CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215383Orig1s000

MULTI-DISCIPLINE REVIEW

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

NDA Multi-disciplinary Review and Evaluation

FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA). While the application review is completed by the FDA, the application is still under review at the other regulatory agencies.

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Application Type	NDA
Application Number(s)	215383
Priority or Standard	Priority
Submit Date(s)	January 15, 2021
Received Date(s)	January 15, 2021
PDUFA Goal Date	September 15, 2021
Division/Office	DO1/OOD/OND/CDER
Review Completion Date	August 12, 2021
Established Name	Belzutifan
(Proposed) Trade Name	Welireg
Pharmacologic Class	Hypoxia-inducible factor inhibitor
Applicant	Merck Sharp & Dohme Corp.
Formulation(s)	Tablets
Dosing Regimen	120 mg, orally, once daily (three 40 mg tablets)
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with Von Hippel-Lindau disease (VHL)-associated renal cell carcinoma (RCC), not requiring immediate surgery.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma, central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
PLT=Patient Labeling Team
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
DPV=Division of Pharmacovigilence

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Project Orbis #27 - Medicines and Healthcare products Regulatory Agency (MHRA; United Kingdom) Review team	
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GLOSSARY

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AUC	area under the curve
BID	twice daily
BLA	biologics license application
BMI	body mass index
BOR	best overall response
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BTD	breakthrough therapy designation
CBER	Center for Biologics Evaluation and Research
ccRCC	clear cell renal cell carcinoma
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
Cmax	maximum concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COA	clinical outcome assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRSD	cumulative running safety dataset
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DCR	disease control rate
DDI	drug-drug interaction
DMC	data monitoring committee
DMF	Drug Master File
DOR	duration of response
DO1	Division of Oncology 1
ECG	electrocardiogram
eCTD	electronic common technical document
EOP2	End of Phase 2
EPO	erythropoietin
E-R	exposure-response

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ESA	erythropoiesis-stimulating agent(s)
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
FFP	fit for purpose
FMF	final market formulation
FMI	final market image
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM	geometric mean
GRMP	Good Review Management Practice
hERG	human ether-á-go-go related gene
Hgb	hemoglobin
HIF-2α	hypoxia-inducible factor 2-alpha
IC_{50}	half-maximal inhibitory concentration
ICH	International Conference on Harmonization
IND	Investigational New Drug
(i)PSP	(initial) Pediatric Study Plan
IRC	independent review committee
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LGR	linear growth rate
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NOAEL	no-observed adverse-effect level
OCS	Office of Computational Science
ODD	Orphan Drug Designation
OOPD	Office of Orphan Products Development
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics

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PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PM	poor metabolizer
PMC	postmarketing commitment
PMR	postmarketing requirement
pNET	pancreatic neuroendocrine tumor
pop-PK	population pharmacokinetics
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QD	once daily
RBC	red blood cell
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
REMS	risk evaluation and mitigation strategy
RP2D	recommended Phase 2 dose
rINN	recommended international nonproprietary name
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment-emergent adverse event
Tmax	time of maximum concentration
TTR	time to response
US	United States
USAN	United States Adopted Name
VEGF	vascular endothelial growth factor
VHL	Von Hippel-Lindau
WHO	World Health Organization
WOCBP	woman of childbearing potential
WONCBP	woman of non-childbearing potential
WRO	written response only

3 EXECUTIVE SUMMARY

3.1 Product Introduction

Belzutifan (Welireg) is a hypoxia inducible factor (HIF)-2α inhibitor that is a first-in class, new molecular entity and that has not previously received marketing approval for any indication from any regulatory body. Approval of belzutifan represents the first approval of a drug that specifically targets the HIF-2a pathway.

Belzutifan is being evaluated for the treatment of patients with Von Hippel-Lindau disease (VHL)-associated renal cell carcinoma (RCC) as well as other VHL-associated malignancies. The Applicant submitted clinical pharmacology, nonclinical pharmacology, pharmacokinetic, and toxicology studies in support of this new drug application (NDA).

The Applicant's proposed indication for the NDA was:

> *WELIREG is indicated for the treatment of patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), not requiring immediate surgery.*

FDA's recommended indication is:

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

The dosing regimen proposed for belzutifan is 120 mg, orally, once daily (three 40 mg tablets).

Belzutifan was initially developed by Peloton Therapeutics Inc, and after initiation of the phase 2 study, MK-6482-004, was acquired by Merck.

3.2 Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for this application is obtained from the ongoing, single-arm, international Phase 2 study MK-6482-004 that enrolled patients with VHL disease-associated RCC.

Patients with VHL disease are at risk for developing tumors that affect various organs, including RCC, CNS hemangioblastoma, pNET, and retinal hemangioblastoma. Surgeries and procedures to treat these tumors may be associated with morbidity including renal insufficiency and CNS deficits. There is no medical therapy approved for this indication, and this represents a population of patients for which an unmet medical need exists.

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Enrollment criteria for MK-6482-004 included at least 1 measurable solid RCC tumor and no RCC tumor >3.0 cm that required immediate surgery, diagnosed radiologically and/or histologically. Patients may have had VHL disease-associated tumors in other organs. The trial excluded those who received prior systemic anticancer therapy and those with metastatic disease. The primary endpoint was ORR in VHL disease-associated RCC using RECIST v1.1 per IRC, and the major secondary endpoint was duration of response (DOR). Evaluation of efficacy in VHL disease-associated non-RCC tumors (retinal and CNS hemangioblastomas, pancreatic, adrenal, endolymphatic sac tumor and epididymal cystadenomas) was included as one of several secondary endpoints.

For the 61 patients enrolled in MK-6482-004, the median tumor size and range for RCC lesions at study entry was 2.2 cm (1.0-6.1). Nine patients per investigator and 18 patients per IRC (7 patients in common in both assessments) had at least 1 RCC tumor that was ≥ 3.0 cm in diameter. Most of these patients were not diagnosed immediately prior to enrollment. The median time from diagnosis of VHL-associated RCC to enrollment on MK-6482-004 was 17.9 months (range 2.8 - 96.7). VHL-RCC is slow-growing with median linear growth rate (LGR) of 3-4 mm/year and many of the patients did not require any treatment for several years after diagnosis. Seventy-seven percent of patients had prior surgical procedures for RCC, including 52% with prior nephrectomy. Diagnosis was confirmed histologically in 62% of patients for the lesion that led to trial enrollment; all patients enrolled in the trial had a germline VHL mutation identified by a variety of local tests. Diagnosis of the RCC lesion that led to trial enrollment was made radiologically in all cases by the presence of a solid enhancing lesion located in the kidney in CT scan or MRI.

ORR per IRC review based on an updated data cutoff date with a median follow-up time of 21.8 months (range 4.2, 30.1) was 49.2%% (36.1, 62.3). All responses were partial responses. All patients who responded had a minimum follow up of 18 months from treatment initiation. Median duration of response was not reached (range 2.8+ to 22.3+ months). Two patients had progressive disease, and 6 others had disease that increased by at least 20% prior to the DCO date but whose disease hadn't reached the minimum of a 5 mm increase needed to qualify for RECIST V1.1 progression, as lesions were small overall. One patient underwent surgery despite a best response of SD per IRC. The protocol did not specify any objective criteria in terms of when a patient would be referred for surgery or other procedures.

All patients enrolled in MK-6482-004 had other VHL-associated non-RCC tumors, although the study was not primarily designed to evaluate efficacy in these tumors. The sponsor elected to pursue IRC review of CNS and retinal hemangioblastomas and pancreatic lesions including pNET after enrollment was completed. ORR for 12 patients with evaluable pNET was 83% (51.6%, 97.9%) and was 62.5% (4.2, 30.1) for 24 patients with evaluable CNS hemangioblastomas. Median duration of response was not reached, with a median follow-up time of 22 months. There were major issues with accurate measurement of retinal hemangioblastomas (b) (4)

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(b) (4)

Although responses were seen in non-pNET pancreatic tumors, these responses were not considered of sufficient clinical relevance (b) (4).

To better assess the natural history of VHL-associated RCC, and to put the RCC-specific responses into context, a supportive analysis was conducted of the linear growth rate (LGR) of RCC lesions in these 61 patients. This analysis found that for patients enrolled in MK-6482-004 the overall median LGR before treatment was approximately 3.63 mm/year. After treatment with MK-6482, the median LGR was -4.48 mm/year.

Safety data for belzutifan in patients with VHL-disease associated RCC (n=61) are obtained primarily from MK-6482-004. In addition, supportive safety data was analyzed from patients who received belzutifan at 120 mg (n=58) in MK-6482-001, a Phase 1, dose-escalation and expansion study in patients with advanced solid tumors that progressed or that was intolerant to standard of care and/or approved treatment options. The median duration of exposure was longer in MK-6482-004 (68 weeks) vs. MK 6482-001 (25 weeks). Patients in MK-6482-001 were older, more heavily pre-treated with anticancer therapies, had metastatic disease, and had more chronic co-morbidities vs. patients in MK-6482-004.

No patients died from study drug toxicity on either study, although one patient died of a fentanyl overdose on MK-6482-004. The most common ($\geq$ 25%) adverse reactions including laboratory abnormalities were decreased hemoglobin, anemia, fatigue, increased creatinine, headache, dizziness, increased glucose, and nausea.

Anemia and hypoxia on-target adverse effects of belzutifan and are labeled as Warnings and Precautions in belzutifan product labeling. The presumed mechanism of belzutifan-induced anemia suggests that erythropoiesis stimulating agents (ESAs) would be expected to provide mitigation; however, secondary malignancies are a known adverse effect of ESAs, and patients with VHL disease are already at heightened risk for a variety of new malignancies. Because of this risk, the use of ESAs in patients who develop anemia while taking belzutifan was not recommended in product labeling for belzutifan.

The degree of embryofetal toxicity seen in nonclinical studies of belzutifan was comparable to that observed with many oncology drug products approved in recent years; however, the patient population for whom belzutifan will be indicated is young and the expected duration of exposure is long. Further, drug-drug interactions with belzutifan may render some hormonal contraceptives ineffective. Because of these considerations, the review team placed a boxed warning for embryofetal toxicity in the product label in addition to having this as a Warning and Precaution.

All disciplines were in favor of regular approval of belzutifan. Extended follow-up of patients on MK-6482-004 for safety will be required as a PMR and extended follow-up for efficacy will serve

as a PMC. Submission of results of a clinical trial further evaluating efficacy of belzutifan in patients with VHL disease-associated non-RCC tumors such as pheochromocytoma/ paraganglioma and pNET will serve as a PMC. Safety PMRs, to be conducted under SPA agreements, will evaluate carcinogenicity in mice and rats.

This application was reviewed under Project Orbis in conjunction with MHRA, TGA, and Health Canada.

3.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Patients with VHL disease are at risk for developing tumors affecting various organs, including RCC, CNS hemangioblastoma, pNET, and retinal hemangioblastoma. Surgeries and procedures to treat these tumors may be associated with morbidity including renal insufficiency and CNS deficits. This represents a population of patients for which an unmet medical need exists.

Belzutifan is a breakthrough-therapy designated HIF-2α inhibitor evaluated in the single-arm Phase 2 study MK-6482-004, which enrolled 61 patients with VHL-associated RCC, with no tumor >3.0 cm requiring immediate surgery. Patients may have had VHL disease-associated tumors in other organs. Efficacy was assessed via independently-determined confirmed response rate and duration of response in patients who received belzutifan at a dose of 120 mg daily, the proposed dose for approval. Data from an additional 58 patients in study MK-6482-001, which evaluated belzutifan in patients with advanced solid tumors, were also reviewed for a comprehensive safety evaluation of the dose under review.

The IRC-assessed ORR with a median follow-up time of 22 months (range 4.2, 30.1) was 49.2%% (36.1, 62.3) for VHL-RCC; all partial responses. Median DoR was not reached (range 2.8+ to 22.3+ months). Responses were also seen in other VHL-associated non-RCC tumors, including an ORR of 83% (51.6%, 97.9%) for 12 patients with evaluable pNET and an ORR of 62.5% (4.2, 30.1) for 24 patients with evaluable CNS hemangioblastomas; these tumor types will be included in the indication statement along with RCC. Median DoR for measurable pNET and CNS hemangioblastomas was also not reached, with a median follow-up time of 22 months. Data on retinal hemangioblastomas (b) (4) issues with accurate measurement, and responses seen for non-pNET pancreatic tumors were not considered of sufficient clinical relevance (b) (4).

The safety profile of belzutifan is acceptable in this setting. No patients died from study drug toxicity on MK-6482-004 although one patient died of a fentanyl overdose. Permanent treatment discontinuation occurred in 3%, and Grade 3-4 AEs occurred in 25%. The most common (≥ 25%) all grade AEs including laboratory abnormalities, were decreased hemoglobin, anemia, fatigue, increased creatinine, headache, dizziness, increased glucose and nausea.

Anemia, hypoxia, and embryo-fetal toxicity are labeled as Warnings and Precautions. Because of the relatively young patient population for whom belzutifan will be indicated and the expected long duration of exposure, the review team placed a boxed warning for embryofetal toxicity in the product label.

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Regular approval of belzutifan is recommended by all disciplines. Extended follow-up of patients on MK-6482-004 for safety will be required as a PMR and extended follow-up for efficacy will be serve as a PMC. Submission of results of a clinical trial further evaluating efficacy of belzutifan in patients with VHL disease-associated non-RCC tumors will serve as a PMC. Safety PMRs will evaluate carcinogenicity in mice and rats.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients with VHL disease have a genetic predisposition putting them at high risk for developing various tumors including RCC, CNS hemangioblastoma, pNET, and retinal hemangioblastoma. • This represents a population of patients for which an unmet medical need exists.	Patients with VHL disease have a serious and potentially life-threatening condition with limited treatment options.
Current Treatment Options	• Surgery and other procedures may treat individual VHL-associated tumors, often with substantial associated morbidity. • While small studies describe the use of kinase inhibitors to treat localized VHL-associated RCC tumors, these data have not been FDA-reviewed and this represents off-label use. Additionally, these agents are relatively difficult to tolerate for long-term use as would be required in this setting. • Efficacy data for use of kinase inhibitors in other VHL-associated tumors is even less well-characterized.	Patients with VHL disease may be treated with surgery or other procedures, although these are often morbid. Off-label use of kinase inhibitors has been described for VHL-associated RCC, although this is difficult to tolerate long-term.
Benefit	• In a single-arm trial, the confirmed response rate by IRC for belzutifan in 61 patients with RCC evaluated at the proposed dose was 49% (95% CI 36, 62). The median duration of response was not reached (range 3+ to 22+ months).	Belzutifan has demonstrated a good response rate with what appears to be a good duration of response and an acceptable safety profile.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Responses were also seen in other VHL-associated tumors, including an ORR of 83% (52, 98) for 12 patients with evaluable pNET and an ORR of 63% (4, 30) for 24 patients with evaluable CNS hemangioblastomas.	
Risk and Risk Management	• No REMS will be required. • The most commonly reported treatment emergent adverse events were decreased hemoglobin, anemia, fatigue, increased creatinine, headache, dizziness, increased glucose and nausea. Anemia, Hypoxia, and Embryo-Fetal Toxicity are labeled as Warnings and Precautions. Embryo-Fetal Toxicity is also a boxed warning due to the young age of patients and long-term use in the otherwise relatively healthy approval population. • The Applicant will submit extended follow-up of patients on MK-6482-004 for efficacy as a PMC and safety as a PMR. Submission of results of a clinical trial further evaluating efficacy of belzutifan in patients with VHL disease-associated non-RCC tumors will serve as a PMC.	The risk-benefit profile of belzutifan is acceptable in the approved patient population. Extended follow-up for MK-6482-004 will be required as a PMC/PMR to provide further data on the efficacy and safety of belzutifan, and a PMC trial will evaluate efficacy in non-RCC VHL-associated tumors.

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3.4 Patient Experience Data

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

□	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
			□	Patient reported outcome (PRO)	
			□	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.				

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X

Chana Weinstock, MD

Cross-Disciplinary Team Leader

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4 THERAPEUTIC CONTEXT

4.1 Analysis of Condition

The Applicant's Position:

VHL disease is a hereditary cancer syndrome transmitted in an autosomal dominant fashion characterized by a germline mutation in or a deletion of the *VHL* gene in which affected individuals are at risk for the development of tumors and fluid-filled sacs (cysts) in a number of organs [1] [2] [3] [4] [5]. Tumors are often found in multiple organs in a simultaneous, multicentric fashion, and affected individuals continue to develop recurrent tumors throughout their life. Tumors may be either noncancerous or cancerous and can initially appear during young adulthood; however, the signs and symptoms of VHL syndrome can occur throughout life [6]. The prevalence of VHL disease has been reported to be between 1 in 91,111 and 1 in 38,951 individuals based on data from different geographic populations, which equals 0.110 and 0.333 per 10,000 individuals. This prevalence would correspond to approximately 3,600 to 11,000 individuals with VHL disease in the US.

Patients affected with VHL disease are at risk to develop renal cysts and ccRCC, pheochromocytomas, pancreatic cysts, pNETs, hemangioblastomas of the brain and spinal cord, retinal angiomas, inner ear endolymphatic sac tumors, and epididymal and broad ligament cystadenomas.

VHL disease-associated renal tumors, which are uniformly the ccRCC histological subtype, are malignant tumors that can metastasize and can be fatal [7]. Renal cell carcinoma occurs in about 70% of individuals with VHL disease [8]. Patients affected with VHL disease are at risk for the development of up to 600 renal tumors and 1100 renal cysts in each kidney as extrapolated from microscopic examination of renal parenchyma from VHL disease patients [9] [7]. Approximately one-third of patients who have VHL disease (13% to 42%) die of metastatic RCC disease [10] [7] [11] [12] [13] [8].

While renal tumors are a leading cause of mortality, other VHL disease-associated tumors also pose a significant risk to these patients. Cerebellar hemangioblastomas may be associated with headache, vomiting, gait disturbances, ataxia or loss of function. Spinal hemangioblastomas and related syrinx may present with pain or loss of function. Sensory and motor loss may develop with spinal cord compression. Retinal angiomas may be the initial manifestation of VHL disease and, if untreated, can cause vision loss. Small pheochromocytomas can be asymptomatic; however, untreated they can cause episodic or sustained malignant hypertension, myocardial infarction and stroke. VHL disease-associated pancreatic neuroendocrine tumors are malignant, may metastasize and lead to death. VHL disease-associated pancreatic lesions rarely cause endocrine or exocrine insufficiency. Endolymphatic sac tumors are low grade, malignant tumors with a low propensity to metastasize. However, if untreated these tumors will lead to hearing

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loss. Epididymal cystadenomas are relatively common in men and are most often asymptomatic [14].

The FDA's Assessment:

FDA agrees with the Applicant's statement.

VHL disease is divided into two types: Patients with VHL disease type 1 have a low incidence of pheochromocytoma. In contrast, patients with VHL disease type 2 have a high risk of developing pheochromocytoma. VHL disease type 2 is further classified into type 2A, 2B, and 2C. The incidence of RCC is low in type 2A and high in type 2B VHL disease. Patients with type 2C VHL disease only develop pheochromocytoma (Lonser et al).

4.2 Analysis of Current Treatment Options

The Applicant's Position:

There are currently no approved non-surgical interventions for VHL disease. The clinical management of VHL disease-associated tumors requires a skilled and dedicated multidisciplinary team committed to lifelong management of patients affected with this disorder. The goal of current management or treatment options is to prevent the development of cancer metastasis for those tumors with malignant potential described above while preserving normal organ function as much as possible. Current management of patients with VHL disease most often involves extensive lifelong surveillance and multiple surgeries on the kidneys, pancreas, adrenal glands, brain, and/or spinal cord.

To inform the Applicant's understanding of the natural history of VHL disease, a structured review of the available medical and scientific literature was conducted with consultation of scientific experts. The structured literature review included searches for a period of the last 20 years (01-JAN-2000 to 05-JUN-2020 inclusive) for bibliographic databases and the last 3 years (01-JAN-2017 to 05-JUN-2020) for conference searches with search terms for VHL disease, RCC, pancreatic neuroendocrine tumor, CNS hemangioblastoma, retinal angioma, growth kinetics, interventions and organ function, metastasis, and survival. Studies of linear growth kinetics, surgical interventions, ablations and the outcomes on interventions in VHL disease (genetically confirmed VHL germline mutation or clinically diagnosed VHL disease) and RCC, pNET, CNS hemangioblastoma, and retinal angioma were included in this review. A total of 1267 unique records were retrieved during the initial search of which 52 met the inclusion criteria, with most studies including patients with VHL disease-associated RCC, and with a limited number of studies for patients with other tumor types. This literature review was further supplemented with additional publications prior to 2000 to capture some of the seminal papers published on VHL disease as well as other relevant articles.

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The clinical management of VHL disease-associated renal tumors involves active surveillance until the largest renal tumor reaches the 3-cm diameter threshold, at which time nephron-sparing surgical intervention is recommended [9] [7]. Currently, surgical management is the only way to remove lesions that are >3 cm and avoid the risk of metastasis. Renal tumor size is an independent negative prognostic factor for overall survival of VHL disease-associated RCC. Reducing the size of the lesions or restricting growth to <3 cm may be beneficial to patients [10].

Renal cancer surgery for VHL disease is often very extensive; as many as 90 tumors may be removed from a kidney during a single surgery. Surgical management may involve NSS – open partial nephrectomy or enucleation – in an effort to preserve renal function or complete nephrectomy in the rare cases where the kidney cannot be preserved and thus is the only option. Thus, even after NSS, microscopic tumors will be left in otherwise healthy renal tissue and the need for monitoring remains [7] [10].

Surgery does not "cure" patients with VHL disease of RCC, it is solely intended to prevent the development of metastasis. In the great majority of patients, the tumors continue to present (14.5% at 2 years, 45.6% at 5 years and 83.7% at 10 years) [12] and repeated surgeries are required to prevent death from metastatic kidney cancer. Complications from such repeat surgeries for VHL disease-associated RCC are not uncommon and can include decrease in renal function, significant blood loss, infection, loss of the kidney, pulmonary emboli, and death [15] [13] [10].

Sunitinib, pazopanib and vandetanib were evaluated in clinical studies in patients with VHL disease [16] [17] [18]. While these agents demonstrated activity, tolerability of the treatment was poor and a significant proportion of patients discontinued treatment. Development of the investigational agents for this disease was discontinued due to poor tolerability.

Once the renal tumors have metastasized the treatment regimen follows that of advanced sporadic ccRCC with immune-modulators, anti-VEGF therapy and mTOR inhibitors.

For pNETs, surgical removal is recommended for those tumors with diameters ≥3 cm in the pancreatic body and ≥2 cm in the head due to risk of malignancy [19]. The mainstay of therapy for VHL disease associated CNS hemangioblastomas is surgical resection judiciously performed for symptomatic tumors [20]. Treatment of peripheral retinal hemangioblastomas includes ablative modalities such as laser photocoagulation, cryotherapy, radiation, photodynamic therapy and transpupillary thermotherapy or radical intervention through vitreoretinal surgery [21].

The FDA's Assessment:

FDA agrees with the Applicant's statement.

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According to the literature, the clinical trials of anti-VEGF therapies in patients with VHL-associated RCC, resulted in ORR ranging from 3%-52%. However, these were small single arm clinical trials and efficacy endpoints were investigator-assessed. There was a high rate of treatment discontinuation or withdrawal from these studies due to treatment-related toxicities (see Applicant's reference # 16-18). These therapies are therefore of limited clinical use to patients although are sometimes used off-label.

Percutaneous ablative techniques, such as radiofrequency ablation (RFA) and microwave ablation (MWA) are an alternative to surgery in carefully selected patients with VHL-RCC who have renal tumors less than 3 cm in size. However, these techniques are not appropriate for renal tumors that are in proximity with adjacent structures such as major vessels or intraabdominal organs, or cannot be easily reached by the probe (Carrion et al).

In addition to renal tumor-reducing procedures, surgical interventions for non-RCC tumors are associated with morbidity and mortality as well. Surgical procedures for CNS hemangioblastomas and abdominal tumors can be complicated by peri- or post-operative bleeding or infection. Repeated abdominal surgeries for removal of kidney, adrenal or pancreatic neuroendocrine tumors can lead to formation of adhesion bonds. Furthermore, frequent need for surgical procedures has significant impact on quality of life of affected patients.

5 REGULATORY BACKGROUND

5.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

The proposed indication for belzutifan in this application is:

> TRADEMARK™ (belzutifan) is indicated for the treatment of patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), not requiring immediate surgery.

This is the first marketing application for belzutifan. Belzutifan has been recommended by WHO and the USAN council as the rINN and USAN for the molecule also known as MK-6482 (formerly known as PT2977).

The FDA's Assessment:

FDA agrees with the Applicant's statement.

5.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

During the development of belzutifan, regulatory guidance on the design of MK-6482-001 and MK-6482-004 were obtained from the FDA. A summary of key interactions during the belzutifan clinical development program for the proposed indication is presented in [Table 1].

Table 1 Applicant – Summary of Key Interactions for Belzutifan Development

Type of Meeting/ Correspondence	Date	Purpose/Summary
Type B (EOP2) Meeting	10-JUN-2020	FDA DO1 provided advice on the development program for MK-6482 in the VHL disease-associated RCC indication and generally agreed with the registrational intent of MK-6482-004; requested the Sponsor to present the topline data before NDA submission.
Orphan Drug Designation Granted	24-JUN-2020	FDA OOPD granted ODD to MK-6482 in the indication of VHL disease; #DRU-2020-7458.
Request for Proprietary Name Review	2-JUL-2020 20-OCT-2020	The Applicant submitted request for proprietary name review. On 20-OCT-2020, FDA conditionally accepted the proposed proprietary name.
Type C CMC Meeting (WRO)	10-JUL-2020	FDA agreed with the Applicant's proposal on the choice of regulatory starting material for drug substance.
Breakthrough Therapy	23-JUL-2020	FDA DO1 granted BTD to MK-6482.

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Designation Granted		
Pediatric Scientific Advice (Type F Meeting)	5-AUG-2020	FDA concurred with planned request for a waiver in the iPSP under FDARA.
Agreed PSP submission	30-OCT-2020	iPSP was prepared under FDARA requirements and submitted to FDA on 04-SEP-2020. Following FDA comments, the Applicant submitted the agreed PSP to FDA on 30-OCT-2020. In this PSP, the Applicant indicated the plan to request a waiver for pediatric development under FDARA.
Pre-Submission Meeting with CDRH Regarding VHL Testing	28-AUG-2020 29-SEP-2020	FDA CDRH informed the Applicant that VHL genetic testing needs to be developed as a Class II or a Class III device.
Type C CMC Meeting	28-AUG-2020	FDA agreed with the 9-month stability data to support NDA submission and supplementation of 12-month stability data within ~ 60 days of NDA dossier submission completion.
Project Orbis	17-JUN-2020 25-SEP-2020 23-OCT-2020	On 17-JUN-2020, FDA inquired about the Applicant's interests in participating in Project Orbis for the upcoming NDA submission. On 25-SEP-2020, the Applicant informed FDA of interest in participating in Project Orbis and proposed a submission plan regarding Project Orbis. On 23-OCT-2020, the Applicant provided an updated submission plan to FDA.
Type B NDA Content/Format Meeting	23-OCT-2020	The Applicant requested FDA advice regarding the NDA submission structure, content, format and schedule. The Applicant and FDA agreed upon: • The Table of Content of the NDA submission. • The Applicant's proposal of NDA rolling submission: Wave 1 (15-DEC-2020); Wave 2 (15-JAN-2021). • Other submission schedules including CMC, Efficacy Update Report, Safety Update Report. • Proposed structure of Integrated Summary of Safety, OSI deliverables. In addition, FDA requested the Applicant to submit a report and datasets regarding family history and diagnosis methods from Study MK-6482-004, and a report and datasets regarding pharmacogenetic analysis.
Type B Pre-NDA Meeting	12-NOV-2020	The Applicant presented topline results from the Study MK-6482-004 and requested FDA feedback on NDA submission, participation of RTOR pilot, and labeling.

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		• FDA agreed that: 1) NDA submission can proceed; 2) the Applicant's proposal on participating in the RTOR pilot; 3) AOM can be scheduled after NDA submission. • FDA advised that labeling topic will be an NDA review issue. • FDA agreed that a REMS is not likely for belzutifan. Final decision will be based on NDA review. FDA requested the Applicant to conduct multi-level analysis to estimate LGR from MK-6482-004 and requested a report and SAS program be submitted to support the review. FDA requested that multi-disciplinary and chemistry Assessment Aids should be submitted in Wave 2 (15-JAN-2021). FDA and the Applicant agreed that the food effect study should be conducted with the to-be-marketed formulation. The Applicant agreed to submit the summary of process changes between FMF and FMI to IND to facilitate FDA review.

The FDA's Assessment:

FDA agrees with the Applicant's summary of their presubmission/submission interactions with FDA in general.

In the Type B (EOP2) Meeting, FDA asked the sponsor to provide a plan for a confirmatory clinical trial.

In the Type B Pre-NDA Meeting, FDA advised that labeling indication will be an NDA review issue.

6 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

6.1 Office of Scientific Investigations (OSI)

For this NDA for belzutifan, the clinical team requested that OSI verify the integrity of the submitted clinical data from Study MK-6482-004. Three clinical investigators [Dr. Ramaprasad Srinivasan (Site 032), Dr. Eric Jonasch (Site 011), and Dr. Kimryn Rathmell (Site 015)] and the study sponsor Merck Sharp & Dohme Corporation were selected for clinical inspection. The three investigator inspections confirmed that the submitted clinical data were verifiable with source records at the study sites, with no evidence of underreporting of adverse events. In general, based on the inspections of the three clinical investigators and the sponsor, the inspectional findings support validity of data as reported by the sponsor to the Agency. The clinical data generated by the three investigators appear to be reliable in support of this NDA for belzutifan.

6.2 Product Quality

The OPQ review team found that the CMC information in the NDA acceptable. All manufacturing and controls facilities are deemed acceptable. For further details, refer to separate Product Quality review.

6.3 Clinical Microbiology

Not applicable

6.4 Devices and Companion Diagnostic Issues

No companion diagnostic device was approved concomitantly with the approval of belzutifan.

While Merck had informed FDA that they were considering several VHL assay developers, they have not provided any further information on whether they had made a final decision on a potential device partner, other than stating that VHL assay will not be available as contemporaneous companion diagnostic.

(b) (4)

. No such test is currently FDA cleared.

7 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

7.1 Executive Summary

The FDA's Assessment

Hypoxic microenvironments are observed in normal physiology as well as pathology conditions, in settings such as embryogenesis and tumor development and progression. Hypoxia-inducible factors (HIFs) are oxygen-regulated proteins that mediate transcriptional responses during

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hypoxia. Particularly, HIF-1α or HIF-2α proteins dimerize with HIF-1β, also known as aryl hydrocarbon receptor nuclear translocator (ARNT), through their PAS-B domains. The heterodimer forms a transcriptional complex to induce transcription of genes involved in various cellular processes that allow cells to adapt to low oxygen conditions. HIF-1β is constitutively expressed; thus, formation of the transcriptional complex is mainly regulated by the stabilization of the HIF-α subunit. During normoxic conditions, HIF-α is hydroxylated at specific proline residues, which allows for the binding of von Hippel-Lindau (VHL) protein to HIF-α, targeting HIF-α for ubiquitin-proteasomal degradation. In contrast, during hypoxic conditions or impairment of VHL protein, HIF-α is not degraded. It is stabilized and translocates to the nucleus where it binds to HIF-1β to stimulate expression of transcriptional target genes by binding to hypoxia-response elements (HRE) in their promoters.

VHL disease is a genetic disorder caused by deletion or mutation in the VHL tumor suppressor gene, preventing expression or impairing function of VHL protein. Patients with VHL disease have an increased risk of developing benign or malignant lesions in multiple organs, including central nervous (CNS) hemangioblastomas, retinal hemangioblastoma, renal cell carcinoma (RCC), and pancreatic neuroendocrine tumors (PNET). Up to 70% of patients with VHL disease develop RCC and is the leading cause of mortality. CNS hemangioblastomas are benign but can be fatal due to bleeding in the brain. There are currently no approved therapies for VHL disease-associated cancers or CNS hemangioblastomas, and treatment is limited to active surveillance and surgical resection to alleviate symptoms from lesions or prevent cancer from metastasizing.

Belzutifan (Welireg, MK-6482, PT2977) is a first-in-class oral small molecule with an established pharmacological class of hypoxia-inducible factor inhibitor that binds to HIF-2α. In pharmacology studies, belzutifan bound to the PAS-B domain of HIF-2α with an $IC_{50} \leq 15$ nM. Functional assays using VHL protein-deficient and VHL protein-proficient cells demonstrated that belzutifan interfered with heterodimerization of HIF-2α and HIF-1β and inhibited HRE-driven luciferase activity and expression of HIF-2α downstream genes in vitro and in vivo. In contrast, belzutifan did not interrupt dimerization of HIF-1α and HIF-1β nor inhibit transcription of HIF-1α downstream genes. Belzutifan exhibited in vivo anti-tumor activity in VHL protein-deficient tumor models. In secondary pharmacology studies, belzutifan at concentrations up to 12.5 μM did not show off-target activity against screening panels consisting of 78 receptors, 8 ion channels, 40 protein kinases, and 2 protein phosphatases.

Safety pharmacology assessments were incorporated in repeat-dose toxicology studies. There were no belzutifan-related adverse effects on respiratory parameters measured after Day 1, nor neurological behavior parameters in rats receiving up to 200 mg/kg/day for 21 days. Belzutifan was a low-potency hERG blocker in vitro ($IC_{50} > 50$ μM) and did not influence QTc in dogs dosed up to 30 mg/kg/day for 3 months.

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Following a single oral administration of belzutifan to fed rats, Tmax occurred at 1.3 h with a half-life of 5 h and an oral bioavailability of 17%. In fasted dogs, a single oral administration of belzutifan had a Tmax of 2 h with a half-life of 17.2 h and an oral bioavailability of 33%. Due to the shorter half-life and lower bioavailability of belzutifan in rats versus dogs, rats were dosed twice a day in the repeat-dose studies. Following a single oral dose of radiolabeled belzutifan to rats, the highest radioactivity was observed in liver, kidney, and small intestine. Radioactivity was eliminated primarily via biliary excretion, followed by fecal elimination. Belzutifan was metabolized by glucuronidation and oxidative metabolism. There were no unique human metabolites detected in vitro in hepatic microsomes or hepatocytes. The major metabolite, PT3317, a glucuronide conjugate formed by UGT2B17 enzyme, was noted across all species tested. PT13317 was quantified in both repeat-dose studies and clinical studies. In dogs, the metabolite to parent ratios were 0.19 to 0.52 for AUC. In humans, the metabolite exposure was approximately 30% of belzutifan exposure. In a primary pharmacology study, PT3317 had > 6,000x reduction in binding to HIF-2α versus belzutifan. In consultation with the FDA clinical pharmacology team, animal to human exposure multiples were calculated using the AUC value at steady-state of 16.7 μg*hr/mL. The rat AUC12h was doubled to compare with human AUC24h.

The safety of belzutifan was evaluated in GLP-compliant repeat-dose toxicology studies up to 3-month duration in rats and dogs using the intended oral route of administration. In the 3-month rat study, there was one male in the 200 mg/kg/day high dose group euthanized at Day 18 due to adverse clinical signs. Declining health was most likely related to liver toxicity, and the animal also presented moderate neuronal degeneration/necrosis in brain. While the study report proposed that brain findings may be related either to belzutifan treatment or may be incidental, the Applicant considers findings to be incidental given that it occurred only in one animal and rats treated at 200 mg/kg/day for the full 3-month period and in the 28-day study did not have brain findings nor CNS effects. Based on the totality of the data, the brain findings are most likely incidental.

Belzutifan caused reversible decreases in red blood cell parameters at ≥ 2 mg/kg/day in rats and ≥ 1 mg/kg/day in dogs (approximately ≥ 0.05 times the human exposure at the recommended human dose of 120 mg daily). Hematology changes were generally not associated with microscopic changes in the bone marrow except for the 28-day repeat-dose study in dogs where up to moderate hypocellularity in bone marrow of femur and sternum were noted. These results are in line with work demonstrating that conditional deletion of HIF-2α in adult mice resulted in anemia, which was associated with decreased levels of circulating erythropoietin (EPO; Gruber et al. 2007). The Applicant measured circulating EPO levels in the 28-day repeat-dose dog study anticipating belzutifan might decrease this parameter, but instead increased EPO levels were noted in all groups, including controls. Based on the available animal findings, the mechanism of belzutifan-related anemia is unclear. In the clinic, anemia occurred in 90% of patients with VHL disease who had at least one measurable tumor

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localized to kidney receiving belzutifan at the recommended dosing regimen; of these patients, 7% experienced Grade 3 anemia. The label includes a warning and precaution for anemia.

Testes and epididymis were the major target organs in the rat studies with belzutifan-related findings including reduced organ weights, degeneration/atrophy of the testes and hypospermia and cellular debris of the epididymis at ≥ 2 mg/kg/day (≥ 0.1 times the human exposure at the recommended human 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) and did not reverse at the end of a 26-week recovery period. Belzutifan had no adverse effects on male reproductive organs in repeat-dose studies in dogs.

One male at end of 3-month treatment and the early decedent (euthanized on Day 18) at 200 mg/kg/day (approximately 1 time the clinical AUC at 120 mg daily) showed moderate hepatocellular necrosis with sinusoidal congestion/hemorrhage with and without inflammation. Both animals had elevated ALT and AST levels and early decedent also had high ALP levels. The Applicant considers both of these findings to be incidental based on the location of the necrosis in the early decedent (caudate lobe of liver, which is a known frequent site of incidental torsion leading to necrosis) or because incidence is within historical control range. Increases in AST and ALT were noted in the clinic.

Belzutifan was not mutagenic in the in vitro bacterial reverse mutation (Ames) test or clastogenic in the in vitro micronucleus assay in human peripheral blood lymphocytes or the in vivo bone marrow erythrocyte micronucleus test in rats.

The Applicant did not conduct carcinogenicity studies to support this NDA. VHL disease manifests in young adults (mean age of onset in MK-6482-004: 41 years old) as a variety of benign and malignant tumors in multiple organs. Belzutifan is intended for use as non-urgent treatment for VHL-associated cancers or CNS hemangioblastomas. During the review cycle, the Applicant submitted a preliminary weight-of-evidence assessment, which did not adequately address the carcinogenicity potential of belzutifan for chronic use. In the 3-month toxicology studies, proliferative changes consisting of minimal to moderate hyperplasia and minimal metaplasia were noted in various organs in both species, but interpretation of findings were confounded by observations noted in control animals and lack of dose relationship. Additionally, there were two rats that had malignant lesions at 6 mg/kg/day and another two that had benign lesions at 200 mg/kg/day. Given the indication, the long-life expectancy and prolonged treatment, it is important to address the carcinogenicity potential of belzutifan for chronic use. Two post-marketing requirements (PMRs) to conduct carcinogenicity studies in mice and rats were communicated to the Applicant.

The Applicant conducted a pilot embryo-fetal development study in rats. Oral administration of belzutifan at doses up to 200 mg/kg/day to pregnant rats during the period of organogenesis caused embryo-fetal lethality (post-implantation loss) at ≥ 60 mg/kg/day (approximately ≥ 1 time the human exposure at the recommended dose of 120 mg daily), with complete litter loss

noted at 200 mg/kg/day. Reduced fetal body weight and fetal skeletal malformations occurred at doses of 6 and 60 mg/kg/day (approximately ≥ 0.2 times the human exposure at the recommended dose of 120 mg daily). Belzutifan-related findings in fetuses included incomplete ossification of sternebra, malformed ribs and domed head. The embryo-fetal lethality may be related to the reported roles of oxygen tension and HIFs in vasculogenesis, placental development and embryogenesis and is consistent with embryonic loss noted in HIF-2α knockout mice between E9.5 and E13.5 (Tian et al. 1998, Peng et al 2000, and Compernolle et al. 2002). The embryo-fetal toxicity noted with belzutifan is comparable to other oncology drugs; however, given the chronic use of belzutifan in a younger population than other targeted oncology drugs, the review team recommended the label contain a boxed warning for embryo-fetal toxicity. Since belzutifan may render some hormonal contraceptives ineffective, the label also advises females of reproductive potential to use effective non-hormonal contraception during treatment and for one week after the last dose of Welireg. Males with female partners of reproductive potential should use effective contraception during treatment and for one week after the last dose of Welireg. These recommendations for duration of contraception are consistent with FDA guidance, "Oncology Pharmaceutical: Reproductive Toxicity Testing and Labeling Recommendations," for non-genotoxic drugs that are teratogenic and have short half-lives (belzutifan half-life = ~14 h).

The Applicant did not conduct studies to investigate the effects of belzutifan on fertility. In repeat-dose toxicity studies up to 3-month duration in rats, belzutifan treatment resulted in irreversible toxicity in testes and epididymis. Belzutifan had no adverse effects on female reproductive organs in repeat-dose toxicity studies; however, belzutifan caused post-implantation loss in pregnant rats given oral doses ≥ 60 mg/kg/day (≥ 1 time the human exposure at recommended human dose of 120 mg daily). Based on findings in animals, belzutifan may impair male and female fertility. The reversibility of the effect on fertility is unknown.

Recommendation

The nonclinical data submitted to this NDA are adequate to support approval of Welireg for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma, central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. Given the proposed indication and chronic use, the pharmacology and toxicology team recommends two post-marketing requirements to assess the carcinogenicity potential of belzutifan for chronic use in mice and rats.

7.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position:

No cross-reference is made by the Applicant to any other NDA/BLA/DMF.

