with advanced RCC. Lower baseline Hgb was associated with a greater risk of anemia. There were no clear E-R relationship between belzutifan exposure and hypoxia.

Figure 15: Incidence of Anemia All Grades, Anemia ≥ grade 3, Hypoxia All Grades and Hypoxia ≥ grade 3 vs. AUCavg, with Incidence Grouped by AUCavg Quartile and a Linear Logistic Regression Fit





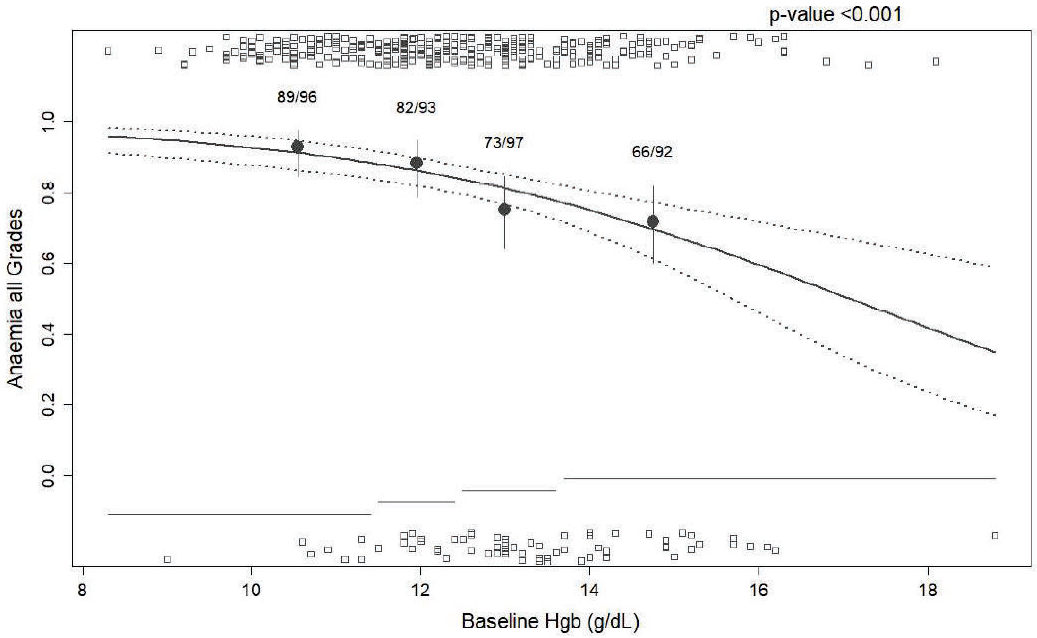
Source: QuantilePlot-NOSTRT-Anaemia-AUCfullAnaemia-allGrades-no.png, QuantilePlot-NOSTRT-Anaemia-AUCfullAnaemia-grade3-no.png, QuantilePlot-NOSTRT-Hypoxia-AUCfullHypoxia-allGrades-no.png, QuantilePlot-NOSTRT-Hypoxia-AUCfullHypoxia-grade3-no.png, ER-analysis-31-May-2023.html, ER-analysis-31-May-2023.Rmd

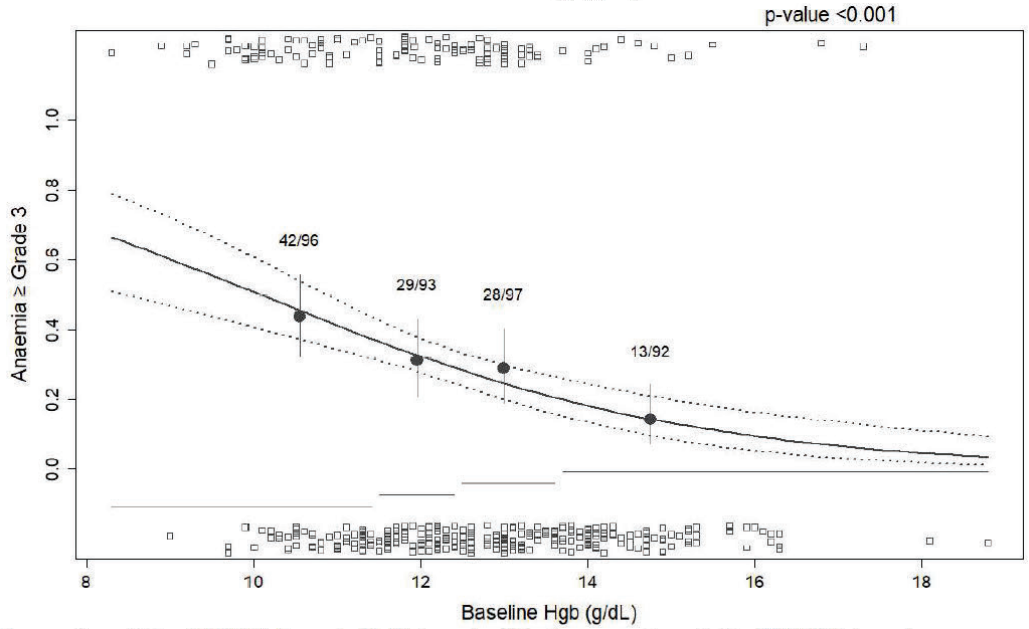
Note: Open squares represent individual values, i.e., patients with event (at the top) and patients with no event (at the bottom). Observations were jittered for improved visualization. Numbers depict n/N for each exposure quartile, with n being the number of patients with an event and N being the total number of patients. Solid dot and vertical line represent incidence and 95% CI of observation at mean exposure within quartile; solid line represents logistic regression fit of the form logit(prob[event]) AUC × slope + intercept; dashed lines represent 95% CI; and horizontal lines represent width of exposure quartiles.

Abbreviations: AUC=area under the plasma concentration-time curve; AUCavg=steady state AUC based on average dose intensity up to the event; CI=confidence interval

Source: Figure 12 in the ER report 08bvhj.

Figure 16: Incidence of Anemia All Grades, Anemia ≥ grade 3 vs. Baseline Hgb, with Incidence Grouped by Baseline Hgb Quartile and a Linear Logistic Regression Fit





Source: QuantilePlot-NOSTRT-Anaemia-BASEAnaemia-allGrades-no.png QuantilePlot-NOSTRT-Anaemia-BASEAnaemia-grade3-no.png, ER-analysis-31-May-2023.html, ER-analysis-31-May-2023.Rmd

Note: Open squares represent individual values, i.e., patients with event (at the top) and patients with no event (at the bottom). Observations were jittered for improved visualization. Numbers depict n/N for each exposure quartile, with n being the number of patients with an event and N being the total number of patients. Solid dots and vertical lines represent incidence and 95% CI of observation at mean exposure within quartile; solid lines represent logistic regression fit of the form logit(prob[event]) AUC × slope + intercept; dashed lines represent 95% CI; and horizontal lines represent width of exposure quartiles.

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; Hgb=hemoglobin

Source: Figure 13 in the ER report 08bvhj.

19.4.2.4. ER (safety) Assessment Summary

The Applicant's Position:

E-R for safety has been applied to Study 005 and the results are described in Sec. 6.3.2. and are consistent with the findings in the original NDA in patients with VHL-RCC.

The FDA's Assessment:

In general, the Applicant's E-R analyses for belzutifan are considered acceptable for the purpose of supporting the objectives of the analyses. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

19.4.2.5. ER Review Issues

No substantive issue.

19.4.2.6. Reviewer's Independent Analysis

Reviewer's independent analysis was not performed.

19.4.2.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

Refer to Sec. 6.3.2.

The FDA's Assessment:

Not Applicable. Refer to other clinical pharmacology sections of the Assessment Aid for the FDA review

19.5. Additional Safety Analyses Conducted by FDA

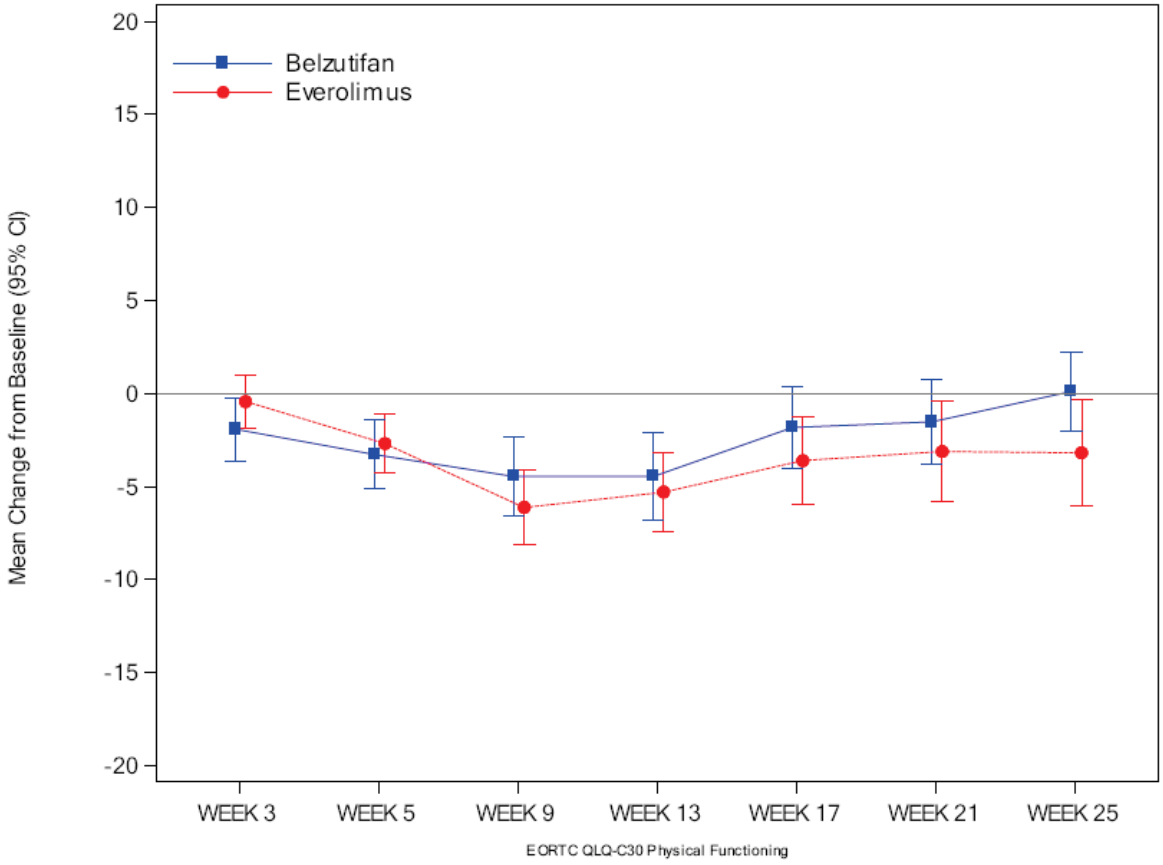
The FDA's Assessment:

No additional safety analyses were conducted by FDA.

19.6. Additional Patient Report Outcomes

Additional supportive PRO data came from the Applicant's IR response date December 5, 2023, and one of the supportive figures is presented below. This figure demonstrates the descriptive mean changes from baseline for the physical functioning subscale for each treatment group and PRO assessment time point. Mean change scores from baseline were stable over time and similar for each treatment arm but show greater worsening in everolimus after week 5. These PRO results further support that everolimus impacted functioning more negatively than belzutifan over time.

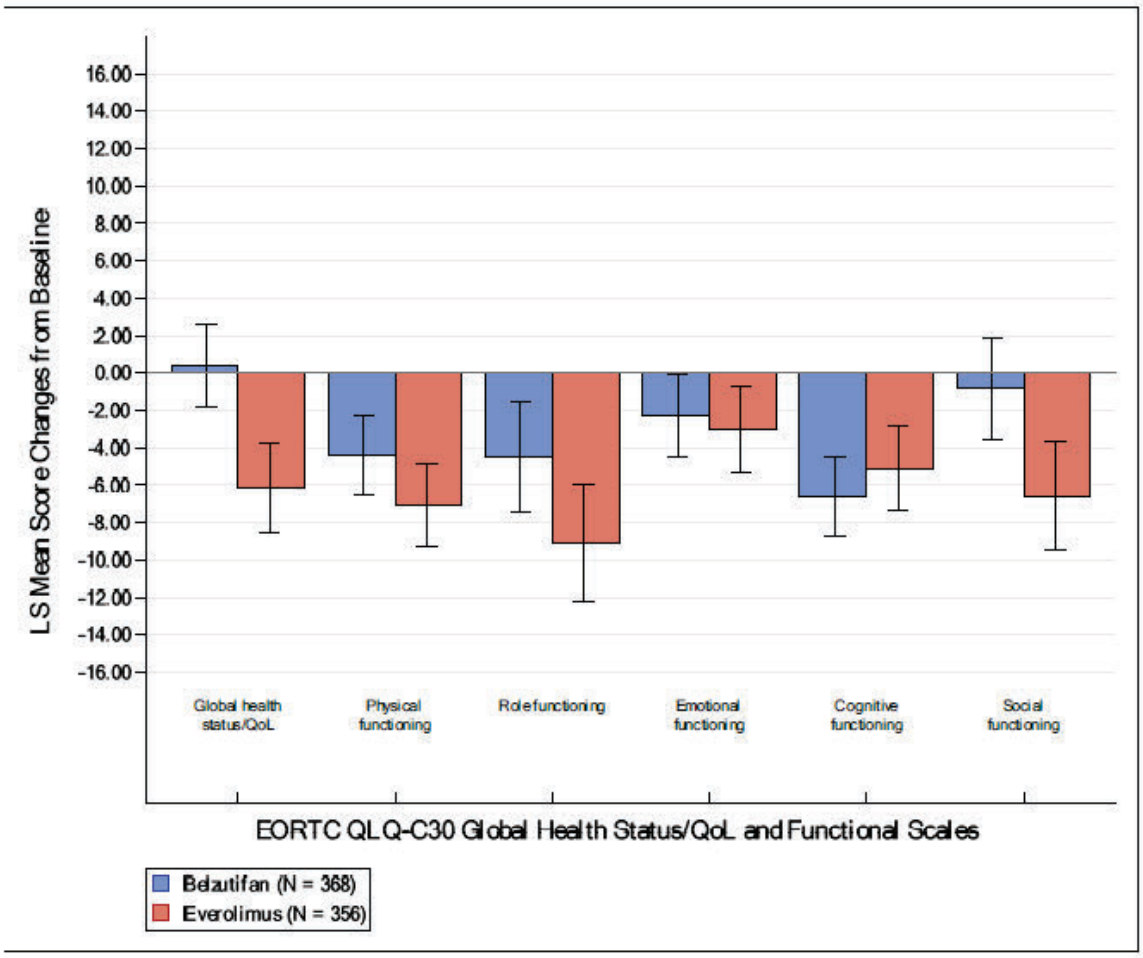
Figure 17: Descriptive Means for Change from Baseline and 95% CI for the EORTC QLQ-C30 Physical Functioning Over Time by Treatment Group (PRO Expected Population)