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7.3 Pharmacology

Primary Pharmacology

The FDA's Assessment:

Binding Affinity

A scintillation proximity assay evaluated the binding of PT2977 (7 lots tested) and its glucuronide metabolite, PT3317, by monitoring their ability to displace a radiolabeled probe from the Per-ARNT-Sim-B (PAS-B) domain of HIF-2α (Study# PD005MK6482). The PAS-B domain is involved in protein-protein interactions, including the heterodimerization of HIF-2α to HIF-1β (ARNT) to form a transcriptional HIF complex. PT2977 at ≤ 0.015 μM displaced 50% to 80% of the radioactive probe. IC_{50} values ranged from < 0.005 μM to 0.015 μM with the seven lots tested of PT2977. In contrast, the metabolite showed < 50% displacement at the maximum concentration tested (100 μM), suggesting poor binding.

Functional Activity

The pharmacodynamic effect of PT2977 was evaluated in vitro and in vivo using RCC cell lines that are VHL protein-deficient (786-O and A498) or a hepatoma cell line that is VHL protein-proficient (Hep3B). A variety of assays, including a luciferase reporter assay, ELISA, QPCR and immunoprecipitation assays, followed by western blotting were conducted to measure transcriptional activity, gene and protein expression and to characterize the HIF-2α-HIF-1β interaction.

In vitro

Containing a mutated VHL gene, 786-O cells express constitutively active HIF-2α but no functional HIF-1α. PT2977 inhibited luciferase activity in 786-O-Hif-Luc cells (786-O cells expressing a HRE luciferase reporter) in a dose-dependent manner, suggesting inhibition of HIF-2α transcriptional activity, with an IC_{50} of 0.015 μM (Study# PD001MK6482). The ability for PT2977 to interfere with dimerization of HIF-2α and ARNT to form functional transcription factors was evaluated in co-immunoprecipitation experiments and by measuring mRNA expression of HIF-2α target genes in 786-O cells (Study# PD003MK6482). In general, PT2977, in a dose-dependent-manner, downregulated mRNA expression of HIF-2α target genes tested (cyclin D1 [CCND1], serpin family E member 1 [SERPINE1], vascular endothelial growth factor A [VEGFA] and solute carrier family 2 member 1 [SLC2A1]). As expected, given that HIF-1α is not expressed in 786-O cells, PT2977 had no effect on phosphoglycerate kinase 1 (PGK1) mRNA expression, a gene that is regulated by HIF-1α. An ARNT antibody was used to form immunoprecipitate from cell lysates from 786-O cells treated with PT2977, followed with immunodetection of HIF-2α and ARNT. In a dose-dependent manner, PT2977 decreased co-immunoprecipitation of HIF-2α and ARNT in 786-O cells. In HepB3 cells that are VHL protein-proficient and express both HIF-1α and HIF-2α proteins, hypoxia induced dimerization of HIF-

1α and HIF-2α to ARNT. In these cells, PT2977 reduced dimerization of HIF-2α to ARNT in a dose-dependent manner but had no effect on HIF-1α to ARNT dimerization (Study# PD004MK6482). Furthermore, PT2977 reduced mRNA expression of HIF-2α target genes (SERPINE1 and EPO) but not HIF-1α target genes (PGK1 and pyruvate dehydrogenase kinase 1 [PDK1]) in HepB3 cells. Lastly, PT2977 reduced VEGFa secretion in a 786-O cell-based assay with an IC_{50} = 0.0183 μM (Study# PD002MK6482).

In vivo

A dose-related decrease in mRNA levels for CCND1, SERPINE1, VEGFA and SLC2A1 was observed in tumor tissue from 786-O tumor-bearing mice exposed to PT2977 at 0.3, 1 and 3 mg/kg twice daily for 3 days. In blood samples, circulating VEGFa levels were decreased in mice treated with PT2977 at ≥ 1 mg/kg, twice daily for 3 days compared to vehicle control animals (Study# PD008MK6482). The Applicant also evaluated the pharmacokinetic and pharmacodynamic effects of PT2977 in a renal cancer A498 xenograft model that is VHL protein-deficient and expresses both HIF-1α and HIF-2α (Study# PD009MK6482). Blood and tissue samples were collected at 12 h, 24 h and 36 h from tumor-bearing mice treated by oral gavage with 0, 0.3 and 1 mg/kg/dose PT2977, twice daily for 6 doses (3 days total). A dose-dependent increase in PT2977 plasma concentrations was noted at 12h, which was fully or partially reversible by ≥ 24 h. PT2977 reduced expression of CCND1, SERPINE1, SCL2A1 and VEGFA in a dose-dependent manner but had no effect on HIF-1α genes (PGK1 and PDK1) in tumor samples collected 12 h after the last dose. Reflecting PK results, mRNA levels of HIF-2α genes were generally reversible by ≥ 24 h of treatment with PT2977. Immunohistochemistry (IHC) analysis of tumor tissues collected 12 h after the final dose of PT2977 suggested a dose-related decrease in Ki67 (proliferation marker) and CD31 (endothelial/angiogenesis marker) staining and an increase in activated caspase-3 (apoptosis marker) staining compared to tumor tissues from control animals; however, tissue analyses were limited as they were not quantitative, and the study report provided only one representative image per animal (n=3 mice/group).

In mice bearing subcutaneous 786-O xenografts, oral doses of 0.3, 1 and 3 mg/kg PT2977, twice daily for 28 days inhibited tumor growth by 87% to 93% compared to vehicle treated mice (Study# PD006MK6482). Similarly, in a patient-derived xenograft mouse model of human clear cell RCC (CTG-0824), PT2977 (3 mg/kg, twice daily for 28 days) decreased tumor volume by 89% compared to vehicle control group (Study# PD007MK6482).

Overall, the in vitro and in vivo results demonstrate that PT2977 binds to HIF-2α, disrupts the formation of the HIF-2α-ARNT transcriptional complex and inhibits expression HIF-2α downstream targets under the conditions tested. Anti-tumor activity was observed in mouse xenograft models of clear cell renal cell carcinoma.

Secondary Pharmacology

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The Applicant's Position:

Belzutifan showed no off-target activity against a panel of 76 receptors and 8 ion channels, and no off-target activity against a panel of 40 protein kinases and 2 protein phosphatases.

The FDA's Assessment:

The FDA agrees with the Applicant's conclusion.

Safety Pharmacology

The Applicant's Position:

Potential effects of belzutifan on critical organ (ie, neurobehavioral, respiratory, and cardiovascular)systems were evaluated in safety pharmacology studies conducted as stand-alone or as components of repeat-dose toxicity studies. The in vitro hERG assay yielded an IC_{50} value of >50 μM, which is >26-fold higher than free plasma concentration (1.95 μM) at steady state Cmax for human dose of 120 mg/day (calculated using pop-PK analysis). No belzutifan-related effects were observed in any of these studies up to the highest dose tested. The no-observable-effect-level for safety pharmacology endpoints in the rat and dog studies corresponds to systemic exposure (AUC0-24) similar to human exposure at 120 mg/day.

The FDA's Assessment:

The FDA agrees that there were no adverse effects of belzutifan on cardiovascular, respiration or neurological behavior parameters in animals. Noteworthy results and study methods are presented below.

Respiration:
Respiratory parameters were assessed on Day 1 in conscious female rats using plethysmograph chambers connected to the respiratory monitoring acquisition system in the 28-day repeat-dose study. Findings were reviewed under IND 132120, and no toxicologically significant changes were noted with doses up to 200 mg/kg/day.

Functional observation battery (FOB):
FOB parameters were assessed only in males, during pre-treatment and on Day 21 at approximately 60 min, 4 h and 23 h post-dosing of twice daily regimen. Findings were reviewed under IND 132120, and no toxicologically significant changes were noted with doses up to 200 mg/kg/day.

Cardiovascular assessment:

In the in vitro hERG assay, PT2977 concentrations of 10 and 50 μM inhibited the hERG current by 7% and 16%, respectively (Study# TT167824). Solubility limitations prevented evaluating higher concentrations of PT2977. The positive control, 60 nM terfenadine, inhibited the hERG current by 85%.

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In vivo, cardiovascular parameters were assessed during pre-treatment and on Week 13 of the 13-week repeat-dose dog study. Findings were reviewed under general toxicology study section below. There were no toxicologically significant changes observed at doses up to 30 mg/kg/day.

7.4 ADME/PK

The Applicant's Position:

Oral bioavailability was low in rats (18%), moderate in dogs, (33%) and high in mice (~ 100%). Exposure to belzutifan in rats was dose proportional up to doses of 30 mg/kg, and less than dose proportional from 30 to 300 mg/kg, while exposure in dogs was less than dose proportional from 1 to 100 mg/kg.

In a quantitative whole-body autoradiography study in rats, [^{14}C]belzutifan-derived radioactivity was readily absorbed after an oral dose, and rapidly and extensively distributed to most tissues. The [^{14}C]belzutifan-derived radioactivity tissue distribution was reversible in both pigmented and non-pigmented rats. Belzutifan is a substrate of rat P-gp and a weak substrate of human P-gp, however, moderate brain penetration (brain to plasma ratio of 0.36 to 0.53) was observed in rats in vivo indicating that P-gp is not preventing access to the brain. The plasma protein binding of belzutifan was moderate and similar across species, and belzutifan is roughly equally distributed between red blood cells and plasma.

In bile duct cannulated rats, the majority (85.0% of the administered dose) was recovered in the bile, primarily as oxidative metabolites. Studies with liver preparations and recombinant enzymes demonstrated that belzutifan is metabolized by glucuronidation catalyzed by UGT2B17 and by oxidative metabolism, catalyzed by CYP2C19, and to a lesser extent by CYP3A4. All human metabolites observed in liver preparations in vitro were also observed in the preclinical safety species. The glucuronide metabolite of belzutifan, PT3317, was quantified in clinical studies and circulates in plasma at ~ 32% of belzutifan exposures. As an O-glucuronide, PT3317 is not considered of toxicological concern. Furthermore, PT3317 levels at the NOAEL in dogs were comparable to human levels at the clinically efficacious dose and therefore adequately characterized. PT3317 does not have activity against HIF-2α.

The FDA's Assessment:

The FDA generally agrees with the Applicant's summary of study results. Additional noteworthy results and comments on Applicant's summary are presented in table below. See the clinical pharmacology Section 6 for information regarding human data and drug interaction studies.

Data (presented by FDA):

Type of Study	Major Findings
Absorption	

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<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Pharmacokinetics of PT2977 in male SD rats single dose intravenous and oral administration (Study# PK007MK6482)</td><td>Rat
Following a single IV or oral dose administered under fed conditions to male rats (n=3/group):
<table><tr><th>Dose, route</th><th>Cmax µg/mL</th><th>Tmax h</th><th>T1/2 h</th><th>$AUC_{0\text{-}inf}$ µg·h/mL</th><th>CL mL/h/kg</th><th>Vss L/kg</th><th>BA %</th></tr><tr><td>1 mg/kg IV[a]</td><td>NA</td><td>NA</td><td>1.09</td><td>1.02</td><td>983</td><td>1.27</td><td>NA</td></tr><tr><td>10 mg/kg oral[b]</td><td>0.28</td><td>1.33</td><td>5.30</td><td>1.78</td><td>NA</td><td>NA</td><td>17.5</td></tr></table>a: vehicle was 10% dimethylacetamide, 10% ethanol, 40% PEG400, 40% water
b: vehicle was 10% ethanol, 30% PEG400, 60% (0.5% methylcellulose and 0.5% Tween 80 in water)</td></tr>
<tr><td>Pharmacokinetics of PT2977 in male beagle dogs following single dose intravenous or oral administration (Study# PK010M6482)</td><td>Dog
Following a single IV or oral dose administered under fasted conditions to male dogs (n=3/group):
<table><tr><th>Dose, route</th><th>Cmax µg/mL</th><th>Tmax h</th><th>T1/2 h</th><th>$AUC_{0\text{-}inf}$ µg·h/mL</th><th>CL mL/min/kg</th><th>Vss L/kg</th><th>BA %</th></tr><tr><td>1 mg/kg IV[a]</td><td>NA</td><td>NA</td><td>9.65</td><td>12.25</td><td>1.35</td><td>1.81</td><td>NA</td></tr><tr><td>5 mg/kg oral[b]</td><td>1.51</td><td>2</td><td>17.2</td><td>25.29</td><td>NA</td><td>NA</td><td>33</td></tr></table>a: vehicle was 40% PEG400, 20% ethanol, 40% water
b: vehicle was 0.5% methylcellulose and 0.5% Tween 80 in water</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>PT2977 blood plasma partitioning study in blood of different species (Study# PK017MK6482)</td><td>Blood to plasma ratio of PT2977 (1 µM) was similar across species, ranging from 0.88 to 1.06 in mice, rat, dog, monkey, and human blood.</td></tr>
<tr><td>Determination of in vitro protein binding of PT2977 in mouse, rat, dog, monkey and human plasma (Study# PK018MK6482)</td><td>Average protein binding of belzutifan (% bound):
Mouse: 56%
Rat: 55%
Dog: 61%
Monkey: 52%
Human: 45%</td></tr>
</table>

Type of Study	Major Findings
Determination of the tissue distribution of PT2977 and its metabolite PT3317 in male SD rats following a single oral gavage dose of PT2977 at 30 mg/kg (Study# PK020MK6482)	**Rat** Following a single oral dose administration of belzutifan at 30 mg/kg to male rats (n=3/group): - C_{max} in plasma and tissues occurred at 4 h post-dose -Tissues with the highest belzutifan exposure were small intestine and liver -Concentration of metabolite PT3317 was lower than belzutifan and detected only in liver, plasma, and small intestine. -The amount of belzutifan and PT3317 in small intestine washout content was highest at 4 h and was 0.633 mg and 0.039 mg, respectively.
Absorption, distribution, metabolism, and excretion of ^{14}C-PT2977 after an oral dose to rats (Study# PK021MK6482)	**Rat** Following a 10 mg/kg single oral administration of [^{14}C]PT2977: To nonpigmented SD rats (n=1/sex/timepoint): - Tissues with the highest radioactivity exposures were liver (M/F), cecum (M/F), kidney (M/F), Harderian gland (M/F), small intestine (M/F), myocardium (F) and Fat, brown (F) at 0.5 and 4 h. To pigmented LE rats (n=1/sex/timepoint): - Tissues with the highest radioactivity exposures were liver (M/F), kidney (M/F), small intestine (M/F), myocardium (M), Harderian gland (M) and eye uveal tract (M) at 0.5 and 4 h.
Metabolism	
Metabolism of [14C]MK-6482 in hepatocyte suspensions, HEPATOPAC co-cultures and recombinant human UGT enzymes (Study# PK038MK6482)	- The major metabolite M16 (PT3317, a glucuronide conjugate) was noted across all species tested, following incubation of [^{14}C]PT2977 with rat, dog, or human hepatocytes for 2 h or HEPATOPAC co-cultures (hepatocytes + stromal cells) for 7 days. -No human specific metabolites were observed -Incubation with recombinant human UGT enzymes identified PT3317 is formed with UGT2B17
Absorption, distribution, metabolism, and excretion of ^{14}C-PT2977 after an oral dose to rats (Study# PK021MK6482)	**Rat** Following a 10 mg/kg single oral administration of [^{14}C]PT2977 to bile duct-intact (intact) or bile duct-cannulated (BDC) rats: -PT2977 was metabolized to produce 23 radioactive components (14/23 were identified). -In plasma, belzutifan was the major component comprising of 46% (M) and 59% (F) of radioactivity. The second most abundant component was M2 (unidentified) metabolite comprising of 24% (M) and 30% (F) of radioactivity. Other metabolites noted in both sexes were M9, M11 and M15 at ≤ 10%. -Metabolite profiles in bile showed M4 was the major component comprising of ~20% of radioactivity. Other metabolites noted were co-eluting metabolites M8/M9 (22.8% combined values for M8 and M9), PT3317 (M16, 9% M, 7% F), M7 (10%M, 11%F), M6 (7%), M11 and M12 at ≤ 5%

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<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Excretion</td><td></td></tr>
<tr><td>Absorption, distribution, metabolism, and excretion of ^{14}C-PT2977 after an oral dose to rats (Study# PK021MK6482)</td><td>Rat
Following a 10 mg/kg single oral administration of [^{14}C]PT2977 to bile duct-intact (intact) or bile duct-cannulated (BDC) rats:
-In intact rats, fecal excretion accounted for 72% (sex combined) of radioactive dose and urinary excretion accounted for 19% (sex combined) of radioactive dose
-In BDC rats, bile excretion accounted for 83% (sex combined) of radioactive dose, while urine and fecal excretion accounted for 12% and 1.5% (sex combined) of radioactive dose, respectively.</td></tr>
<tr><td>TK data from general toxicology studies
A 13-week oral gavage toxicity study followed by 28-day and 26-week recovery period in rats (Study# TT187809)</td><td>Rat
Accumulation: 2x Cmax and AUC exposure at 2 mg/kg in males and 2x Cmax at 6 mg/kg in females (Days 91 vs Day 1)
Dose proportionality: A less than dose proportional increase for most dose levels
<table><tr><th>Day</th><th>Sex</th><th>Dose (mg/kg)</th><th>C_{max} (μg/mL)</th><th>$AUC_{(0\text{-}12)}$ (μg·hr/mL)</th></tr><tr><td rowspan="7">1</td><td rowspan="4">M</td><td>2</td><td>0.12</td><td>0.408</td></tr><tr><td>6</td><td>0.32</td><td>1.28</td></tr><tr><td>20</td><td>0.82</td><td>4.11</td></tr><tr><td>200</td><td>1.47</td><td>10.8</td></tr><tr><td rowspan="3">F</td><td>6</td><td>0.30</td><td>1.16</td></tr><tr><td>20</td><td>0.67</td><td>3.36</td></tr><tr><td>200</td><td>1.27</td><td>9.80</td></tr><tr><td rowspan="7">91</td><td rowspan="4">M</td><td>2</td><td>0.21</td><td>0.822</td></tr><tr><td>6</td><td>0.40</td><td>1.68</td></tr><tr><td>20</td><td>0.92</td><td>4.20</td></tr><tr><td>200</td><td>1.20</td><td>7.85</td></tr><tr><td rowspan="3">F</td><td>6</td><td>0.51</td><td>1.48</td></tr><tr><td>20</td><td>0.89</td><td>3.88</td></tr><tr><td>200</td><td>1.54</td><td>9.93</td></tr></table></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>A 13-week oral gavage toxicity study followed by 28-day recovery periods in Beagle dogs (Study# TT187808)</td><td>Dog
Accumulation: 2x AUC exposure at 30 mg/kg in males only (Days 91 vs Day 1)
Dose proportionality: Lower than dose proportional increase at all doses.
Sex differences: On Day 1, females at 30 mg/kg had up to 2.7x higher Cmax and AUC exposure than males.
Metabolite PT3317: Metabolite to parent ratios ranged from 0.25 to 0.70 for Cmax and 0.19 to 0.52 for AUC
<table>
<tr><th>Day</th><th>Sex</th><th>Dose (mg/kg)</th><th>C_{max} (μg/mL)</th><th>$AUC_{(0-24)}$ (μg·hr/mL)</th></tr>
<tr><td rowspan="6">1</td><td rowspan="3">M</td><td>1</td><td>0.38</td><td>4.46</td></tr>
<tr><td>5</td><td>0.78</td><td>9.87</td></tr>
<tr><td>30</td><td>1.22</td><td>14.5</td></tr>
<tr><td rowspan="3">F</td><td>1</td><td>0.37</td><td>4.87</td></tr>
<tr><td>5</td><td>1.01</td><td>12.4</td></tr>
<tr><td>30</td><td>3.24</td><td>31.8</td></tr>
<tr><td rowspan="6">91</td><td rowspan="3">M</td><td>1</td><td>0.57</td><td>6.75</td></tr>
<tr><td>5</td><td>1.34</td><td>16.9</td></tr>
<tr><td>30</td><td>1.94</td><td>29.0</td></tr>
<tr><td rowspan="3">F</td><td>1</td><td>0.56</td><td>7.13</td></tr>
<tr><td>5</td><td>1.40</td><td>19.7</td></tr>
<tr><td>30</td><td>2.12</td><td>30.2</td></tr>
</table></td></tr>
<tr><td>TK data from reproductive toxicology studies
Preliminary oral embryo-fetal developmental toxicity and toxicokinetic study in rats (Study# TT207004)</td><td>Rat
<table>
<tr><th>Gestational Day</th><th>Dose (mg/kg/day)</th><th>C_{max} (μg/mL)</th><th>$AUC_{(0-12)}$ (μg·hr/mL)</th></tr>
<tr><td rowspan="3">7</td><td>6</td><td>0.53</td><td>1.30</td></tr>
<tr><td>60</td><td>1.30</td><td>7.43</td></tr>
<tr><td>200</td><td>1.69</td><td>14.1</td></tr>
</table>
Values are mean of n=6</td></tr>
</table>

LE: Long Evans; SD: Sprague-Dawley: M: males; F: females

7.5 Toxicology

7.5.1 General Toxicology

Data (presented by FDA):

Study title/ number: PT2977: A 13-week oral gavage toxicity study followed by 28-day and 26-week recovery periods in Sprague-Dawley rats / TT187809

- One mortality at HD, possibly related to PT2977

- PT2977 caused decreases in red cell parameters, increases in bicarbonate and triglycerides.
- The target organs of toxicity were liver and male reproductive organs

GLP compliance: Yes

Methods

Dose and frequency of dosing:	1, 3, 10, 100 mg/kg/dose, twice daily (2, 6, 20, 200 mg/kg/day) for 13 weeks
Justification of doses:	Based on non-reversible testicular toxicity and fluctuations of hematology parameters, including anemia, observed in a 28-day study evaluating doses of 3, 10 and 100 mg/kg, twice daily. Per Applicant, rats were dosed twice daily based on the shorter half-life and lower bioavailability of MK-6482 in rats versus dogs.
Route of administration:	Oral, gavage
Formulation/Vehicle:	0.5% methylcellulose and 0.5% tween 80 in water
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	15/sex/group (main; except for 2 mg/kg/day group – M only); 5/sex/group (recovery – 28 days); and 5 M/group (recovery – 26 weeks)
Age:	6 weeks old
Satellite groups/ unique design:	TK groups – 5/sex in control; 9/sex/group in treatment groups, except no TK females at 2 mg/kg/day There were two recovery periods: 28-days (M and F) and 26-week (M only) The 2 mg/kg/day dose level was evaluated in M only.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings

<table>
<tr><td>Mortality</td><td>There were four early deaths during the study.
<u>Control</u>:
Male# 1026 was found dead on Day 228, cause of death is unknown
<u>2 mg/kg/day:</u>
Male# 2011 was found dead on Day 61. Animal was observed gasping prior to death and microscopic findings showed moderate alveolar edema, which may have contributed to mortality.
Male# 2034 was found dead on Day 171, cause of death is unknown
<u>200 mg/kg/day:</u>
Male# 5009 was euthanized on Day 18 due to clinical signs (recumbent, gasping, uncoordinating behavior, weakness, unresponsive to stimuli, eyes close and increased activity). Animal presented moderate hepatocellular necrosis with sinusoidal congestion/hemorrhage, which was associated with high ALT, AST and ALP levels; and moderate bilaterally symmetrical neuronal degeneration/necrosis in brain. While no other animal presented brain findings, it could not be ruled out that this was not a PT2977-related effect given the bilateral distribution of the lesion. Other findings were degeneration of seminiferous tubules in testes and hypospermia and increased cellular debris in epididymis.</td></tr>
<tr><td>Clinical Signs</td><td>There were generally no PT2977-related findings. There was no dose relationship for the malignant ventral cervical mass noted in individual female at 6 mg/kg/day.

<table>
<tr><td></td><td colspan="5">Males</td><td colspan="4">Females</td></tr>
<tr><td>mg/kg/day</td><td>0</td><td>2</td><td>6</td><td>20</td><td>200</td><td>0</td><td>6</td><td>20</td><td>200</td></tr>
<tr><td>Penis
Red discharge
White discharge
Yellow discharge
Skin red
Swelling soft/firm</td><td>
1R

1R

</td><td>

</td><td>
1R
1

</td><td>

1
2
1</td><td>
1

3,1R
1</td><td>

</td><td>

</td><td>

</td><td>

</td></tr>
<tr><td>Ventral cervical mass (malignant mammary carcinoma)</td><td></td><td></td><td></td><td></td><td></td><td></td><td>1</td><td></td><td></td></tr>
</table>
R: recovery period</td></tr>
<tr><td>Body Weights</td><td>Females at 200 mg/kg/day showed statistically significant decreases compared to control on Days 84, 91 and 105 but differences were ≤ 10% and lacked a dose-response.</td></tr>
<tr><td>Ophthalmoscopy</td><td>Unremarkable</td></tr>
</table>

Hematology

% change from control following 13-week exposure with PT2977 in rats

	Males				Females		
	mg/kg/day				mg/kg/day		
	2	6	20	200	6	20	200
n	15	15	15	14	15	15	15
RBC	**-7**	**-11**	**-15**	**-25**	**-8**	**-11**	**-17**
HGB	**-8**	**-12**	**-18**	**-28**	-10	**-15**	**-20**
HCT	**-8**	**-12**	**-18**	**-27**	-9	**-14**	**-19**
NEUT	23	7	34	-4	-14	-18	-19
WBC	5	-2	-2	-17	7	-11	1
LYMPH	2	-4	-9	-19	11	-9	5
BASO	-6	-26	-29	**-45**	57	-14	**29**
RET	1	-7	-7	**-23**	-6	**-21**	**-26**

Values in bold are statistically significant from control

Parameters were partially or fully reversible by end of 28-day recovery, except for reticulocytes in males at 200 mg/kg/day (-31%; p≤0.05 vs control); and neutrophils in females at 6 mg/kg/day (-28%) and 20 mg/kg/day (-31%), although this was not dose-dependent nor statistically significant. For males by end of week 26, reticulocytes were partially reversible at 200 mg/kg/day (-11%).

Coagulation

A decrease in APTT was noted in males at all doses (up to -11%) but was not dose-related and not noted in females. Reversibility was noted by 28-day recovery but was decreased again by end of Week-26 recovery (p≥0.05 at 2 mg/kg/day, -19%) but not dose-dependent.

Clinical Chemistry

% change from control following 13-week exposure with PT2977 in rats

	Males				Females		
	mg/kg/day				mg/kg/day		
	2	6	20	200	6	20	200
n	15	15	15	14	15	15	15
AST	-4	6	7	**36**	-19	-12	-24
ALT	5	-5	12	39	-14	-11	-14
CHOL	-4	8	8	22	-2	13	3
TRIG	-19	-22	-18	-2	-24	-11	**-38**
Cl	0	**-1**	**-3**	**-4**	-1	**-3**	**-2**
HCO3	5	**9**	**13**	**14**	6	5	**14**
Iron	**-21**	**-19**	**-19**	-13	-9	-16	-16

Values in bold are statistically significant from control

Full or partial reversibility were noted at 28-day recovery, except for triglycerides in females at 20 mg/kg/day (-48%, p≤0.05) and 200 mg/kg/day (-40%, n.s.)

Urinalysis

Unremarkable

Gross Pathology

Small and/or soft epididymis and testes in males, mainly at ≥ 20 mg/kg/day
Enlargement and swelling of penis in one male at 20 mg/kg/day
Discolored (red or pale) or enlargement in liver in individual treated males

Organ Weights

Males had reduced testicular weights associated with degeneration/atrophy in histopathology. Reduced epididymis weight correlated with hypospermia and/or increased cellular debris and decreased fluid production, secondary to testis findings. These changes did not resolve after a 26-week recovery period.

Males had a reversible dose-related increase in heart weights at ≥ 20 mg/kg/day (statistically significant); however, it lacked correlates and this change was not present in females.

Other statistically significant changes noted in kidney and pituitary were considered incidental as changes differed between sexes, were of low magnitude (≤ 10%) and/or lacked a dose-relationship

% change from control following 13-week exposure with PT2977 in rats

	Males				Females		
PT2977 mg/kg/day	2	6	20	200	6	20	200
n	14	13-15	14-15	14	15	15	15
Epididymis, Left							
Organ	-4	-10	**-34**	**-36**			
Organ:BW	-2	-12	**-33**	**-37**			
Organ:Brain	-3	-10	**-34**	**-35**			
Epididymis, Right							
Organ	-	**-13**	**-35**	**-38**			
Organ:BW	-	-15	**-33**	**-39**			
Organ:Brain	-	**-13**	**-35**	**-37**			
Prostate							
Organ	-11	**-12**	-7	**-14**			
Organ:BW	-9	**-14**	-5	**-16**			
Organ:Brain	-11	-12	-7	-13			
Testis, bilateral							
Organ	-	-	**-48**	**-47**			
Organ:BW	-	-	**-48**	**-48**			
Organ:Brain	-	-	**-48**	**-46**			
Heart							
Organ	4	8	**10**	**17**			
Organ:BW	6	5	**13**	**14**			
Organ:Brain	4	8	**10**	**20**			
Uterus							
Organ					-6	-11	-16
Organ:BW					-	-13	-11
Organ:Brain					-5	-10	-16

Values in bold are statistically significant from control

Male Reproductive Assessment	Motility: A reduction in sperm motility was noted with PT2977 at ≥ 6 mg/kg/day, with statistically significant changes noted at ≥ 20 mg/kg/day. Partial recovery was noted in some animals at ≥ 20 mg/kg/day, but in some animals, it was non-reversible (see table below). Spermatozoa count: A dose dependent decrease in sperm concentration (millions/g, epididymis organ weight) was noted with PT2977 at ≥ 6 mg/kg/day. • 6 mg/kg/day: -29% (in general, reversibility was noted in mean values by recovery Day 28 and Week 26, -18% and -9%, respectively; however, one male had -61% counts versus mean control by the end of 26-week recovery period) • 20 mg/kg/day: -64%, p≤0.001 (non-reversible by recovery Day 28 and Week 26, -73%, p≤0.01 and -62%) • 200 mg/kg/day: -84%, p≤0.001 (non-reversible by recovery Day 28 80%, p≤0.01 and partial reversibility by Week 26, -38%) Spermatozoa morphology: A statistically significant dose-dependent increase in the percentage of abnormal sperm was reported at ≥ 6 mg/kg/day (32% at 6 mg/kg/day, 83% at 20 mg/kg/day and 90% at 200 mg/kg/day). In contrast, control and 2 mg/kg/day had a ≤ 8% abnormal sperm. The most frequent abnormality was normal-shaped head separated from the flagellum at end of main and recovery periods. Abnormal sperm persisted at ≥ 20 mg/kg/day by recovery Day 28 and showed partial reversibility by recovery Week 26, although up to 77% abnormal sperm was still noted at 20 mg/kg/day. Overall, these findings correlated with the degeneration and/or atrophy noted in testes and epididymides at ≥ 6 mg/kg/day

Motility assessment

	0	2	6	20	200
End of Main Study					
N	15	15	15	15	14
Grade					
1				9	12
2				4	2
3			4	2	
4	11	9	8		
5	4	5	3		
6					
Recovery - Day 28					
N	5	5	5	5	5
Grade					
1				5	5
2	1				
3	1	2	1		
4	3	1	4		
5		2			
6					
Recovery – Week 26					
N	4	4	5	5	5
Grade					
1			1	4	2
2					
3					
4	4	4	4	1	3
5					
6					

Grades: 1) no motility 2) small number of motile sperm 3) moderate number of motile sperm 4) large number of motile sperm 5) some wave motion 6) fast wave motion

Histopathology Adequate battery: Yes	See table below for histopathology findings, includes findings from end of treatment and 28-day recovery, 26-week recovery, and unscheduled deaths.

End of treatment period/28-day recovery (R)

	Males					**Females**			
PT2977 mg/kg/day	**0**	**2**	**6**	**20**	**200**	**0**	**6**	**20**	**200**
n, main study[a] **n, 28-day recovery[a]**	**15** **5**	**14** **5**	**15** **5**	**15** **5**	**14** **5**	**15** **5**	**15** **5**	**15** **5**	**15** **5**
Epididymis (paired)									
Hypospermia[b]									
Minimal			1						
Mild				1					
Moderate					1R				

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	Males					Females			
PT2977 mg/kg/day	**0**	**2**	**6**	**20**	**200**	**0**	**6**	**20**	**200**
n, main study[a] **n, 28-day recovery[a]**	**15** **5**	**14** **5**	**15** **5**	**15** **5**	**14** **5**	**15** **5**	**15** **5**	**15** **5**	**15** **5**
Marked				3	10/3R				
Severe		1		11/5R	4/1R				
Cellular debris[b]									
Minimal			7/2R	2	1R				
Mild			6	5/1R	5/2R				
Moderate				3/1R	6/1R				
Marked				2R	3				
Cibriform change[b]									
Mild				3R	1R				
Moderate		1		1R					
Kidneys									
Inflammation; pelvis; Bilateral									
Mild				2		1			
Inflammation; pelvis; Unilateral									
Minimal							1		2
Mild	1R	1R	1						
Moderate			2						
Increased hyaline droplets; tubular; epithelium; bilateral									
Mild	2	1	1	1	6/1R				
Basophilia; tubular; bilateral									
Minimal	2	1	1/1R	3/3R	3/1R	2		1	1
Mild	1	1R		1					
Basophilia; tubular; unilateral									
Minimal	2	6/2R	6/1R	5	7/2R	2/2R	3	2	3/1R
Dilatation; pelvis; bilateral									
Minimal	2	2	1	1			2	1	1
Mild		1R	1						
Moderate				1					
Dilatation; pelvis; unilateral									
Minimal	1	1/1R		2R	1		2/1R	1	1
Mild			1	1R			1R	1	
Moderate		1			1R				
Inflammation; chronic; Interstitial; bilateral									
Mild				1					
Inflammation, chronic; Interstitial; unilateral									
Minimal			2	1		1	1		1/1R
Mild			1R						
Cyst, bilateral or unilateral									
Minimal	1	1			1/2R		1/1R		
Mild				1					
Moderate				1R					
Nephroblastoma; malignant, primary, incidental			1R						
Liver									

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	Males					Females			
PT2977 mg/kg/day	**0**	**2**	**6**	**20**	**200**	**0**	**6**	**20**	**200**
n, main study[a]	**15**	**14**	**15**	**15**	**14**	**15**	**15**	**15**	**15**
n, 28-day recovery[a]	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**
Necrosis; hepatocellular									
Minimal		2	1	2	3/1R	1		1	
Mild	1R	1R							
Moderate					1				
Vacuolation; hepatocellular									
Minimal	3/4R	1/3R	4/3R	4/1R	5/4R	1/3R	1	1R	1/1R
Mild	1	1	3/1R	1/1R	3				
Tension lipidosis									
Minimal		2/1R	1/5R	4	1/2R	1	3	1/1R	2R
Mild							1R		
Lungs									
Examined at Main		NE	NE	n=1			NE	NE	
Examined at Recovery		n=1	NE	NE			NE	NE	
Hemorrhage									
Minimal	2	1R			5/1R	1R			3
Inflammation, interstitial									
Minimal					1				
Infiltration, eosinophilic									
Minimal					1				
Mild					1				
Lymph node, tracheobronchial									
Examined at Main	NE	NE	NE	n=1	NE	NE	NE	NE	NE
Hyperplasia, lymphoid									
Mild				1					
Penis									
Examined at Main	NE	NE	NE	n=1	NE				
Hemorrhage									
Mild				1					
Inflammation									
Severe				1					
Prostate									
Inflammation									
Minimal	9/3R	11	9/1R	9/4R	10/4R				
Mild	2/1R	2/1R	3/1R	3/1R	3				
Moderate	1R	2R	1	1					
Marked			2	1					
Severe		1R		1					
Skin & Subcutis									
Examined at Main	NE	n=1	NE	NE	NE	NE	n=2	NE	NE
Carcinoma, mammary; Malignant, incidental							1		
Hyperplasia; epidermis									
Mild							1		
Inflammation; dermis									
Moderate		1							
Ulceration; dermis									

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	Males					Females			
PT2977 mg/kg/day	**0**	**2**	**6**	**20**	**200**	**0**	**6**	**20**	**200**
n, main study[a] **n, 28-day recovery[a]**	**15** **5**	**14** **5**	**15** **5**	**15** **5**	**14** **5**	**15** **5**	**15** **5**	**15** **5**	**15** **5**
Minimal							1		
Marked		1							
Crust; serocellular									
Mild							1		
Moderate		1							
Granulation tissue; dermis									
Mild		1							
Testis (paired)									
Atrophy, tubular[b]									
Minimal			2	1	5				
Mild			1		5/2R				
Moderate				1	2/1R				
Marked				7	1/1R				
Severe		1		6/5R	1R				
Degeneration, tubular[b]									
Minimal		3	8/5R	6/4R	1R				
Mild			6	4	1/1R				
Moderate			1	2	10/2R				
Marked					3/1R				
Retained spermatids in/on the surface of epithelium[b]									
Minimal		3	9	3	8/2R				
Mild			6		2				
Moderate				1	1				
Retained spermatid heads at basement of membrane[b]									
Minimal			11	2	3				
Mild					1				
Retained large residual bodies[b]									
Minimal		3	8	2	5				
Mild			4	3	2				
Moderate				2	7				
Multinucleated giant cells[b]									
Minimal			3	1	6/1R				
Mild				4	5/1R				
Moderate				3	3/1R				
Vacuolated spermatid nuclei[b]									
Minimal			1	1/1R	6/1R				
Mild				2	3/1R				
Moderate				5	1/1R				
Exfoliated epithelial cells into lumen[b]									
Minimal			8	3/1R	1/2R				
Mild			2	6	1				
Moderate				1/1R	11				

	Males					Females			
PT2977 mg/kg/day	**0**	**2**	**6**	**20**	**200**	**0**	**6**	**20**	**200**
n, main study[a] **n, 28-day recovery[a]**	**15** **5**	**14** **5**	**15** **5**	**15** **5**	**14** **5**	**15** **5**	**15** **5**	**15** **5**	**15** **5**
Marked					1/1R				
Apoptotic pachytene and Meiotic germ cells[b]									
Minimal			1	2/2R	6				
Mild					4/1R				
Moderate					3/1R				
Apoptosis/disorganization of elongating spermatids									
Minimal			6	1	1				
Mild			6	2	2				
Moderate			1	9/1R	8/3R				
Marked					3/1R				
Decreased elongating Spermatids[b]									
Minimal			6	1					
Mild			6	2	1				
Moderate			1	9/1R	9/3R				
Marked					4/1R				
Focal germ cell dropout[b]									
Minimal			7/5R	1/1R	1R				
Mild			6	2	1				
Moderate			1	9/2R	9/3R				
Marked					4/1R				
Vacuolation of Sertoli cells[b]									
Minimal			9/2R	5	8/5R				
Mild			5/2R	4	3				
Moderate				1	3				
Interstitial cell hyperplasia/ hypertrophy									
Minimal				13/4R	7/3R				
Sperm granuloma[b]									
Minimal				1					
Thymus									
Examined at Main Examined at Recovery		n=2 n=1	n=7 NE	n=10 NE			n=1 n=1	n=13 n=1	
Atrophy; lymphoid									
Minimal	12/4R	1R	6	8	13/3R	13/2R		1	7/4R
Mild	1R				2R	1/3R	1	1R	6
Hemorrhage									
Minimal	8/1R	2	4	7	4	5	1/1R	2/1R	2
Mild			3	2	2				
Trachea									
Examined at Main		NE	NE	NE			NE	NE	
Metaplasia; squamous									
Minimal					1				
Urinary bladder									
Examined at Main		n=1	NE	n=2			NE	NE	
Hemorrhage; epithelium									

	Males					Females			
PT2977 mg/kg/day	**0**	**2**	**6**	**20**	**200**	**0**	**6**	**20**	**200**
n, main study[a] **n, 28-day recovery[a]**	**15** **5**	**14** **5**	**15** **5**	**15** **5**	**14** **5**	**15** **5**	**15** **5**	**15** **5**	**15** **5**
Mild				1					
Hyperplasia; epithelium									
Marked				1					
Inflammation; submucosa									
Mild				1					

a: unless otherwise indicated; b: incidence reflects unilateral and bilateral findings; NE: not examined

End of 26-week recovery

	Males				
PT2977 mg/kg/day	**0**	**2**	**6**	**20**	**200**
n[a]	**4**	**4**	**5**	**5**	**5**
Adrenal glands					
Examined			NE	NE	
Cystic degeneration; unilateral					
Minimal					1
Epididymis (paired)					
Hypospermia[b]					
Mild				1	
Severe			1	4	2
Cellular debris[b]					
Minimal			1	1	
Mild			1	1	1
Eyes					
Examined		NE	NE	NE	
Atrophy; retina; bilateral					
Moderate					1
Marked	1				
Atrophy; retina; unilateral					
Mild					1
Kidneys					
Dilatation; pelvis; unilateral					
Minimal					1
Moderate			1	1	
Cyst					
Minimal		1		2	1
Mild				1	
Liver					
Necrosis; hepatocellular					
Minimal	2		1	1	1
Vacuolation; hepatocellular					
Minimal	4	3	3	3	3
Mild				1	1
Moderate			1		1
Tension lipidosis					
Minimal	1	1	1	3	2
Hyperplasia; bile duct					
Minimal	1	4	2	2	2

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	Males				
PT2977 mg/kg/day	**0**	**2**	**6**	**20**	**200**
n[a]	**4**	**4**	**5**	**5**	**5**
Pituitary glad					
Examined		NE	NE	NE	
Adenoma; pars distalis; benign Primary; incidental					2
Cyst					
Minimal	1				2
Moderate					1
Hyperplasia; pars distalis; focal					
Minimal					1
Hypertrophy; pars distalis; focal					
Minimal	2				
Prostate gland					
Inflammation					
Minimal		1	1	4	3
Mild	3	1	2		1
Moderate	1			1	
Stomach					
Hemorrhage; mucosa					
Minimal	1	1	1		3
Testis (paired)					
Atrophy, tubular[b]					
Minimal			1		1
Mild					1
Moderate			1	1	
Severe			1	4	2
Degeneration, tubular[b]					
Minimal			1		3
Mild				1	
Exfoliated epithelial cells into lumen[b]					
Mild				1	
Focal germ cell dropout[b]					
Minimal			1	1	2
Sperm statis					
Minimal			1		
Thymus					
Examined	n=2	n=1	n=1	n=1	n=4
Atrophy; lymphoid					
Minimal	1				
Mild		1	1	1	2
Moderate	1				2

a: unless otherwise indicated; b: incidence reflects unilateral and bilateral findings; NE: not examined

Unscheduled deaths

	Males		
PT2977 mg/kg/day	**0**	**2**	**200**
n	**1**	**2**	**1**
Brain			
Dilatation; lateral ventricle, Unilateral			
Moderate			1
Spongiosis; neuropil; Bilateral			
Minimal			1
Degeneration/necrosis; neuron; bilateral			
Moderate			1
Fluoro-Jade B: neuronal Degeneration/necrosis; Bilateral			
Moderate			1
Kidneys			
Infiltrate, mononuclear cell; Interstitial; unilateral			
Minimal	1	1	
Cast, hyaline/granular; Bilateral			
Mild			1
Liver			
Necrosis; hepatocellular			
Moderate			1
Vacuolation; hepatocellular			
Mild	1		
Infiltrate, mononuclear cell			
Minimal		1	
Mild	1		
Lungs			
Edema; alveolar			
Moderate		1	
Histocytosis; alveolar			
Minimal		1	
Infiltration, eosinophilic			
Minimal		1	
Hemorrhage			
Minimal			1
Mandibular lymph node			
Erythrocytosis/hemorrhage			
Minimal		1	
Pancreas			
Atrophy; exocrine			
Minimal		1	
Fibrosis; islet			
Minimal		1	
Hemorrhage; islet			
Minimal		1	

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	Males		
PT2977 mg/kg/day	**0**	**2**	**200**
n	**1**	**2**	**1**
Hyperplasia; islet			
Minimal		1	
Infiltrate, mononuclear cell			
Minimal		1	
Pigmentation; islet			
Minimal		1	
Prostate			
Inflammation			
Minimal	1	1	
Mild		1	
Spleen			
Atrophy; lymphoid			
Minimal			1
Thymus			
Atrophy; lymphoid			
Mild	1	1	1
Hemorrhage			
Mild		1	
Moderate		1	

Study title/ number: PT2977: A 13-week oral gavage toxicity study followed by a 28-day recovery periods in Beagle dogs / TT187808

- All animals survived
- Decreases in red cell parameters, reversible increases in bicarbonate
- Target organs: no major microscopic changes during main study; one recovery male at HD had abnormal sperm, no spermatozoa motility and low count but histopathology was limited to minimal unilateral focal tubular hypoplasia

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 1, 5, 30 mg/kg/day, once daily for 13 weeks
Justification of doses:	Based on hematology toxicity (anemia, reduced reticulocytes) observed in a 28-day study evaluating doses of 1, 5 and 30 mg/kg/day.
Route of administration:	Oral, gavage
Formulation/Vehicle:	0.5% methylcellulose and 0.5% tween 80 in water
Species/Strain:	Dog/Beagle
Number/Sex/Group:	4/sex/group (main); 2/sex/group (recovery)

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Age:	13 to 14 months
Satellite groups/ unique design:	None/ No
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	None that were belzutifan-related. Signs noted were also present in control, were transient and/or had no dose-relationship.
Body Weights	Unremarkable; changes noted were dose-dependent and were generally < -10%, except for males at MD (up to -16% vs control during recovery period, Days 98 to 120).
Ophthalmoscopy	One male at LD had optic nerve atrophy in the right eye, which was considered as a spontaneous change in the study population
ECG	At HD, males had a decrease in PR of -12% ($p \leq 0.05$) compared to control and -10% (n.s.) compared to baseline. Females had a decrease in PR of -14% (n.s.) compared to control but similar to baseline levels. A -23% ($p \leq 0.05$) and -11% decrease in diastolic pressure was noted in males at HD compared to control and baseline, respectively. Of note, control males also had a -9% decrease compared to baseline. In females, up to -12% decrease in diastolic pressure was noted at HD versus control and baseline levels. Nevertheless, changes were not dose-dependent. The sponsor considered changes noted in males to be incidental.
Hematology	

% change from control following 7- and 13-week exposure with PT2977 in dogs

	PT-2977 mg/kg/day					
	Males			Females		
	1	5	30	1	5	30
Test	Day 44 Week 7/Day 86 Week 13					
RBC	**-36**/**-39**	**-39**/**-43**	**-39**/**-43**	**-35**/-39	**-40**/**-46**	**-46**/**-55**
HGB	**-35**/**-37**	**-40**/**-41**	**-39**/**-41**	**-37**/-38	**-42**/**-45**	**-48**/**-53**
HCT	**-35**/**-36**	**-40**/**-39**	**-39**/**-41**	**-37**/38	**-42**/**-44**	**-48**/**-52**
MCV	-/**5**	-2/**6**	-/**4**	-3/1	-3/4	**-4**/4
RDW	**8**/6	**7**/**12**	6/**12**	9/4	4/5	2/10
PLT	-5/16	-6/35	-9/34	-4/28	-9/**44**	-7/**45**
WBC	-12/-23	-21/-25	-12/-11	-22/-24	-42/-15	**-33**/-26
LYMPH	-21/**-29**	-27/**-36**	-15/**-24**	**-25**/**-25**	**-42**/**-29**	**-37**/**-34**
NEUT	-8/-19	-19/-20	-12/-2	-23/-22	-23/-5	-31/-21
MONO	7/-27	0/-19	5/-7	-3/-9	-42/-5	-17/-20
BASO	-58/-56	**-67**/**-63**	**-58**/**-63**	**-45**/**-64**	**-52**/**-46**	**-61**/**-64**
LUC	-35/-54	-48/**-63**	-45/-31	-17/-35	-42/-22	-29/-30
RET	**-61**/-53	**-58**/9	**-56**/31	**-62**/-44	**-42**/-23	**-77**/-22

Values in bold are statistically significant from control

At recovery (Day 117), most parameters were partially or fully reversible except for:

- WBC (-16% MD; -31% HD) and LYMPH (-46% MD; -42%HD) remained decreased in females at ≥ 5 mg/kg
- In females, BASO (-46% MD) was non-reversible at MD and partially reversible at HD; LUC was non-reversible (-43%) at MD but reversible at HD

Coagulation	Females treated with PT2977 had up to -6% decrease (p≤0.05) in prothrombin time without a dose-relationship; and up to 19% increase (n.s.) in fibrinogen

<table>
<tr><td>Clinical Chemistry</td><td>% change from control following 13-week exposure with PT2977 in dogs
<table>
<tr><td></td><td colspan="6">PT2977 mg/kg/day</td></tr>
<tr><td></td><td colspan="3">Males</td><td colspan="3">Females</td></tr>
<tr><td>Test - Day 86</td><td>1</td><td>5</td><td>30</td><td>1</td><td>5</td><td>30</td></tr>
<tr><td>ALT</td><td>-9</td><td>-12</td><td>11</td><td>-21</td><td>-21</td><td>-18</td></tr>
<tr><td>AST</td><td>8</td><td>9</td><td>23</td><td>9</td><td>48</td><td>30</td></tr>
<tr><td>TRIG</td><td>-42</td><td>-17</td><td>-13</td><td>-4</td><td>-19</td><td>-19</td></tr>
<tr><td>CK</td><td>25</td><td>4</td><td>15</td><td>29</td><td>159</td><td>44</td></tr>
<tr><td>CREA</td><td>-9</td><td>1</td><td>-6</td><td>-19</td><td>-24</td><td>-26</td></tr>
<tr><td>ALB</td><td>-1</td><td>-2</td><td>-6</td><td>-5</td><td>-10</td><td>-8</td></tr>
<tr><td>LDH</td><td>77</td><td>45</td><td>166</td><td>49</td><td>141</td><td>254</td></tr>
<tr><td>Ca</td><td>-1</td><td>1</td><td>-2</td><td>-2</td><td>-5</td><td>-4</td></tr>
<tr><td>PHOS</td><td>-7</td><td>-4</td><td>-12</td><td>-1</td><td>1</td><td>-11</td></tr>
<tr><td>HC03</td><td>15</td><td>15</td><td>10</td><td>6</td><td>7</td><td>8</td></tr>
<tr><td>Iron</td><td>-25</td><td>-31</td><td>-29</td><td>-21</td><td>-26</td><td>-7</td></tr>
</table>
Values in bold are statistically significant from control

Increase in CK in F at MD was driven mainly by Female# 3502, which also showed a 557% increase compared to baseline levels.
LDH levels fluctuated (up and down) during dosing period, including in controls. While increases were noted at end of study, some of these values were also present at baseline levels.

At recovery,
AST was not reversible in females at ≥ 5 mg/kg (47% vs control).
Iron was further decreased at all dose levels, in a dose-dependent manner in females but not males (up to -62%M; up to -41%F)
In females, lipase increased in what appears a dose-dependent manner in females (6%, 13% and 65% at 1, 5 and 30 mg/kg/day). At MD and HD, it was driven by one animal.</td></tr>
<tr><td>Urinalysis</td><td>Unremarkable</td></tr>
<tr><td>Gross Pathology</td><td>Thymus: small, correlating microscopically with up to marked lymphoid hypocellularity
Other findings were present in controls, not dose-related, low incidence and/or lacked histopathology correlates</td></tr>
<tr><td>Organ Weights</td><td>Spleen: Decrease (up to -45%) at ≥ LD in M and ≤ MD in F, which was reversible except in M at HD (-55% at recovery).
Testes: Reversible increases (up to 22%) at ≥ MD
Thymus: Partially reversible decreases in M at HD (-13%) and F at ≥ MD (up to -60%)
Uterus: At recovery, a decrease (up to -79%) in organ weight (absolute, organ to body weight and organ to brain) was noted at all dose levels.</td></tr>
</table>

Male Reproductive Assessment	End of treatment: There were no significant PT2977-related changes in sperm motility, concentration, or morphology End of 28-day recovery: HD: Right epididymal semen sample from Male# 4005 had no spermatozoa motility, reduced sperm concentration and abnormal sperm morphology (increased number of detached heads). There no histopathology findings noted in right testis associated with these findings. The left testis had minimal focal tubular hypoplasia.
Histopathology Adequate battery: Yes	See table below for main study and recovery histopathology findings.

M: male; F: female; LD: low dose; MD: mid dose; HD: high dose; n.s.: not significant
-: indicates reduction in parameter relative to control

End of treatment period/28-day recovery (R)

	Males				Females			
PT2977 mg/kg/day	**0**	**1**	**5**	**30**	**0**	**1**	**5**	**30**
n, main study[a]	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
n, 28-day recovery[a]	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Liver								
Increase pigment Kupffer cell								
Minimal				1			1	
Mild				1				
Necrosis/inflammation								
Minimal				1			1	
Fibrosis								
Mild			1R					
Lungs with bronchi								
Histocytosis								
Minimal				1				
Inflammation, interstitial								
Minimal		1						
Mild				1				
Inflammation, alveolar-interstitial								
Mild							1R	
Thymus								
Cyst								
Minimal		1		1R			1R	
Mild				1				
Hypocellularity, lymphoid								
Minimal					1/1R			
Mild	1	1/1R	1R	1R	2/1R	1		
Moderate	3/2R	1/1R	1	1/1R	1	3	1/2R	1R
Marked		2	3/1R	3		2R	3	4/1R
Thyroids								
Cyst, unilateral								
Minimal		1	1	2R				

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	Males				Females			
PT2977 mg/kg/day	**0**	**1**	**5**	**30**	**0**	**1**	**5**	**30**
n, main study[a]	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
n, 28-day recovery[a]	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Hyperplasia; unilateral								
Minimal							1R	
Mild						1		
Trachea								
Metaplasia, mucosal								
Minimal			1					

a: unless otherwise indicated; NE: not examined

General toxicology; additional studies

The 28-day repeat-dose toxicity studies were initially reviewed by the FDA under IND 132120. The summaries of these studies are based on and adapted from original review.

Study title/ number: PT2977: A 28-day oral gavage toxicity study followed by a 28-day and a 90-day recovery periods in Sprague-Dawley rats / TT167820

Rats received belzutifan twice daily for a total of 0, 6, 20 and 200 mg/kg/day for 28 days. There were no belzutifan-related deaths. Belzutifan caused dose-dependent anemia in both sexes and decreased white blood cells and neutrophils, more so in females. Decreases in bicarbonate levels (up to 24%) in both sexes and increase in triglycerides were noted in females at ≥ 20 mg/kg/day. Clinical pathology findings were reversible. All doses caused significant impairment of the male reproductive system (up to moderate hypospermatogenesis, germ cell degeneration and multinucleated giant cells in testes and up to marked oligospermia and cellular debris in epididymis) that were non-reversible. Macroscopically, some rats had cardiac hyperplasia accompanied by microscopic cardiac myopathy, which may be a compensatory response to the anemia. This study included assessment of functional observational battery (males only; pre-treatment and Day 21) and respiratory function (females only; Day 1). No toxicologically significant changes were noted with belzutifan treatment in central nervous system and respiratory parameters.

Study title/ number: PT2977: A 28-day oral gavage toxicity study followed by a 28-day and a 90-day recovery periods in Beagle dogs / TT167821

Dogs received belzutifan orally at 0, 1, 5, and 30 mg/kg/day for 28 days. Key study findings were reversible decreased red blood cell parameters and reticulocytes, associated with up to moderate hypocellularity in bone marrow of femur and sternum. There were no belzutifan-related changes in male reproductive organs in dogs at end of main study. Abnormal sperm was slightly increased at ≥ 5 mg/kg/day after recovery period but lacked histopathology correlates.

The Applicant's Position:

Belzutifan-related effects on the RBC mass were observed consistently in the rat and dog toxicity studies up to 13-week duration. The effects on the RBC compartment were dose-dependent. The effects on the RBC compartment were reversible, and were related to the pharmacology of belzutifan involving HIF-2α regulation of EPO expression in the kidney [22].

In rats, there were adverse belzutifan-related testicular and epididymal effects. These effects included hypospermatogenesis, germ cell degeneration and multinucleated giant cells (testes), and oligospermia (epididymides) that were not reversible within the 26-week recovery period. These findings were associated with decreased sperm motility and sperm counts, and increased number of abnormal sperms. For some animals, the sperm findings were partially reversed at the 28-day recovery necropsy. Based on the histologic degenerative changes in the testes/epididymides, the NOAEL in male rats was 6 mg/kg/day and 2 mg/kg/day for the 28-day and 13-week studies, respectively. For female rats, the NOAEL in both the 28-day and 13-week studies was 200 mg/kg/day. In dogs, no adverse belzutifan-related toxicity was identified, including the lack of effects on sperm evaluation and testes/epididymides histopathology, in either the 28-day or 13-week studies. The NOAEL in dogs was 30 mg/kg/day.

The FDA's Assessment:

The FDA generally agrees with the Applicant's summary of study results. In the 13-week rat study (Study# TT187809), one male at 200 mg/kg/day (HD) was euthanized on Day 18 due to poor conditions. The animal showed hepatoxicity (discussed below) and moderate bilaterally symmetrical neuronal degeneration/necrosis in brain. No other animal presented brain findings in this study nor in the 28-day repeat-dose rat study using doses up to 200 mg/kg/day belzutifan, including CNS adverse effects.

The Applicant suggests that decreases in red blood cell parameters are due to dysregulation of erythropoietin by inhibition of HIF-2α with belzutifan. While this may be an explanation of a potential mechanism for findings based on literature, in the 28-day repeat-dose dog study, an increase in EPO was noted in all groups, including controls, suggesting it was not belzutifan-related. EPO levels were not measured in the 13-week repeat-dose studies. Based on the available data, the mechanism of anemia in animal studies is unclear.

Based on irreversible histological findings and functional assessments of male reproductive organs in rats at ≥ 6 mg/kg/day (≥ 0.2 times the exposure at the human recommended dose based on AUC), belzutifan may impair male reproduction function and fertility. No effects on male reproductive organs were noted in male dogs administered belzutifan for 13-weeks; however, one recovery male at HD had abnormal sperm, no spermatozoa motility and low sperm count, but histopathology was limited to minimal unilateral focal tubular hypoplasia.

In the 13-week study in rats, hepatocellular necrosis was noted across all groups, including in controls, at end of treatment and recovery periods. However, above these background levels,

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moderate hepatocellular necrosis with sinusoidal congestion/hemorrhage with and without inflammation was noted in one male at end of treatment and in early decedent (euthanized on Day 18) at 200 mg/kg/day (1 time the human exposure at the human recommended dose based on AUC). The early decedent had high ALT, AST, and ALP levels. In MK-6482-004, 16% and 20% of patients had increased AST and ALT, respectively.

Other histopathology findings noted in 13-week repeat-dose studies in both rats and dogs were increased incidence of hyperplasia or metaplasia in various organs. These findings did not appear to be drug-related, as they lacked a dose relationship and were seen in control animals. Additionally, in rats, two incidences of malignant lesions were noted in kidney (nephroblastoma) and skin and subcutis (mammary carcinoma) at 6 mg/kg/day and benign adenoma of pituitary gland was reported in two recovery males at 200 mg/kg/day. Evaluating the carcinogenic potential of belzutifan for chronic use should elucidate whether the proliferative changes noted in repeat-dose toxicity studies are incidental or adverse findings.

7.5.2 Genetic Toxicology

Data (presented by FDA):

In vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/number: Bacterial reverse mutation assay/TT16-7825 (DEV-138)

Key Study Findings:

- PT2977 (PT2977-17) was not mutagenic under the conditions tested.

GLP compliance: Yes
Test system: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and Escherichia coli $Wp2_{uvr}A$; up to 5000 μg/plate; +/- S9
Study is valid: Yes

In vitro Assays in Mammalian Cells

Study title/number: In vitro mammalian cell micronucleus assay in human peripheral blood lymphocytes (HPBL) /TT16-7826 (DEV-139)

Key Study Findings:

- PT2977 (PT2977-17) was not clastogenic under the conditions tested.

GLP compliance: Yes
Test system: HPBL cells from healthy female donors; up to 383 μg/mL (1 mM); +/- S9
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title/ number: Two day oral (gavage) in vivo mammalian bone marrow erythrocyte micronucleus test in rat/ TT20-9018
Key Study Findings:

- PT2977 was not clastogenic under the conditions tested

GLP compliance: Yes
Test system: Rat/Sprague-Dawley (n=3/sex/group for dose range finding phase; 5/sex/group for main study phase), bone marrow micronuclei; dosed twice daily at 0, 10, 30, 100 mg/kg/dose (0, 20, 60 and 200 mg/kg/day) for 2 days; collection was ~48 h after the first dose
Study is valid: Yes

The Applicant's Position:

Belzutifan was not genotoxic when evaluated in the in vitro microbial mutagenesis assays and in vitro and in vivo micronucleus assays.

The FDA's Assessment:

The FDA agrees with the Applicant's conclusion.

7.5.3 Carcinogenicity

The Applicant's Position:

No carcinogenicity studies were conducted with belzutifan.

The FDA's Assessment:

The NDA submission, including a preliminary weight-of-evidence assessment, did not adequately address the carcinogenicity potential of belzutifan for chronic use. Given the early cancer indication and long-life expectancy, studies in mice and rats should be conducted to determine the risk of carcinogenicity from belzutifan. Two nonclinical post-marketing requirements (PMRs) for rodent carcinogenicity studies were communicated to the Applicant.

7.5.4 Reproductive and Developmental Toxicology

Data (presented by FDA):

Embryo-Fetal Development:

Study title/ number: Preliminary oral embryo-fetal developmental toxicity and toxicokinetics study in rats /TT207004

Key Study Findings

- MK-6482 given to pregnant rats during period of organogenesis caused post-implantation losses at ≥ 60 mg/kg/day, with complete litter loss noted at 200 mg/kg/day; decreased number of live fetuses and reduced fetal body weight at ≤ 60 mg/kg/day
- Nine fetuses at 60 mg/kg/day had incomplete ossification of sternebra and 1 fetus at 6 mg/kg/day and 2 fetuses at 60 mg/kg/day had a rib malformation (hypoblastic and/or 13th absent)

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- Four fetuses at 60 mg/kg/day had an external malformation (domed head). 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).

GLP compliance: No

Methods

Dose and frequency of dosing:	0, 3, 30, 100 mg/kg, twice daily from Day 6 to Day 17 of gestation
Route of administration:	Oral gavage
Formulation/Vehicle:	Vehicle: 0.5% (w/v) methylcellulose and 0.5% (w/v) polysorbate 80 in deionized water
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	8 females/group
Satellite groups:	6 females/group evaluated for TK and hematology parameters
Study design:	Mated female rats of approximately 10 weeks of age were treated with MK-6482 on GD 6-17 (14 females/group). A subset of females (n=6/group) were assigned for TK analysis and hematology evaluation, collected on GD 7 and GD 18, respectively. The remaining females were euthanized on GD 21 for EFD evaluation (n=8/group).
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	There was no maternal mortality.
Clinical Signs	Unremarkable
Body Weights	Maternal: Reduced mean maternal body weights versus control were -14% and -22% on GD 21 for 60 and 200 mg/kg/day, respectively. Reduced mean body weight gain was observed at ≥ 60 mg/kg/day starting on GD 6, with maximal decrease noted on DG 18 to DG 21 (-79% to -96% versus control), which was associated with post-implantation loss and/or reduced fetal body weights. Gravid uterine weights were -77% and -96% lower than control at 60 and 200 mg/kg/day, respectively.

<table>
<tr><td></td><td>Fetal: Reduced live fetal weight, -11% M/-12% F and -42% M/-46% F of control at 6 mg/kg and 60 mg/kg/day, respectively</td></tr>
<tr><td>Food Consumption</td><td>Reductions in mean maternal food intake at ≥ 60 mg/kg/day (up to -20%) on GD 20</td></tr>
<tr><td>Hematology</td><td>Decreases in red cell mass parameters (up to -23%) and reticulocytes (up to -35%) at ≥ 6 mg/kg/day</td></tr>
<tr><td>Necropsy findings Cesarean Section Data</td><td>Pregnancy occurred in all rats, except for one female in control
Complete litter loss reported in 3/8 dams at 60 mg/kg/day and 8/8 dams at 200 mg/kg/day

<table>
<tr><td></td><td colspan="4">Litter data (mean)</td></tr>
<tr><td>Dose mg/kg/day</td><td>0</td><td>6</td><td>60</td><td>200</td></tr>
<tr><td>Corpora lutea</td><td>14.6</td><td>14.6</td><td>14.4</td><td>14.5</td></tr>
<tr><td>Implantation sites</td><td>10.7</td><td>13.9</td><td>12.5</td><td>12.5</td></tr>
<tr><td>Live fetuses
Females
Males</td><td>69
37
32</td><td>104
51
53</td><td>18
5
13</td><td>0
0
0</td></tr>
<tr><td>Peri-implantation loss (%)</td><td>23.6</td><td>5.2</td><td>12.3</td><td>14.6</td></tr>
<tr><td>Post-implantation loss (%)</td><td>10.2</td><td>5.9</td><td>82.7</td><td>100</td></tr>
</table></td></tr>
<tr><td>Necropsy findings Offspring</td><td>A lower sex ratio was noted at 60 mg/kg/day (0.35) versus control (0.5).

Fetal external:
<table>
<tr><td></td><td colspan="4">Dose mg/kg/day</td></tr>
<tr><td>Findings</td><td>0</td><td>6</td><td>60</td><td>200</td></tr>
<tr><td>No. examined litter/fetus</td><td>7/69</td><td>8/104</td><td>5/18</td><td>N/A</td></tr>
<tr><td>Domed head</td><td></td><td></td><td>2/4</td><td></td></tr>
<tr><td>Protruding tongue</td><td></td><td>1/1</td><td></td><td></td></tr>
</table>
Fetal visceral:
<table>
<tr><td></td><td colspan="4">Dose mg/kg/day</td></tr>
<tr><td>Findings</td><td>0</td><td>6</td><td>60</td><td>200</td></tr>
<tr><td>No. examined litter/fetus</td><td>7/69</td><td>8/104</td><td>5/18</td><td>N/A</td></tr>
<tr><td>Pancreas variation</td><td></td><td>1/1</td><td></td><td></td></tr>
</table>
Fetal skeletal:
<table>
<tr><td></td><td colspan="4">Dose mg/kg/day</td></tr>
<tr><td>Findings</td><td>0</td><td>6</td><td>60</td><td>200</td></tr>
<tr><td>No. examined litter/fetus</td><td>7/69</td><td>8/104</td><td>5/18</td><td>N/A</td></tr>
<tr><td>Rib malformation – hypoplastic and/or absent 13th</td><td></td><td>1/1</td><td>2/2</td><td></td></tr>
<tr><td>Supernumerary rib</td><td>2/10</td><td>2/5</td><td></td><td></td></tr>
<tr><td>Sternebra incomplete ossification</td><td></td><td></td><td>3/9</td><td></td></tr>
</table>
<table>
<tr><td></td><td colspan="4">Dose mg/kg/day</td></tr>
<tr><td>Findings</td><td>0</td><td>6</td><td>60</td><td>200</td></tr>
</table></td></tr>
</table>

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	Ossified sacrocaudal vertebrae (mean)	10.4	9.4	7.2	N/A

GD: gestational day

The Applicant's Position:

In the preliminary embryo-fetal developmental toxicity study in rats, belzutifan was administered to pregnant rats at doses of 6, 60 and 200 mg/kg/day from gestation day 6 through 17. Developmental toxicity occurred at all dose levels tested and consisted of increased embryo-fetal lethality at ≥60 mg/kg/day (corresponding to subtherapeutic exposure), and reduced fetal body weight, reduced ossification, and malformations at 6 and 60 mg/kg/day (no available embryos at 200 mg/kg/day due to 100% embryofetal lethality). The NOAEL for developmental toxicity in rats was not determined.

The FDA's Assessment:

The FDA agrees with the Applicant's conclusion. The animal-to-human AUC ratio for EFD findings was determined by doubling the animal AUC12h to compare with human AUC24h. 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).

No fertility studies were conducted with belzutifan; however, based on the post-implantation loss noted in the pilot embryo-fetal development study, belzutifan may affect female fertility. Based on results from general toxicology studies in rats, belzutifan may impair fertility in males of reproductive potential. Results from these studies will be included in Section 13.1 of the label.

7.5.5 Other Toxicology Studies

The Applicant's Position:

Belzutifan was not phototoxic and was classified as a non-irritant and as a non-dermal sensitizer in safety occupational handler assays. All specified belzutifan impurities above the qualification threshold and degradation products were qualified according to ICH Q3A(R2) and ICH Q3B(R2) guidelines by virtue of their presence in the batch evaluated in the 13-week toxicity study in dogs. Potential and actual impurities, including identified impurities in each starting material, intermediate, and drug substance/product, were assessed for mutagenic potential according to ICH M7 guidance.

The FDA's Assessment:

The FDA agrees with the Applicant's conclusion. Assessment by FDA Computational Toxicology Consultation Service confirmed that belzutifan impurities were predicted to be non-mutagenic using (Q)SAR methodologies.

X	X
Claudia Miller Primary Reviewer	Tiffany Ricks Supervisor

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8 CLINICAL PHARMACOLOGY

8.1 Executive Summary

The FDA's Assessment:

Belzutifan is a small molecule inhibitor of hypoxia inducible factor 2 alpha (HIF 2α), which is overexpressed in many tumors. Belzutifan binds to HIF-2α and prevents its heterodimerization and its subsequent binding to DNA leading to decreased transcription and expression of HIF-2α target genes that regulate hypoxia and promote tumor survival.

To support the proposed indication, a single-arm study (MK-6482-004; study 004) was conducted in 61 patients with VHL-associated RCC receiving 120 mg QD dose of belzutifan. The overall response rate was 49.2% (95% CI: 36.1, 62.3). Supportive safety information was obtained from study MK-4862-001 (study 001), a dose-escalation and expansion study in patients with advanced solid tumors.

The recommended daily dose of 120 mg was selected based on the evaluation of PK, PD, and safety information from study 001. Doses ranging from 20 mg QD to 240 mg QD as well as 120 mg BID were investigated, and an MTD was not reached. Saturation in the reduction of circulating epoietin levels was observed at the 120 mg dose. Exposure-safety analysis identified a relationship between exposure and the probability of Grade 3+ anemia. This relationship was dependent on the baseline hemoglobin levels. In the VHL population, typically with high baseline hemoglobin levels, the relationship between exposure and Grade 3+ anemia was shallow compared to patients with advanced solid tumors, who had lower baseline hemoglobin levels. Therefore, dose modifications based on baseline hemoglobin levels are not recommended for the VHL population.

No dose modifications are recommended for intrinsic factors (age, sex, body weight, mild to moderate renal impairment, and mild hepatic impairment) and extrinsic factors (food intake and concomitant medications) based on population PK analysis. From a safety perspective, these factors were found to increase belzutifan exposure by 30% to 60%. The primary adverse reaction was anemia, which is relatively late onset (median onset of approximately 10 weeks) and clinically monitorable. Frequent monitoring of anemia along with dose reductions and dose interruptions as detailed in the USPI provide adequate management strategy and prespecified dose modifications are not necessary.

Patients who are dual UGT2B17 and CYP2C19 poor metabolizer (PM) are predicted to have 3.2-fold higher exposures (steady state $AUC_{0\text{-}24hr}$) compared to a patients who are UGT2B17 normal metabolizer (NM) and CYP2C19 non-poor (ultrarapid, rapid, normal, and intermediate) metabolizer. As the predicted exposure for dual PMs would be above the observed clinical exposure range, patients who are dual PMs should be closely monitored for adverse reactions.

8.2 Summary of Clinical Pharmacology Assessment

8.2.1 Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical pharmacology development program evaluated the PK and pharmacodynamics of belzutifan in patients with VHL disease-associated RCC, advanced cancer patients and healthy participants. Characterization of belzutifan PK was largely derived from data contributed from 95 patients with solid tumors who received multiple daily belzutifan doses up to 240 mg (including 120 mg BID) and 83 healthy participants who received single belzutifan doses up to 200 mg.

Two formulations were used in the clinical pharmacology development program: an oral (b) (4) tablet (FFP) and a film-coated tablet (FMF). The biopharmaceutics program established the clinical comparability between the 2 formulations and evaluated the impact of food on belzutifan PK.

In vitro, the major metabolic pathways of belzutifan are glucuronidation catalyzed by UGT2B17 and oxidation catalyzed by CYP2C19. The impact of functional variants of UGT2B17 and CYP2C19 (both are polymorphic enzymes) on belzutifan PK was assessed in a Phase 1 trial in Japanese and Caucasian healthy WONCBP. An integrated, cross-study exploratory pharmacogenetic (PGx) analysis also evaluated the impact of UGT2B17 and CYP2C19 phenotype variations on exposure.

The impact of key intrinsic factors, including the above metabolizing enzyme phenotypes, was assessed using a population-PK analysis and the PK impact is contextualized using the E-R relationship for efficacy and safety. Key extrinsic factors were evaluated based on in vitro experiments to determine the victim and/or perpetrator effects of belzutifan.

E-R analyses were performed for efficacy, safety, and biomarker levels to support dose justification. For the E-R efficacy analysis, various tumor specific categorical/continuous and time to event response variables (ORR, DCR, BOR, TTR, TTS, DOR and PFS) were evaluated against exposure. The E-R safety analysis evaluated endpoints of anemia ≥Grade 3 and hypoxia ≥Grade 3. Exposure dependence on time to dose reduction, dose interruption and dose discontinuation was also evaluated.

The effect of belzutifan concentration on QTc interval was evaluated using by-timepoint and concentration-QTc analyses to assess the mean change from baseline using data from MK-6482-004. Based on these analyses, large mean increases (>20 ms) in QTc interval due to belzutifan were excluded.

There are 4 additional ongoing or planned Phase 1 studies in healthy participants as described in Section 6.2.2.3.

The FDA's Assessment:

FDA agrees with the Applicant. The effect of intrinsic factors (age, sex, weight, mild to moderate renal impairment, mild hepatic impairment) was evaluated using population PK analysis. The effect of extrinsic factors (inhibition of UGT2B17 or CYP2C19) was evaluated using population PK based on information obtained from patients who have no UGT2B17 or CYP2C19 enzyme activity (i.e., poor metabolizers). The effect of food intake on belzutifan bioavailability was evaluated with the early formulation FFP; a food effect study is currently being conducted to evaluate the effect of intake on the bioavailability of the to-be-marketed FMI formulation. None of the evaluated intrinsic or extrinsic factors are likely to have a clinically meaningful effect on the exposure of belzutifan.

A clinical study was conducted to evaluate the effect of belzutifan, a CYP3A inducer, at the recommended dose of 120 mg QD on the pharmacokinetics of midazolam. Midazolam exposure decreased by 40% when administered concomitantly with belzutifan. Additionally, PBPK modeling was used to predict the effect of high belzutifan exposure (i.e., dual UGT2B17 and CYP2C19 poor metabolizers) on midazolam PK. Midazolam exposure is predicted to decrease by up to 70% at the high exposure scenarios. As such, appropriate recommendations regarding the concomitant use of oral hormonal contraceptives (CYP 3A4 substrates) were included in the USPI for the VHL population, who are typically young and of child-bearing age.

Based on population PK analysis, a patient who receives the recommended dose and is a UGT2B17, CYP2C19, or dual UGT2B17 and CYP2C19 poor metabolizer (PM) is predicted to have 2.0-, 1.6-, or 3.2-fold higher exposures (steady state $AUC_{0\text{-}24hr}$), respectively, compared to a patient who is a UGT2B17 normal metabolizer (NM) and CYP2C19 non-poor (ultrarapid, rapid, normal, and intermediate) metabolizer. As the predicted exposure for dual PMs would be above the observed clinical exposure range, patients who are dual PMs should be closely monitored for adverse reactions.

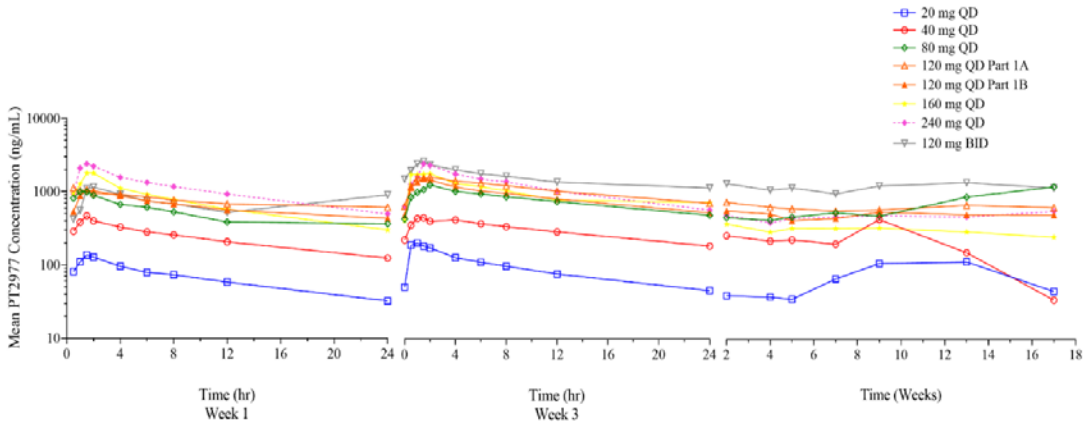
In addition, exploratory analyses suggested lower ORRs and longer median time to response (mTTR) in the subgroup of VHL-RCC patients with VHL complete or partial gene deletion compared to those with other VHL mutation types, suggesting an heterogeneity of response to belzutifan based on mutation type.

8.2.2 General Dosing and Therapeutic Individualization

8.2.2.1 General Dosing

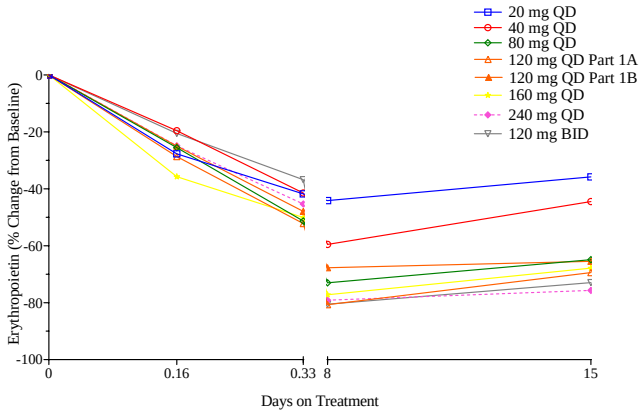
Data:

Figure 1 Applicant - Mean Plasma Concentrations of MK-6482 (PT2977; ng/mL) Versus Nominal Time (Semi-Log Scale)- Study MK-6482-001



Source: [Ref. 5.3.5.2: P001V01MK6482: Figure 11-6]

Figure 2 Applicant - Mean Percentage Change in Erythropoietin from Baseline for First 15 Days – Study MK-6482-001



Note: Predose values on nominal Day 8 (Week 2) and Day 15 (Week 3) are shown in the figure, representing 7 and 14 days of treatment.
Source: [Ref. 5.3.5.2: P001V01MK6482: Figure 11-10]

The Applicant's Position:

MK-6482-001 was a combined dose-escalation and dose-expansion trial in participants with advanced solid tumors. In the dose escalation portion, Part 1A (N=43), the PK, pharmacodynamics, safety, and efficacy of belzutifan doses ranging from 20 to 240 mg (including 120 mg BID) were evaluated. The MTD was not reached. Based on the observations of possible plateauing of exposure [Figure 1] and pharmacodynamic response, suppression of EPO [Figure 2], at higher doses, the RP2D was determined to be 120 mg QD.

The safety and efficacy of belzutifan 120 mg QD was evaluated in the pivotal Phase 2 trial in patients with VHL disease-associated RCC, MK-6482-004. Based on the 01-JUN-2020 data

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cutoff, the confirmed ORR (primary efficacy endpoint) per RECIST 1.1 was 36.1% (22 out of 61; 95% CI: 24.2%, 49.4%). In addition, the DCR was 98.4% based on a median duration of follow-up of 15.8 (4.2 to 24.1) months. While the median TTR was 31.1 weeks (min 11.6, max 61.0), the median DOR, PFS and TTS were not reached. See Section 8.1.1 for additional details.

The 120 mg QD dose of belzutifan also showed clinically meaningful ORR in VHL disease-associated non-RCC tumors including CNS hemangioblastomas, pancreatic lesions, and pancreatic neuroendocrine tumors.

Treatment with 120 mg belzutifan was tolerable based on the safety analysis which was comprised of all enrolled participants in MK-6482-004 who received at least 1 dose of belzutifan. The median duration of treatment was 68 weeks. All participants on study experienced an AE. The most common AEs (≥20% incidence) were anemia (90.2%), fatigue (60.7%), headache (37.7%), dizziness (36.1%), and nausea (31.1%). The most frequent Grade 3 to 5 AEs (>1 participant) were anemia (6.6%), fatigue (4.9%), and hypertension (3.3%). No treatment-related Grade 4 or Grade 5 events occurred. Overall, the 120 mg QD dose was tolerable, with no occurrence of treatment-related Grade 4 or Grade 5 events and low rates of drug-related AEs leading to dose interruption [14 participants (23.0%)], dose reduction [6 participants (9.8%)] or dose discontinuation [1 participant (1.6%)]. To date, the important ADRs for belzutifan are anemia due to decreased erythropoietin and hypoxia. Grade 3 anemia occurred in 4 participants (6.6%). Grade 3 hypoxia occurred in 1 participant (1.6%). Overall, most cases of anemia were mild to moderate, manageable with ESA administration and/or blood transfusion along with dose interruption or reduction.

The 120-mg dose of belzutifan is recommended as a new therapeutic option for patients with VHL disease-associated RCC and is supported by both efficacy and safety results from MK-6482-004 and an overall favorable risk-benefit profile. Exposure-response analyses for efficacy and safety further support the dose recommendation (Sections 6.3.2.2 and 6.3.2.3).

The FDA's Assessment:

FDA agrees with the Applicant.

8.2.2.2 Therapeutic Individualization

The Applicant's Position:

Intrinsic factors such as age, sex, body weight/BMI, race, ethnicity, disease status/cancer type (healthy, patients with VHL disease-associated RCC, advanced RCC, or other advanced non-RCC solid tumors), renal impairment (mild and moderate impairment) and hepatic impairment (mild impairment as categorized by NCI index) as well as the phenotype status of any single metabolic enzyme (UGT2B17, CYP2C19) do not have a clinically meaningful impact on MK-6482 exposures (AUC) and no dose adjustment is recommended based on any of these factors. The pop-PK analysis demonstrated that the UGT2B17/CYP2C19 dual PM phenotype is anticipated to be associated with greater than 2X increases (~ 2.3X) in MK-6482 AUC compared to a reference group, UGT2B17 IM/CYP2C19 non PMs. Based on E-R analyses for efficacy and safety, and the

overall benefit-risk profile at these higher exposures in VHL-RCC patients, no dose adjustment is recommended. Of note, in the overall US population, the expected frequency of the UGT2B17/CYP2C19 dual PM phenotype is estimated to be approximately 0.5%.

Drug administration with food did not have a clinically meaningful impact on belzutifan PK and belzutifan can be administered without regard to food.

Given that UGT2B17 and CYP2C19 poor metabolizers have no enzyme activity, the safety profile observed in subjects who are poor metabolizers can be extrapolated to support the lack of a clinically relevant drug interaction effect when belzutifan is co-administered with inhibitors of UGT2B17 or CYP2C19 and no dose adjustment is recommended in such scenario. A study to evaluate the impact of a strong CYP2C19 inducer (rifampin) on belzutifan PK is planned.