Number of Subjects							
Belzutifan	318	318	306	264	229	209	197
Everolimus	287	304	286	235	188	158	144

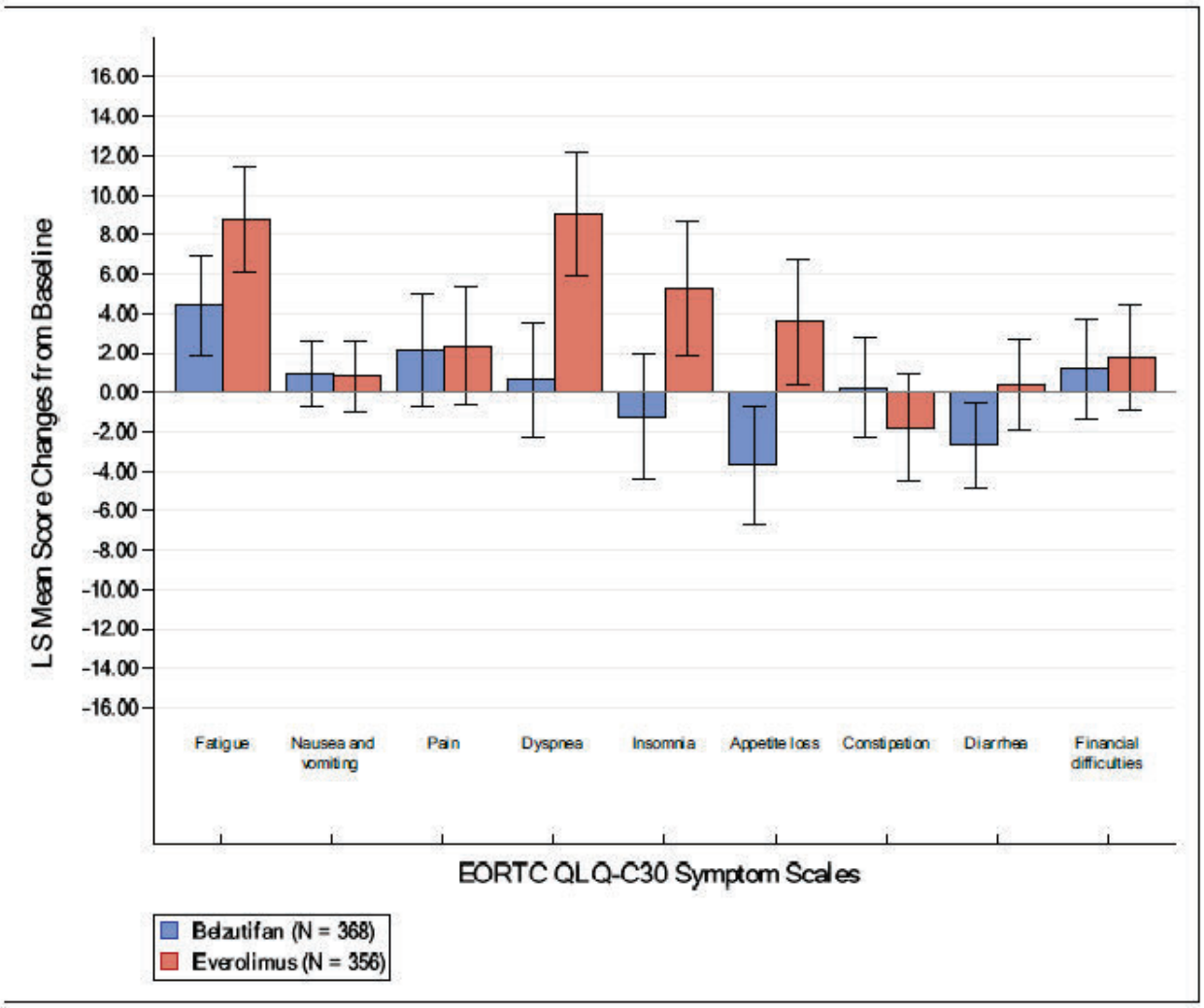
From the Applicant's IR Response dated December 5, 2023 (SDN 447)

Figure 18: LS Mean Change from Baseline to Week 17 and 95% CI in EORTC QLQ-C30 Global Health Status/QoL and Functional Scales (PRO FAS Population)



From Applicant CSR, Figure 11-11

Figure 19: LS Mean Change from Baseline to Week 17 and 95% CI in EORTC QLQ-C30 Symptom Scales (PRO FAS Population)



From Applicant CSR, Figure 11-12

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/s/

CHANA WEINSTOCK
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DANIEL L SUZMAN
10/07/2024 01:38:56 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215383Orig1s006

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 4, 2023

To: Benjamin Chukwurah, Regulatory Health Project Manager, DO1

Chana Weinstock, Associate Director for Labeling

From: Mispa Ajua-Alemanji, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for WELIREG™ (belzutifan) tablets, for oral use

NDA: 215383-S-006

In response to DO1's consult request dated July 21, 2023, OPDP has reviewed the proposed product labeling (PI), Medication Guide (MG) for supplement S-006 for WELIREG™ (belzutifan) tablets, for oral use. This supplement proposes revisions to the drug labeling to include a new indication for the treatment of adult patients with advanced renal cell carcinoma (RCC) following a PD-1 or PD-L1 inhibitor and a VEGF-TKI.