The FDA's Assessment:

FDA agrees with the Applicant. The proposed dosing regimen of 120 mg QD is acceptable. Intrinsic (mild hepatic impairment, mild to moderate renal impairment, body weight, age, and enzyme polymorphisms) and extrinsic factors (concomitant medications and food intake) may alter belzutifan exposure. However, the change in exposure is not likely to be clinically meaningful. Patients with mild to moderate renal impairment, mild hepatic impairment, lower body weight, or with concomitant medications that inhibit UGT2B17 or CYP2C19 are likely to have increased exposure. The change in exposure in each of these cases ranges from 30% to 60% relative to the typical subject. Given that the primary adverse reaction for belzutifan is anemia, which is relatively late onset, manageable, and monitorable, no dose modifications are recommended based on these factors.

8.2.2.3 Outstanding Issues

The Applicant's Position:

Additional ongoing or planned Phase 1 studies in healthy participants include: an absorption, metabolism, and excretion study with [^{14}C]-belzutifan (MK-6482-008), a DDI study to evaluate the potential of belzutifan to induce CYP3A4 (MK-6482-009), a DDI study to evaluate the impact of a strong CYP2C19 inducer (rifampin) on belzutifan PK (MK-6482-017), and a definitive food effect study with the commercial tablet formulation (MK-6482-014). These studies have not been completed at the time of this submission.

The Applicant will continue to monitor the safety and efficacy of participants enrolled in MK-6482-004, which will provide further insights on the long-term implications of belzutifan treatment and exposure variations. (b) (4)

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(b) (4)

The FDA's Assessment:

FDA agrees with the Applicant.

8.3 Comprehensive Clinical Pharmacology Review

8.3.1 General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

An overview of the ADME properties, PK and DDI potential of belzutifan are summarized below.

Absorption

Following oral administration of belzutifan 120 mg, median Tmax is achieved within 1-2 hours under fasted conditions. A high-fat, high-calorie meal delays Tmax, with a median difference (Fed – Fasted) of 2 hours; however, there is no effect on the extent of belzutifan absorption based on comparison of AUC0-t and AUC0-inf, which are contained within the 0.80 to 1.25 reference interval for AUC ratio. Therefore, belzutifan may be administered without regard to food. The absolute bioavailability of belzutifan has not been determined.

Distribution and Protein Binding

Following belzutifan 120 mg once daily in advanced RCC patients, the mean V_z/F (CV) is 138 L (28%) suggesting extensive distribution to tissues. The plasma protein binding of belzutifan is 45%. Based on pop-PK analysis, for 120 mg QD dosing, the geometric mean (GeoCV%) total volume of distribution (Vd/F) is 130 L (35.2%) in VHL-RCC patients.

Metabolism

An ADME study (MK-6482-008) is currently ongoing. In vitro, belzutifan is metabolized primarily via the polymorphic enzymes UGT2B17 and CYP2C19. UGT2B17 is the major route of elimination in subjects who express that enzyme, with the fraction eliminated via UGT2B17 dependent on both the UGT2B17 and CYP2C19 phenotype. In subjects not expressing UGT2B17, CYP2C19 is a major route of elimination. Belzutifan glucuronide (PT3317), a major human metabolite formed by UGT2B17, circulates at exposures ~ 32% of the belzutifan exposure at steady state. PT3317 does not inhibit HIF-2α and has low potential to be a perpetrator of drug interactions. PT3317 exposures were well below human levels in 13 week rat GLP safety studies and comparable to clinical exposures in 13 week dog GLP safety studies (~ 1.8x exposure multiples relative to a 120 mg clinical dose of belzutifan).

Steady-State

Following once-daily dosing of 20 mg to 240 mg in patients with advanced solid tumors, the mean AUC accumulation ratio (CV) at steady state for belzutifan is 1.27 to 1.54 (21% to 49%). In patients with advanced RCC, the mean (CV%) accumulation ratio for AUC is 1.49 (48%) for 120 mg QD belzutifan. Based on the pop-PK analysis, for 120 mg QD belzutifan in VHL-RCC patients,

the geometric mean (GeoCV%) AUC accumulation ratio is predicted to be 1.41 (18.7%) for FFP and 1.44 (19.5%) for FMF, respectively.

Linearity and Dose Proportionality

Based on single and multiple dose data from patients with advanced solid tumors and single dose data from healthy participants, belzutifan PK (Cmax and AUC) appears generally dose-proportional up to 200 mg.

Clinical Pharmacokinetics

In patients with advanced RCC, the steady-state GM Cmax and AUC0-tau for 120 mg QD were 1.7 µg/mL (4.4 µM) and 18.1 µg•hr/mL (47.3 µM•hr). Based on the pop-PK model analysis, the steady-state GM for Cmax and AUC0-tau for 120 mg in VHL disease-associated RCC patients are predicted to be 1.4 µg/mL (3.6 µM) (and 1.3 µg/mL for FMF) and 16.7 µg•hr/mL (43.6 µM•hr), respectively. The slightly lower predicted Cmax and AUC values in VHL disease-associated RCC patients compared to non-VHL disease patients with advanced RCC may reflect the underlying age and chronic comorbidity (including renal impairment) differences between the populations.

Comparison of observed single-dose mean Cmax and AUC values in healthy participants across studies to Cmax and AUC values in VHL and non-VHL patients for 120 mg MK-6482 shows that these parameters are generally similar between patients and healthy participants, supporting the conduct and extrapolation of results from studies in healthy participants to patients.

Intrinsic Factors

The effects of age, gender, disease status/cancer type (healthy volunteers, and patients with VHL-RCC, advanced RCC, or other advanced non-RCC solid tumors), phenotype (UGT2B17 and CYP2C19 polymorphisms), body weight/BMI, race, ethnicity, renal impairment and hepatic impairment on belzutifan PK have been characterized in Phase 1 studies and/or pop-PK analyses. With the exception of the UGT2B17 and CYP2C19 dual PM phenotype, the effects of evaluated intrinsic factors are generally small (<2X increase in AUC), and unlikely to be clinically meaningful.

However, in a typical VHL disease-associated RCC patient weighing 74 kg, the combined UGT2B17/CYP2C19 dual PM phenotype is projected to result in a 2.3X increase in AUC (43.6 µg•hr/mL) compared to the reference group, UGT2B17 IM/CYP2C19 non-PMs (19.0 µg•hr/mL). An exploratory pharmacogenetic analysis predicted a larger magnitude of effect on AUC (~3X) for the combined UGT2B17/CYP2C19 dual PM phenotype relative to the same reference population. Since the pop-PK analysis includes a larger data pool, particularly participants from the pivotal trial, MK-6482-004, the pop-PK model estimates should be more representative of the observed effects of UGT2B17 and CYP2C19 phenotype in the VHL-RCC population.

Extrinsic Factors

No extrinsic factor evaluation studies were completed at the time of the submission. Belzutifan is metabolized by UGT2B17 and CYP2C19. Given that UGT2B17 and CYP2C19 poor metabolizers have no enzyme activity, the safety profile observed in subjects who are poor metabolizers can

be extrapolated to support the lack of a clinically relevant drug interaction effect when belzutifan is co-administered with inhibitors of UGT2B17 or CYP2C19, in that exposures in these PM subjects would recapitulate a theoretically maximal effect of enzyme inhibition. A study to evaluate the impact of a strong CYP2C19 inducer (rifampin) on belzutifan PK is planned (MK-6482-017).

Based on an in vitro risk assessment, belzutifan has the potential to induce CYP3A4. To quantify this risk, a physiologically based pharmacokinetic (PBPK) model was built to project the impact of repeat dosing of 120 mg QD belzutifan on midazolam exposures. These projections suggest that belzutifan may be a moderate CYP3A4 inducer in humans. The effect of belzutifan on midazolam PK is currently being assessed clinically in a Phase 1 trial in healthy participants, MK-6482-009. The preliminary PK data from the study suggests a reduction in AUC0-inf in the range of ≥20% to <50% for midazolam after 7 day administration of 120 mg QD belzutifan, suggesting a weak CYP3A4 induction potential for belzutifan (ongoing analysis; data on file and not submitted).

The FDA's Assessment:

PHARMACOLOGY	
Mechanism of Action	Belzutifan is a small molecule inhibitor of HIF-2α, which is overexpressed in many tumors. Belzutifan binds to HIF-2α and prevents its heterodimerization and its subsequent binding to DNA, leading to decreased transcription and expression of HIF-2α target genes that regulate hypoxic signaling and promote tumor survival.
Active Moiety	Belzutifan.
QT Prolongation	In study MK-6482-004 in patients VHL disease at the recommended dose (120 mg QD), belzutifan did not cause large mean increases (I.e., > 20 msec) in the QT interval. The point estimate and the 90% CI corresponding to the largest upper bound of ΔQTCF was 2.5 msec (0.6 to 4.4) at 1380 ng/mL.
GENERAL INFORMATION	
Molecular Weight	383.34 g/mol
Formulation Development	FFP formulation was initially developed used in the FIH dose escalation study 001, Phase 2 efficacy study MK-6482-004, and food effect study MK-6482-002. A film-coated FMF formulation was developed and used in the expansion phase of study 001 and study 004. Study 006 was conducted to compare the bioavailability of the FMF compared to the FFP formulation; the GMR (90% CI) of $AUC_{0\text{-}inf}$ was 0.93 (0.88-0.98) and C_{max} was 0.87 (0.77-0.99). The to-be-marketed (FMI) formulation is manufactured with very

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	minor process changes and embossing compared to FMF is was bridged using in vitro dissolution.
Bioanalysis	Belzutifan and the glucuronide metabolite were measured using a validated LC/MS/MS method.
Dose Proportionality	The PK of belzutifan exhibited dose-proportional increase in AUC and C_{max} after single and multiple doses ranging from 20 mg to 240 mg QD.
Accumulation	The accumulation of AUC_{0-24h} values on Day 15 relative to Day 1 was approximately ranged from 1.27 to 1.54.
Variability	The intersubject variability (CV%) was 13% to 65% for C_{max} and 30% to 64% for AUC at steady-state across the dose escalation range (20 mg QD, 40 mg QD, 80 mg QD, 120 mg QD, 160 mg QD, 240 mg QD, and 120 mg BID).
ABSORPTION	
Absolute Bioavailability	The absolute bioavailability of belzutifan has not been characterized.
T_{max}	In patients with advanced solid tumors, the peak belzutifan plasma concentration was achieved within 1 to 2 hours after oral administration.
Food Effect	A high-fat and high-calorie meal resulted in a small decrease in AUC 3%) but a more substantial decrease in C_{max} (35%) relative the fasted state. Of note, the food effect study (study MK-6482-002) was conducted with the FFP formulation. A food-effect study with the FMI formulation is ongoing.
Substrate Transporter Systems	Belzutifan is a substrate of P-gp but is not a substrate of BCRP.
DISTRIBUTION	
Volume of Distribution	The total mean volume of distribution (% CV) after a 120 mg oral dose of belzutifan was 130 (35%) L.
Plasma Protein Binding	45%
Blood-to-Plasma ratio	0.88
ELIMINATION	
Mean Terminal Half-Life	The mean terminal half-life of belzutifan is 14 hours
METABOLISM	
Primary Metabolic Pathways	Belzutifan is metabolized by the polymorhpic enzymes UGT2B17 and CYP2C19.
Transporter Substrate	In vitro, belzutifan is not a substrate of OATP1B1 or OATP1B3.
DDI Potential	Enzyme Inhibition

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	In vitro, belzutifan did not inhibit CYP enzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5). Enzyme Induction Belzutifan did not induce CYP1A2 or CY2B6. However, belzutifan is an inducer of CYP3A4. At 120 mg QD, belzutifan decreased midazolam AUC by 40% and C_{max} by 34%. PBPK modeling predicts a more substantial decrease in midazolam AUC (up to 70%) in subjects with higher belzutifan exposure (eg., dual UGT2B17 and CYP2C19 poor metabolizers). Transporter Inhibition Belzutifan inhibits MATE2K in vitro but did not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, or OAT3.
EXCRETION	
Primary Excretion Pathway	Routes of elimination have not been identified. Mass balance study (Study MK-6482-008) is ongoing.

FDA agrees with the use of popPK analysis to model the impact of UGT2B17 and CYP2C19 phenotype on belzutifan exposure. However, FDA recommended comparison of dual UGT2B17/CYP2C19 PMs to a reference group of UGT2B17 NM/CYP2C19 non-PMs in the presentation of changes in exposure (Information Request dated April 8, 2021). In the revised analysis by the Applicant, in a typical VHL disease-associated RCC patient weighing 74 kg, the combined UGT2B17/CYP2C19 dual PM phenotype is projected to result in a 3.2X increase in AUC (43.6 µg•hr/mL) compared to the reference group, UGT2B17 NM/CYP2C19 non PMs (13.7 µg•hr/mL). Also see section 8.3.2.3.

8.3.2 Clinical Pharmacology Questions

8.3.2.1 Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

The Applicant's Position:

The E-R relationships for efficacy, safety and biomarker/pharmacodynamic markers provide supportive evidence of effectiveness for the 120 mg QD dose as described below further in Section 6.3.2.2 and 6.3.2.3.

The FDA's Assessment:

Yes, the clinical pharmacology program provides evidence of effectiveness. Primary evidence of efficacy was obtained from study 004 in 61 patients with VHL-associated RCC receiving 120 mg QD dose of belzutifan. The overall response rate was 49.2% (95% CI: 36.1, 62.3).

The 120 mg dose was selected based on PK, PD, and safety information obtained from the FIH study (study 001) in patients with advanced solid tumors. In the escalation portion of study 001, escalating doses of belzutifan (20 mg, 40 mg, 80 mg, 120 mg, 160 mg, and 240 mg QD and 120

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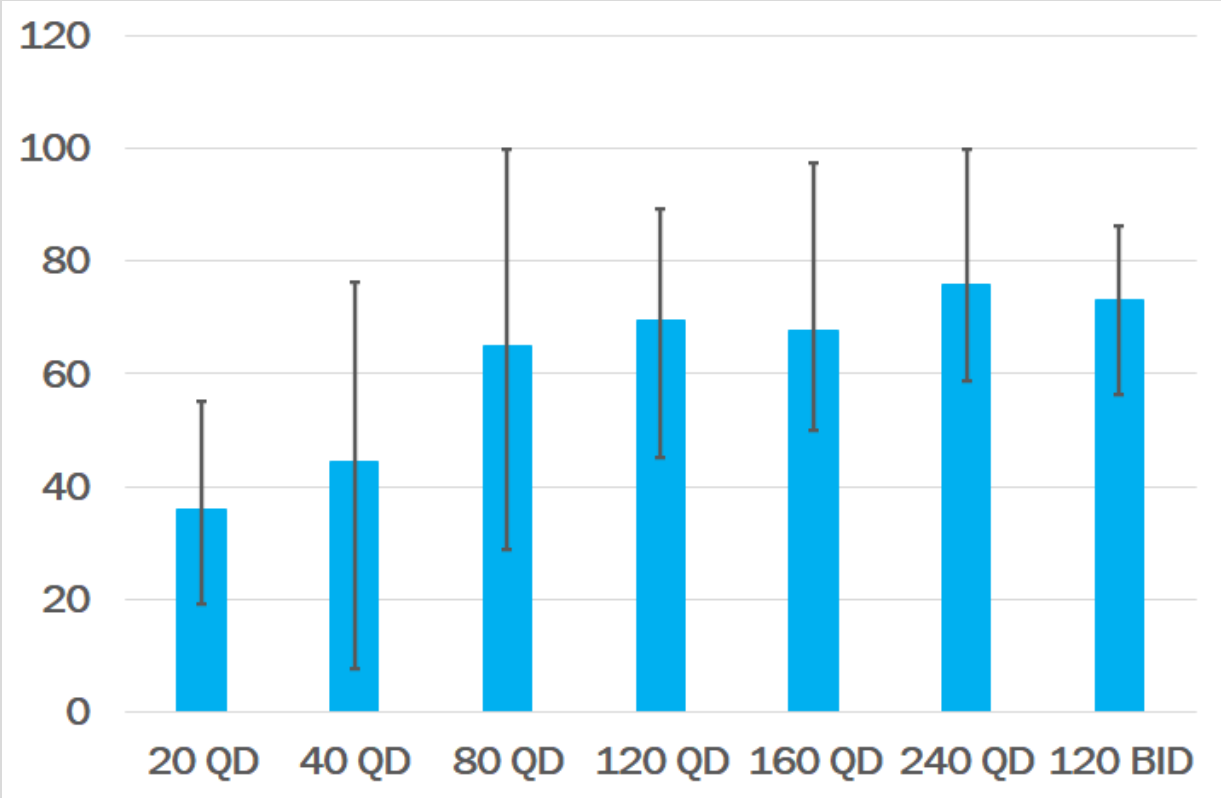
mg BID) were investigated. The MTD was not reached at any of the investigated cohorts; however, PD (% epoetin inhibition by week 3) information demonstrated saturation of effect at doses greater than 120 mg QD (Figure 3). The 120 mg QD dose was selected for investigation in the expansion phase of study 001 and for study 004.

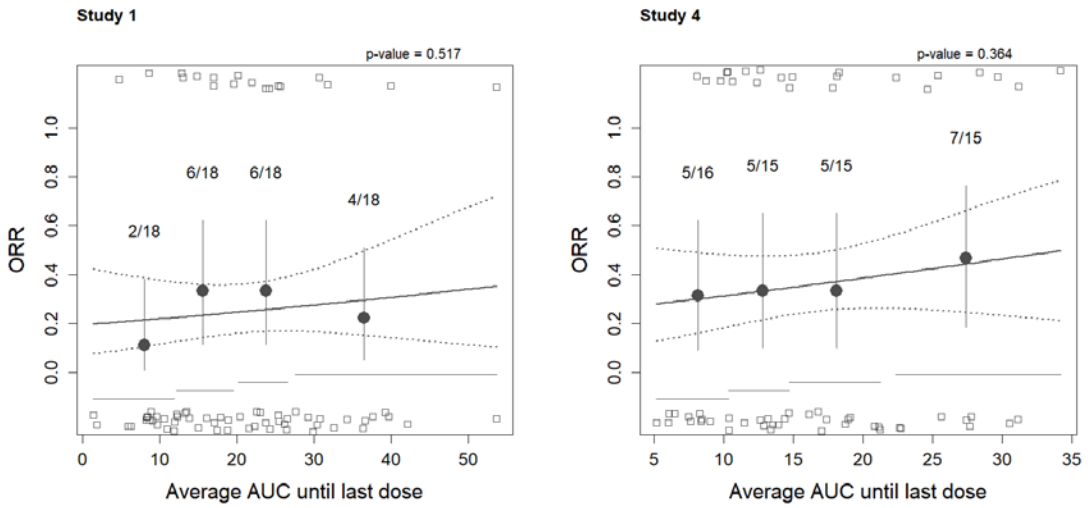
Figure 3: Relationship between PD effect (% epoietin inhibition) and administered belzutifan dose at week 3 of treatment in patients with advanced solid tumors.



8.3.2.2 Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

Data:

Figure 4 Applicant - Plots of ORR for RCC Tumors Versus AUCavgeot Relationship, with ORR Grouped by AUCavgeot Quartiles and a Linear Logistic Regression Fit by Study (Study 1: MK-6482-001; Study 4: MK-6482-004)



Abbreviations: AUCavgeot=average area under the concentration-time curve until end of treatment
Notes: Open squares represent individual values, represent subjects with event (at the top) and subjects with no event (at the bottom). Observations were jittered for improved visualization. Numbers depict n/N for each exposure quartile, with n being number of subjects with an event and N being total number of subjects.
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.
Source: [Ref. 5.3.3.5: 05MSSH: Figure 16]

The Applicant's Position:

The 120 mg QD dose of MK-6482 for patients with VHL-RCC is supported by efficacy and safety results from MK-6482-004, E-R relationships for efficacy, safety and biomarker/ pharmacodynamic markers, and an overall favorable risk-benefit profile.

As described in Section 6.2.2.1, the 120 mg QD dose of MK-6482 evaluated in MK-6482-004 showed (i) clinically meaningful efficacy in renal as well as non-renal (CNS hemangioblastomas, pancreatic lesions, and pancreatic neuroendocrine tumors) tumors, (ii) reasonable safety/tolerability, with no occurrence of treatment-related Grade 4 or Grade 5 events and low rates of drug-related AEs responsible for dose interruption, dose reduction or dose discontinuation, (iii) low incidence of Grade 3 anemia and Grade 3 hypoxia, and (iv) anemia being manageable with ESA administration and/or blood transfusion along with dose interruption or reduction.

Although only a single dose level (120 mg) was evaluated in MK-6482-004, there was an ~ 7-fold AUC range of 5.16 to 34.2 µg•hr/mL based on average AUC until end of treatment and ~ 8.5-fold AUC range of 5.2 to 43.5 µg•hr/mL based on nominal steady state AUC with 120 mg QD due to the inter-individual variability, enabling E-R analyses of key clinical efficacy endpoints in patients with VHL-RCC across a broad range of exposures. Efficacy E-R analyses were also

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conducted for non-VHL disease patients with advanced RCC in MK-6482-001 in parallel for general comparison.

Within the broad exposure range achieved at a single dose level (120 mg QD), no significant relationship between exposure (AUC) and various efficacy endpoints (ORR, DCR, PFS, BOR, TTR, DOR) was observed for patients with VHL-RCC or non-VHL disease patients with advanced RCC. However, a slight positive trend for ORR for RCC lesions, which was not statistically significant, was observed for both patient groups [Figure 3]. In non-VHL disease patients with advanced RCC in MK-6482-001, a slight positive trend was also observed for DCR for RCC lesions.

Given the relatively long TTR for RCC lesions observed for patients with VHL-RCC treated with belzutifan, the completed E-R analyses may not yet fully reflect the potential underlying relationship for ORR and DCR for RCC lesions. Furthermore, based on the slight improving trend in ORR with higher exposure for RCC lesions in VHL patients, dose adjustments to achieve lower exposures may not be desirable in the setting of acceptable safety and tolerability. In addition, since the number and percentage of responders was similar in the lowest exposure quartile compared to the other quartiles, these patients appear to derive satisfactory treatment response while having lower risk of exposure-related safety issues.

In general, E-R analyses for safety do not show significant safety concerns associated with higher MK-6482 exposures. A positive E-R relationship was observed for Grade 3 anemia in both patients with VHL-RCC and non-VHL disease patients with advanced RCC or other solid tumors. Notably, a strong relationship between baseline Hgb and Grade 3 anemia was also observed. Since non-VHL disease patients with advanced RCC had lower median baseline Hgb than patients with VHL-RCC (11.8 g/dL versus 14.0 g/dL), this difference could explain the observed higher incidence of Grade 3 anemia (27.3% [15 in 55 patients] versus 6.6% [4 in 61 patients]) at 120 mg QD dose in the former compared to the latter. Thus, although higher belzutifan exposures are associated with a greater risk of Grade 3 anemia, this risk is considered relatively low in VHL-RCC patients because of their higher baseline Hgb values. Furthermore, anemia was clinically well managed. No clear E-R relationship for Grade 3 hypoxia was detected in either patients with VHL-RCC or non-VHL disease patients with advanced RCC.

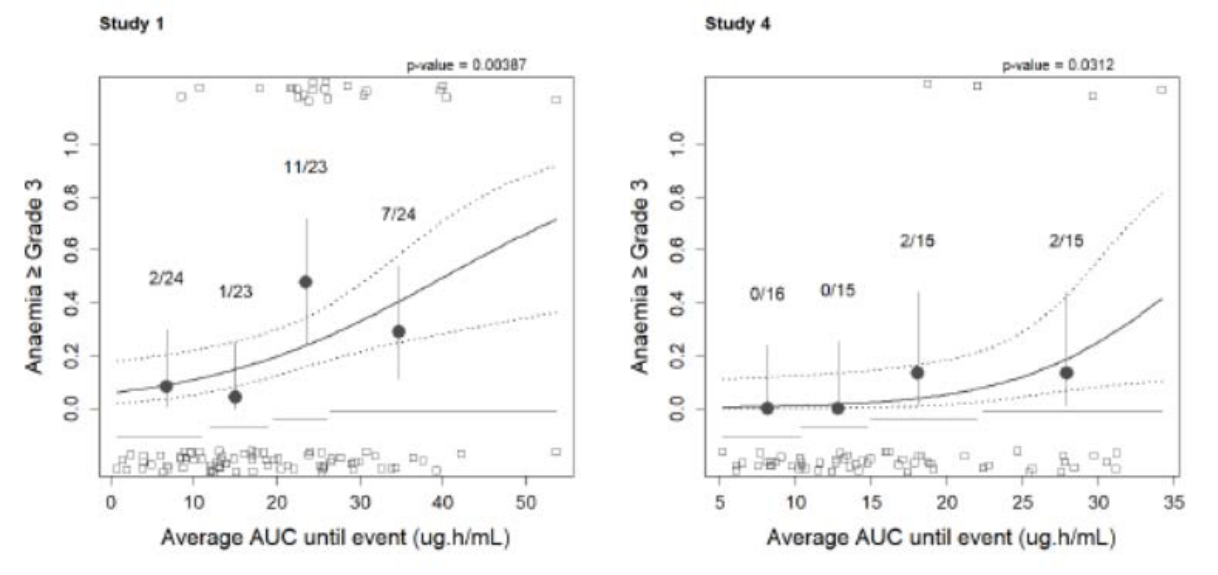
The FDA's Assessment:

FDA agrees with the Applicant. There is a trend of increased probability of Grade 3+ anemia with increased belzutifan exposure in study 004 (Figure 5). However, the relationship is shallow and the probability of anemia is low even at the highest exposure range. The low incidence of anemia in the VHL population is primarily due to the high baseline hemoglobin levels in this population, relatively young population with no prior chemotherapy treatment. The proposed 120 mg QD dose achieves and acceptable balance of safety and efficacy in the VHL population.

In patients with low hemoglobin levels (< 12 g/dL) in study 001 , the probability of anemia increased dramatically (Figure 5). As such, a different dosing regimen may be required to

balance safety and efficacy in a patient population that is heavily pre-treated and has low levels of baseline hemoglobin.

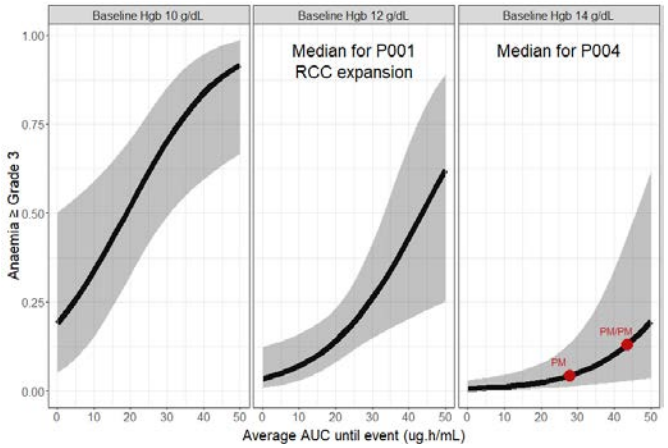
Figure 5: Relationship between Grade 3+ anemia and belzutifan exposure in study 001 (left panel) and study 004 (right panel)



8.3.2.3 Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

Data:

Figure 6 Applicant - Predicted Incidence of Grade 3 Anemia Versus AUCavg Based on Linear Logistic Regression Model Including AUCavg and Baseline Hgb as Predictors for Three Baseline Hgb Scenarios



Notes: Rightmost panel depicts projected risk at expected exposures (red dots) for typical reference VHL-RCC patient with UGT2B17 PM phenotype (1.5X exposure; AUCss=27.9 µg•hr/mL and corresponding model predicted Grade 3 anemia incidence [95% CI] of 4.2% [1.3%, 13.3%]) and UGT2B17/CYP2C19 dual PM phenotype (2.3X Exposure; AUCss=43.6 µg•hr/mL and

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corresponding model predicted Grade 3 anemia incidence [95% CI] of 13.0% [2.8%, 43.1%]), assuming baseline Hgb of 14 g/dL (median observed in Study MK-6482-004).

Solid line and shaded area represent model predicted incidence and 95% CI based on the logistic regression fit of the form logit(prob[event]) AUC × $slope_{AUC}$ + Baseline Hgb × $slope_{Hgb}$ + intercept. CI = confidence interval. The projection of incidence of Grade 3 anemia are shown by red dots for the expected exposures for typical reference patient in the study with UGT2B17 poor metabolizer (PM) and UGT2B17/CYP2C19 dual PM (PM/PM) phenotype.

Source: [Ref. 5.3.3.5: 05MSSH: Figure 70] [Ref. 5.3.3.5: 05MSSH: Table 64]

The Applicant's Position:

AUC is reasoned to be the most critical PK parameter for MK-6482 since it represents an overall measure of average daily concentration. Furthermore, all of the identified efficacy (tumor reduction) and safety parameters (anemia, hypoxia) of interest in VHL-disease patients are more likely the result of sustained drug effects associated with prolonged cumulative belzutifan exposures, rather than caused by brief low or high concentrations (ie, which would otherwise track or correlate more with Cmin or Cmax, respectively). The effects of age, sex, metabolizer phenotype (UGT2B17 and CYP2C19 polymorphisms), 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 (mild and moderate impairment) and hepatic impairment (mild impairment as categorized by NCI index) on MK-6482 PK have been evaluated in Phase 1 studies and/or pop-PK analysis. The results from the pop-PK analysis indicate that the individual effects of the majority of evaluated intrinsic factors are associated with less than a 2X increase in MK 6482 exposures (AUC) and no dose adjustment is recommended based on any of these single factors.

UGT2B17 and CYP2C19 phenotype were identified as the most important intrinsic or extrinsic factor impacting MK-6482 PK. The pop-PK analysis indicates that the combined UGT2B17/CYP2C19 dual PM phenotype is associated with a 2.3X higher MK-6482 AUC compared to the reference group, UGT2B17 IM/CYP2C19 non-PMs, in a typical 41-year, 74-kg subject. In contrast, UGT2B17 EM/CYP2C19 non-PMs are predicted to have 0.7X lower AUC compared to the same UGT2B17 IM/CYP2C19 non-PMs reference typical subject. Generally similar magnitude effects are predicted based on an exploratory PGx analysis; this cross-validation supports the strength of the model predictions from both approaches.

In the MK-6482 clinical development program, doses up to 240 mg QD and 120 mg BID have been evaluated for safety and tolerability, and are associated with a steady-state GM for AUC0-24 up to 42.4 µg•hr/mL (120 mg BID). For reference, based on the pop-PK model analysis, the steady-state GM AUC0-24 in VHL-RCC patients is predicted to be 16.7 µg•hr/mL at the 120 mg QD dose. To date, no MTD for belzutifan has been established with dosing up to 120 mg BID. Although only the 120-mg dose has been evaluated for safety and efficacy in VHL-RCC patients, individual belzutifan AUCs spanned an ~ 7-fold AUC range of 5.16 to 34.2 µg•hr/mL based on average AUC until end of treatment and ~ 8.5-fold AUC range of 5.2 to 43.5 µg•hr/mL based on nominal steady state AUC with 120 mg QD. No DLTs were identified in patients with VHL-RCC in MK-6482-004, which included 5 UGT2B17 PMs and no UGT2B17/CYP2C19 dual PMs.

As described earlier, E-R analyses for safety showed a positive relationship for Grade 3 anemia, but no apparent relationship for Grade 3 hypoxia. In VHL-RCC patients at 120 mg QD, the overall incidence of Grade 3 anemia was low (6.6%; 4 in 61 patients), and was clinically well managed. There were no dose discontinuations due to drug-related anemia AEs; 3 (4.9%) patients had a dose interruption and 1 (1.6%) patient had dose reduction based on drug-related anemia AEs. The lower incidence of Grade 3 anemia in VHL patients relative to that in advanced RCC patients is attributed to the generally normal baseline Hgb values (median ~ 14 g/dL) in this population. In this context, the risk of Grade 3 anemia at the higher exposures expected with UGT2B17/CYP2C19 dual PMs is projected to be low in VHL patients [Figure 4].

Regarding efficacy, the E-R analyses for various efficacy endpoints in VHL-RCC patients were relatively flat, with a slight positive trend (albeit not statistically significant) between belzutifan exposure and ORR and BOR for RCC lesions, supporting the possibility of greater benefit with higher exposures. Thus, in this instance, dose adjustment for safety may not outweigh the potential therapeutic benefit in the setting of acceptable safety and tolerability. Therefore, no dose-adjustment is proposed for the above described intrinsic factors that result in higher exposures.

The relatively flat E-R relationships between belzutifan exposure and ORR, DCR and BOR in VHL-disease patients suggest that individuals at the lower end of the exposure range receive satisfactory benefit from belzutifan treatment, while having a lower risk of exposure-related safety issues. Further long-term data may elucidate whether these patients gain further tumor reduction with continued treatment. Dose adjustments to achieve higher belzutifan exposures in these individuals is not supported by the totality of the evidence. Therefore, no dose-adjustment is proposed for the above described intrinsic factors that result in modest decrease in exposures.

The FDA's Assessment:

Intrinsic factors such as body weight, renal function, hepatic function, age, and enzyme polymorphisms were found to be significant covariates for belzutifan exposure.

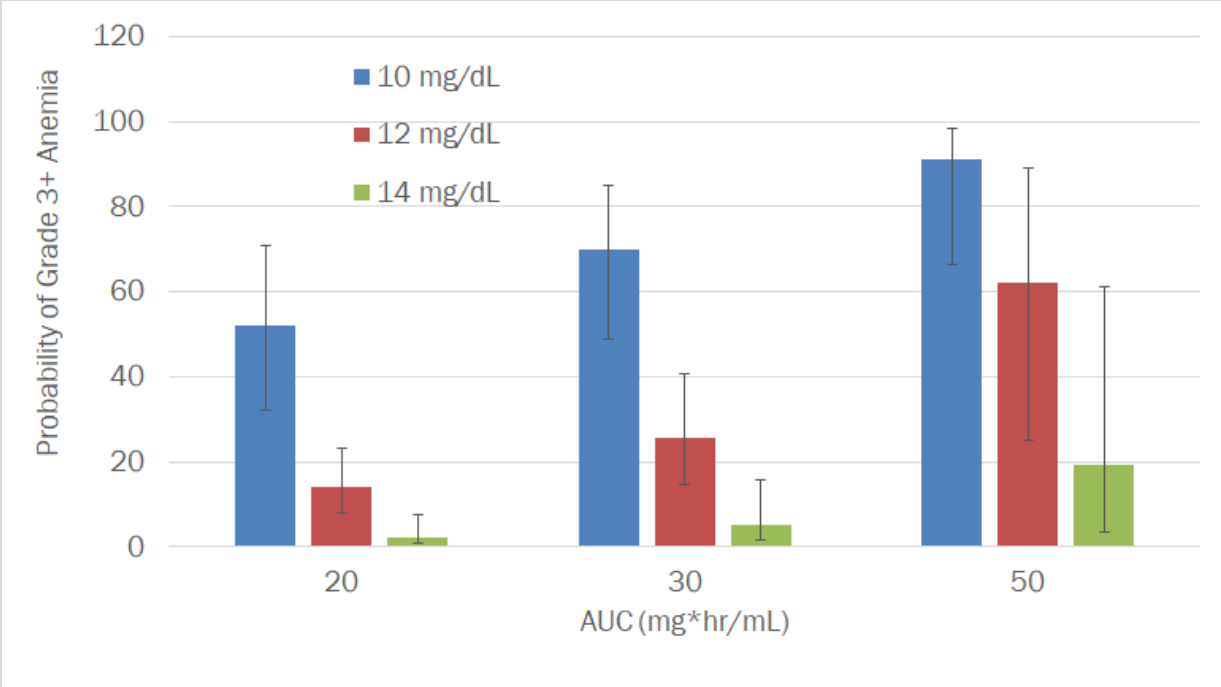
Body weight is predicted to result in exposure change from increase of 25% at 5th percentile (53 kg) to a decrease of 30% in exposure at the 95th percentile (130 kg). Patients with mild hepatic impairment (n=8) are predicted to have a 37% increase in belzutifan exposure compared to patients with normal hepatic function (n=109). Similarly, patients with mild (n=42) or moderate (n=37) renal impairment are predicted to have 44% and 53% increase in exposure compared to patients with normal renal function (n=37). Exposure is predicted to decrease by 20% in subjects at the 5th percentile of the age range (26 years) compared to an increase of 17% in patients at the 95th percentile (74 years).

A dosage modification recommendation is not warranted in the VHL population because the baseline hemoglobin level are high and a change in exposure from the target 20 mg*hr/mL up to 50 mg*hr/mL (i.e. 150% increase in exposure) is predicted to have a modest increase in the

predicted probability of Grade 3+ anemia. Additionally, the observed anemia in study 004 was relatively late onset (median time to incidence is ~10 weeks) and is reversible and monitorable. As such, frequent monitoring for anemia along with dose interruptions and reductions is an adequate management strategy for patients with VHL disease.

It is important to note, however, that risk-benefit ratio in other populations (i.e., heavily pre-treated populations with low baseline hemoglobin levels) may warrant a different management strategy; one that is based on prespecified dose modifications based on hemoglobin levels as the predicted probability of Grade 3+ anemia might be substantially higher (Figure 7).

Figure 7: Relationship based on predicted Grade 3+ anemia and exposure at different baseline hemoglobin levels.



UGT2B17 and CYP2C19 Poor Metabolizers

The Applicant estimates that overall, 0.5% of the United States population are dual PMs, however frequencies can reach 15% in certain populations such as in Japanese (Table 2).

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Table 2. Estimated CYP2C19 and UGT2B17 Poor Metabolizer Frequency

Phenotype	Expected Phenotype Frequency (%)						
	European	East Asian	Japanese	African American	South Asian	Latino	United States[f]
CYP2C19 PM[a]	2.39	13.02	19.19	4.76[d]	8.16[e]	1.16	3.12
UGT2B17 PM[b]	14.51	68.65	76.92	5.75	38.24	11.24	15.94
Dual CYP2C19 and UGT2B17 PMs[c]	0.35	8.94	14.76	0.27	3.12	0.13	0.50

CYP2C19=cytochrome P450 enzyme 2C19; PM=poor metabolizer; UGT2B17=uridine diphosphate glucuronosyltransferase 2B17

[a] CYP2C19 Frequencies and phenotype definitions from https://www.pharmgkb.org/page/cyp2c19RefMaterials, March 2020, except for Japanese column derived from [Ref. 5.4: 05LLGB].
[b] Frequencies from 1000 genomes Phase3v5. Frequencies for Latinos taken from "Admixed American" category; frequencies for African Americans taken from "African" category.
[c] Expected frequency for dual-PMs is calculated by multiplying frequency of CYP2C19 and UGT2B17 PM, assuming the incidence of each is independent in each population.
[d] Frequency is calculated across both African-American and Afro-Caribbean populations, however the majority of subjects used to generate the estimate are African-American.
[e] Frequency is calculated across both South and Central Asians, however the majority of subjects used to generate the estimate are South Asian.
[f] Derived from CYP2C19 frequencies and phenotype definitions from PharmGKB (https://www.pharmgkb.org/page/cyp2c19RefMaterials) March 2020, UGT2B17 frequencies from 1000 Genomes Phase 3v5, weighted by expected frequencies of each race/ethnic group from the American Community Survey 2018 1-Year estimates: 60.2% White, 18.3% Hispanic or Latino, 12.3% Black or African-American, 4.3% East Asian, 1.3% Asian Indian (Imputed as South Asian), and 3.6% Other (https://data.census.gov/cedsci/table?t=Asian&tid=ACSDP1Y2018.DP05&hidePreview=false) (assume phenotype frequencies for Other category is the average of the reported frequencies for Europeans, East Asians, African Americans, South Asians and Latinos).

To assess the impact of UGT2B17 and CYP2C19 variants on belzutifan PK in the popPK analysis, blood samples of 250 participants from 5 studies (MK-6482-001, MK-6482-002, MK-6482-004, MK-6482-006, and MK-6487-007) were genotyped for CYP2C19 reduced function (*2, *3 *4, *5, *6, *7, *8, *9, *10, *35) and increased function (*17) and UGT2B17 reduced function (*2) alleles using TaqMan assays and the Affymetrix Pharmacoscan array. Phenotypes were inferred based on genotypes. Consistent with expected frequencies, the only clinical and PK data with dual PMs came from the Phase 1 healthy volunteer study MK-6482-007, which included 10 female participants who were dual UGT2B17 and CYP2C19 PMs (9 Japanese and 1 White). The mean AUC0-inf in these 10 patients was 27329 h*ng/mL compared to 6411 h*ng/mL in patients who were CYP2C19 NM/UGT2B17 NM (N=4; reviewer analysis). The popPK model estimated a 3.2 fold increase in this phenotype subgroup (see FDA's Assessment in Section 8.3.1).

The Applicant also conducted an exploratory analysis to ascertain if there was an association between CYP2C19 or UGT2B17 phenotype and frequency and severity of safety events in studies MK-6482-004 (N=58/61) and MK-6482-001 (N=55/58). However, results were inconclusive due to the limited number of patients who were PMs for CYP2C19 or UGT2B17 (2 and 3 patients, respectively, in MK-6482-001, and 1 and 5 patients, respectively, in MK-6482-004) and confounding concomitant and comorbidity conditions.

Given the lack of clinical data with the proposed dose of 120 mg in dual PMs, the large range of individual belzutifan AUCs observed in the VHL-RCC patient population (which did not include dual PMs) and the manageable safety profile of belzutifan, the FDA agrees with the Applicant's proposal of not establishing a dose adjustment for dual poor metabolizers at this time.

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VHL Mutation Type

In study MK-6482-004, VHL mutations were confirmed retrospectively for all patients (N=61) using central Sanger sequencing, with Multiplex Ligation-dependent Probe Amplification (MLPA) used to detect copy number variations. A total of 35 unique mutations were identified in 43 patients, with the remaining having complete (N=3) or partial (N=15) VHL gene deletions. Approximately 84% of patients had Type 1 disease. In an exploratory analysis by the reviewer, an 11% ORR was observed in the subgroup of patients with complete or partial gene deletions (17 Type 1 and 1 unknown VHL Type) compared to 65% in the subgroup of patients with other VHL mutation types (Table 3).

Table 3: RCC Response by VHL disease subtype and VHL mutation type in Study MK-6482-004 (N = 61) (cutoff date 01Dec-2021)

VHL Disease Subtype	VHL Mutation Type	Number of Patients N	Number of RCC Responses n (ORR)	
Type 1 (N=51)	Missense	16	9 (56)	25 (49)
	Nonsense	10	8 (80)	
	Frameshift	7	6 (86)	
	Splice Site	1	0	
	Complete (N=3) or Partial* Deletion	17	2 (12)	
Type 2A (N=2)	Missense	2	1 (50)	1 (50)
Type 2B (N=6)	Missense	5	2 (40)	3 (50)
	Splice Site	1	1 (100)	
Unknown (N=2)	Nonsense	1	1 (100)	1 (50)
	Partial* Deletion	1	0	

Source: Reviewer exploratory analysis. ORR per RECIST 1.1 as assessed by IRC in RCC. *Partial deletion: VHL Type 1 [exon 1 deletion (N=1), exon 2 deletion (N=3), exon 3 deletion (N=11)]; unknown VHL Type [exon 3 deletion (N=1)].

In response to an FDA Information Request dated April 23, 2021, the Applicant concurred with these exploratory findings, and noted that the median time to response (mTTR) for VHL-RCC tumors with VHL deletion tended to be longer compared with those with other mutation types (Table 4), which could explain the difference in ORR. For non-RCC tumors, although ORRs (VHL deletion vs VHL mutation) were comparable in pNET, pancreatic lesions and CNS hemangioblastomas, the mTTR also tended to be longer for the tumors with VHL deletion. A review of the literature suggested that VHL-null tumors display lower basal HIF-2α expression, and that VHL ccRCC tumors may display variable HIF-2α dependency and thus variable sensitivity to HIF-2 α inhibition (Tarade et al. 2018). A longer follow up in patients with gene deletions vs other mutation types will be requested as part of a clinical PMC (see Section 16 for details).

Table 4: Summary of Time to Response in RCC Tumors by VHL Alteration Status in Patients with Confirmed Response in RCC per RECIST 1.1 based on IRC assessment (Efficacy Analysis Set)

	VHL Deletion	VHL Mutation
Participants with RCC Response	2	28
Time to Response (weeks)		
Participants with data	2	28
Mean	64.6	39.9
SD	9.0	22.0
Median	64.6	35.7
Range	58.3 to 71.0	11.6 to 82.9
RCC Response: confirmed partial or complete response as best overall response per RECIST 1.1 based on IRC assessment in RCC Tumors Date of Data Cut-off: 01DEC2020		

Source: [P004V01MK6482: adam-adsl; adtte; adxc]

Source: Applicant's Table in response to FDA Information Request dated April 23, 2021.

8.3.2.4 Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

The Applicant's Position:

The impact of food on belzutifan exposure was studied using an oral (b) (4) tablet (FFP) formulation. Consumption of a high-fat, high-calorie meal prior to belzutifan administration delayed Tmax, with a median difference (Fed – Fasted) of 2 hours. However, a high-fat, high-calorie meal had no effect on the extent of belzutifan absorption based on comparison of AUC0-t and AUC0-inf, which were contained within the 0.80 to 1.25 reference interval for AUC ratio. Cmax was approximately 35% lower under fed conditions, suggesting that food may impact the rate of belzutifan absorption. The effects of a high-fat, high-calorie meal on belzutifan Tmax and Cmax are not considered clinically meaningful.

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The potential for belzutifan to inhibit metabolizing enzymes or transporters was evaluated in vitro. Belzutifan demonstrated low potential to inhibit major CYP or UGT enzymes and major drug transporters. In vitro studies and PBPK modelling suggest that belzutifan may be a moderate CYP3A4 inducer. Consequently, a study to assess the impact of belzutifan administration on midazolam PK has been initiated (MK-6482-009), although the final study report is not available at the time of filing. The preliminary PK data from the study suggests a reduction in AUC0-inf in the range of ≥20% to <50% for midazolam after 7 day administration of 120 mg QD belzutifan, suggesting a weak CYP3A4 induction potential for belzutifan (ongoing analysis; data on file and not submitted).

As noted earlier, belzutifan is metabolized by UGT2B17, CYP2C19, and to a lesser extent by CYP3A4. The relative contribution of UGT2B17 and CYP2C19 to the elimination of belzutifan was further elucidated by a dedicated single-dose PK trial in Japanese and Caucasian healthy subjects, an integrated cross-study pharmacogenetic analysis and population PK analysis. Collectively, these analyses indicate that UGT2B17 is the major elimination pathway, while CYP2C19 likely plays a lesser role. A [^{14}C]-belzutifan human mass balance study is ongoing and will further elucidate the relative contribution of CYP2C19, UGT2B17 and other pathways to the elimination of belzutifan. The exploratory pharmacogenetic analysis results for both UGT2B17 and CYP2C19 poor metabolizers (ie, no enzyme activity) and pop-PK analysis submitted in the NDA, provides an understanding of the potential impact of strong inhibitors of UGT2B17 and CYP2C19 on belzutifan PK. A study to evaluate the impact of a strong CYP2C19 inducer (rifampin) on belzutifan PK is planned.

Belzutifan is a weak substrate of P-gp, as well as OATP1B1 and OATP1B3. Given the weak nature of these interactions, clinically meaningful effects are not anticipated for inhibitors of P-gp or OATP1B1/B3.

Belzutifan and its (b) (4) intermediate do not exhibit reduced solubility at elevated pH. Thus, belzutifan FMI may be administered without any restrictions for agents that modulate gastric pH (e.g., proton-pump inhibitors).

The FDA's Assessment:

FDA agrees with the Applicant. Food intake did not have a clinically meaningful effect on belzutifan exposure with the FFP formulation. The effect of food intake on the bioavailability of the FMI formulation is being characterized in an ongoing study. However, given the safety profile of belzutifan and the fact that anemia is a monitorable and relatively late onset adverse reaction, as highlighted above, administration without regard to food is acceptable.

Concomitant medications that are known to inhibit UGT2B17 or CYP2C19 are predicted to result in an exposure increase of 50% to 60%. Similar to the rationale for intrinsic factors highlighted in section 6.3.2.3, dosage modifications are not recommended.

Of note, belzutifan is an inducer of CYP3A4. The coadministration of belzutifan decreased midazolam exposure by 40%. Given that some patients may have substantially higher exposure

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of belzutifan (e.g., dual PM or lighter patients with organ disfunction), the degree of CYP3A induction may substantially increase. This VHL population is typically younger and of child-bearing age; thus, a recommendation to avoid the use of oral hormonal contraceptives (CYP3A4substrates) is included in the label.

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9 SOURCES OF CLINICAL DATA

9.1 Table of Clinical Studies

The Applicant's Position:

[Table 5] presents details of the MK-6482-004 study that supports the safety and efficacy in the proposed indication, as well as the additional studies which are included throughout the submission.

Table 5 Applicant – Listing of Clinical Trials Relevant to this NDA

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow up	No. of participants enrolled	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety							
MK-6482-004/ NCT03401788	Phase 2 open-label study of MK-6482 in participants with VHL disease	120 mg QD of belzutifan orally	Primary: ORR per RECIST 1.1 in VHL disease-associated RCC Secondary: DOR, TTR, PFS, and TTS in VHL disease-associated RCC ORR, DOR, TTR, PFS and TTS in VHL disease-associated non-RCC Safety and PK in all participants	Treatment continued until meeting protocol-defined discontinuation criteria. All participants underwent long-term follow up (every 6 months) until death, withdrawal of consent, or the end of the study.	61 participants	Adult participants with VHL disease with at least 1 measurable RCC tumor without prior systemic therapy	11 centers in 4 countries (8 in US; 1 each in UK, DN, FR)
Studies to Support Safety							
MK-6482-001/ NCT02974738	Phase 1, dose-escalation and expansion study of MK-	Escalating doses of belzutifan QD/BID orally	Primary: To identify the MTD and/or RP2D of belzutifan Secondary: Safety, PK, PD, ORR, PFS and DOR	Treatment continued for 1 year or until meeting a protocol-defined discontinuation	95 participants in Part 1 (43 in Part 1A; 52 in Part 1B)	Adult patients with locally advanced or metastatic solid tumor	8 centers in 1 country

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Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow up	No. of participants enrolled	Study Population	No. of Centers and Countries
	6482 in participant with advanced solid tumors			criteria. Participants deriving clinical benefit were eligible to continue receiving extended treatment beyond 1 year.	21 participants in Part 2	that has progressed or been intolerant to standard of care and/or approved treatment options.	
Other Studies Relevant to the Submission							
MK-6482-002	Phase 1, open-label, randomized, 2-period trial in healthy participants	Single 120 mg (3 x 40-mg tablet FFP formulation, fasted) Single 120 mg (3 x 40-mg tablet FFP formulation, fed)	Primary: To determine the effect of food on the PK of a single dose of 120 mg of MK-6482 in normal healthy adults Secondary: To assess the safety and tolerability of 120 mg of MK-6482 in normal healthy adult subjects	Single-dose administration	Enrolled=16 Complete=13	Adult healthy female or vasectomized male volunteers	1 center in 1 country
MK-6482-006	Phase 1, open-label, randomized, 3-period trial in healthy participants	Single 120 mg (3 x 40-mg tablet FFP formulation) Single 120 mg (3 x 40-mg tablet FMF formulation) Single 200 mg (5 x 40-mg tablet FMF formulation)	Primary: To characterize the safety, bioavailability, and PK of a single dose of FFP, 120 mg of MK-6482; a single dose of FMF, 120 mg of MK-6482; and a single dose of FMF, 200 mg of MK-6482 administered to normal, healthy, adult subjects. Secondary: To assess the safety and tolerability of MK-6482 in normal healthy adult subjects	Single-dose administration	Enrolled=18 Completed=17	Adult healthy female or vasectomized male volunteers	1 center in 1 country
MK-6482-007	Phase 1, open-label, non-randomized,	40 mg MK-6482	Primary: To obtain plasma pharmacokinetic data of MK-6482 and its metabolite in healthy Japanese and Caucasian female participants	Single-dose administration	Enrolled=49 Completed=49	Adult healthy WONCBP	2 centers in 1 country

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Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow up	No. of participants enrolled	Study Population	No. of Centers and Countries
	no-controlled, multi-site trial in healthy female participants		Secondary: To compare plasma PK data following a single oral dose of MK-6482 among healthy Japanese EMs, IMs and PMs of CYP2C19 Secondary: To evaluate the safety and tolerability following a single oral dose of MK-6482 in healthy Japanese and Caucasian female participants				
MK-6482-008	Phase 1, open-label, 1-period trial in healthy participants	Single 120 mg (~200 µCi) dose of [14C]MK-6482	Primary: To investigate route(s) of elimination and mass balance of MK-6482 after administration of a single 120 mg (~ 200 µCi) dose of [14C]MK-6482 in healthy adult participants Primary: To quantitate total radioactivity concentration equivalents and PK of MK-6482 in plasma after administration of a single 120 mg (~ 200 µCi) dose of [14C]MK-6482 in healthy participants Primary: To examine the metabolism of MK-6482 in humans and identify major metabolites in biological specimens Secondary: To evaluate the safety and tolerability of a single 120 mg (~ 200 µCi) dose of [14C]MK-6482 in healthy adult participants	Single-dose administration	(N=6 to 8), planned	Adult healthy female or vasectomized male volunteers	1 center in 1 country
MK-6482-009	Phase 1, open-label, fixed-sequence, 2-period, multiple-dose trial in healthy	MK-6482 120 mg qd on Days 2 to 8 (Period 2) Midazolam 2 mg on Day 1 (Period 1) and Day 8 (Period 2)	Primary: To compare the PK profile of midazolam following a single oral 2-mg dose of midazolam given alone or after multiple doses of MK-6482 Secondary: To evaluate the safety and tolerability of MK-6482 with co-administration of	Single-dose administration	(N=15), planned	Adult healthy WONCBP	1 center in 1 country

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Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow up	No. of participants enrolled	Study Population	No. of Centers and Countries
	participants		midazolam in healthy adult participants				
MK-6482-014	Phase 1, open-label, randomized, 2-period trial in healthy participants	Single 120 mg (3 x 40-mg tablet FMI formulation, fasted) Single 120 mg (3 x 40-mg tablet FMI formulation, fed)	Primary: To assess the effect of a high-fat meal on plasma PK of a single dose of MK-6482 120 mg administered using the final market image tablet formulation relative to plasma PK in the fasted state in healthy adult participants Secondary: To evaluate the safety and tolerability of MK-6482 120 mg in healthy adult participants	Single-dose administration	(N=14), planned	Adult healthy female or vasectomized male volunteers	1 center in 1 country
MK-6482-017	Phase 1, open-label, fixed-sequence, 2-period trial in healthy participants	MK-6482 120 mg on Day 1 (Period 1) and Day 18 (Period 2) Rifampin 600 mg qd on Days 4 to 20 (Period 2)	Primary: To compare the pharmacokinetic profile of MK-6482 following a single oral 120-mg dose of MK-6482 given alone or after multiple doses of rifampin Secondary: To evaluate the safety and tolerability of MK-6482 with coadministration of rifampin in healthy adult participants	Single-dose administration	(N=14), planned	Adult healthy female or vasectomized male volunteers	1 center in 1 country

The FDA's Assessment:

The FDA agrees with the Applicant's table of clinical trials of belzutifan relevant to this submission. MK-6482-004 (Phase 2, open-label study of belzutifan in patients with VHL disease-associated non-metastatic RCC) formed the basis for evaluation of the efficacy of belzutifan in the indicated population.

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10 STATISTICAL AND CLINICAL EVALUATION

10.1 Review of Relevant Individual Trials Used to Support Efficacy

10.1.1 MK-6482-004

Trial Design

The Applicant's Description:

Study MK-6482-004 is an ongoing single-arm open-label Phase 2 study to evaluate the efficacy and safety of belzutifan in participants with VHL disease and at least 1 measurable RCC tumor (as defined by RECIST 1.1). Participants received belzutifan 120 mg by oral administration once daily. Participants were evaluated radiologically approximately 12 weeks after initiation of study intervention and every 12 weeks thereafter while continuing in the study to assess response to treatment for VHL disease-associated RCC and non-RCC areas of disease that were present at screening per investigator. Participants continued to receive treatment until unacceptable treatment-related toxicity or disease progression.

Key inclusion criteria for the study include having a diagnosis of VHL disease based on germline VHL alteration, having at least 1 measurable solid RCC tumor (with no RCC tumor >3 cm). A key exclusion criterion for the study was receiving prior systemic anticancer therapy.

Radiographic assessments for VHL disease-associated RCC tumors were made by an IRC, and IRC results were used for the primary analysis. Radiographic outcomes were also determined by investigators, and investigator-determined results were considered to be supportive. Radiographic assessments of additional organ systems and ophthalmic evaluation were made depending on the other documented non-RCC VHL-associated lesions present at screening.

The FDA's Assessment:

The Applicant states above that "Key inclusion criteria for the study include having a diagnosis of VHL disease based on germline VHL alteration, having at least 1 measurable solid RCC tumor (with no RCC tumor >3 cm)." This is inaccurate. According to the protocol for Study MK-6482-004, patients with "at least 1 measurable solid RCC tumor and no RCC tumor greater than 3.0 cm that requires immediate surgical intervention" were eligible for enrollment. This means that those with RCC tumors >3 cm were actually able to enroll at the discretion of the investigator if they determined that it was feasible to do so in terms of the patient not needing immediate surgery, although criteria for making that determination were not defined in the protocol.

Per investigator assessment, 9 patients had at least one RCC tumor > 3.0 cm in diameter at the time of enrollment. According to the Applicant, the factors used to make the clinical decision that these patient did not require surgical resection of the tumor at the time of enrollment included the patient's medical condition, RCC tumor growth rate, and the patient's preference:

Participant ID	Lesion Size (mm) by Investigator	Reason of not having surgery for RCC ≥ 3 cm according to the investigator
(b) (6)	32.0	The 3 cm cutoff is not absolute and the decision to initiate systemic therapy versus performing procedure depends on prior procedures, location of lesion, patient preference.
	35.0	Clinical decision made in consultation with urologic surgeons based on multifactorial consideration. “Patients with tumors in the 3-3.5 cm range seldom need immediate surgery”.
	32.0 31.0	Clinical decision made in consultation with urologic surgeons based on multifactorial consideration. “Patients with tumors in the 3-3.5 cm range seldom need immediate surgery.”
	31.5	Prior total left nephrectomy and right laparoscopic nephrectomy. The decision was to observe for a complex cystic lesion with the solid component less than 3 cm.
	34.4 37.5	Prior nephrectomies with half of both kidneys removed. In addition, solid component matters. For complex cystic lesions presented in the patient, the solid components were less than 3 cm. The decision was to observe.
	31.1 31.0	Multiple prior interventions, tumor growth rates were slow; it was most appropriate to continue standard of care and avoid too frequent surgical interventions.
	39.4	Relative frequent prior procedures and surgeries due to multiple lesions in both kidneys, tumor growth rates were slow; decision made to wait and preserve renal function by reducing the frequency of interventions.
	38.0	Following a very detailed discussion with multiple health care providers, the patient ultimately opted for the study. Although 3cm is a guideline cut-off, we regularly encounter patients that prefer continued observation and they certainly have our support.
	30.0	The tumor was near threshold for typical consideration of local therapy, but not rapidly growing. Following extensive discussion regarding local therapy versus trial participation, the patient

clearly preferred to delay /avoid surgery if possible, and elected to proceed with trial therapy.

Another key exclusion criteria in study MK-6482-004 was any history of metastatic disease.

Study Endpoints

The Applicant's Description:

The primary efficacy outcome for MK-6482-004 was ORR per RECIST 1.1 for VHL disease-associated RCC. Secondary measures of efficacy were DOR, TTR, PFS, and TTS for RCC tumors and for non-RCC tumors associated with VHL disease in individual organ systems.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the primary and secondary measures of efficacy for study MK-6482-004.

We also note that ORR and DOR in non-RCC tumors was an additional efficacy endpoint.

Radiographic outcomes for VHL disease-associated RCC were determined by investigators as well as an independent review committee (IRC). IRC measurements were used for the primary analysis. Radiology scans and ophthalmic evaluation for all non-RCC VHL associated lesions were performed during the treatment period, only if there are documented lesions at baseline.

RECIST 1.1 criteria was used for assessment of solid lesions for each VHL-associated organ system. All patients enrolled in the study were required to have at least one measurable solid renal target lesion, as defined by RECIST 1.1. VHL-associated non-renal organ systems could have measurable and/or non-measurable lesions. A measurable solid component of a cystic lesion could be assigned as a target lesion for that tumor type. The tumor response assessment will be made separately for each organ system.

Confirmed ORR per RECIST 1.1 that is of sufficient magnitude, combined with a DOR of reasonable duration, are appropriate efficacy endpoints for a single arm study in the setting of a reasonable safety profile. This is because spontaneous shrinkage of a tumor that meets RECIST criteria would be unlikely, and any tumor shrinkage that meets RECIST criteria is therefore thought to be directly attributable to the anti-tumor effect of the investigational drug itself. Time to response (TTR) in this setting is helpful in terms of providing information to patients and clinicians on how fast the VHL-tumor in each organ system is expected to shrink with treatment and can be important in making an informative treatment decision.

Progression-free survival (PFS) is a time-to-event endpoint and results are uninterpretable in a single arm study without a comparator arm. Time to surgery (TTS) results are also difficult to interpret in this setting because although in theory it would be helpful to know about surgical decisions, there were no objective criteria in the protocol that dictated when the decision for a patient to undergo nephrectomy or other RCC-directed procedures was made and this subjectivity limits interpretability.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Participants were assessed with clinical and laboratory evaluations according to the Schedule of Events in the study protocol. Participants were evaluated radiologically Q12W while continuing in the study to assess response to treatment for VHL disease associated RCC and non-RCC areas of disease that were present at screening per investigator.

The APaT population was used for all analyses of efficacy and safety. The APaT population consists of all allocated participants who received at least one dose of belzutifan.

All changes to the statistical analysis plan were made via protocol amendments and are summarized in [Table 6].

The FDA's Assessment:

FDA agrees with the Applicant's description of the statistical analysis plan.

Although patients were evaluated radiologically Q12W to assess response to treatment for both VHL disease-associated RCC and non-RCC areas of disease that were present at screening per investigator, the images obtained were often not optimized for pancreatic tumors which led to uncertainty with measurement of these tumors as described more fully in section 10.1.2.

APaT stands for All Patients as Treated.

Protocol Amendments

The Applicant's Description:

The original protocol was finalized on 10-NOV-2017 and subsequently was amended 13 times (with 7 major versions). [Table 6] summarizes the key changes in each amendment.

Table 6 Applicant – Summary of Key Changes to the MK-6482-004 Protocol

Protocol Version (Approval Date)	Key Changes
Version 1.0 (10-NOV-2017)	Original Protocol
Version 2.0 (19-DEC-2017)	Several commitments to FDA including specific guidance for dose delays/modifications/discontinuations and updated exclusion criterion regarding history of metastatic disease.

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Version 2.1 (18-APR-2018)	Various changes per MHRA recommendation, including only allowing the use of highly effective methods of contraception and changing the SAE reporting window.
Version 2.2 (03-MAY-2018)	Per ANSM recommendation, added monthly pregnancy testing after Week 25 and extended the required window for contraceptive use to 95 days after last dose.
Version 2.3 (30-AUG-2018)	Minor wording changes to inclusion/exclusion criteria per French EC recommendation.
Version 3.0 (21-FEB-2019)	Increased the window of time between last participant enrolled and the data cutoff date, added additional background information on the testicular findings from the dog 28-day study, and included information on tablet formulation change.
Version 3.1 (20-MAR-2019)	
Version 3.2 (20-MAR-2019)	
Version 4.0 (13-SEP-2019)	Included additional information on tablet formulation change and added additional PK sampling to confirm exposure from the new formulation.
Version 4.1 (13-SEP-2019)	
Version 4.2 (16-SEP-2019)	
Version 5.0 (07-FEB-2020)	Revisions to reflect change in sponsorship of the study, and various changes throughout the protocol to reflect the Sponsor's preferred terminology and definitions of analysis populations.
Version 6.0 (31-MAR-2020)	Contraceptive guidelines were updated to reflect the updated preclinical toxicologic findings with regard to embryofetal lethality. Contraception was required during and up to 95 days after treatment and monthly pregnancy testing was advised.
Version 7.0 (07-MAY-2020)	Updates to contraceptive guidance were made to be consistent across the belzutifan program

The FDA's Assessment:

FDA agrees with the protocol amendments described by the Applicant in the table. Additionally, the Sponsor decided to pursue IRC review of CNS hemangioblastoma, retinal hemangioblastoma, and pancreatic tumors including pNET after enrollment in the study was completed. The IRC review and analyses were initially incorporated into the revised Statistical Analysis Plan (version 2.0, dated 12-JUL-2020), which was submitted to the IND 137354 on July 15th, 2020. Subsequently, the IRC review and analyses were consolidated into the global protocol amendment MK-6482-004-14 (version 8.0, dated March 2nd, 2021), which was submitted to IND 137354 on 11-MAR-2021.

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10.1.2 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

MK-6482-004 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:

The FDA agrees with the Applicant's statement.

Financial Disclosure

The Applicant's Position:

Disclosure of financial interests of the investigators who conducted the MK-6482-004 study has been collected and submitted by the Applicant.

The FDA's Assessment:

The FDA agrees with the Applicant's statement.

Patient Disposition

The Applicant's Position:

Sixty-one participants received belzutifan 120 mg once daily. The median duration of exposure to belzutifan was 68 weeks (range: 8.4 to 104.7), and 57 of the 61 participants (93.4%) received treatment for ≥12 months. The median duration of follow up was 15.8 months (range: 4.2 to 24.1). Treatment with study intervention is ongoing for 56 participants (91.8%) as of the data cutoff.

The FDA's Assessment:

FDA agrees with the Applicant statement. The Applicant submitted an efficacy update report with data-cut off as of December 1, 2020 (the data cut-off date in the previous report was June 1, 2020, and the associated exposure and follow up duration numbers above are associated with the June 2020 date). In the updated report, the median duration of follow up increased to 21.8 months (range: 4.2, 30.1 months). In the updated report, the median duration of drug exposure increased from 15.6 months) to 21.6 months (range: 1.9, 30.1 months). Fifty-seven (93.4%) patients received treatment for ≥12 months and 55 [90.2%] for ≥18 months.

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In the updated report, two more patients discontinued study treatment, 1 patient (1.6%) due to disease progression and 1 patient (1.6%) due to patient decision to discontinue (54 [88.5%] of 61 patients were still receiving study treatment). The number of patients on study remained unchanged (58 [95.1%]) from the initial report.

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.

The number of major protocol deviations was low and is not expected to impact the overall safety or integrity of the study. Major protocol deviations were reported for 3 participants. No participants' data were excluded from analyses due to an important protocol deviation. No major protocol deviation was classified as a serious GCP compliance issue.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. The protocol deviations did not affect the overall ability of the trial to support an approval.

Major protocol deviations were reported for 3 participants:

- One participant did not meet inclusion criteria (ECOG of 2); this protocol deviation was approved by the investigator and IRB and was not considered clinically important.
- One participant had a clinically important deviation related to study intervention compliance as the participant was off treatment for more than 3 weeks due to lack of access to study treatment due to COVID-19.
- One participant had a clinically important deviation related to discontinuation criteria as the participant was off treatment for more than 3 weeks allowed by the protocol due to an AE of abdominal pain.

Table of Demographic Characteristics

Data:

Most participants were white, not Hispanic or Latino, and had an ECOG performance status of 0. The age of participants ranged from 19 to 66 years with a median age of 41 years, and most participants had VHL Type I subtype (83.6%) [Table 4].

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Consistent with the presence of tumors in multiple organs in VHL disease all participants had other non-RCC VHL-disease associated tumors as assessed by investigator: 51 (83.6%) participants had CNS hemangioblastomas, 31 (50.8%) had pancreatic lesions, 17 (27.9%) had retinal lesions, 10 (16.4%) had epididymal cystadenomas, 3 (4.9%) had adrenal lesions, 2 (3.3%) had other lesions (not specified), and 1 (1.6%) had endolymphatic sac tumors [Table 7].

Table 7 Applicant – Demographics and Baseline Characteristics

	MK-6482 (N=61)
Age (years)	
Median	41.0
Min, Max	19, 66
Sex, n(%)	
Male	32 (52.5)
Female	29 (47.5)
Ethnicity, n(%)	
Hispanic or Latino	6 (9.8)
Not Hispanic or Latino	54 (88.5)
Unknown	1 (1.6)
Race, n(%)	
American Indian or Alaska Native	0
Asian	1 (1.6)
Black or African American	2 (3.3)
Native Hawaiian or Other Pacific Islander	1 (1.6)
White	55 (90.2)
Unknown	2 (3.3)
ECOG Performance Status, n(%)	
0	50 (82.0)
1	10 (16.4)
2	1 (1.6)
VHL Subtype, n (%)	
Type 1	51 (83.6)
Type 2A	2 (3.3)
Type 2B	6 (9.8)
Type 2C	0
Missing	2 (3.3)
VHL-associated Non-RCC tumors, n (%)	
Pancreatic Lesions	31 (50.8)
Adrenal Lesions (Pheochromocytomas)	3 (4.9)
CNS Hemangioblastoma	51 (83.6)
Endolymphatic Sac Tumors	1 (1.6)
Epididymal Cystadenomas	10 (16.4)
Retinal Lesions	17 (27.9)
Other	2 (3.3)
Number of Prior Surgeries per Subject	
Median	5.0
Min, Max	1, 15

Date of Data Cut-off: 01JUN2020
Source: [P004V01MK6482: adam-adsl; addc]

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The Applicant's Position:

The baseline demographic and disease characteristics of participants in MK-6482-004 were generally representative of a patient population with VHL disease-associated RCC.

The FDA's Assessment:

The FDA agrees with the Applicant's description of baseline demographics and disease characteristics presented in the table in general.

The median age was 41 years (range 19-66 years), which points to a relatively young age for trial enrollees overall; only 3.3% were age 65 or over.

Additional clinically relevant disease characteristics are as follows:

The median diameter of RCC target lesions per IRC was 2.2 cm (range 1 - 6.1).

- Diagnosis was not confirmed histologically in 38% of patients for the lesion that led to trial enrollment. However, all patients enrolled in this trial had a germline VHL mutation. Diagnosis of the RCC lesion that led to trial enrollment was made radiologically in all cases by the presence of a solid enhancing lesion located in the kidney in CT scan or MRI. This is consistent with current clinical practice, in which patients with known/ confirmed VHL disease often do not have a biopsy performed to confirm the histologic diagnosis of a renal tumor with a characteristic appearance on imaging. The review team determined that this approach was acceptable.

- The median time from the initial radiographic diagnosis of VHL-associated RCC tumors that led to enrollment on MK-6482-004 to the time of treatment with belzutifan was 17.9 months (range 2.8 - 96.7). This fact was added to product labeling to clarify that treatment with belzutifan need not start immediately when an RCC lesion is found in a patient with VHL-disease associated RCC, but might be appropriately deferred until such time as the physician and patient deem it necessary to begin treatment.

- Seventy-seven percent of patients had prior surgical procedures for RCC: 5 patients had excision of renal tumor, 32 patients had nephrectomy (including 4 with radical/total nephrectomy), 14 patients had cryoablation and 6 patients had radiofrequency ablation. These numbers may overlap as some patients had various prior procedures for RCC at different timepoints.

- More than 80% of the patients in MK-6482-004 had type 1 VHL disease, which has a low incidence of pheochromocytoma. This explains the small number of patients with concomitant adrenal tumors in this study. MK-6482-004 enrolled a subgroup of patients with VHL-disease who had RCC tumor, therefore the percentage of patients with various

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non-RCC tumors in this study is different from what has been reported in the Natural History Study and in the literature.

Other Baseline Characteristics (eg, disease characteristics, important concomitant drugs)

The Applicant's Position:

In accordance with the inclusion criteria for the study, all participants had VHL disease-associated RCC. Consistent with the presence of tumors in multiple organs in VHL disease, all participants also had additional VHL-disease associated tumors other than RCC, including CNS hemangioblastomas, pancreatic lesions, retinal lesions, epididymal cystadenomas, adrenal lesions, and endolymphatic sac tumors. While [Table 4] presents the investigator-assessed presence of non-RCC lesions at baseline, efficacy data is presented for those participants with IRC-assessed presence of non-RCC lesions at baseline.

The FDA's Assessment:

FDA agrees with the Applicant's position and has the following additional clarifications:

Per IRC assessment, 61 patients (i.e. all patients) had pancreatic lesions (cysts, cystadenomas, and pNET), 50 patients had CNS hemangioblastoma, and 17 patients had retinal hemangioblastoma.

The primary review team requested several consult opinions from review teams within the FDA for review of these data; the Division of Gastroenterology for review of benign pancreatic lesions, the Gastroenterology Malignancies team for review of pNET; the Nervous System, Pediatric, and Rare Tumors team for review of CNS hemangioblastoma, and the Division of Ophthalmology for review of retinal hemangioblastoma.

- **Pancreatic Lesions (pNET and non-pNET)**:

  In MK-6482-004, pancreatic lesions were initially evaluated by the IRC following the RECIST 1.1 criteria as defined in the Pancreatic Independent Review Procedures Document, "pancreatic disease will be classified as VHL disease associated lesions within the pancreas and associated regional malignant lymphadenopathy (N0 or N1 disease)". A measurable solid lesion and a measurable solid component of a cystic lesion could be considered as a target lesion; simple cysts did not qualify as target lesions. This initial pancreatic review resulted in the identification of baseline pancreatic lesions in all 61 participants (encompassing cystic lesions, cystadenomas, and pNETs), including target lesions in 56 participants. The information regarding locations of the lesions in the pancreas (head vs body/tail of pancreas) was not captured in the Applicant's database. Information regarding single pancreatic cysts and multiple cystic pancreatic lesions were

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not collected. No further sub-classification of the cystic lesions was performed within the non-pNET lesion group.

The discrepancy between the numbers of pancreatic lesions at baseline as assessed by investigators (n=31) vs. IRC (n=61) was attributed to the difference in lesion selection criteria by the investigator vs. by the IRC in addition to a lack of protocol-defined specific selection criteria in the context of highly heterogeneous nature of the pancreatic lesions manifested in VHL disease.

IRC performed further evaluation of the lesions selected at the initial pancreatic review by distinguishing pNETs and non-pNET lesions. According to the IRC pNET Procedures Document, no adjudication was done during pNET review. Among 61 patients with pancreatic lesions, 22 (36%) patients had pNET identified by IRC. Of these, for 5 patients there was agreement between 2 IRC readers that there was a pNET at baseline and for 17 patients there was no agreement between the 2 IRC readers, but for 7 of those adjudication was done and it was determined that those patient had a pNET at baseline by a third radiologist. Adjudication was performed only for pancreatic lesions as a whole per the IRC Pancreatic Procedures Document. Thus overall, 12 (20%) of 61 patients had pNET at baseline as determined by at least two blinded radiologists (although adjudication overall was not done consistently).

The Applicant provided the following rationale for this frequent discordance in diagnosis of pNET between the IRC readers:

1) Frequent discordance between readers 1 and 2 is primarily due to a difference in the identification of pNET tumors

2) Scan acquisition was not optimized for pNET detection on a number of parameters, including contrast timing and slice thickness.

3) These scans were acquired to assess renal cell carcinoma, with pancreatic reviews added later to the study.

4) Intrinsic differences in pNET appearances on scans may also lead to discordance between primary readers.

5) All of these challenges are especially difficult in the setting of VHL disease where there may be a background of multiple pancreatic cystic lesions.

- **CNS Hemangioblastoma**:

In the IRC assessment, 50 (82%) of 61 patients had CNS hemangioblastoma at baseline. Solid tumors and cysts were measured together in the IRC assessments per RECIST v1.1

in the initial submission. Further review of the CNS procedures document and images provided in the Applicant's response to an information request by the FDA suggested that IRC review included brain and spine edema in tumor volume measurements. The FDA therefore requested that the Applicant provide a re-review of the CNS hemangioblastoma imaging data with the following changes:

1) Define maximal tumor diameter as the maximal contrast-enhancing diameter measured using post-contrast T1-weighted MRI. Do not include peri-tumoral cyst diameter in tumor measurements.

2) Include patients with measurable disease at baseline only.

The Applicant provided a fresh re-review of the CNS imaging data on July 8, 2021, identifying 24 (39%) of 61 patients with measurable disease at baseline.

- **Retinal Hemangioblastoma**:

Per the consult report from the Division of Ophthalmology at FDA, retinal photographs was only available in 16 (26%) of 61 patients and of the 16, only 11 (18%) of 61 patients were documented with retinal hemangioblastomas.

According to historical data, approximately 50% of patients with VHL-disease have retinal hemangioblastoma. A lower proportion of patients reported to have retinal hemangioblastomas in MK-6482-004 may be due to absence of pre-planned screening for retinal lesions in all participants at the time of enrollment and the actual incidence may in fact be higher.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Participants were generally compliant with the study intervention. Study intervention was dispensed to participants for oral administration, and the number of tablets returned at a visit was used to assess compliance. There was 1 major protocol deviation related to study intervention compliance, where the participant was off treatment for >3 weeks due to lack of access to study treatment due to the COVID-19 pandemic. No AEs of overdose were reported.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The confirmed ORR (per RECIST 1.1 by IRC) for VHL disease-associated RCC tumors was 36.1% (95% CI=24.2% to 49.4%), with all responders having a PR [Table 5]. As of the data cutoff,

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7 participants (11.5%) with unconfirmed PR are awaiting confirmatory scans, bringing the total ORR (confirmed and unconfirmed) to 47.6%. Disease control, which included any participant with a best overall response of CR, PR, or stable disease, was achieved by 98.4% of participants. No participants had PD as best overall response (one participant was not evaluable (NE) due to discontinuation prior to first follow-up visit). A total of 91.8% of participants (56/61) had a decrease in the sum of target tumor diameters [Figure 8]. Approximately 50% of participants had a >30% reduction in tumor size (including participants with both confirmed and unconfirmed responses).

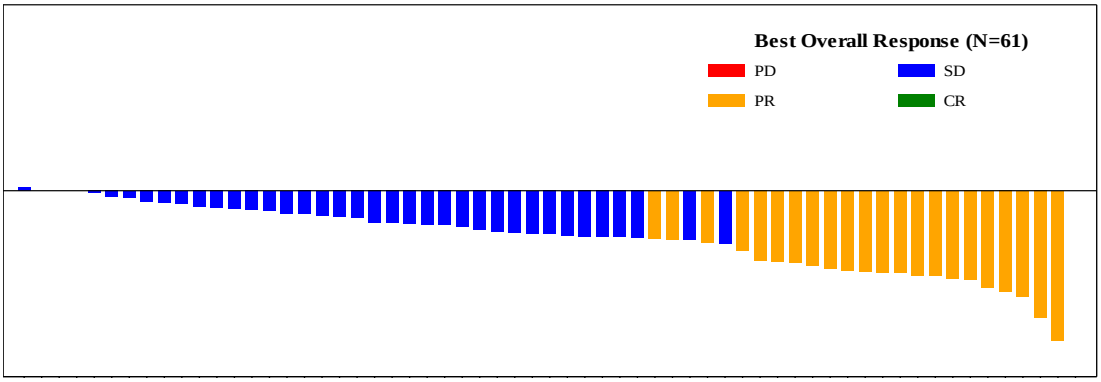
Table 8 Applicant – Summary of Best Overall Tumor Response for RCC Tumors (RECIST 1.1) – IRC (Efficacy Analysis Set)

	MK-6482 (N=61)
Best Overall Response, n (%)	
Complete Response (CR)	0
Partial Response (PR)	22 (36.1)
Stable Disease (SD)	38 (62.3)
Progressive Disease (PD)	0
Not Evaluable (NE)	1 (1.6)
Ongoing with unconfirmed response, n (%)	7 (11.5)
Ongoing without a response, n (%)	27 (44.3)
Objective response rate CR + PR (ORR), n (%)	22 (36.1)
95% Confidence interval	(24.2, 49.4)
Disease Control Rate CR + PR + SD (DCR), n (%)	60 (98.4)
95% Confidence interval	(91.2, 100.0)

Note: 95% confidence intervals are constructed using 2-sided Clopper-Pearson method. Best overall response of RCC CR and PR should be confirmed by a second assessment at least 4 weeks after the initial response.
Date of Data Cut-off: 01JUN2020

Source: [P004V01MK6482: adam-adsl; adeff]

Figure 8 Applicant – Waterfall Plot – Percentage Change in Total Sum of RCC Target Lesions Diameters From Baseline to Post-Baseline Maximum % Reduction



Subjects without either post-baseline lesion measurements or target lesions or with all post-baseline non-evaluable time-point responses are shown to the right of the last visible bar in the figure.
Number (%) of patients with maximum % reduction in sum of diameters of target lesions < 0 = 56 (91.8)
Date of Data Cut-off: 01JUN2020

Source: [P004V01MK6482: adam-adeff]

The Applicant's Position:

Over the course of treatment with belzutifan, participants with VHL disease associated RCC had a clinically meaningful ORR. Additionally, the totality of these data, including disease control rate and percentage of participants who experienced a decrease in the sum of target tumor diameters, suggest the benefit of MK-6482 beyond the participants who attained a RECIST 1.1 response.

The FDA's Assessment:

The FDA agrees with the reported ORR and DoR results for VHL-RCC in Table 5, which a DCO of June 1, 2020. The Applicant submitted an updated reported of efficacy results with DCO as of December 1, 2020.The efficacy results at these two DCO dates per IRC and investigator (INV) assessment are shown in the table below:

Table 9. Efficacy Results (IRC and INV assessment) for WELIREG for VHL-Associated RCC

	Original IRC-assessed (cut-off date: 01-JUN-2020)	Updated IRC-assessed (cut-off date: 01-DEC-2020)	Original INV-assessed (cut-off date: 01-JUN-2020)	Updated INV-assessed (cut-off date: 01-DEC-2020)
	N=61			
ORR, % (n)	36 (22)	49 (30)	38 (23)	44 (27)
CR, % (n)	0	0	0	0
PR, % (n)	36 (22)	49 (30)	38 (23)	44 (27)
PD, % (n)	0	0	0	0

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

DoR (median, 95% CI) in months	NE (NE, NE)	NE (17, NE)	NE (NE, NE)	NE (17, NE)
TTR, median (range) in months	7 (3, 14)	8 (3, 19)	8 (3, 14)	8 (3, 20)

In the updated efficacy report, 8 additional patients had PR as best overall response (BOR):

- 5 of 8 patients had unconfirmed responses by the DCO of June 1, 2020 and response was confirmed later.
- 3 of 8 patients had decrease in tumor size by June 1, 2020, but it did not originally meet RECIST criteria for PR. The change from baseline was more than 30% after the first DCO and they were counted as having confirmed PR by DCO as of Dec 1, 2021.