PI and MG: OPDP's comments on the proposed labeling are based on the draft PI and MG received by electronic mail from DO2 on November 20, 2023, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed and comments on the proposed MG were sent under separate cover on November 20, 2023.

Thank you for your consult. If you have any questions, please contact Mispa Ajua-Alemanji at Mispa.Ajua-Alemanji@fda.hhs.gov.

	Statement from Draft (if applicable)	OPDP Comment
HIGHLIGHTS OF PRESCRIBING INFORMATION: ADVERSE REACTIONS	(b) (4)	OPDP notes that the statement of the adverse reactions in the Highlights and order or adverse reactions are inconsistent with the adverse reactions presented in tables in section 6 (see tables 4 and 5). We recommend revising the adverse reactions statement in the Highlights section and section 6 so that it is consistent with the information presented in both tables 4 and 5 and are presented in descending order.
6.1 Clinical Trials Experience	(b) (4)	As previously noted above, please consider revising the adverse reaction statement in section 6.1 so that it is consistent with the information presented in tables 4 and 5 and are presented in descending order.

17 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MISPA L AJUA-ALEMANJI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 28, 2023
To:	Benjamin Chukwurah, PharmD Regulatory Project Manager **Division of Oncology I (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Mispa Ajua-Alemanji, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	WELIREG (belzutifan)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215383
Supplement Number:	S-006
Applicant:	Merck Sharp & Dohme LLC

1 INTRODUCTION

On July 17, 2023, Merck Sharp & Dohme LLC submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their New Drug Application (NDA) 215383/S-006 for WELIREG (belzutifan) tablets. With this supplement, the Applicant proposes an additional indication for the treatment of adult patients with advanced renal cell carcinoma (RCC) following immune checkpoint and anti-angiogenic therapies.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology I (DO1) on July 21, 2023 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for WELIREG (belzutifan) tablets.

2 MATERIAL REVIEWED

- Draft WELIREG (belzutifan) tablets MG received on July 17, 2023, and received by DMPP and OPDP on November 17, 2023.
- Draft WELIREG (belzutifan) tablets Prescribing Information (PI) received on July 17, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 17, 2023, and November 20, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
11/28/2023 10:29:21 AM

MISPA L AJUA-ALEMANJI
11/28/2023 11:29:16 AM

BARBARA A FULLER
11/28/2023 11:33:07 AM

LASHAWN M GRIFFITHS
11/28/2023 12:46:04 PM

LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 17, 2023
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 215383/S-006
Product Name, Dosage Form, and Strength:	Welireg (belzutifan) tablets, 40 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Merck Sharp & Dohme LLC
FDA Received Date:	July 17, 2023 and September 28, 2023
TTT ID #:	2023-5667
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 REASON FOR REVIEW

Merck Sharp & Dohme LLC submitted a Efficacy Supplement for Welireg (belzutifan) tablets to propose the following additional indication: *treatment of adult patients with advanced renal cell carcinoma (RCC) following immune checkpoint and anti-angiogenic therapies*. Subsequently, the Division of Oncology 1 (DO1) requested that we review the proposed Welireg prescribing information (PI) and Medication Guide (MG) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed changes to Section 2 Dosage and Administration section of the Welireg PI and determined that the proposed changes are acceptable from a medication error perspective. We note that there are no changes to Section 3 Dosage Forms and Strengths, Section 16 How Supplied/Storage and Handling, and Section 17 Patient Counseling Information. We reviewed the proposed changes to Welireg Medication Guide and find them acceptable from a medication error perspective. Additionally, our routine postmarket safety surveillance did not identify any medication errors related to labels and labeling that is relevant for this review. Therefore, we have no recommendations for the proposed Welireg PI and Medication Guide from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The proposed Welireg PI and Medication Guide are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

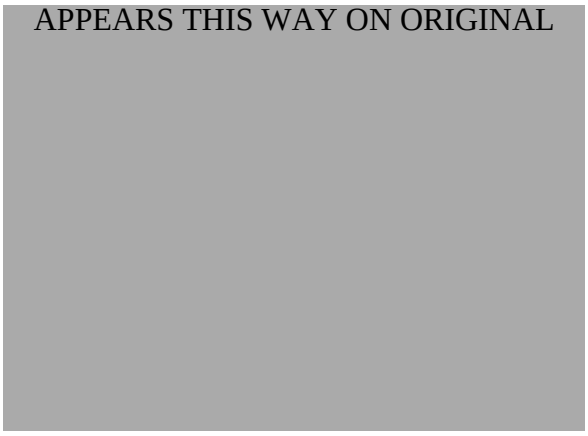
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Welireg received on September 28, 2023 from Merck Sharp & Dohme LLC.