For demonstration of efficacy in a single arm trial, FDA relies on ORR and DoR in single arm trial. While stable disease may be clinically meaningful on an individual level, it may not be definitively attributed to the drug effect. Thus the FDA disagrees with the Applicant statement above that "the totality of these data, including disease control rate and percentage of participants who experienced a decrease in the sum of target tumor diameters, suggest the benefit of MK-6482 beyond the participants who attained a RECIST 1.1 response." In addition, waterfall plots (provided by the Applicant here and elsewhere in the review) should be interpreted with caution as they do not incorporate progressive disease.

Data Quality and Integrity

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 carried out in accordance with GCP guidelines. The Applicant independently assessed quality through a comprehensive, risk-based audit program to ensure adherence with applicable GCP, Good Pharmacovigilance Practices regulations and applicable company policies and procedures. Audit information and serious GCP compliance issues (including significant quality issues, unblinding events that have impacted data integrity and compliance issues reported to health authorities) were submitted by the Applicant separately.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

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Efficacy Results – Secondary and Other Relevant Endpoints

Data:

Duration of Response

Among confirmed responders, the median DOR was not reached (range: 11.9+, 62.3+) [Table 10]. As of the data cutoff or before end of treatment, no confirmed responder had either progressed or died [Figure 9].

Table 10 Applicant – Summary of Duration of Response for RCC Tumors (RECIST 1.1) – IRC: Efficacy Analysis Set

	MK-6482 (N=61)
Patients with Confirmed Response, n (%) (as of data cut-off)	22 (36.1)
Patients who Progressed or Died (%)	0
Duration of Response (Weeks) 95% CI	
N	22
Mean [1]	36.3
Median (95% CI)	NE (NE, NE)
Min, Max	11.9+, 62.3+
Number (%) of Patients with Extended Response Duration [2]	
>=3 Months	20 (100.0)
>=6 Months	14 (100.0)
>=9 Months	7 (100.0)
>=12 Months	3 (100.0)

NE: Not Estimable.
Duration of Response is analyzed using the Kaplan-Meier estimator. Median is reported along with 95% Brookmeyer-Crowley confidence intervals.
[1] Arithmetic mean.
[2] % is calculated by Kaplan-Meier method.
+ indicates there was no progressive disease by the time of last disease assessment.
Date of Data Cut-off: 01JUN2020
Source: [P004V01MK6482: adam-adsl; adtte]

Time to Response

The median TTR (per RECIST 1.1 by IRC) among the 22 confirmed responders was 31.1 weeks (range, 11.6 to 61.0) [Table 11].

Table 11 Applicant – Summary of Time to Response for RCC Tumors (RECIST 1.1) – IRC: Efficacy Analysis Set

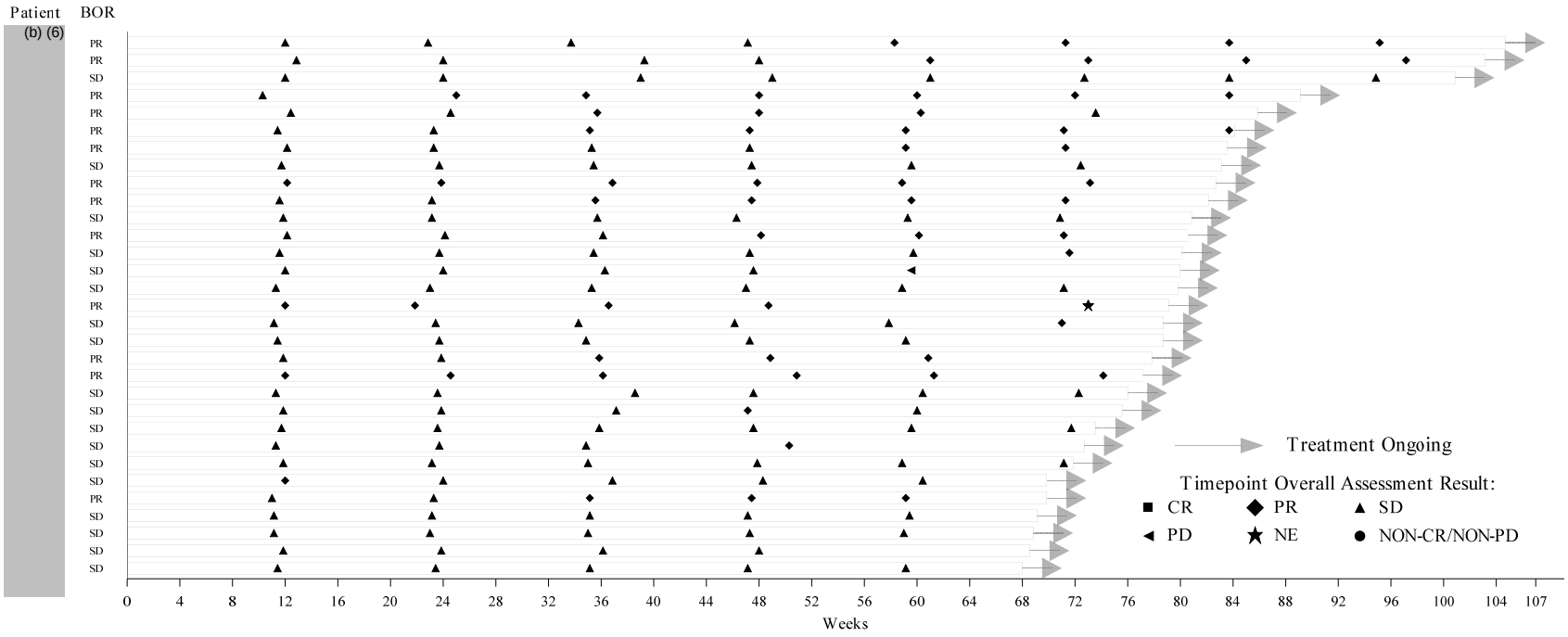
	MK-6482 (N=61)
Patients with Confirmed Response, n (%) (as of data cut-off)	22 (36.1)

	MK-6482 (N=61)
Time to Response (Weeks)	
N	22
Mean (SD)	30.7 (16.54)
Median	31.1
Min, Max	11.6, 61.0

Date of Data Cut-off: 01JUN2020
Source: [P004V01MK6482: adam-adtte; adeff]

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

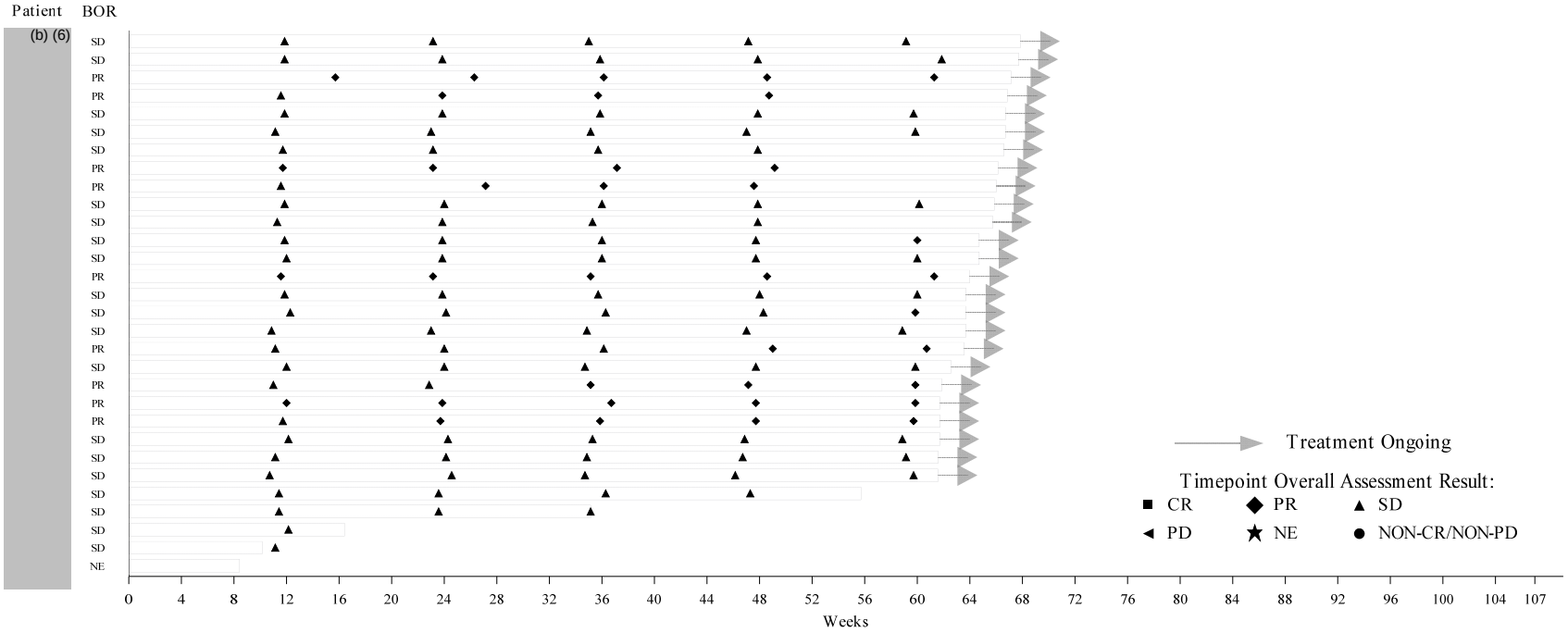
Figure 9 Applicant – Swimmers Plot: Duration of Treatment and Overall Timepoint Assessments for RCC Tumors (RECIST 1.1) – IRC (Efficacy Analysis Set)



Tumor responses were assessed by RECIST 1.1 criteria. Horizontal bars represent treatment duration for each patient. For ongoing patients, data cut-off date was used for treatment duration.
Date of Data Cut-off: 01JUN2020

Source: [P004V01MK6482: adam-adeff]

Figure 9 (continued) Applicant – Swimmers Plot: Duration of Treatment and Overall Timepoint Assessments for RCC Tumors (RECIST 1.1) – IRC (Efficacy Analysis Set)



Tumor responses were assessed by RECIST 1.1 criteria. Horizontal bars represent treatment duration for each patient. For ongoing patients, data cut-off date was used for treatment duration.

Date of Data Cut-off: 01JUN2020

Source: [P004V01MK6482: adam-adeff]

Progression-free Survival

As of the data cutoff, the median PFS (per RECIST 1.1 by IRC) was not reached. There was only a single PFS event, and that was a death that was unrelated to either the disease under study or the study treatment (the participant died of an opioid overdose).

Time to Surgery

The median TTS for VHL disease-associated RCC was not estimable as of the data cutoff date as only 1 participant had undergone a surgery. IRC assessed SD as BOR for this participant and the participant was censored for PFS at the time of last disease assessment prior to new anti-cancer therapy as the surgery constituted a new anticancer intervention.

Efficacy in VHL Disease-associated Non-RCC Tumors

Table 12 Applicant – Summary of Best Overall Tumor Response for VHL Disease-associated Non-RCC Tumors (RECIST 1.1) - IRC

	MK-6482 (N=61)		
	Pancreatic Lesions	CNS Hemangioblastoma	Pancreatic Neuroendocrine
Patients with VHL Disease-associated Non-RCC Tumors at Baseline, N1 (N1/N%)	61 (100.0)	50 (82.0)	20 (32.8)
Best Overall Response, n (n/N1%)			
Complete Response (CR)	4 (6.6)	1 (2.0)	1 (5.0)
Partial Response (PR)	35 (57.4)	15 (30.0)	15 (75.0)
Stable Disease (SD)	21 (34.4)	29 (58.0)	4 (20.0)
Progressive Disease (PD)	0	2 (4.0)	0
Not Evaluable (NE)	1 (1.6)	3 (6.0)	0
Ongoing with unconfirmed response, n (n/N1%)	6 (9.8)	2 (4.0)	2 (10.0)
Ongoing without a response, n (n/N1%)	12 (19.7)	28 (56.0)	1 (5.0)
Objective response rate CR + PR (ORR), n (n/N1%)	39 (63.9)	16 (32.0)	16 (80.0)
95% Confidence interval	(50.6, 75.8)	(19.5, 46.7)	(56.3, 94.3)
Disease Control Rate CR + PR + SD (DCR), n (n/N1%)	60 (98.4)	45 (90.0)	20 (100.0)
95% Confidence interval	(91.2, 100.0)	(78.2, 96.7)	(83.2, 100.0)

Note: 95% confidence intervals are constructed using 2-sided Clopper-Pearson method.
Best overall response of RCC CR and PR should be confirmed by a second assessment at least 4 weeks after the initial response.
Patients evaluable at baseline per IRC are included Pancreas tumor assessments followed RECIST 1.1 criteria and thus measurable solid lesions or the measurable solid component of a mixed solid/cystic lesion could've been chosen as target tumors such as pNETs or cystadenomas, respectively.
Date of Data Cut-off: 01JUN2020

Source: [P004V01MK6482: adam-adsl; adeff]

Table 13 Applicant - Summary of Duration of Response for VHL Disease-associated Non-RCC Tumors (RECIST 1.1) – IRC: Efficacy Analysis Set

	MK-6482 (N=61)		
	Pancreatic Lesions	CNS Hemangioblastoma	Pancreatic Neuroendocrine
Patients with VHL Disease-associated Non-RCC Tumors at Baseline, N1/N	61 (100.0)	50 (82.0)	20 (32.8)
Patients with Confirmed Response, n (n/N1%) (as of data cut-off)	39 (63.9)	16 (32.0)	16 (80.0)
Patients who Progressed or Died (%)	1 (2.6)	0	1 (6.3)
Duration of Response (Weeks) 95% CI			
Mean [1]	33.1	38.8	38.7
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (36.3, NE)
Q1 (95% CI)	NE (36.3, NE)	NE (NE, NE)	NE (36.3, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	11.1+, 71.0+	11.6+, 72.4+	12.3+, 71.0+
Number (%) of Patients with Extended Response Duration [2]			
>=3 Months	28 (100.0)	12 (100.0)	15 (100.0)
>=6 Months	21 (100.0)	11 (100.0)	11 (100.0)
>=9 Months	14 (94.4)	8 (100.0)	7 (90.0)
>=12 Months	5 (94.4)	4 (100.0)	2 (90.0)

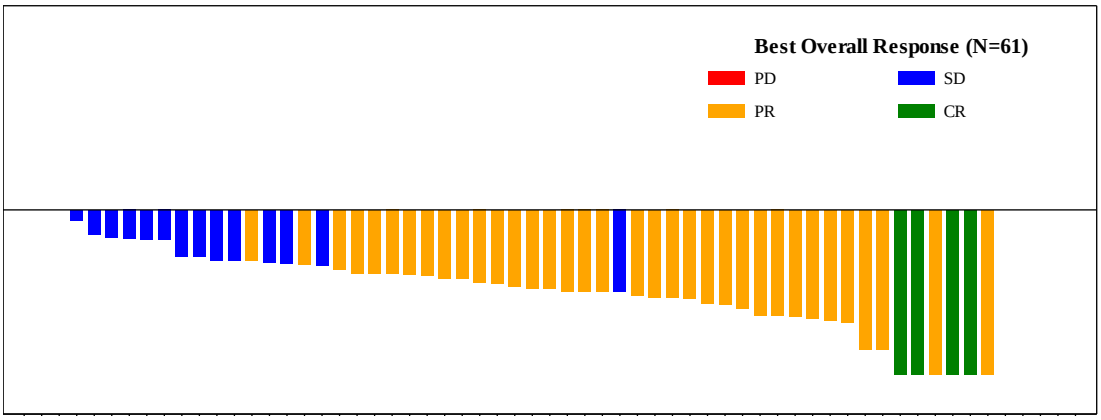
NE: Not Estimable.
Duration of Response is analyzed using the Kaplan-Meier estimator. Median, first and third quartiles of Duration of Response are reported along with 95% Brookmeyer-Crowley confidence intervals.
[1] Arithmetic mean.
[2] % is calculated by Kaplan-Meier method.
+ indicates there was no progressive disease by the time of last disease assessment.
Date of Data Cut-off: 01JUN2020

Source: [P004V01MK6482: adam-adsl; adtte]

Pancreatic Neoplasms

The ORR of belzutifan by IRC for pancreatic neoplasms (including both pNETs and cystadenomas/cystic lesions) was 63.9% (95% CI=52.6% to 74.2%): 4 CRs and 35 PRs. Additionally, there were 21 participants with stable disease and none with PD [Table 12]. Among participants with measurable disease at baseline, 53/61 of participants (86.9%) had a decrease in the sum of their target tumor diameters [Figure 10]. The median DOR in pancreatic lesions has not been reached, and 94.4% of participants remained in a response at 12 months [Table 13].

Figure 10 Applicant – Waterfall Plot – Percentage Change in Total Sum of Pancreatic Target Lesions Diameters from Baseline to Post-Baseline Maximum % Reduction



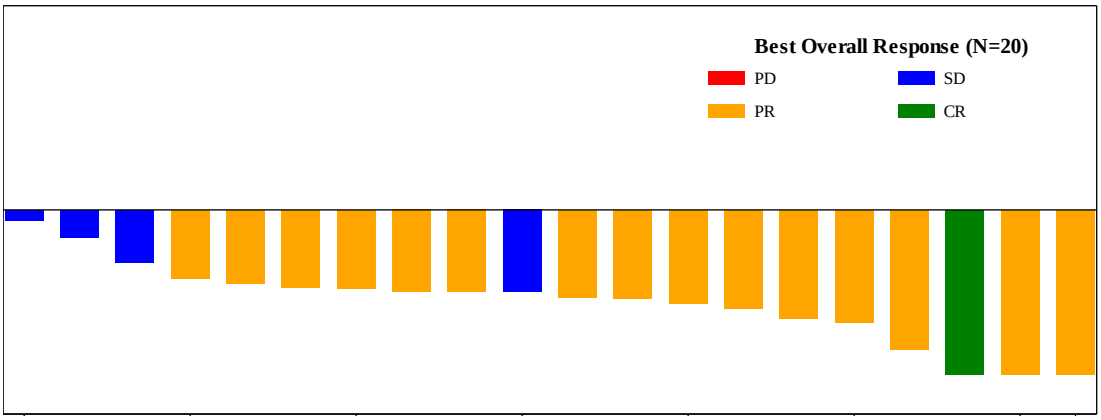
Subjects without either post-baseline evaluable lesion measurements or target lesions or with all post-baseline non-evaluable time-point responses are shown to the right of the last visible bar in the figure.
Number (%) of patients with maximum % reduction in sum of diameters of target lesions < 0 = 53 (86.9)
Date of Data Cut-off: 01JUN2020

Source: [P004V01MK6482: adam-adeff]

Pancreatic Neuroendocrine Tumors

The ORR of belzutifan by IRC for the pNET subset of all pancreatic neoplasms was 80.0% (95% CI=56.3% to 94.3%); 1 CR and 15 PRs were observed in 20 participants. Additionally, there were 4 participants with stable disease and none with PD. There is a suggestion of benefit beyond those who achieve a RECIST 1.1 response based on the assessment of response in target lesions, as 100% of participants with pNETs had a decrease in the sum of their target tumor diameters [Figure 11]. The DCR for participants with pNETs was 100%. The median DOR in pNETs has not been reached, and by Kaplan-Meier estimation, 90% of responders had a response that lasted ≥12 months.

Figure 11 Applicant – Waterfall Plot – Percentage Change in Total Sum of Target Lesions Diameters for Pancreatic Neuroendocrine Tumors from Baseline to Post-Baseline Maximum % Reduction



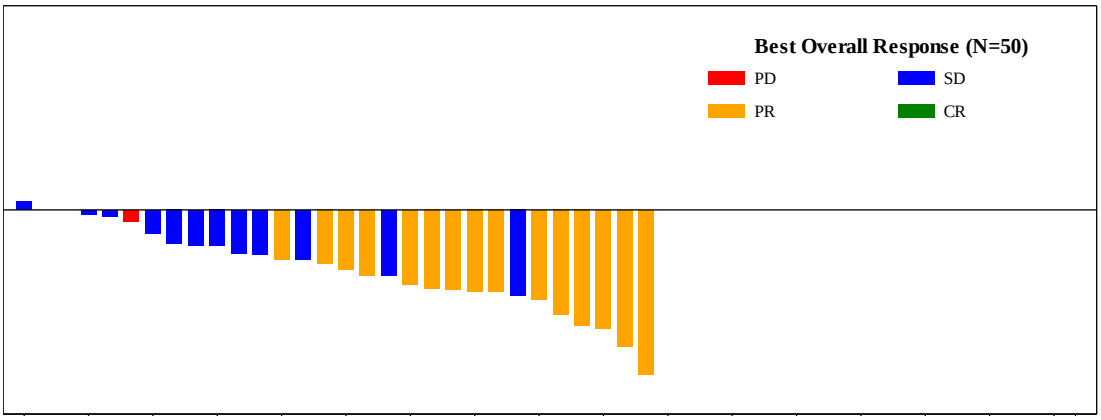
Subjects without either post-baseline evaluable lesion measurements or target lesions or with all post-baseline non-evaluable time-point responses are shown to the right of the last visible bar in the figure.
Number (%) of patients with maximum % reduction in sum of diameters of target lesions < 0 = 20 (100.0)
Date of Data Cut-off: 01JUN2020

Source: [P004V01MK6482: adam-adeff]

CNS Hemangioblastomas

The ORR of belzutifan by IRC for CNS hemangioblastomas was 32.0% (95% CI=19.5% to 46.7%); 1 CR and 15 PRs were observed in 50 participants [Table 8]. Additionally, there were 29 participants with stable disease and 2 participants with PD. Among the participants with measurable disease at baseline, 27/50 participants (54.0%) had a decrease in the sum of their target tumor diameters; 20/50 participants (40.0%) were without either post-baseline lesion measurements or target lesions and are shown on the right-hand side of the figure [Figure 12]. The DCR for CNS hemangioblastomas was 90.0%. The median DOR in CNS hemangioblastomas has not been reached and 4 participants remained in a response at 12 months.

Figure 12 Applicant – Waterfall Plot – Percentage Change in Total Sum of CNS Hemangioblastoma Target Lesions Diameters from Baseline to Post-Baseline Maximum % Reduction (RECIST 1.1) – IRC: Efficacy Analysis Set



Subjects without either post-baseline lesion measurements or target lesions or with all post-baseline non-evaluable time-point responses are shown to the right of the last visible bar in the figure.
Number (%) of patients with maximum % reduction in sum of diameters of target lesions < 0 = 27 (54.0)
Date of Data Cut-off: 01JUN2020
Source: [P004V01MK6482: adam-adeff]

The Applicant's Position:

Responses to belzutifan were durable in all confirmed responders. The observed slow kinetics of response (as shown by long TTR) may underestimate the benefit of MK-6482 treatment. The absence of meaningful tumor growth, as demonstrated by the high DCR (98.4%), high PFS rate at 52 weeks (98.3%), and negative post-treatment LGR indicate that additional participants may have derived clinical benefit despite not reaching PR or CR. The need for surgery is potentially prevented or delayed in participants who have reductions or no increases in tumor size.

There was only a single PFS event, and that was a death that was unrelated to either the disease under study or the study treatment.

Treatment with belzutifan also resulted in clinically meaningful ORR, DCR, and DOR for other VHL-associated tumors, including pancreatic lesions (encompassing cystadenomas and pNETs) and CNS hemangioblastomas. The ORR and durable responses demonstrated, along with reduction in tumor lesion size, offers benefit in reducing or delaying the need for surgical interventions for these tumors.

The FDA's Assessment:

The FDA agrees with the assessment of efficacy in Table 12 and Table 13; these data reflect the original DCO date of June 1, 2020. The table below shows DoR for VHL-RCC at two timepoints; both the original DCO date and the updated date of Dec 1, 2020:

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

Table 14. Duration of response (IRC assessment) for WELIREG for VHL-Associated RCC

	Original IRC-assessed (cut-off date: 01-JUN-2020)	Updated IRC-assessed (cut-off date: 01-DEC-2020)
N=61		
DoR, median (range) in months	Not reached (3+, 14+)	Not reached (3+, 22+)
% (n) with DoR >12 months	13% (3 of 22 responders)	56 (17 of 30 responders)
TTR, median (range) in months	7 (3, 14)	8 (3, 19)

Of the 30 patients who responded, two patients had progressive disease per RECIST v1.1 after they achieved PR as BOR. Six others had disease that was increasing in size prior to the Dec 1, 2020 DCO date, and in fact met or exceeded a 20% increase from nadir, but whose disease hadn't reached the minimum of 5 mm cutoff increase needed to qualify for RECIST V1.1 progression. This underscores the fact that most lesions of patients on the trial were quite small overall and different than most trials that use RECIST v1.1-based metrics for response assessment.

The median time to response (TTR) among 30 patients with confirmed response with DCO as of Dec 1, 2020 was 8 months (ranging from 3 to 19). The relatively long TTR indicates that belzutifan use may not be appropriate for patients who require an urgent tumor reduction procedure for life-threatening conditions or severe symptoms.

Progression-free survival (PFS) is a time-to-event endpoint and results are uninterpretable in a single arm study without a comparator arm. Time to surgery (TTS) results are also difficult to interpret in this setting because although in theory it would be helpful to know about surgical decisions, there were no objective criteria in the protocol that dictated when the decision for a patient to undergo nephrectomy or other RCC-directed procedures was made and this subjectivity limits interpretability. (b) (4)

One patient underwent surgery despite IRC-assessed SD as his best response. The protocol did not specify any objective criteria in terms of when a patient would be referred for surgery or other procedures. (b) (4)

Non-RCC tumors

- **Pancreatic lesions**: For assessment of benign pancreatic lesions, the consult opinion from Division of Gastroenterology at the FDA stated the following, and the primary review team agreed:

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There were no protocol-defined selection criteria for these lesions despite the heterogeneous presentation known to occur in patients with VHL. Accordingly, there was a noteworthy discrepancy between lesions identified by the IRC and those identified by investigators. Without standard classification and agreement on lesion identification, the ability of the data to support the evaluation of a treatment effect is significantly limited.

(b) (4)

Although the natural history of these lesions has not been well-characterized, in patients with non-pNET pancreatic lesions have been shown to have a heterogenous rate of progression that includes spontaneous regression and resolution. Furthermore, there is no known association between tumor size for these lesions and clinical outcomes. Although benign pancreatic lesions are very common in von Hippel-Lindau disease, the vast majority of these lesions do not cause symptoms or require medical or surgical intervention (Charlesworth et al., 2012; Mukhopadhyay et al., 2002).

In the absence of data to support a treatment effect above that expected based on the natural history of these lesions, evidence is lacking to support that a decrease or maintenance of stability in size for these lesions is predictive of a clinical benefit for patients.

(b) (4)

(b) (4)

- **Pancreatic neuroendocrine tumors (pNET):**

Overall assessment of data for pNET was done in conjunction with the consult opinion of the Gastroenterology Malignancies team from the Division of Oncology 2 at the FDA.

Per the Applicant: “The scan acquisition was not optimized for pNET detection on a number of parameters, including contrast timing and slice thickness.” IRC review of pancreatic lesions was added later to the study” (i.e. after enrollment was complete).

In the 61 enrolled patients in the study, there were 22 who had pNET identified by IRC. Of these, 5 had agreement between 2 IRC readers that there was a pNET at baseline and 17 did not, but 7 of those were adjudicated and were determined to have a pNET at baseline by a third radiologist. Thus overall, there were 12 patients with pNET at baseline as determined by at least two blinded radiologists (although adjudication overall was not done consistently). However, of the 12 patients with pNET at baseline according to at least 2 radiologists, 10 responded with ORR of 83.3% (51 , 97. There were 10 patients who had

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pNET per 1 of the 2 IRC readers but no adjudication was done and all 10 patients (100%) achieved a response.

The FDA review team concluded that overall, given the high response rate of 83.3% in the 12 patients with pNET determined by two independent radiologists, supported by the 100% response rate in the 10 patients who had pNET per 1 IRC reviewer, that belzutifan demonstrated a high overall degree of clinical efficacy in pNET. The ORR in the 12 patients with pNET at baseline according to at least 2 radiologists was therefore added to the efficacy results in Section 14 of product labeling. Additionally, pNET was added to the indication statement for belzutifan.

- **CNS hemangioblastomas**

Overall assessment of data for CNS hemangioblastomas was done in conjunction with the consult opinion of the Nervous System, Pediatric, and Rare Tumors team from the Division of Oncology 2 at the FDA.

IRC review of CNS hemangioblastomas was pursued after study enrollment was completed. Fifty patients had CNS hemangioblastoma at baseline per IRC, which consisted of a solid and/or cystic component. Of those, 24 patients had a measurable solid component at baseline per RECIST v1.1; 23 out of 24 patients had post-baseline measurements. The median and range of the solid component in patients with measurable CNS hemangioblastoma at study entry was 1.4 cm (range 1.0-2.8). The sum diameters of the tumors reduced for all 23 patients. Per RECIST v1.1, the confirmed ORR was 62.5% (40.6, 81.2). 11 of 11 evaluable patients had ongoing responses at 1 year. The mean DOR was 63.4 weeks, median is NE. Decreases in size of CNS hemangioblastoma-associated peri-tumoral cysts and syringes were observed as well. The MRI protocols were considered appropriate for measuring hemangioblastomas.

The table below shows efficacy results for PNET and CNS hemangioblastoma at the DCO date of December 1, 2020.

Table 15. Efficacy Results (IRC assessment) for WELIREG for VHL-Associated Subgroups with pNET or CNS Hemangioblastoma

	TRADEMARK 120 mg daily N=61	
Endpoint	**Patients with pNET n=12**	**Patients with ECNS Hemangioblastomas n=24**
Overall Response Rate		
ORR, % (n) (95% CI)	83% (n=10) (52%, 98%)	63%, (n=15) (41%, 81%)
Complete response	17% (2)	4% (1)
Partial response	67% (8)	58% (14)
Duration of Response‡		
Median in months (range)	Not reached (11+, 19+)	Not reached (4+, 22+)
% (n) with duration ≥ 9 months	100% (10)	80% (12)
% (n) with duration ≥ 12 months	50% (5)	73% (11)
Time to Response		
Median in months (range)	8 (3, 11)	**10 (3, 11)**

- **Retinal hemangioblastomas:** For assessment of efficacy in retinal hemangioblastoma, a consult opinion was requested from Division of Ophthalmology at FDA. IRC review of retinal hemangioblastomas was pursued after study enrollment was completed. IRC assessment was therefore limited to those participants who investigators had originally assessed as having retinal hemangioblastomas at screening and were thus followed every 12 weeks with fundus photography. Those patients who, per investigator assessment, were not considered as having retinal lesions at baseline did not have follow-up fundus photography imaging. Responses were measured at eye level. The best overall response at the patient level was based on the following assessment: the patient was considered improved if 1 eye was improved; the patient was considered to have progressed if 1 eye progressed (regardless of the status of the other eye); the patient was considered stable if both eyes were stable. Responses needed to be confirmed at a subsequent timepoint.

There were major concerns about the accuracy of diagnosis and measurement of response for retinal hemangioblastomas (b) (4)

Per the consult report from the Division of Ophthalmology at FDA, retinal photographs were only available in 16 (26%) of 61 patients. Of the 16 patients (32 eyes) theoretically available for retinal evaluation, three (3) did not have any images in one or both eyes. Of the 28 eyes with images, 13 eyes did not have any lesions at baseline. Of the 15 eyes remaining, 1 eye had no

light perception (completely blind) at baseline, 7 eyes had laser treatment potentially resulting in lesion improvement and 2 eyes without laser treatment were already showing fibrosis, a stage of improvement. The remaining 5 eyes (16%) of the eyes followed in this trial appeared to have improvement per IRC without potentially confounding circumstances. Grade 4 decreased vision occurred in two patients, due to retinal detachment (1 patient) and central retinal vain occlusion (1 patient). Information about these events are covered more fully in the safety section of this review.

At Week 49, as per investigator's assessment, 61.3% of the patients with retinal hemangioblastomas had improved compared with baseline and 38.7% were stable compared with baseline. No patients with retinal lesions underwent surgeries as of the DCO.

Reviewer's Comment: Ultimately, the review team determined that the ORR and DoR for enrolled and evaluable patients with pNET and CNS hemangioblastoma were clinically meaningful and of sufficient magnitude to warrant inclusion in product labeling, both in the indication statement and in Section 14. (b) (4)

Dose/Dose Response

The Applicant's Position:

A single dose level (120 mg once daily) was assessed in the study, so a dose: response analysis was not performed. Exposure: response analyses were performed and demonstrated that, within the broad exposure range achieved at the single dose level, a significant positive relationship between exposure (AUC) and various efficacy endpoints (ORR, DCR, PFS, BOR, TTR, DOR) was not observed. However, a slight positive trend for ORR for RCC lesions was observed, but was not statistically significant.

The FDA's Assessment:

FDA agrees with the Applicant's statement.

Durability of Response

The Applicant's Position:

Durability of response is a secondary objective in MK-6482-004 and is discussed in the Secondary Objectives section above.

The FDA's Assessment:

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

VHL-disease associated RCCs are slow growing tumors in general with median LGR 3-4 mm/year and patients may not require treatment for several years. The median time from initial radiographic diagnosis of VHL-associated RCC tumors that led to enrollment on MK-6482-004 to the time of treatment with WELIREG was 17.9 months (range 2.8 - 96.7). Median duration of follow up on study 004 was 22 months which is relatively short when compared with the slow growth of VHL disease-associated RCC tumors. Longer follow up is needed to better assess the duration of response in this setting.

Persistence of Effect

The Applicant's Position:

Time to surgery is a secondary objective in MK-6482-004 and is discussed in the Secondary Objectives section above.

The FDA's Assessment:

MK6482-004 is a single arm clinical trial and time-to event endpoints such as time to surgery are uninterpretable in single arm studies without a comparator arm. Additionally, objective criteria for the decision for a patient to undergo surgery or other procedures were left to the discretion of the investigator and were not specified in the protocol. (b) (4)

Efficacy Results – Secondary or Exploratory COA (PRO) endpoints

The Applicant's Position:

Patient-reported outcome data were not collected in MK-6482-004.

The FDA's Assessment:

FDA agrees with the Applicant's statement. While patient-reported tolerability data might have been informative, it was not collected.

Additional Analyses Conducted on the Individual Trial

Data:

For VHL disease-associated RCC, the overall median LGR before treatment was approximately 3.63 mm/year (with median LGR across the four quartiles of approximately 0.97, 2.70, 4.34 and 7.81 mm/year), demonstrating pre-treatment tumor growth in all participants across quartiles. After treatment with MK-6482, the median LGR was -4.48 mm/year (with median LGR across the four pre-treatment quartiles of approximately -4.07, -3.60, -5.78 and -4.83 mm/year), demonstrating changes in growth kinetics of tumors across all pre-treatment LGR quartiles [Table 10] [Figure 10].

Notably, both participants who achieved PR and participants who did not achieve PR had a decrease in LGRs from baseline, demonstrating the benefit achieved by participants even in the absence of a RECIST 1.1 response [Table 17].

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Table 16 Applicant – Patient-level Summary of After Treatment Linear Growth Rate for RCC Tumors by Quartiles of Before Treatment LGR – IRC – Efficacy Analysis Set

LGR (mm/year) Before Treatment		MK-6482 (N=61) Before Treatment	MK-6482 (N=61) After Treatment
All Patients (-3.47323, 33.10120)	n	57	54
	Median	3.63145	-4.48117
	Q1, Q3	1.46243, 5.64417	-7.27779, -1.83086
	Min, Max	-3.47323, 33.10120	-12.75732, 5.11382
(Min, Q1) (-3.47323, 1.46243)	n	14	13
	Median	0.97262	-4.07304
	Q1, Q3	-0.13539, 1.16469	-6.68826, -2.77025
	Min, Max	-3.47323, 1.43178	-7.92359, 1.74896
(Q1, Q2) (1.46243, 3.63145)	n	14	14
	Median	2.70522	-3.60902
	Q1, Q3	1.87078, 3.08857	-7.32378, -1.65971
	Min, Max	1.46243, 3.57729	-12.75732, -0.02278
(Q2, Q3) (3.63145, 5.64417)	n	14	13
	Median	4.34393	-5.78302
	Q1, Q3	3.98810, 4.91792	-8.36855, -1.51820
	Min, Max	3.63145, 5.35358	-10.24327, 5.11382
(Q3, Max) (5.64417, 33.10120)	n	15	14
	Median	7.81460	-4.83404
	Q1, Q3	6.12523, 9.26750	-7.85203, -2.61607
	Min, Max	5.64417, 33.10120	-10.04725, 1.72704

LGR = Linear growth rate; Q1:1st quartile; Q2: Median; Q3: 3rd quartile. Patients with less than 3 before treatment scans are not included in the table.
Patient level linear tumor growth rate for target tumors pre and post dose treatment are calculated for patients with at least 3 scans respectively by using linear regression applied to the tumor sizes with time as continuous variables and individual tumor as categorical variables.
The linear growth rate is derived as the coefficient of time.
Date of Data Cut-off: 01JUN2020

Source: [P004V01MK6482: adam-adsl; adtrg]

Table 17 Applicant – Patient-level Summary of Before- and After-treatment LGR for RCC Tumors by Best Overall Response – IRC – Efficacy Analysis Set

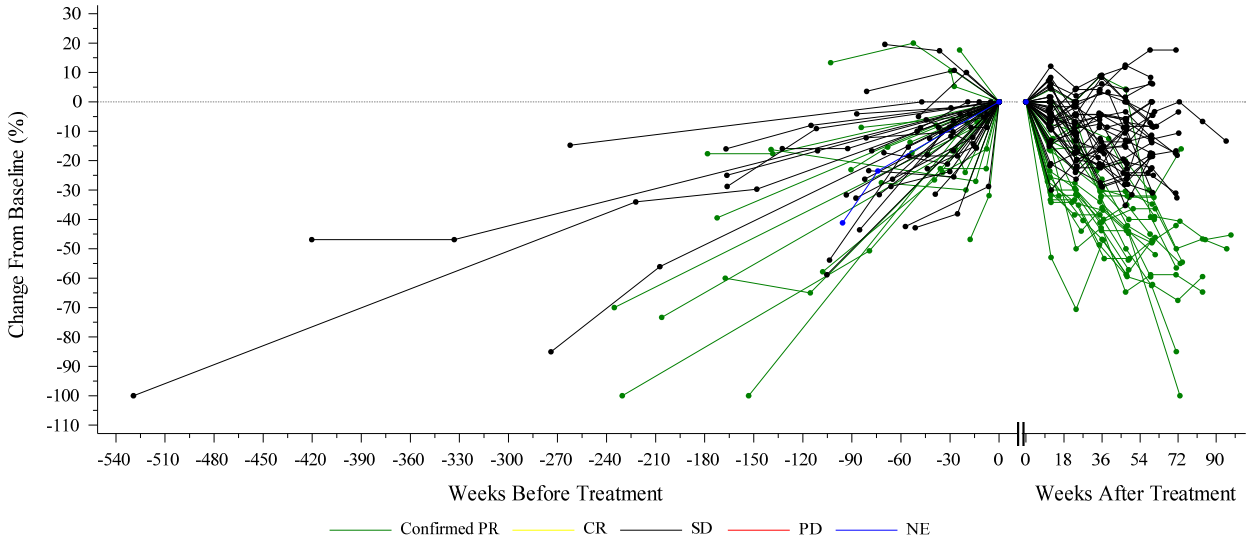
Best Overall Response Statistics	Before Treatment	After Treatment
Complete Response (CR)		
n	0	0
Partial Response (PR)		
n	21	22
Mean (SD)	4.94 (7.155)	-7.63 (2.357)
Median	4.10	-7.25

Best Overall Response Statistics	Before Treatment	After Treatment
Min, Max	-3.1, 33.1	-12.8, -4.1
Stable Disease (SD)		
n	35	36
Mean (SD)	3.83 (3.048)	-2.67 (3.023)
Median	3.58	-2.69
Min, Max	-3.5, 10.1	-10.0, 5.1
Progressive Disease (PD)		
n	0	0
Not Evaluable (NE)		
n	1	0
Mean (SD)	3.67 (-)	
Median	3.67	
Min, Max	3.7, 3.7	
No Evidence of Disease (NED)		
n	0	0

Patient level linear tumor growth rate for target tumors pre and post dose treatment are calculated for patients with at least 3 scans respectively by using linear regression applied to the tumor sizes with time as continuous variables and individual tumor as categorical variables.
The linear growth rate is derived as the coefficient of time.
Date of Data Cut-off: 01JUN2020

Source: [P004V01MK6482: adam-adsl; adeff; adtrg]

Figure 13 Applicant – Spider Plot – Percentage Change in Total Sum of RCC Target Lesion Diameters from Baseline in Scan Before and After Treatment – IRC – Efficacy Analysis Set



Date of Data Cut-off: 01JUN2020

Source: [P004V01MK6482: adam-adtrs; adeff]

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

The Applicant's Position:

LGR is an indicator of the aggressiveness of the disease. Given that renal tumor burden is an independent negative prognostic factor for overall survival of VHL disease-associated RCC patients [10], reducing the size of the lesions or restricting growth to <3 cm may be beneficial to these patients. Currently, surgical management is the only way to manage lesions that are >3 cm and to avoid the risk of metastasis.

Irrespective of growth rate prior to treatment, the median growth rate after treatment with belzutifan decreased in all quartiles of before treatment LGR. Importantly, participants with a BOR of stable disease also had a reduction in LGR, suggesting clinical benefit despite not attaining an objective response.

The FDA's Assessment:

In MK-6482-004, 6 patients had decrease in tumor size in the pre-treatment LGR assessments, as shown in the spider plot. According to the Applicant, these changes were up to 20% overall in total size and were mainly due to variations in IRC assessments rather than due to true regressions. However, this points to the fact that these lesions are generally small overall and measurement accuracy and consistency between scans may be problematic.

FDA disagrees with the statement that clinical benefit was obtained in those who did not attain an objective response, as these patients technically are classified as having stable disease per RECIST v1.1. In the absence of objective responses per RECIST v1.1, it is unclear that clinical benefit can be attributed to belzutifan on a trial level although some tumor shrinkage is likely beneficial to an individual patient.

10.1.3 Natural History Study

Trial Design

The Applicant's Description:

The natural history study is a retrospective, non-interventional study of patients with VHL disease-associated RCC using data registered by the NCI in a hereditary database of patients with VHL syndrome. The study population consisted of patients treated at the NCI with confirmed VHL syndrome with ≥1 renal solid identified and measured during the study period (31-JUL-2004 to 30-JUN-2020), who are residents of the US or Canada, and with no investigational therapy, oncologic therapy, or renal tumor reduction procedures within 30 days proximate to patient-level index date, defined as the first date that a patient had at least one solid tumor measured within the study period. Patients were followed until the first of date of death or last clinical encounter.

The primary research outcome is an assessment of LGR for renal solid tumors under active surveillance and in a similar setting as MK-6482-004 in the absence of treatment. Additional outcomes which are intended to support MK-6482-004 clinical benefit include an assessment of

the expected rates of surgery and time to surgery, and an assessment of renal function in patients receiving standard of care.

Analyses were conducted in the Primary Study Population of patients who met the study eligibility criteria and a subgroup of patients ('Trial Population Subgroup') who met additional key eligibility criteria that closely matched that of the MK-6482-004 clinical study with a focus on the growth rate assessment. An analysis of linear growth rate for renal solid tumors was performed for a subset of patients in the Primary Study Population and Trial Population Subgroup with at least three serial tumor measurements for unique tumor(s) prior to the first of: date of death or last clinical encounter, initiation of investigational or oncologic therapy, or first renal tumor reduction procedure impacting the tumor.

The FDA's Assessment:

FDA agrees with the Applicant's statement.

10.1.4 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

The natural history study 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 FDA's Assessment:

FDA agrees with the Applicant's statement.

Financial Disclosure

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's statement.

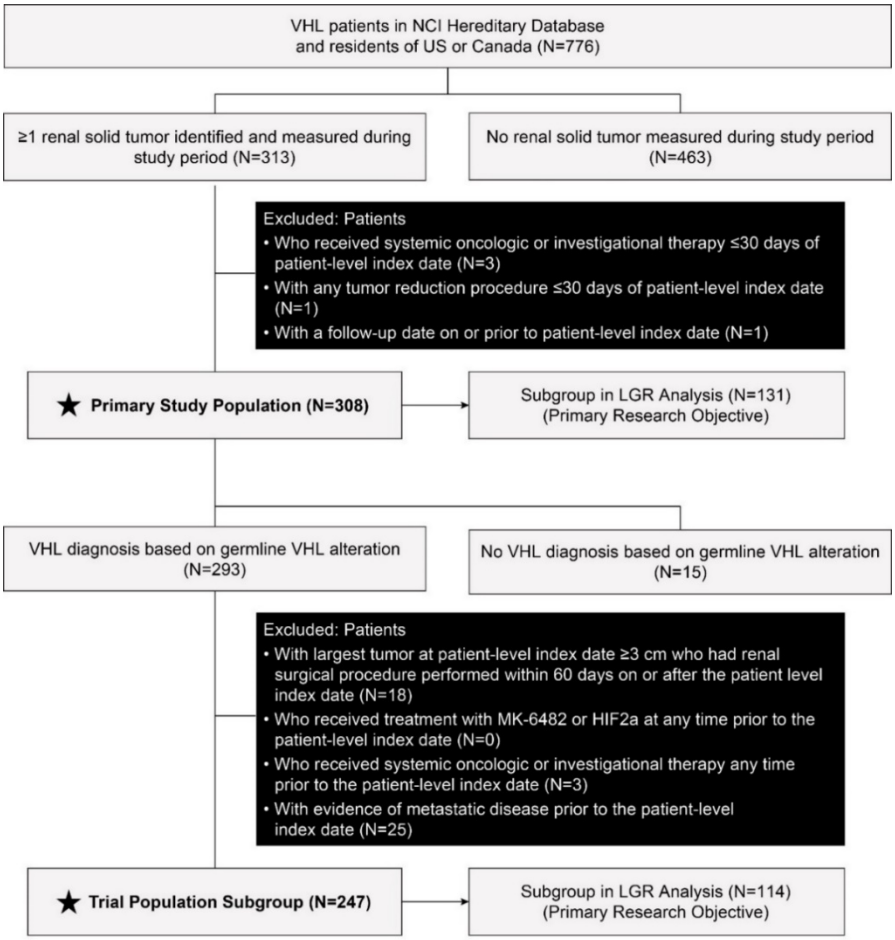
Patient Disposition

The Applicant's Position:

Of 776 VHL patients in the NCI hereditary database, a total of 308 patients with at least 1 solid renal tumor met the eligibility criteria and were included in the Primary Study Population. After applying additional eligibility criteria that closely matched key MK-6482-004 trial criteria with a

focus on the tumor growth rate assessment, 247 patients (80%) were included in the Trial Population Subgroup [Figure 14]. A subgroup of 131 patients and 114 patients in the Primary Study Population and Trial Population Subgroup, respectively, had ≥3 serial measurements for at least one solid renal tumor during the study period that qualified them for inclusion in the LGR analysis (primary research objective). Secondary research objectives were addressed in the broader Primary Study Population and Trial Population Subgroup.

Figure 14 Applicant - Natural History Study Disposition Flowchart



The FDA's Assessment:

FDA agrees with the Applicant's statement.

Protocol Violations/Deviations

The Applicant's Position:

Not Applicable.

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The FDA's Assessment:

FDA agrees with the Applicant's statement.

Table of Demographic Characteristics

Data:

Patients in the Primary Study Population had a median age of 41.9 years (range: 17.6 to 79.4 years) at the patient-level index date, defined as date the first renal solid tumor was identified and measured during the study period, and 44.2% were female. The median length of follow-up after the patient-level index date was 9 years (107.2 months: range, 0.03 to190.2 months), with 87.7% and 70.5% having at least 2 and 5 years of follow-up, respectively. Most (95%) patients had a genetic diagnosis of VHL and the majority of the VHL alterations were missense mutations (41.6%) and complete/partial deletions (24.7%). Based on investigator assessment, patients with ≥1 renal solid tumor had a record of other clinical manifestations at the patient-level index date including 78.6% and 71.4% with a history of brain and spine hemangioblastomas, respectively; 91.6% had renal cysts, 34.1% had pancreatic solid tumors, 76.9% had pancreatic cysts, 56.8% had retinal angiomas, 8.8% had endolymphatic sac tumors and 26.2% (of males) had epididymal cystadenomas. Sixty-two percent (192/308) of patients had a prior renal tumor reduction procedure, with a median of 45.9 months (Q1 to Q3: 20.3 to 83.9) from the time of the last procedure to the patient-level index date. The median baseline tumor size (cm) of the largest renal solid tumor at the patient-level index date, based on local NCI assessment, was 2.1 cm (Q1 to Q3: 1.5 to 2.8) [Table 18].

Table 18 Applicant – Demographic and Clinical Characteristics – Natural History Study: Primary Study Population and Trial Population Subgroup

	Primary Study Population		Trial Population Sub-Group	
	All Patients (N=308)	Patients with ≥3 Serial Measurements[1] (N=131)	All Patients (N=247)	Patients with ≥3 Serial Measurements[1] (N=114)
Length of Follow-up, months				
Minimum, Maximum	0.03, 190.2	24.0, 190.2	0.03, 190.2	24.0, 190.2
Median	107.2	157.6	123.2	160.1
Q1, Q3	50.1, 164.0	116.4, 176.4	58.0, 169.3	131.0, 176.4
2-year follow-up: n (%) [2]	270 (87.7%)	130 (99.2%)	220 (89.1%)	113 (99.1%)
5-year follow-up: n (%) [2]	217 (70.5%)	127 (96.9%)	185 (74.9%)	112 (98.2%)
Age, years				
At Patient-level index date				
Minimum, Maximum	17.6, 79.4	17.6, 66.5	17.6, 76.2	17.6, 66.5
Median	41.3	41.3	41.1	40.8
Q1, Q3	32.2, 51.5	32.0, 49.8	32.0, 51.4	30.8, 49.4
At VHL diagnosis				
N of included patients	113	47	94	40
Minimum, Maximum	5.0, 53.0	11.0, 53.0	5.0, 53.0	11.0, 53.0
Median	27.0	27.0	27.0	29.0

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

	Primary Study Population		Trial Population Sub-Group	
	All Patients (N=308)	Patients with ≥3 Serial Measurements[1] (N=131)	All Patients (N=247)	Patients with ≥3 Serial Measurements[1] (N=114)
Q1, Q3	19.0, 34.0	18.0, 36.0	18.0, 34.0	18.5, 34.5
Sex: n (%)[2]				
Female	136 (44.2%)	59 (45.0%)	115 (46.6%)	55 (48.2%)
Male	172 (55.8%)	72 (55.0%)	132 (53.4%)	59 (51.8%)
Baseline tumor size of the largest renal solid tumor[3], cm				
Minimum, Maximum	0.600, 19.500	0.600, 3.820	0.600, 6.350	0.600, 3.700
Median	2.064	1.900	1.910	1.820
Q1, Q3	1.500, 2.800	1.455, 2.460	1.432, 2.600	1.400, 2.330
Non-RCC VHL lesions at Patient-level index date[4]: n (%)[2]				
Kidney cyst	282 (91.6%)	119 (90.8%)	224 (90.7%)	102 (89.5%)
Pheochromocytoma / paraganglioma	67 (21.8%)	26 (19.8%)	49 (19.8%)	22 (19.3%)
Pancreatic solid tumor	105 (34.1%)	43 (32.8%)	84 (34.0%)	36 (31.6%)
Pancreatic cyst	237 (76.9%)	103 (78.6%)	193 (78.1%)	90 (78.9%)
Brain hemangioblastoma	242 (78.6%)	108 (82.4%)	192 (77.7%)	93 (81.6%)
Spine hemangioblastoma	220 (71.4%)	93 (71.0%)	178 (72.1%)	81 (71.1%)
Retinal angioma	175 (56.8%)	74 (56.5%)	144 (58.3%)	66 (57.9%)
Endolymphatic sac	27 (8.8%)	12 (9.2%)	24 (9.7%)	10 (8.8%)
Epididymal cystadenoma (males only)[5]	45 (26.2%)	17 (23.6%)	37 (28.0%)	14 (23.7%)
Genetic confirmation of VHL: n (%)[2]				
Yes	293 (95.1%)	130 (99.2%)	247 (100.0%)	114 (100.0%)
No	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not done / missing	14 (4.5%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
VHL mutation type: n (%)[2]				
Missense	128 (41.6%)	56 (42.7%)	105 (42.5%)	48 (42.1%)
Complete or partial deletion	76 (24.7%)	43 (32.8%)	69 (27.9%)	37 (32.5%)
Nonsense	33 (10.7%)	14 (10.7%)	28 (11.3%)	13 (11.4%)
Frameshift	30 (9.7%)	8 (6.1%)	25 (10.1%)	8 (7.0%)
Other[6]	41 (13.3%)	10 (7.6%)	20 (8.1%)	8 (7.0%)
VHL type: n (%)[2]				
1	177 (57.5%)	88 (67.2%)	148 (59.9%)	78 (68.4%)
2	76 (24.7%)	36 (27.5%)	60 (24.3%)	29 (25.4%)
Missing	55 (17.9%)	7 (5.3%)	39 (15.8%)	7 (6.1%)
Renal tumor reduction procedures prior to Patient-level index date, n				
Minimum, Maximum	0, 9	0, 7	0, 9	0, 7
Median	1	1	1	1
Q1, Q3	0, 2	0, 2	0, 2	0, 2
Time from most recent renal tumor reduction procedure to Patient-level index date, months				
N of included patients	192	90	158	76

	Primary Study Population		Trial Population Sub-Group	
	All Patients (N=308)	Patients with ≥3 Serial Measurements[1] (N=131)	All Patients (N=247)	Patients with ≥3 Serial Measurements[1] (N=114)
Minimum, Maximum	1.3, 302.2	2.0, 213.8	2.0, 302.2	2.0, 213.8
Median	45.9	43.2	46.5	43.2
Q1, Q3	20.3, 83.9	25.5, 71.0	21.3, 89.2	23.5, 74.0

VHL=von Hippel-Lindau; AA= amino acid; Q1= first quartile (25th percentile); Q3=third quartile (75th percentile); Patient-level index date= date of earliest radiology report at the NCI of a solid renal tumor during the study period.

[1] All patients with ≥3 renal solid tumor serial measurements after the patient-level index date and within the assessment window.
[2] %=n/N.
[3] At patient-level index date.
[4] Age at detection of lesion was ≤ patient age at index date.
[5] % of males only.
[6] Included AA deletion, splice acceptor, splice donor, no mutation detected, unknown, or missing

The Applicant's Position:

The Primary Study Population is generally representative of a patient population with VHL-associated disease.

The FDA's Assessment:

FDA agrees with the Applicant's assessment and notes the similarity of the patient population to that of MK-6482-004 in many aspects including the overall young age of patients. In the Natural History Study, 20% and 58% of the patients in the trial population subgroup had pheochromocytoma/paraganglioma and retinal angioma, respectively. These tumors are notably underrepresented in MK-6482-004, which is likely due to lack of preplanned optimized screening for these non-RCC tumors in MK-6482-004. Additionally, a higher proportion of patients in MK-6482-004 had type 1 VHL disease which is another reason for notably lower number of patients with adrenal tumors in MK-6482-004 compared to the percentages reported in the literature and the Natural History Study.

Other Baseline Characteristics (eg, disease characteristics, important concomitant drugs)

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Maximal tumor diameter measurements just prior to each tumor reduction procedure were not available in the Natural History Study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Not applicable.

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The FDA's Assessment:

FDA agrees with the Applicant's statement.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The median tumor-level LGR for the Trial Population Subgroup was 3.69 mm/year (Q1 to Q3: 2.86, 4.66) [Table 19], falling within the range of growth rate observed in the published literature [23] [24] [25] [26] [12]. There was a positive change in maximal tumor diameter for most (99%) unique tumors and 100% of the patient-level analyses. Similar results were observed for patient-level LGR analyses, and patient-level and tumor-level analyses using similar regression model used in MK-6482-004 [Table 20]. Results were also similar for patients included in the Primary Study Population of patients with at least 3 serial tumor measurements (N=131 patients, N=201 unique tumors).

Table 19 Applicant – Patient-level and Tumor-level Linear Growth Rate for Renal Solid Tumors: Primary Analysis Using Linear Mixed (Multi-level) Model – Natural History Study – Primary Study Population and Trial Population Subgroup

	Primary Study Population	Trial Population Subgroup
	Patients with ≥3 Serial Measurements (N=131)[1]	Patients with ≥3 Serial Measurements (N=114)[1]
Patient-Level LGR (mm/year)		
Mean	3.99	3.84
Standard deviation	0.75	0.77
Minimum, Maximum	2.36, 7.44	2.19, 7.36
Median	3.90	3.74
Q1, Q3	3.55, 4.47	3.43, 4.25
Increase in Maximal Tumor Diameter[3]	100%	100%
	Tumors with ≥3 Serial Measurements (N=201)[2]	Tumors with ≥3 Serial Measurements (N=173)[2]
Tumor-Level Linear Growth Rate (mm/year)		
Mean	3.99	3.84
Standard deviation	1.48	1.49
Minimum, Maximum	-0.03, 10.34	-0.08, 10.19
Median	3.84	3.69
Q1, Q3	2.99, 4.86	2.86, 4.66
Increase in Maximal Tumor Diameter[3]	99.5%	99.4%

Q1= first quartile (25th percentile); Q3=third quartile (75th percentile);
Linear Growth Rate estimated using linear mixed (multi-level) model including 3 levels including unique patients, unique tumors nested within unique patients, and tumor measurements nested within unique tumors.

[1] All patients with ≥3 serial measurements of ≥1 renal solid tumor(s) after the patient-level index date and within the assessment window.
[2] All unique tumor(s) with ≥3 serial measurements after the patient-level index date and within the assessment window.
[3] Positive change in maximal tumor diameter between baseline and last measurement within the assessment window.

Table 20 Applicant – Patient-level and Tumor-level Linear Growth Rate for Renal Solid Tumors: Secondary Analysis Using Linear Regression Model – Natural History Study – Primary Study Population and Trial Population Subgroup

	Primary Study Population	Trial Population Subgroup
	Patients with ≥3 Serial Measurements (N=131)[1]	Patients with ≥3 Serial Measurements (N=114)[1]
Patient-Level LGR (mm/year)		
Mean	4.00	3.80
Standard deviation	2.30	2.22
Minimum, Maximum	-2.32, 11.23	-2.32, 9.78
Median	3.70	3.54
Q1, Q3	2.56, 5.63	2.48, 5.40
	Tumors with ≥3 Serial Measurements (N=201)[2]	Tumors with ≥3 Serial Measurements (N=173)[2]
Tumor-Level LGR (mm/year)		
Mean	4.24	4.10
Standard deviation	2.88	2.91
Minimum, Maximum	-2.32, 19.50	-2.32, 19.50
Median	3.62	3.56
Q1, Q3	2.47, 5.66	2.37, 5.60

LGR=linear growth rate; Q1= first quartile (25th percentile); Q3=third quartile (75th percentile)
Tumor-level LGR was determined using linear regression model by regressing tumor size on time since tumor-level index date as a continuous variable at a tumor-level. Patient-level LGR was determined using linear regression model by regressing tumor size on time since tumor-level index date as a continuous variable and individual tumor as categorical variable.

[1] All patients with ≥3 serial measurements of ≥1 renal solid tumor(s) after the patient-level index date and within the assessment window.
[2] All unique tumor(s) with ≥3 serial measurements after the patient-level index date and within the assessment window.

The Applicant's Position:

These data demonstrate that spontaneous regression is unlikely to occur as part of the natural history of VHL-disease associated RCC tumors.

The FDA's Assessment:

Data Quality and Integrity

The Applicant's Position:

Not applicable.

The FDA's Assessment:

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The natural history study was a non-interventional retrospective study based upon a NCI database. Since the natural history study is being used as supportive information only, the data quality and integrity appear to be sufficient quality to support the conclusions made below.

Efficacy Results – Secondary and Other Relevant Endpoints

Data:

Frequency and Type of Tumor Reduction Procedures

Of the 308 patients in the Primary Study Population, 232 (75.3%) patients had ≥1 tumor reduction procedure during the study period including 225 (73.1%) patients with surgical procedures (96% of which were partial nephrectomies), 16 (5.2%) patients with ablation procedures, and 1 (0.3%) patient who received radiation therapy [Table 21]. Similar treatment patterns were observed in the Trial Population Subgroup.

During 2-year and 5-year follow-up for patients in the Trial Population Subgroup, 71 (28.7%) and 138 (55.9%) patients had ≥1 tumor reduction procedure, respectively. Among patients with ≥1 tumor reduction procedure, approximately 60% of patients in the Primary Study Population and Trial Population Subgroup had ≥2 procedures, including 11/71 (15.5%) patients and 34/138 (24.6%) patients in the Trial Population Subgroup with ≥2 procedures within 2 years and 5 years of follow-up, respectively. The median number of tumor reduction procedures in the Primary Study Population and Trial Population Subgroup was 2 and ranged from 1 to 9 procedures. During 2-year and 5-year follow-up for patients in Trial Population Subgroup, the median number of procedures was 1 and ranged from 1 to 3 and 1 to 4 procedures, respectively [Table 21].

Median estimated blood loss for those who received surgery in the Primary Study Population and Trial Population Subgroup was 1.5L (Q1 to Q3: 0.6, 2.6) and 1.3L (Q1 to Q3: 0.6, 2.5), respectively, which represents an approximate 30% blood loss in an average adult patient and increases the potential need for transfusion [27] [28] [29] [12] [15]. Among the 217 patients in the Primary Study Population and 175 patients in the Trial Population Subgroup receiving at least ≥1 partial nephrectomy, 30% had experienced a complication associated with surgery. In the Primary Study Population and Trial Population Subgroup, 2/223 (0.9%) and 1/178 (0.6%) patients, respectively, undergoing surgery at the NCI experienced perioperative mortality.

Table 21 Applicant – Summary of Tumor Reduction Procedures During Study Period – Natural History Study – Primary Study Population and Trial Population Subgroup

	Patients in the Primary Study Population (N=308)		Patients in the Trial Population Subgroup (N=247)	
Renal Solid Tumor Reduction Procedures	All Available Follow-up	All Available Follow-up	During 2-year Follow-up	During 5-year Follow-up
Number of Patients with Tumor Reduction Procedures: n (%)[1]				

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	Patients in the Primary Study Population (N=308)	Patients in the Trial Population Subgroup (N=247)		
Renal Solid Tumor Reduction Procedures	All Available Follow-up	All Available Follow-up	During 2-year Follow-up	During 5-year Follow-up
≥1 tumor reduction procedure	232 (75.3%)	184 (74.5%)	71 (28.7%)	138 (55.9%)
≥1 surgical procedure	225 (73.1%)	177 (71.7%)	68 (27.5%)	132 (53.4%)
≥1 partial nephrectomy	217 (70.5%)	175 (70.9%)	65 (26.3%)	128 (51.8%)
≥1 ablation procedure	16 (5.2%)	13 (5.3%)	3 (1.2%)	7 (2.8%)
≥1 radiation procedure	1 (0.3%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
≥2 procedures[2]	136 (58.6%)	114 (62.0%)	11 (15.5%)	34 (24.6%)
Number of Tumor Reduction Procedures, n				
N of included patients	232	184	71	138
Mean	2.1	2.1	1.2	1.3
Standard deviation	1.2	1.2	0.4	0.6
Minimum, Maximum	1.0, 9.0	1.0, 9.0	1.0, 3.0	1.0, 4.0
Median	2.0	2.0	1.0	1.0
Q1, Q3	1.0, 3.0	1.0, 3.0	1.0, 1.0	1.0, 1.0

Q1= first quartile (25th percentile); Q3=third quartile (75th percentile)
Tumor reduction procedures include surgery, ablation, and radiation procedures.

[1] %=n /N
[2] % of patients with ≥1 procedure

The Applicant's Position:

Consistent with what has been reported previously for patients with VHL disease-associated RCC, participants in the Primary Study Population and Trial Population Subgroup underwent frequent surgical procedures (most commonly partial nephrectomies), many of which were associated with complications.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. Overall, the number of renal solid tumor reduction procedures reported in the Natural History Study is consistent with the number of RCC-related procedures prior to enrollment in MK-6482-004. We note that despite the baseline median tumor size of approximately 2 cm and a growth rate per year of approximately 4 mm, nearly 30% of patients underwent tumor reduction procedures within 2 years of trial follow-up. This points to the fact that these procedures may be pursued even in the absence of patients reaching the 3 cm mark and that there may be some degree of subjectivity in the decision to undergo these procedures.

While the Natural History Study provided supportive information, there was no part of reported data that was appropriate for inclusion in labeling. The Natural History Study was a retrospective study and the results should be interpreted with caution due to potential selection bias and confounding factors affecting the result.

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10.1.5 Integrated Review of Effectiveness

The FDA's Assessment:

See section 8.1.7

10.1.6 Assessment of Efficacy Across Trials

The Applicant's Position:

This is not applicable as the efficacy of belzutifan is presented from one study (MK-6482-004). All efficacy data is summarized in the section on MK-6482-004 above.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Additional Efficacy Considerations

The FDA's Assessment:

N/A

10.1.7 Integrated Assessment of Effectiveness

The Applicant's Position:

Treatment of patients in VHL-disease associated RCC and other VHL-associated tumors with belzutifan resulted in clinically-meaningful ORR and DCR in MK-6482-004. Additionally, the percentage of patients who experienced a decrease in the sum of target tumor diameters demonstrates the benefit of MK-6482 beyond the participants who attained a RECIST 1.1 response. The benefits were shown to be durable, with a long DOR and TTS. High response rates were also observed for VHL-disease associated non-RCC tumors. A similar pattern of efficacy to belzutifan was observed in VHL-disease associated RCC and other VHL-associated tumors, underscoring the common underlying pathophysiology in VHL disease and the ability of belzutifan to meaningfully impact benign or malignant neoplasms driven by VHL loss in multiple organs. Efficacy is also supported by decreases in intra-patient LGR in target renal tumors and pancreatic tumors after belzutifan treatment versus before belzutifan treatment. Comparisons to LGR data from the tumor growth kinetics of patients with VHL disease-associated RCC in the natural history study also shows that belzutifan reverses the trajectory of tumor growth and meaningfully changes the natural history of the disease. The data from MK-6482-004 strongly suggest that clinical benefit from belzutifan extends beyond patients who achieve a confirmed objective response. Nearly all patients treated achieved disease control, no patient had a best response of progressive disease, and the PFS analysis showed only a single event (which as a death unrelated to progression of the underlying disease). Only 1 patient of the 61 in the study required surgical excision of a single RCC tumor compared to the approximately 25% of patients with VHL disease associated RCC that would be expected to require surgery for their RCC if they

were observed for a similar period of time based on the results of the natural history study, underscoring the potential value of belzutifan in preventing or delaying the need for surgical excision of RCC tumors.

The FDA's Assessment:

For demonstration of efficacy in this application, FDA relied on ORR and DoR in the single arm trial MK-6482-004. Stable disease and DCR, while often clinically meaningful on individual level, may not be definitively attributed to the drug effect. Time-to-event endpoint results (e.g., time to surgery, and progression-free survival) are uninterpretable in a single arm study without a randomized comparator.

Regarding VHL-associated RCC, data from MK-6482-004 supports the efficacy of belzutifan by demonstrating a high overall rate of measurable decreases in tumor size for an extended duration of time, which is directly attributable to drug effect. Given the magnitude and durability of results and the relative rarity of the population and disease under study, the review team determined that a regular approval was appropriate despite the small size of the cohort of patients enrolled in MK-6482-004. Further follow up is needed to assess whether the decrease in tumor size results in a decrease in the rate of renal tumor reduction procedures and associated morbidity as stated by the Applicant, although this may be a logical assumption.

In MK-6482-004, patients with RCC ≥ 3.0 cm were enrolled and results showed there were durable responses in this subgroup as well. However, the size of tumor remained ≥ 3.0 cm at the time of DCO as of December 1, 2020 for all the 18 patients who had at least 1 RCC tumor ≥ 3.0 cm per IRC at the time of enrollment. The goal of surgery for VHL-disease RCC is to prevent metastasis which is a risk for patients with RCC ≥ 3.0 cm in size. In MK-6482-004, duration of follow up was relatively short and data is not adequate to assess whether treatment with belzutifan in patients with RCC ≥ 3.0 cm prevents metastasis, particularly if the size of tumor remains ≥ 3.0 despite treatment.

Most of the patients were not diagnosed immediately prior to enrollment in MK-6482-004 and the median time from diagnosis of VHL-associated RCC to enrollment on this trial was 18 months. VHL-disease RCC is slow-growing and there is likely little risk of metastasis for RCC tumors < 3.0 cm. Therefore, patients with VHL-disease RCC may not require any treatment for several years after diagnosis and a decision to initiate medical treatment is multifactorial and likely subjective, based on patient and disease characteristics, to avoid unnecessary exposure to toxicities of the drug when treatment is not required.

Belzutifan showed efficacy in non-RCC tumors such as pancreatic tumors (pNET, non-pNET), and CNS hemangioblastoma. Overall, the FDA review team determined that these data were clinically meaningful enough to include these in the indication statement of product labeling despite the Applicant not originally proposing their inclusion.

In terms of VHL-disease associated pNET, these tumors may regress, progress, or remain stable and can rarely metastasis. Therefore, the decision to start medical treatment should be based on multiple factors such as the growth pattern of the tumor and patient's medical condition.

In patients enrolled on MK-6482-004 there was generally a high rate of discordance regarding the baseline presence of pNET in some of the patients; however after review of the data the review team determined that there were 12 patients who had pNET agreed on per at least two radiologists. The ORR was high among both the larger group of all 22 patients who had PNET per Applicant's assessment (ORR 90%) and in the subgroup of 12 patients for whom at least two IRC radiologists had agreement on the presence of a PNET-pancreatic lesion (ORR 85%). Thus this very high response rate in the context of scientific rational for efficacy across VHL diseases was thought to be of sufficient magnitude to include these patients in the indication statement and in section 14 of labeling despite the small sample size.

Belzutifan demonstrated efficacy in the 24 patients with VHL-disease CNS hemangioblastoma, with ORR 62% in the subgroup with a measurable solid component in CNS hemangioblastoma. Additionally, there was radiologic decrease in cysts and syrynges as well. Although data on neurologic function, PRO data and presence of related symptoms are not available for patients enrolled in MK-6482-004, overall the review team determined that the high response rate and durations in this disease type in the context of scientific rational for efficacy across VHL diseases translates into clinically meaningful effects for patients especially as the treatment for enlarging, symptomatic lesions would otherwise involve potentially morbid surgical or other procedures. Thus CNS hemangioblastomas were included in the indication statement and in section 14 of product labeling.

Non-PNET benign pancreatic lesions may regress, remain stable or progress over time and are usually asymptomatic and rarely require treatment in situations that a tumor becomes very large and presses on the organs. In the rare case that the tumor becomes symptomatic, surgical procedures may be needed. The review team determined that provided data in MK-6482-004 is not adequate to support a favorable risk: benefit assessment in non-PNET pancreatic tumors (b) (4)

Efficacy data from MK-6482-004 in retinal hemangioblastoma is only available in a small proportion of patients. Overall after review of the data, the FDA review team determined that the reported efficacy data for retinal tumors in MK-6482-004 was not reliable due to concerns about accuracy in measurement (b) (4)

TTR in VHL-disease RCC, PNET and CNS hemangioblastoma was relatively long. Therefore, belzutifan is not an alternative for urgent procedures required for management of life-threatening conditions or severe symptoms caused by VHL-disease tumors.

10.2 Review of Safety

The Applicant's Position:

Overall, the belzutifan 120 mg QD dose as administered in VHL-associated RCC population in MK-6482-004 Study is tolerable and has a manageable safety profile. The tolerability is supported by the low frequencies of AEs leading to study intervention discontinuation. The manageable safety profile is supported by the mild to moderate AEs observed, which were responsive to standard medical care. There were no Grade 4 or Grade 5 drug-related AEs

The FDA's Assessment:

The overall review of the safety of belzutifan is discussed in detail in the sections below.

In terms of the Applicant's Position stated above, while the FDA agrees that few patients (2 [3.3%]) in MK-6482-004 discontinued study intervention due to AEs, a relatively high proportion of patients experienced Grade 3-4 AEs (15 [24.6%]), SAEs (9 [14.8%]), AEs leading to dose interruption (24 [39.3%]), and AEs leading to dose reduction (8 [[13.1%]). TEAEs reported with frequencies above 20% were anemia, fatigue, headache, dizziness, and nausea. Serious safety concerns with the use of belzutifan for the proposed indication include anemia, hypoxia, secondary malignancies, and embryofetal toxicities. These concerns are discussed in detail in the sections below.

10.2.1 Safety Review Approach

The Applicant's Position:

Analyses of safety data for belzutifan in participants with VHL-disease associated RCC from the pivotal Study MK-6482-004 and the proposed indicated dose of 120 mg once daily are included (n=61). Supportive safety data from participants with advanced solid tumors in MK-6482-001 (120 mg once daily group; n=58) are also included to further characterize the safety of belzutifan monotherapy at the 120mg dose. Direct comparison of these 2 studies is challenging due to the differences between the VHL-disease associated RCC and advanced solid tumor populations (median age, ECOG status, disease status, pretreatment, chronic comorbidities and baseline hemoglobin level at study entry), treatment durations, and follow-up times. However, taking these differences into consideration, the observed safety profile has been consistent between studies.

Data from each of the 2 individual studies (MK-6482-004 [n= 61]; MK-6482-001 [n=58]), pooled results from both studies at the 120 mg once daily dose (n=119), and pooled results from both studies at any dose of belzutifan (CRSD, n=177) are presented [Table 22].

Table 22 Applicant – Summary of Safety Datasets

Safety Population	Definition	Data Cutoff(s)
MK6482-004 Safety Dataset	Includes all subjects who received at least 1 dose of belzutifan 120 mg QD in MK-6482-004.	MK-6482-004: 01-JUN-2020
MK6482-001 Safety	Includes all subjects who received at least 1 dose of	MK-6482-001: 01-

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Dataset	belzutifan 120 mg QD in MK-6482-001 Part 1A and 1B.	JUN-2020
Pooled Safety Dataset	Includes all subjects who received at least 1 dose of belzutifan 120 mg QD in MK-6482-001 Part 1A and 1B, and MK-6482-004	MK-6482-001: 01-JUN-2020 MK-6482-004: 01-JUN-2020
Cumulative Running Safety Dataset	Includes all subjects who received at least 1 dose of belzutifan at 20mg QD (N=6), 40mg QD (N=6), 80mg QD (N=6), 120mg QD (N=119), 160mg QD (N=6), 240mg QD (N=7), 120mg BID (N=27) in MK-6482-001 Part 1A, 1B, MK-6482-001 Part 2 and MK-6482-004	MK-6482-001: 01-JUN-2020 MK-6482-004: 01-JUN-2020

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. To highlight toxicities observed in the proposed patient population, the adverse event table presented in product labeling will display information from MK-6482-004 but not from MK-6482-001.

10.2.2 Review of the Safety Database

Overall Exposure

Data:

The median duration of exposure was longer in MK-6482-004 (68 weeks) compared with MK-6482-001 (25.36 weeks) [Table 23].

Table 23 Applicant – Study Drug Exposure (Safety Analysis Set)

	MK6482-004 Data for MK6482 120 mg QD (N=61)	MK6482-001 Safety Dataset for MK6482 120 mg QD (N=58)	Pooled Safety Dataset for MK6482 120 mg QD (N=119)	Cumulative Running Safety Dataset for MK-6482 (N=177)
Number of patients exposed	61	58	119	177
Duration of exposure (weeks) [1]				
n	61	58	119	177
Mean (SD)	69.12 (17.407)	43.97 (42.979)	56.86 (34.724)	44.54 (37.734)
Median	68.00	25.36	64.43	35.14
Min, Max	8.4, 104.7	1.1, 145.9	1.1, 145.9	1.1, 145.9
Cumulative dose received (mg/subject)				
n	61	58	119	177
Mean (SD)	54849.8 (15584.97)	36800.0 (36201.09)	46052.4 (28959.26)	39447.0 (36773.00)

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

Median	56040.0	21300.0	51920.0	32040.0
Min, Max	4680, 84720	960, 122520	960, 122520	280, 189360

Each subject is counted once on each applicable duration category row.
[1] Duration of Exposure is calculated as (last dose date - first dose date + 1)/7.

Source: [ISS: adam-adsl; adex]

The Applicant's Position:

As of the DCO of 01-JUN-2020, a total of 93.4% (57/61) of participants in MK-6482-004 remained on study treatment for ≥1 year and 91.8% (56/61) remained on study treatment at the time of the data cutoff. The median duration of exposure was longer in MK-6482-004 compared with MK-6482-001.

The FDA's Assessment:

Safety data for belzutifan in patients with VHL-disease associated RCC (n=61) are obtained primarily from MK-6482-004. In addition, supportive safety data was analyzed from patients who received belzutifan at 120 mg (n=58) in MK-6482-001, a Phase 1, dose-escalation and expansion study in patients with advanced solid tumors that progressed or that was intolerant to standard of care and/or approved treatment options.

The FDA verified the information in Table 20 using dataset ADEX and variables AVAL, PARAM, DOSGP1FL, and DOSGP1FL. Although MK-6482-001 was initiated before MK-6482-004, the median duration of exposure was longer (68 vs. 25 weeks) likely because patients with metastatic RCC tend clinically to progress faster than those with early stage disease. The median duration of exposure was longer in MK-6482-004 (68 weeks) vs. MK 6482-001 (25 weeks).

Relevant Characteristics of the Safety Population:

Data:

Table 24 Applicant – Subject Characteristics – Safety Analysis Set

	MK6482-004 Data for MK6482 120 mg QD	MK6482-001 Safety Dataset for MK6482 120 mg QD	Pooled Safety Dataset for MK6482 120 mg QD	Cumulative Running Safety Dataset for MK-6482
	n (%)	n (%)	n (%)	n (%)
Subjects in population	61	58	119	177
Gender				
Male	32 (52.5)	45 (77.6)	77 (64.7)	116 (65.5)
Female	29 (47.5)	13 (22.4)	42 (35.3)	61 (34.5)
Age (Years)				
<65	59 (96.7)	34 (58.6)	93 (78.2)	126 (71.2)

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>=65	2 (3.3)	24 (41.4)	26 (21.8)	51 (28.8)
Mean	41.0	61.4	50.9	54.2
SD	13.46	9.85	15.63	15.51
Median	41.0	62.5	53.0	57.0
Range	19 to 66	39 to 75	19 to 75	19 to 84

Source: [ISS: adam-adsl]

The Applicant's Position:

The relevant characteristics of participants in the MK-6482-004 study were generally representative of a patient population with VHL-associated disease. Participants in the MK-6482-004 Safety Dataset were mostly male, <65 years, and mostly assigned an ECOG status of 0. Participants in MK-6482-001 were older, more heavily pre-treated with anticancer therapies, had metastatic disease, and had more chronic co-morbidities when compared to participants in the MK-6482-004 study [Table 18]. These differences in baseline population characteristics are important to consider when reviewing frequencies and severities of AEs in the different studies and in the pooled safety dataset.

The FDA's Assessment:

The FDA verified the information presented above using Integrated Summary of Safety dataset ADSL. The safety populations of MK-6482-001 and MK-6482-004 differed in terms of demographic and disease characteristics to an extent that results obtained by pooling safety data derived from these two populations would not have been appropriate to inform safety for the population of patients for which belzutifan was primarily evaluated. However, safety data from MK-6482-004 was considered as important supplemental information.

We note that there were no patients >75 treated with belzutifan on either trial at the proposed dose.

Adequacy of the Safety Database:

The Applicant's Position:

The clinical safety data supporting this NDA is derived from MK-6482-004 and MK-6482-001. The safety database is of an adequate size, considering VHL-associated RCC as a rare disease, with 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 safety database for belzutifan is relatively small but was deemed by the review team to be sufficient in size to adequately characterize the safety of belzutifan in the proposed population. This is especially true as despite the small number of patients evaluated in MK-6482-004, the median duration of exposure was relatively long and thus data is available for patients taking

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the drug for a prolonged period of time. The FDA Guidance document entitled, *Rare Diseases: Common Issues in Drug Development Guidance for Industry* states, "The goal of safety evaluation during drug development is to characterize the drug's safety profile in a reasonable number of patients over a reasonable duration of time, consistent with the intended use of the drug". What constitutes a reasonable number of patients for the safety database in a rare diseases requires consideration of feasibility challenges posed by the limited number of patients who have the disease."

Thus the review team concluded that the safety database was adequately large in this case given the rarity of the disease and the extent of exposure.

10.2.3 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 carried out 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 NDA 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:

The data submitted were well organized, complete, and consistent across case report forms, datasets, and clinical study reports.

Categorization of Adverse Events

The Applicant's Position:

AEs were coded using MedDRA (version 23.0). Uncoded preferred terms are presented in their verbatim terms. AEs were reported according to NCI CTCAE Version 4.03. AEs were graded in terms of severity (per NCI CTCAE V4.03) and were classified as serious or non-serious. The causal relationship between any AEs and study intervention was determined by the investigator and confirmed by the Sponsor. Adverse drug reactions are determined after an integrated review of the totality of available safety data. AEs occurring on or after the first day of treatment and within 28 days after administration of the last dose of study intervention were considered treatment-emergent.

The FDA's Assessment:

The use of MedDRA, an adverse event categorization system widely used by the FDA and the biopharmaceutical industry for regulatory purposes, is acceptable. The definition of treatment-emergent, as having begun or increased in severity between the first day of study treatment and 28 days after administration of the last dose, irrespective of attribution, is appropriate.

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Routine Clinical Tests

The Applicant's Position:

Participants underwent routine and sufficient evaluation for safety events including laboratory testing, vital sign measurements, physical examinations, and AE monitoring.

The FDA's Assessment:

The protocols for MK-6482-004 and MK-8482-001 incorporated adequate schedules of safety assessments. These included a physical examination, hematology, serum chemistry panel, serum iron panel, electrocardiography, and pregnancy testing at Weeks 1, 3, 5, 9, 13, 17, 21, and 25, every 12 weeks during extended treatment, 30 days after the last dose of study drug, and every 6 months during long-term follow-up. Tumor assessments by cross-sectional imaging were done every 8 weeks.