Table 2. Relevant Product Information for Welireg	
Initial Approval Date	8/13/2021
Active Ingredient	belzutifan
Indication	Currently approved: • for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. Proposed addition: • for treatment of adult patients with advanced renal cell carcinoma (RCC) following immune checkpoint and anti-angiogenic therapies
Route of Administration	oral
Dosage Form	tablets
Strength	40 mg
Dose and Frequency	120 mg administered orally once daily with or without food. The recommended dose reductions for adverse reactions are: • First dose reduction: WELIREG 80 mg orally once daily • Second dose reduction: WELIREG 40 mg orally once daily • Third dose reduction: Permanently discontinue
How Supplied	Bottles of 90 tablets
Storage	Store at 20°C to 25°C (68°F to 77°F)
Container Closure	100 cc high density polyethylene (HDPE) bottle with induction seal closure and desiccant

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 14, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Welireg. Our search identified 1 previous review[a], and we considered our previous recommendations to see if they are applicable for this current review.



[a] Gao, T. Label and Labeling Review for Welireg (NDA 215383). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Apr 14. OSE RCM No.: 2021-52.

APPENDIX F. LABELS AND LABELING

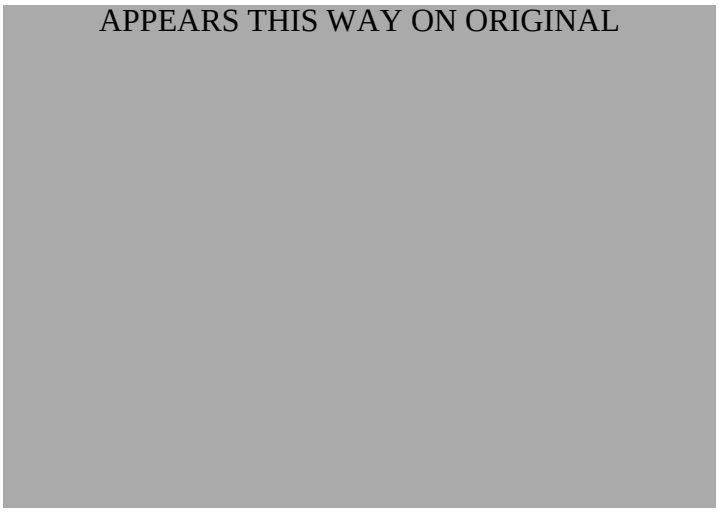
F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Welireg labels and labeling submitted by Merck Sharp & Dohme LLC.

- Prescribing Information (Image not shown) received on September 28, 2023, available from \\CDSESUB1\EVSPROD\nda215383\0421\m1\us\02-wrm-uspi-mk6482-t-rcc2.doc
- Medication Guide received on July 17, 2023, available from \\CDSESUB1\EVSPROD\nda215383\0385\m1\us\01-wrm-usmg-mk6482-t-rcc2.doc

F.2 Label and Labeling Images

N/A



[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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ASHLEIGH V LOWERY
10/24/2023 10:15:24 AM

Clinical Inspection Summary

Date	November 15, 2023
From	Yang-Min (Max) Ning, M.D., Ph.D. Min Lu, M.D., M.P.H. Jenn Seller, M.D., Ph.D. GCPAB/DCCE/OSI/CDER
To	Jaleh Fallah, M.D. Brian Heiss, M.D. Chana Weinstock, M.D. Benjamin Chukwurah, RPM DO1/OOD/CDER
NDA #	215383-S6
Applicant	Merck Sharp & Dohme Corp.
Drug	Belzutifan (MK-6482)
NME (Yes/No)	No
Therapeutic Classification	Inhibitor of hypoxia-inducible factor-2α
Proposed Indication	Treatment of adult patients with advanced renal cell carcinoma following immune checkpoint and anti-angiogenic therapies
Consultation Date	08/08/2023
Summary Goal Date	11/09/2023; extended to 11/17/2023
Action Goal Date	12/08/2023
PDUFA Date	01/17/2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from an ongoing Phase 3 trial (Protocol 6482-005) were submitted to the Agency in support of a supplemental New Drug Application (sNDA) for belzutifan for the indication as described above. Three participating clinical investigators [Drs. Pooja Ghatalia (Site #1506), Walter Stadler (Site #1539), and Elaine Lam (Site #1540)] in the trial were inspected.

The inspections identified no significant regulatory violations in the conduct of this trial by the three investigators. Subjects enrolled and randomized at the investigator sites were found to have met the protocol-specified eligibility criteria and the Applicant's submitted clinical data for these subjects were verifiable with source records reviewed at the sites. There was no evidence of underreporting of adverse events. Overall, the inspection results show that the clinical data generated from these investigator sites are reliable and acceptable for this sNDA.

II. BACKGROUND

Belzutifan has been approved and marketed in the United States since 2021 for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated renal cell carcinoma (RCC), central nervous system hemangioblastomas, or pancreatic neuroendocrine tumors, not requiring immediate surgery. The investigational name of this product was MK-6482 under IND 132120. For this sNDA, the Applicant submitted data from an ongoing Phase 3 trial (Study Protocol 6482-005) and proposed a new indication for belzutifan in patients with advanced RCC who have received both immune checkpoint and anti-angiogenic therapies.

Study 6482-005 [NCT04195750] is a randomized (1:1), open-label, active-controlled trial of belzutifan versus everolimus in subjects with unresectable, locally advanced or metastatic clear cell RCC who had disease progression on or after prior systemic treatments with both a programmed cell death-1/ligand 1 (PD-1/L1) checkpoint antibody and a vascular endothelial growth factor (VEGF) receptor targeted tyrosine kinase inhibitor (TKI), administered either in combination or in sequence. The study has co-primary endpoints, progression-free survival (PFS), as assessed by blinded independent radiology review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and overall survival (OS).

Subjects were required to have: 1) received at least 2 doses of a PD-1/L1 antibody and had radiographic disease progression during or after treatment with a PD-1/L1 antibody and/or a VEGF receptor targeted TKI; 2) had measurable disease per RECIST 1.1 at study entry, as assessed by the Investigator or local radiology; 3) had no more than 3 prior systemic regimens for locally advanced or metastatic RCC; 4) had adequate organ function as specified for the bone marrow, liver, kidney, and other parameters in the protocol. Eligible subjects consented for the study were to be randomized (1:1) to receive either belzutifan or everolimus. Randomization was stratified by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic scores (0, 1-2, or 3-6) and number of prior VEGF receptor targeted TKI for advanced RCC (1 or 2-3).

Following randomization and treatment assignment, subjects were planned to receive belzutifan 120 mg orally once daily or everolimus 10 mg orally once daily. Study treatment was to be continued until disease progression, unacceptable toxicity, consent withdrawal, or other conditions as specified in the protocol. Crossover between treatment arms was not planned for the study.

For the co-primary endpoint PFS, tumor imaging was to be performed with computed tomography (CT)/magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis plus other regions [i.e., bone scan and brain scan as protocol-specified] at Screening (baseline), Week 9 (±7 days) from the date of randomization, then every 8 weeks (±7 days) through Week 49 (±7 days), and thereafter every 12 weeks (±7 days). Imaging scans were to be continued until disease progression as verified by BICR, initiation of a new anticancer treatment, consent withdrawal, death, or occurrence of other pre-specified conditions in Section 8.2 of the protocol. Subjects who discontinued study treatment due to other reasons (e.g., unacceptable toxicity) were to have imaging assessments conducted per the protocol-defined schedules.

For the co-primary endpoint OS, subjects' survival status was to be followed approximately every 12 weeks in the Survival Follow-up Phase (i.e., after verification of disease progression, start of a new anticancer treatment, or conclusion of the study).

For safety assessments, adverse events and protocol-required examinations and laboratory tests were to be collected, monitored, and/or conducted according to "Schedule of Activities" in Table 1.3 of the protocol. All adverse events and changes in laboratory values were to be assessed by the investigator and graded for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

From 02/27/2020 through 11/01/2022 [data cutoff date for analyses included in the current submission], the study enrolled 746 subjects from 146 investigator sites across 23 countries. Seventeen percent (N=129) of the subjects were recruited from 25 sites in the United States. Of the total enrolled, 374 subjects were randomized to the belzutifan arm and 372 to the everolimus arm. Following randomization, 372 subjects received belzutifan and 360 received everolimus as assigned. These treated subjects were included in the safety analysis. For analyses of the efficacy endpoints, all the randomized subjects were included. This study was ongoing as of the data cutoff date of 11/01/2022.

III. RESULTS

1. **Pooja Ghatalia, M.D. (Site #1506)**
   333 Cottman Avenue
   Philadelphia, PA 19111

   Dr. Ghatalia was inspected on September 5-11, 2023, as a surveillance and data audit for Study 6482-005. For the investigator, this was the initial FDA inspection. The site enrolled 16 subjects into the study, with 6 subjects randomized to the belzutifan arm and 10 to the everolimus arm. Following randomization, two subjects (b) (6) (b) (6) in the everolimus arm withdrew their consent and received no study treatment as assigned. As of the data cutoff date of 11/01/2022, one subject (b) (6) in the belzutifan arm remained on study treatment and the rest of subjects in the two arms were discontinued from study treatment due to disease progression or adverse event. At the time of this inspection, the study was active at the site, with the most recent subject visit documented on (b) (6)

   Source records for all the randomized subjects were reviewed and compared with the Applicant's submitted data for the site. Subjects' records reviewed during the inspection included, but were not limited to, the informed consent forms, eligibility documentation, screening and enrollment log, randomization allocation and study treatment administered, study visits, tumor assessments, survival status, adverse events (AE) and serious adverse events (SAE), concomitant medications, and protocol deviations. Documents for the administration and oversight of this study at the site were also examined, including the institutional review board (IRB) approvals of the study protocol/amendments and informed consent forms and related continuing reviews,

delegation of authority log, training performed, Form FDA 1572s, financial disclosures, study monitoring activities, investigational product accountability, and data entry into the Electronic Data Capture (EDC) system [i.e., InForm version 4.6.6.] used for this study.

The inspection found that the investigator has properly conducted the study per protocol and its amendments, with no compliance issues identified. All the enrolled subjects were found to have met the eligibility criteria, received study treatment as planned (except for the above-described two subjects who withdrew their consent), and had protocol-specified assessments performed as scheduled. The Applicant's submitted clinical data for these subjects were verifiable with source records examined at the site, with no discrepancies noted. There was no evidence of underreporting of AEs or protocol deviations.

2. Walter Stadler, M.D. (Site #1539)
5841 South Maryland Avenue MC 2115
Chicago, IL 60637

Dr. Stadler was inspected on September 11-14, 2023, as a surveillance and data audit for Study 6482-005. This was the first FDA inspection of the investigator. The site enrolled 11 subjects into the study, with 8 subjects randomized to the belzutifan arm and 3 to the everolimus arm. All the randomized subjects received study treatment as assigned. As of the data cutoff, one subject (b) (6) in the belzutifan arm remained on study treatment and the rest of subjects in both arms were discontinued from study treatment due to disease progression, consent withdrawal, or adverse event. As of the inspection, the site was actively conducting the study, with continuation of belzutifan treatment for the same subject (b) (6) since the subject randomization in September 2021.

Source records for all the 11 enrolled subjects were audited and compared relevant data with the submitted clinical data for this site. Records reviewed during the inspection included the informed consents, case history and progress notes, eligibility criteria, enrollment and randomization, study visits, protocol-required scans and RECIST assessments, survival status, AEs and SAEs, laboratory tests, concomitant drugs, protocol deviations, and case report forms. The inspection also reviewed site's documents for the conduct and oversight of this study at the site, including the IRB's approvals and correspondence related to the study protocol and amendments, training activities, signed Form FDA 1572, financial disclosures, authorized access to the EDC system InForm and data entry management, control of the investigational product, monitoring visits, and reports to the sponsor.

The inspection identified no significant regulatory violations in Dr. Stadler's conduct of this study at the site. The Applicant's submitted data were verifiable with source records examined at the site. There was no evidence of underreporting of AEs but evidence of delayed reporting of an SAE (i.e., Grade 3 pericardial effusion in Subject (b) (6) not reported until 7 weeks after the site's initial awareness) and an AE

(i.e., a COVID-19 infection event in Subject [redacted] was entered in the EDC system 5 months after the source record documentation). Dr. Stadler acknowledged the delayed reporting issues and promised to evaluate the reporting process to prevent them from reoccurring in the future.

Reviewer's Comments: Subject [redacted] received belzutifan in the study and was hospitalized for Grade 3 pericardial effusion based on the collected source record. This SAE occurred on [redacted] and resolved on [redacted] but was not reported to the sponsor until [redacted] The documented time points for this event at the site are consistent with the Applicant's submitted data. In addition, severe pericardial effusion that was observed in both arms has been included in the submitted clinical study report.

3. Elaine Lam, M.D. (Site #1540)
12631 E. 17th Avenue
Aurora, CO 80045

Dr. Lam was inspected from October 30 through November 3, 2023, as a surveillance and data audit for Study 6482-005. For the investigator, this was the first FDA inspection. The site enrolled 11 subjects into the study, with 3 subjects randomly assigned to the belzutifan arm and 8 to the everolimus arm. Following randomization, one subject [redacted] on the everolimus arm withdrew and receive no study treatment with everolimus as planned. As of the data cutoff date, one subject [redacted] in the everolimus arm remained on study treatment and the rest of subjects in both arms were discontinued due to disease progression or adverse event. At the time of this inspection, the study was ongoing at the site, with Subject [redacted] actively on treatment with everolimus (i.e., from [redacted] per site's Enrollment Report).

The inspection reviewed source records for all the 11 subjects and compared source data with the Applicant's submitted data for the site. Subjects' records reviewed during the inspection included the signed informed consents, eligibility assessment forms, enrollment and randomization log, protocol-specified visits and assessments, survival status, AEs, laboratory tests, case report forms, and protocol deviations. In addition, the inspection covered the authority and administration of the clinical trial at the site, including the IRB's approvals of the study protocol and amendments as well as the corresponding informed consents, Delegation of Authority log, training for the study, Form FDA 1572s, financial disclosures, monitoring activities, data entry into the EDC system InForm, accountability of the investigational product, and reports to the sponsor.

The inspection revealed no significant regulatory violations at the site. All the enrolled subjects were found to have met the eligibility criteria and the reported efficacy data for these subjects were consistent with source data documented at the site. All adverse events were found to have been properly documented, assessed, and reported to the sponsor.

{See appended electronic signature page}

Yang-Min (Max) Ning, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Lead
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Jenn Seller, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Room
Review Division/Division Director
Review Division/Project Manager
Review Division/Clinical Team Lead
Review Division/Clinical Reviewer
OSI/Office Director
OSI/DCCE/Division Director
OSI/DCCE/Acting Branch Chief
OSI/DCCE/Team Lead
OSI/DCCE/GCP Reviewer
OSI/ GCP Program Analysts
OSI/Database PM

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YANGMIN NING
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JENN W SELLERS
11/15/2023 12:00:32 PM