Safety Results

Table 25 Applicant – Overall Summary of Adverse Events

	MK6482-004 Data for MK-6482 120 mg QD		MK6482-001 Safety Dataset for MK-6482 120 mg QD		Pooled Safety Dataset for MK-6482 120 mg QD		Cumulative Running Safety Dataset for MK-6482	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	61		58		119		177	
with one or more adverse events	61	(100.0)	58	(100.0)	119	(100.0)	175	(98.9)
with no adverse event	0		0		0		2	(1.1)
with drug-related† adverse events	60	(98.4)	55	(94.8)	115	(96.6)	159	(89.8)
with toxicity grade 3-5 adverse events	15	(24.6)	41	(70.7)	56	(47.1)	87	(49.2)
with toxicity grade 3-5 drug-related adverse events	8	(13.1)	23	(39.7)	31	(26.1)	43	(24.3)
with serious adverse events	9	(14.8)	24	(41.4)	33	(27.7)	53	(29.9)
with serious drug-related adverse events	2	(3.3)	4	(6.9)	6	(5.0)	9	(5.1)
with adverse events leading to dose reduced	8	(13.1)	6	(10.3)	14	(11.8)	17	(9.6)
with drug-related adverse events leading to dose reduced	6	(9.8)	5	(8.6)	11	(9.2)	13	(7.3)
with adverse events leading to dose interrupted	24	(39.3)	24	(41.4)	48	(40.3)	61	(34.5)
with drug-related adverse events leading to dose interrupted	14	(23.0)	13	(22.4)	27	(22.7)	33	(18.6)
who died	1	(1.6)	5	(8.6)	6	(5.0)	10	(5.6)
who died due to a drug-related adverse event	0		0		0		0	

Adverse events up to 28 days of last dose are included. Grades are based on NCI CTCAE version 4.03.
† Determined by the investigator to be related to the drug.
Source: [ISS: adam-adsl; adae]

Deaths

Data:

One death (up to 28 days after the last dose of study intervention) due to an AE of toxicity to various agents (investigator report term: acute fentanyl overdose) was reported in the 004 Safety Dataset; this event was not considered related to study intervention per investigator and sponsor assessment. In the MK-6482-001 Safety Dataset, the Pooled Safety Dataset, and the CRSD, there were 5 (8.6%), 6 (5.0%), and 10 (5.6%) deaths due to AEs, respectively. None were considered drug-related [Table 26].

Table 26 Applicant – Subjects with Adverse Events Resulting in Death (Incidence >0% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term – Safety Analysis Set

	MK6482-004 Data for MK6482 120 mg QD		MK6482-001 Safety Dataset for MK6482 120 mg QD		Pooled Safety Dataset for MK6482 120 mg QD		Cumulative Running Safety Dataset for MK-6482	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	61		58		119		177	
with one or more adverse events resulting in death	1	1.6)	5	(8.6)	6	(5.0)	10	(5.6)
with no adverse events resulting in death	60	(98.4)	53	(91.4)	113	(95.0)	167	(94.4)
Toxicity to various agents	1	(1.6)	0		1	(0.8)	1	(0.6)
Malignant neoplasm progression	0		1	(1.7)	1	(0.8)	3	(1.7)
Disease progression	0		1	(1.7)	1	(0.8)	2	(1.1)
Acute kidney injury	0		1	(1.7)	1	(0.8)	1	(0.6)
Cardiac arrest	0		1	(1.7)	1	(0.8)	1	(0.6)
Suicide attempt	0		1	(1.7)	1	(0.8)	1	(0.6)
Intestinal perforation	0		0		0		1	(0.6)

Every subject 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.
Adverse events up to 28 days of last dose are included.
The table is be listed by PT in descending order of frequency in MK6482-004 Data for MK6482 120 mg QD, MK6482-001 Safety Dataset for MK6482 120 mg QD and Cumulative Running Safety Dataset for MK-6482.
Source: [ISS: adam-adsl; adae]

The Applicant's Position:

The frequency of deaths due to AEs was low across all datasets. There were no drug-related life-threatening or fatal events.

The FDA's Assessment:

Five patients died while participating in MK-6482-001. Details are as follows:

- Patient (b) (6) was a 67 year old man who enrolled on Study 101 for treatment of a meningioma. On Day 22 the patient underwent a scan to assess possible disease

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progression due to increasing weakness in the right hand. On Day 28, the day before the participant was to receive the scan results, the patient committed suicide. Before death, an increase in depression was seen. The last dose of study medication was taken the same day. The investigator considered that the suicide attempt was not related to study medication.

- Patient (b) (6) was a 75 year old male who enrolled on Study 101 because of metastatic renal cell carcinoma. His medical history included follicular lymphoma, hypothyroidism, pulmonary embolism and hypertension. On Study Day 171, belzutifan was discontinued because of disease progression in the chest, abdomen, and pelvis. The patient was hospitalized because of failure to thrive, poor oral intake, confusion, and hypercalcemia. On Day 190, the patient died under hospice care.

- Patient (b) (6) was a 57 year old man who enrolled on Study 101 because of clear cell RCC metastatic to adrenal gland, kidney, liver, lung, lymph nodes, skin, thyroid, gall bladder, and iliac fossa, previously treated with pazopanib, cabozantinib, and radiation. During the first 12 weeks of study treatment, he had recurring Grade 1 hypotension, Grade 2 proteinuria, Grade 2 increased blood creatinine, and Grade 1-3 anemia for which he was transfused on Days 22 and 43 in addition to receiving darbepoietin. On Day 130, he was hospitalized with pneumonia, hyptension, nephrotic syndrome, and acute kidney injury. Despite antibiotics and an additional blood transfusion, on Day 137 the participant died of acute kidney injury. At the time of death, anemia, hypotension, proteinuria, nephrotic syndrome, and increased blood creatinine had not resolved.

- Patient (b) (6) was a 61 year old man who enrolled on Study 101 because of clear cell RCC metastatic to adrenal, bone, and lung, previously treated with interleukin, sunitinib, nivolumab, cabozantinib, and radiation. On Day 4, he was hospitalized with low blood pressure, Grade 3 decreased urine output, Grade 1 acute kidney injury, Grade 3 adrenal insufficiency, and a Grade 2 pericardial effusion that was felt to likely be malignant. The acute kidney injury and adrenal insufficiency resolved with fluids and steroids. On Day 11, he was transfused for Grade 3 anemia. On Days 15 and 29, he had Grade 2 hypoxia. Belzutifan was interrupted on Day 29. On Day 34, he experienced Grade 4 cardiac arrest. Chest X-ray showed diffuse bilateral interstitial and airspace opacities. Despite endotracheal tube placement and aggressive medical support, he died of a second cardiac arrest on Day 41.

- Patient (b) (6) was a 64 year old man who enrolled on Study 101. His medical history included hypertension, chronic obstructive pulmonary disease and cancer pain. On Day 55, belzutifan was discontinued. On Day 59, because of inability to swallow and progressive hypoxia, his care was transitioned to comfort measures only, and he died of progressive disease.

One patient ((b) (6)) died while participating in MK-6482-004:

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- Patient (b) (6) was a 48 year old male with VHLD-associated RCC and CNS hemangioblastoma. His medical history included illicit drug use, hypertension, back pain, paresthesia, constipation, anxiety, insomnia, fatigue, decreased appetite, hemorrhoids, fungal infection, cholecystitis, nausea, and environmental allergies. Past surgeries included spinal laminectomy, adrenalectomy, intrathecal pump insertion, retinal laser coagulation, and nephrectomy. On Day 47, after taking a double dose of oxycodone, the patient was hospitalized because he had a seizure while visiting a relative, and then, 3 more seizures in the ED. The participant was unresponsive; a dose of naloxone was administered, and the patient became responsive and oriented. Treatment also included anticonvulsants, and seizures resolved the same day. An MRI of the brain showed no abnormalities. On Day 50, an awake and asleep EEG was normal, and the patient was discharged home. Belzutifan was interrupted for 3 days, restarted on Day 50 at 80 mg QD, and increased to 120 mg QD. The last dose of belzutifan was received on Day 115. On Day 127 the participant was taken to the hospital, was treated with epinephrine and naloxone, and died later the same day. An autopsy determined the cause of death as a toxicity to various agents. Fentanyl was present in the postmortem blood, and the brain showed acute hypoxic ischemic changes.

On April 15, 2021, the Applicant submitted a Safety Update Report containing an additional six months of safety data. This reported indicates that one additional death (Patient (b) (6)) occurred on MK-6482-001, and no additional deaths occurred on MK-6482-004. Patient (b) (6) was a 68 year old man who on Day 943 died of cardiogenic shock secondary to acute coronary syndrome.

Reviewer's comment: One of the five deaths that occurred on MK-6482-001 was due to suicide, and the others sound likely to have been due to complications of progressive disease. The death that occurred on MK-6482-004 was due to opioid overdose. This may point to the fact that living with a chronic disease associated with a history of multiple procedures and related morbidity, as is common for patients with VHL disease, may lead to psychologic harm and/or addiction to opioid pain medication.

Serious Adverse Events

Data:

A total of 9 (14.8%) participants experienced 12 SAEs in the MK-6482-004 Safety Dataset [Table 25]. No individual SAE (by preferred term) was reported for >1 participant in the Dataset. The majority of SAEs were Grade 3 in severity. There was 1 Grade 4 SAE of retinal detachment, which was considered not related to study intervention. A total of 24 (41.4%) participants experienced SAE(s) in the MK-6482-001 Safety Dataset. Hypoxia was the most frequent SAE (in ≥5% of participants) in the MK-6482-001 Safety Dataset.

The Applicant's Position:

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The types and frequencies of SAEs observed in the MK-6482-004 Safety Dataset were generally consistent with what is anticipated in the target population of VHL-associated RCC and also what is currently known about the mechanism of action of belzutifan.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. In MK-6482-004, no individual SAE was reported in more than one patient (Table 27).

Table 27. MK-6482-004 Serious Treatment-Emergent Adverse Events

Preferred Term	N (%)
Any	9 (14.8)
Abdominal pain	1 (1.6)
Adrenal insufficiency	1 (1.6)
Anaphylactic reaction	1 (1.6)
Anemia	1 (1.6)
Cholecystectomy	1 (1.6)
Coronary artery dissection	1 (1.6)
Cystitis	1 (1.6)
Dyspnea	1 (1.6)
Hypoxia	1 (1.6)
Hypotension	1 (1.6)
Retinal detachment	1 (1.6)
Seizure	1 (1.6)
Skin laceration	1 (1.6)
Toxicity to various agents	1 (1.6)
Urinary tract infection	1 (1.6)

One Grade 4 SAE was reported on MK-6482-004. Patient (b) (6) was a 63 year old woman whose manifestations of VHL disease at the time of study enrollment were RCC and large retinal hemangioblastomas refractory to intravitreal bevacizumab. Her medical history also included high myopia, hypertension, hyperlipidemia, tendonitis, renal failure, and migraine. Medications at the time of study enrollment were atenolol, hydrochlorothiazide, potassium, and atorvastatin. On Study Day 9, the patient saw an ophthalmologist due to blurry vision and floaters in the right eye. A retinal hole and a Grade 4 retinal detachment was diagnosed. Belzutifan was interrupted on Day 10, and on Day 12, a surgical vitrectomy was performed. On Day 36, the retinal detachment resolved, and belzutifan was resumed. Subsequent vitreous floaters were reported on Days 76 and 433 for which no action was taken with belzutifan.

Reviewer's Comment: Large retinal hemangiomas in patients with VHL disease may grow to displace retinal structures, causing exudative retinal detachment, or may lead to fibrosis of the epiretinal space with tractional retinal detachment. Further, individuals with high myopia, because their eyes are more elongated than normal are at increased risk for rhegmatogenous retinal detachments following macular holes because the elongation causes thinning, and in locations where there is an initial attachment to the vitreous, traction. The retinal detachment

in Patient (b) (6) may have been due to the macular hole and/or the large retinal hemangioblastomas and not due to belzutifan.

Hypoxia was the most frequently reported SAE in MK-6482-001 (Table 28). Individual cases are discussed below in the Treatment Emergent Adverse Events and Adverse Reactions section.

Table 28. MK6482-001 Serious Treatment-Emergent Adverse Events

Preferred Term	**N (%)**
Any	25 (43.1)
Hypoxia	7 (12.1)
Acute kidney injury	2 (3.4)
Adrenal insufficiency	2 (3.4)
Anemia	2 (3.4)
Dyspnea	2 (3.4)
Hemoptysis	2 (3.4)
Pneumonia	2 (3.4)
Abdominal pain upper	1 (1.7)
Acute coronary syndrome	1 (1.7)
Bacteremia	1 (1.7)
Biliary obstruction	1 (1.7)
Blood creatinine increased	1 (1.7)
COVID-19	1 (1.7)
Cardiac arrest	1 (1.7)
Cellulitis	1 (1.7)
Cholangitis acute	1 (1.7)
Cholecystitis acute	1 (1.7)
Complication associated with device	1 (1.7)
Disease progression	1 (1.7)
Duodenal stenosis	1 (1.7)
Hyperbilirubinemia	1 (1.7)
Hypotension	1 (1.7)
Liver function test increased	1 (1.7)
Malignant neoplasm progression	1 (1.7)
Non-cardiac chest pain	1 (1.7)
Osteomyelitis	1 (1.7)
Pain	1(1.7)
Pneumonia	1 (1.7)
Presyncope	1 (1.7)
Pulmonary hemorrhage	1 (1.7)
Respiratory failure	1 (1.7)
Spinal cord compression	1 (1.7)
Suicide attempt	1 (1.7)
Urine output increased	1 (1.7)

On April 15, 2021, the Applicant submitted a Safety Update Report (SUR) containing six more months of follow-up safety data. Compared with the initial clinical study report, two additional patients on MK-6482-004 experienced three additional SAEs (hemorrhage intracranial, skin

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laceration, and urinary tract infection) and one additional patient on MK-6482-001 experienced one additional SAE (hypoxia).

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

There were 2 (3.3%) reports of AEs leading to study intervention discontinuation in the MK-6482-004 Study: 1 due to Grade 1 dizziness and the other due to death by acute fentanyl overdose unrelated to study intervention. The incidences of AEs resulting in study intervention discontinuation were lower in the MK-6482-004 Safety Dataset (3.3%) compared with the MK-6482-001 (10.3%), Pooled (6.7%), and CRSD (7.3%) datasets [Table 29].

Table 29 Applicant – Subjects with Adverse Events Resulting in Treatment Discontinuation (Incidence >0% in One or More Treatment Groups) By Body System or Organ Class and Preferred Term – Safety Analysis Set

	MK6482-004 Data for MK6482 120 mg QD		MK6482-001 Safety Dataset for MK6482 120 mg QD		Pooled Safety Dataset for MK6482 120 mg QD		Cumulative Running Safety Dataset for MK-6482	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	61		58		119		177	
with one or more adverse events leading to study drug discontinuation	2	(3.3)	6	(10.3)	8	(6.7)	13	(7.3)
with no adverse events leading to study drug discontinuation	59	(96.7)	52	(89.7)	111	(93.3)	164	(92.7)
Cardiac disorders	0		1	(1.7)	1	(0.8)	1	(0.6)
Cardiac arrest	0		1	(1.7)	1	(0.8)	1	(0.6)
Gastrointestinal disorders	0		1	(1.7)	1	(0.8)	2	(1.1)
Abdominal pain	0		1	(1.7)	1	(0.8)	1	(0.6)
Intestinal perforation	0		0		0		1	(0.6)
General disorders and administration site conditions	0		2	(3.4)	2	(1.7)	3	(1.7)
Disease progression	0		1	(1.7)	1	(0.8)	1	(0.6)
Fatigue	0		1	(1.7)	1	(0.8)	2	(1.1)
Injury, poisoning and procedural complications	1	(1.6)	0		1	(0.8)	1	(0.6)
Toxicity to various agents	1	(1.6)	0		1	(0.8)	1	(0.6)
Investigations	0		0		0		1	(0.6)
Aspartate aminotransferase increased	0		0		0		1	(0.6)
Metabolism and nutrition disorders	0		1	(1.7)	1	(0.8)	1	(0.6)
Decreased appetite	0		1	(1.7)	1	(0.8)	1	(0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0		0		0		1	(0.6)

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Malignant neoplasm progression	0	0	0	1	(0.6)

Every subject is counted a single time for each applicable row and column. A system organ class or 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. Adverse events up to 28 days of last dose are included.
Source: [ISS: adam-adsl; adae]

The Applicant's Position:

In general, the overall frequencies of AEs and drug-related AEs leading to study intervention discontinuation in the MK-6482-004 Safety Dataset were low. The rates of AEs and drug-related AEs leading to treatment discontinuation were higher in the MK-6482-001 Safety Dataset. This difference was likely due to the more advanced disease status and higher frequencies of chronic co-morbidities and prior treatment in MK-6482-001 participants versus MK-6482-004 participants.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. TEAEs of dizziness and acute fentanyl overdose led to discontinuation of study treatment by one patient each on MK-6482-004. The patient on MK-6482-004 who discontinued study treatment due to acute fentanyl overdose (Patient (b) (6)) is discussed above in the section on deaths.

Patient (b) (6) was a 26 year old man who enrolled on MK-6482-004 with VHL disease-associated RCC and CNS hemangioblastoma. On Day 28, he had Grade 1 fatigue, and on Day 49, he had Grade 1 dizziness and Grade 1 headache. No treatment was reported. On Day 59 he discontinued belzutifan due to dizziness. On Day 88, he withdrew informed consent. The outcomes of dizziness, fatigue, and headache are unknown.

On April 15, 2021, the Applicant submitted a Safety Update Report containing an additional six months of safety data. No new reports of discontinuation of study treatment were received during that additional six months.

Dose Interruption/Reduction Due to Adverse Effects

Data:

In the MK-6482-004 Safety Dataset, 24 participants (39.3%) experienced AEs resulting in interruption of study intervention [Table 19]. The most frequently reported AEs leading to interruption of study intervention were fatigue, anemia, nausea, influenza-like illness, abdominal pain, and headache. Drug-related AEs resulting in interruption of study intervention were reported for 14 participants (23.0%); 7 participants (11.5%) experienced fatigue, 3 (4.9%) experienced nausea, 3 (4.9%) experienced anemia, and 2 (3.3%) experienced headache. All other drug-related AEs that led to interruption of study intervention treatment were reported for 1 participant. In the MK-6482-001 Safety Dataset, the Pooled Safety Dataset, and the CRSD, 24 (41.4%), 48 (40.3%), and 61 (34.5%) participants experienced AEs resulting in study

intervention treatment interruption, and 13 (22.4%), 27 (22.7%), and 33 (18.5%) participants experienced drug-related AEs resulting in study intervention treatment interruption, respectively.

Eight participants (13.1%) reported AEs leading to dose reduction in the MK-6482-004 Safety Dataset. The most frequently reported AE that led to dose reduction (incidence ≥2%) was fatigue (6.6%). Drug-related AEs leading to dose reduction were reported in 6 participants (9.8%). The most frequently reported drug-related AE leading to dose reduction (incidence ≥2%) was fatigue (6.6%). In the MK-6482-001 Safety Dataset, the Pooled Safety Dataset, and the CRSD, 6 (10.3%), 14 (11.8%), and 17 (9.6%) participants experienced AEs resulting in dose reduction, respectively.

The Applicant's Position:

The frequency of participants who had AEs resulting in interruption of study intervention or study intervention dose reduction was generally consistent across datasets. The observed AEs resulting in interruption of study intervention (all cause and drug-related) or dose reduction were consistent with what is anticipated in the target population and also what is currently known of the mechanism of action and safety profile of belzutifan.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. Twenty-six (42.6%) patients in MK-6482-001 experienced AEs leading to treatment interruption. AEs leading to treatment interruption in >1 patient were fatigue, anemia, nausea, abdominal pain, headache, and influenza like illness. On April 15, 2021, the Applicant submitted a Safety Update Report containing six more months of follow-up safety data. Compared with the initial clinical study report, two additional patients on MK-6482-004 experienced two further AEs leading to treatment interruption (fatigue and diarrhea); no additional patients on MK-6482-001 were reported as having experienced AEs leading to interruption.

Significant Adverse Events

Data:

The most frequently reported AEs in the MK-6482-004 Safety Dataset were anemia, fatigue, headache, dizziness, and nausea, and this was generally consistent across datasets [Table 30].

Table 30 Applicant – Subjects with Adverse Events (Incidence ≥20% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term – Safety Analysis Set

	MK6482-004 Data for MK6482 120 mg QD		MK6482-001 Safety Dataset for MK6482 120 mg QD		Pooled Safety Dataset for MK6482 120 mg QD		Cumulative Running Safety Dataset for MK-6482	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	61		58		119		177	
with one or more adverse events	61	(100.0)	58	(100.0)	119	(100.0)	175	(98.9)

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

with no adverse events	0		0		0		2	(1.1)
Anaemia	55	(90.2)	44	(75.9)	99	(83.2)	130	(73.4)
Fatigue	37	(60.7)	41	(70.7)	78	(65.5)	100	(56.5)
Headache	23	(37.7)	14	(24.1)	37	(31.1)	46	(26.0)
Dizziness	22	(36.1)	13	(22.4)	35	(29.4)	36	(20.3)
Nausea	19	(31.1)	20	(34.5)	39	(32.8)	53	(29.9)
Dyspnoea	12	(19.7)	27	(46.6)	39	(32.8)	50	(28.2)
Arthralgia	11	(18.0)	14	(24.1)	25	(21.0)	32	(18.1)

Every subject 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.
Adverse events up to 28 days of last dose are included.
The table is be listed by PT in descending order of frequency in MK6482-004 Data for MK6482 120 mg QD, MK6482-001 Safety Dataset for MK6482 120 mg QD and Cumulative Running Safety Dataset for MK-6482.
Source: [ISS: adam-adsl; adae]

The Applicant's Position:

The frequency, type, and severity of AEs reported in the MK-6482-004 Safety Dataset were generally consistent with what is currently known about the mechanism of action of belzutifan and were generally consistent across datasets.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. TEAEs reported with frequencies above 20% in MK-6482-004 were anemia, fatigue, headache, dizziness, nausea, dyspnea, and arthralgia (Table 31).

Table 31. MK6482-001 and MK6482-004 Adverse Events Reported by ≥20% in One or More Treatment Groups

	MK-6482-004 (N = 61)		**MK-6482-001 at 120 mg QD (N = 58)**	
	All Grades	**Grade 3-4**	**All Grades**	**Grade 3-4**
Any	61 (100%)	14 (23.0%)	58 (100%)	40 (69.0%)
Anemia	55 (90.2%)	4 (6.6%)	44 (75.9%)	16 (27.6%)
Fatigue[a]	39 (63.9%)	3 (4.9%)	41 (70.6%)	3 (5.2%)
Headache[b]	24 (39.3%)	0	14 (24.1%)	1 (1.7%)
Dizziness[c]	23 (37.7%)	0	13 (22.4%)	0
Nausea	19 (31.1%)	0	20 (34.5%)	0
Upper respiratory tract infection[i]	13 (21.3%)	0	14 (24.1%)	0
Dyspnea[d]	12 (19.7%)	1 (1.6%)	32 (55.2%)	3 (5.2%)
Arthralgia	11 (18.0%)	0	14 (24.1%)	0
Musculoskeletal pain[h]	11 (18.0%)	0	25 (43.1%)	1 (1.7%)
Alanine aminotransferase increased	10 (16.4%)	0	8 (13.8%)	4 (6.9%)
Myalgia	10 (16.4%)	0	9 (15.5%)	0
Vision blurred	9 (14.8%)	0	6 (10.3%)	0
Hypertension	8 (13.1%)	2 (3.3%)	7 (12.1%)	3 (5.2%)
Abdominal pain[k]	8 (13.1%)	0	8 (%)	0
Edema[e]	8 (13.1%)	0	17 (29.3%)	0
Constipation	8 (13.1%)	0	12 (20.7%)	0
Weight increased	7 (11.5%)	1 (1.6%)	6 (10.3%)	0

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

Aspartate aminotransferase increased	7 (11.5%)	0	6 (10.3%)	2 (3.4%)
Cough[f]	6 (9.8%)	0	19 (32.8%)	2 (3.4%)
Vomiting	6 (9.8%)	0	16 (27.6%)	0
Blood creatinine increased[g]	5 (8.2%)	0	18 (31.0%)	1 (1.7%)
Diarrhea	5 (8.2%)	0	12 (20.7%)	0
Hypotension[j]	3 (4.9%)	1 (1.6%)	10 (17.2%)	2 (3.4%)
Decreased appetite	3 (4.9%)	0	9 (%)	1 (1.7%)
Insomnia	3 (4.9%)	0	7 (12.1%)	0
Anxiety	2 (3.3%)	0	9 (15.5%)	0
Hyperglycemia	2 (3.3%)	1 (1.6%)	6 (10.3%)	3 (5.2%)
Hypoxia	1 (1.6%)	1 (1.6%)	17 (29.3%)	9 (15.6%)
Hyponatremia	1 (1.6%)	0	7 (12.1%)	1 (1.7%)
Hypophosphatemia	1 (1.6%)	0	7 (12.1%)	3 (5.2%)
Lymphocyte count decreased	1 (1.6%)	1 (1.6%)	6 (10.3%)	2 (3.4%)
Hyperkalemia	1 (1.6%)	0	12 (20.7%)	1 (1.7%)
Dehydration	1 (1.6%)	0	12 (20.7%)	1 (1.7%)
Hypercalcemia	0	0	10 (17.2%)	1 (1.7%)
Proteinuria	0	0	9 (15.5%)	2 (3.4%)
Pyrexia	0	0	9 (15.5%)	1 (1.7%)
Blood alkaline phosphatase increased	0	0	7 (12.1%)	3 (5.2%)

Source: dataset ADAE; variables USUBJID, STUDYID, AEDECOD, AETOXGR, TRTEMFL
[a] includes fatigue and asthenia
[b] includes headache and migraine
[c] includes dizziness and vertigo
[d] includes dyspnea, dyspnea exertional, and orthopnea
[e] Includes face edema, generalised edema, edema genital, edema peripheral, periorbital edema, and scrotal edema
[f] includes cough, hemoptysis, productive cough, and upper airway cough syndrome
[g] includes acute renal failure, blood creatinine increased, and chronic renal failure
[h] includes back pain, bone pain, musculoskeletal pain, musculoskeletal chest pain, neck pain, pain, and pain in extremity
[i] includes bronchitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection
[j] includes hypotension and orthostatic hypotension
[k] includes abdominal discomfort, abdominal pain, abdominal pain lower, and abdominal pain upper

Treatment Emergent Adverse Events and Adverse Reactions

Data:

The most frequently reported drug-related AEs in the MK-6482-004 Safety Dataset were anemia, fatigue, and dizziness, which was generally consistent across datasets [Table 32]. Most events were Grade 1 or 2 in severity.

Table 32 Applicant – Subjects with Drug-related Adverse Events (Incidence ≥20% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term – Safety Analysis Set

	MK6482-004 Data for MK6482 120 mg QD		MK6482-001 Safety Dataset for MK6482 120 mg QD		Pooled Safety Dataset for MK6482 120 mg QD		Cumulative Running Safety Dataset for MK-6482	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	61		58		119		177	
with one or more drug-related adverse events	60	(98.4)	55	(94.8)	115	(96.6)	159	(89.8)
with no drug-related adverse events	1	(1.6)	3	(5.2)	4	(3.4)	18	(10.2)
Anaemia	53	(86.9)	41	(70.7)	94	(79.0)	122	(68.9)
Fatigue	32	(52.5)	33	(56.9)	65	(54.6)	80	(45.2)
Dizziness	13	(21.3)	3	(5.2)	16	(13.4)	16	(9.0)

Every subject 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.
Adverse events up to 28 days of last dose are included.
The table is be listed by PT in descending order of frequency in MK6482-004 Data for MK6482 120 mg QD, MK6482-001 Safety Dataset for MK6482 120 mg QD and Cumulative Running Safety Dataset for MK-6482.
Source: [ISS: adam-adsl; adae]

Eight participants (13.1%) in the MK-6482-004 Safety Dataset had at least 1 drug-related Grade 3 to 5 AE. The most frequently reported Grade 3 to 5 drug-related AEs in the MK-6482-004 Safety Dataset were anemia and fatigue. The frequency of hypoxia was lower in the MK-6482-004 Safety Dataset compared to the MK-6482-001 Safety Dataset. No Grade 4 or 5 drug-related AEs were reported [Table 33].

Table 33 Applicant – Subjects with Grade 3-5 Drug-Related Adverse Events by Decreasing Incidence (Incidence >0% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term – Safety Analysis Set

	MK6482-004 Data for MK6482 120 mg QD		MK6482-001 Safety Dataset for MK6482 120 mg QD		Pooled Safety Dataset for MK6482 120 mg QD		Cumulative Running Safety Dataset for MK-6482	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	61		58		119		177	
with one or more grade 3-5 drug-related adverse events	8	(13.1)	23	(39.7)	31	(26.1)	43	(24.3)
with no grade 3-5 drug-related adverse events	53	(86.9)	35	(60.3)	88	(73.9)	134	(75.7)
Anaemia	4	(6.6)	14	(24.1)	18	(15.1)	23	(13.0)
Fatigue	3	(4.9)	1	(1.7)	4	(3.4)	6	(3.4)
Hypoxia	1	(1.6)	6	(10.3)	7	(5.9)	10	(5.6)
Dyspnoea	0		2	(3.4)	2	(1.7)	2	(1.1)
Alanine aminotransferase increased	0		1	(1.7)	1	(0.8)	2	(1.1)
Headache	0		1	(1.7)	1	(0.8)	1	(0.6)
Hypertension	0		1	(1.7)	1	(0.8)	1	(0.6)

Every subject 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.
Adverse events up to 28 days of last dose are included.
The table is be listed by PT in descending order of frequency in MK6482-004 Data for MK6482 120 mg QD, MK6482-001 Safety Dataset for MK6482 120 mg QD and Cumulative Running Safety Dataset for MK-6482.
Source: [ISS: adam-adsl; adae]

The Applicant's Position:

Based on a comprehensive integrated review of the totality of safety data available in the belzutifan program, the sponsor has determined that the adverse events of anemia due to decreased erythropoietin, hypoxia, fatigue, nausea, dizziness and dyspnea are adverse drug reactions of belzutifan. Anemia due to decreased erythropoietin is consistent with the mechanism of action of MK-6482 (as described below). The other adverse drug reactions are symptoms that are common in advanced cancer populations, irrespective of drug therapy. Fatigue and dyspnea may be nonspecific symptoms of the more specific AEs of anemia and hypoxia.

Anemia due to Decreased Erythropoietin

Anemia was the most frequently reported AE in participants treated with belzutifan and was observed at all dose levels studied. Anemia is expected, given the on-target pharmacology of belzutifan via HIF 2α inhibition and its reduction of EPO levels with resultant reduction in hemoglobin levels. Anemia has been mostly mild to moderate in severity and medically manageable with ESA administration and/or blood transfusion and dose interruption/reduction.

In the MK-6482-004 Safety Dataset, anemia due to decreased erythropoietin assessed as drug related occurred in 53 (86.9%) participants including 4 (6.6%) participants with Grade 3 severity. There was 1 SAE (1.6%) of anemia considered to be drug-related. There were no Grade 4 or 5 events of anemia. No participant discontinued treatment due to anemia.

Given that decreased erythropoietin is the likely etiology of anemia with belzutifan treatment, the administration of ESA is an effective management strategy for belzutifan-induced anemia. In addition, blood transfusion and study intervention dose interruption/reduction are also effective for belzutifan-induced anemia, as indicated. The Week 3 timepoint appeared to show maximum reduction in EPO in MK-6482-004, and EPO values appeared to recover by Weeks 9 and Week 13.

Hypoxia

There was 1 case of hypoxia (1.6%) in the MK-6482-004 Safety Dataset. This event was Grade 3 in severity and was managed by dose interruption and dose reduction to 80 mg once daily; no oxygen supplementation was required.

In the MK-6482-001 Safety Dataset, 17 participants (29.3%) experienced events of hypoxia; these events were Grade 3 in severity for 9 participants. Twelve (20.6%) of these participants

were treated with supplemental oxygen that resulted in event resolution for most participants. There were no Grade 4 or 5 events of hypoxia. SAEs of hypoxia were reported in 6 (10.3%) participants. There were 2 discontinuations from study treatment due to hypoxia AEs.

Hypoxia events occurred across all dose levels. Eighteen (15.1%) participants in total experienced hypoxia at the clinical dose of 120 mg QD, as described above. Most hypoxia AEs occurred during the first 3 months of drug administration.

Other ADRs

In addition to the important ADRs presented above, there are additional ADRs associated with belzutifan based on an overall integrated review of the totality of available safety data. These other ADRs include fatigue, nausea, dyspnea, and dizziness. The events of fatigue, nausea, dyspnea, and dizziness were effectively managed with standard of care protocols and by dose interruption or dose reduction, and most of these events were mild to moderate in severity.

The FDA's Assessment:

Anemia

Anemia was the most commonly reported TEAE in both MK-6482-001 and MK-6482-004. In MK-6482-001, 75.9% and 27.6% of patients in the RCC cohort experienced any grade or a Grade 3-4 TEAE of anemia, respectively. Although it is difficult to draw conclusions because of small patient numbers in the earlier dose-escalation cohorts of MK-6482-001, the risk of experiencing any grade or a Grade 3-4 TEAE of anemia in MK-6482-001 appeared to be dose related at lower doses and then to plateau near the recommended phase 2 dose of 120 mg QD (Table 28). This is consistent with the findings reported in the exposure-safety analysis for belzutifan, which identified a relationship between exposure and the probability of Grade 3+ anemia. This relationship was dependent on the baseline hemoglobin levels. In patients with low hemoglobin levels (< 12 g/dL) in MK-8582-001 , the probability of anemia increased dramatically . This is discussed in the Clinical Pharmacology section above, particularly 6.3.2.2 and figure 5.

Table 34. MK-6482-001 TEAEs of Anemia by Dosing Cohort

Grade	20 mg QD (N = 6)	40 mg QD (N = 6)	80 mg QD (N = 6)	120 mg QD (N = 58)	160 mg QD (N = 6)	240 mg QD (N = 7)	120 mg BID (N = 27)
Any, n (%)	1 (16.7)	2 (33.3)	4 (66.7)	44 (75.9)	5 (83.3)	5 (71.4)	14 (51.9)
3-4, n (%)	0 (0.0)	0 (0.0)	2 (33.3)	16 (27.6)	1 (16.7)	1 (14.3)	1 (3.7)

Source: Applicant's response to FDA Information Request

In MK-6482-004, 90.2% of patients experienced a TEAE of anemia, and 6.6% of patient experienced Grade 3-4 anemia. The risk of experiencing a Grade 3-4 TEAE of anemia was highest among patients in the lowest tertile of baseline hemoglobin (Table 35).

Table 35. MK-6282-004 TEAEs of Anemia by Tertile of Baseline Hemoglobin

Tertile of Baseline Hemoglobin	TEAEs of Anemia	
	All Grades	Grade 3-4

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

Hb ≤ 13.2 g/dL (N = 21)	20 (95.2)	3 (14.3)
13.2 < Hb ≤ 14.6 g/dL (N = 21)	18 (85.7)	1 (4.8)
Hb > 14.6 g/dL (N = 19)	17 (89.5)	0

Source: Applicant's response to FDA Information Request

In MK-6482-004, 12 (19.7%) patients received erythropoiesis stimulating agents (ESAs), and 5 (8.2%) received red cell transfusions, with median times to first dose of ESA and first transfusion of 21.6 weeks and 30.1 weeks, respectively. In MK-6482-004, 17 (19.7%) patients received erythropoietin (n = 7), darbepoietin (n = 7), or methoxy polyethylene glycol epoetin beta (n = 1). ESAs were prescribed as one or more single doses in 6 patients and as standing weekly doses or PRN orders (i.e., as needed) in 5 patients; in 3 patients, the dosing interval was not specified. Of the 5 patients who were prescribed ESAs as standing weekly doses or as PRN orders, 4 continued to receive them at the data cutoff date. In MK-6482-001, higher percentages of patients received ESAs and red cell transfusions compared to MK-6482-004, and the median times to first treatments were shorter (Table 36).

Table 36. Treatments Administered for Anemia

Treatment	**MK-6482-004**	**MK-6482-001**
Erythropoiesis Stimulating Agent		
Patients who received at least one dose (n,%)	12 (19.7)	27 (46.6)
Number of doses per patient (n)		
Mean ± SD	4.4 ± 4.5	4.1 ± 4.3
Median (range)	2.5 (1.0-17.0)	3 (1-21)
Time to first dose (weeks)		
Mean ± SD	29.9 ± 20.5	14.7 ± 23.1
Median (range)	21.6 (8.4-72.1)	8.1 (1.1-120.1)
Red Cell Transfusions		
Patients who received at least one transfusion (n,%)	5 (8.2)	16 (27.6)
Number of transfusions per patient (n)*		
Mean ± SD	1.4 ± 0.9	2.4 ± 1.6
Median (range)	1 (1-3)	2 (1-6)
Time to first transfusion (weeks)		
Mean ± SD	45.0 ± 31.3	5.8 ± 5.3
Median (range)	30.1 (14.6-87.7)	3.7 (1-16.2)

Source: Applicant's response to FDA Information Request (database cutoff date: 1 December 2020)

- Refers to the number of transfusion procedures (the number of units of red cells transfused was not captured on case report forms and may have been more than one during any given transfusion procedure

The presumed mechanism of belzutifan-induced anemia suggests that ESAs would be expected to provide effective mitigation; however, secondary malignancies are a known adverse effect of ESAs. This concern is especially serous in patients with VHL disease because they are already at heightened risk for a wide variety of malignancies. One patient on MK-6482-004 (Patient (b) (6)) experienced a secondary malignancy of vulvar cancer on Study Day 109 after having received one dose of darbepoietin on Study Day 73. In addition, three patients on MK-6482-001 experienced adverse events of progression of their underlying renal cell carcinoma. While these

incidences by themselves are too small to be considered potential signals of carcinogenicity, this is not fully reassuring because ESA-induced growth of existing tumors would have likely been obscured by the primary tumor shrinking activity of belzutifan, and ESA-induced secondary malignancies are rare and follow-up time on both studies was relatively limited.

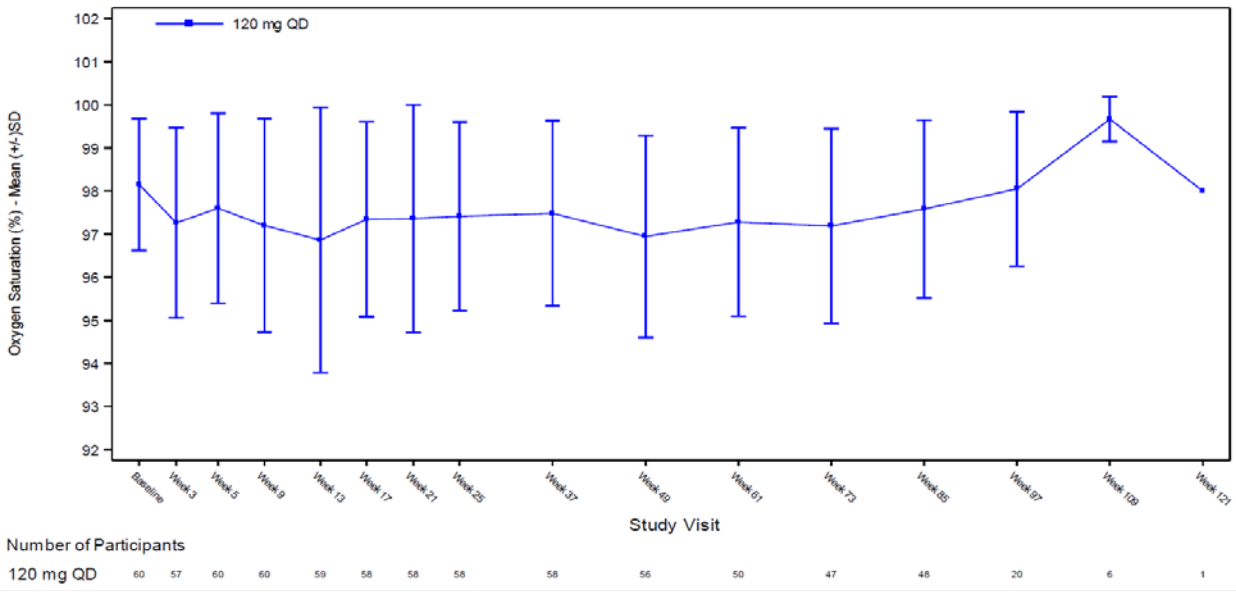
The clinical review team's recommendations for measures to help mitigate the risk of secondary malignancies are discussed in Section 8.2.9 of this Assessment Aid.

Reviewer's Comments: Anemia has been added as a Warning and Precaution to the belzutifan label. In addition, due to concern about the unknown risk of secondary malignancies if ESAs are used, cautionary language about ESA use has been added to the anemia Warning and Precaution.

Hypoxia
Hypoxia is an expected toxicity of belzutifan, as HIF-2α may play a role in hypoxic pulmonary vasoconstriction and may exert act on the carotid body.

No clinically significant change in mean hemoglobin oxygen saturation values was observed over time among the 61 patients in MK-6482-004 (Figure 15).

Figure 15. MK-6482-004 Oxygen Saturation Over Time (Applicant's figure)



The mean and median Day 1 oxygen saturations of patients on MK-6482-004 were similar pre- and post-dosing (Table 37). Two patients ((b) (6)) on MK-6482-004 were outliers in this respect, with oxygen saturations 6 hours after their first dose of belzutifan on Day 1 that were notably lower than pre-dose values. Patient (b) (6) also had lung metastases and a

history of acute respiratory distress syndrome and pulmonary embolism), and Patient (b) (6) also had lung metastases.

Table 37. MK-6482-004 Summary of Day 1 Pulse Oximetry Readings

Pulse Oximetry Reading	***N***	***Mean ± SD***	***Median (range)***
Pre-dose, at rest	*55*	*97.7 ± 1.9*	*98 (92-100)*
Pre-dose, on exertion	*52*	*97.0 ± 2.6*	*97 (87-100)*
6 hours post-dose, at rest	*53*	*96.5 ± 2.7*	*97 (85-100)*
6 hours post-dose, on exertion	*50*	*95.8 ± 3.5*	*96 (84-100)*

One hypoxic TEAE was reported in MK-6482-004:

- Patient (b) (6) was a 50 year old male who was diagnosed with VHL disease-associated RCC approximately 2 years prior to enrollment. Disease manifestations at enrollment were RCC and CNS hemangioblastoma. His medical history included hypertension and glaucoma, and prior medications were amlodipine, enalapril, diuretics, and timolol. His oxygen saturation at baseline was 98%. On Study Day 56, his oxygen saturation was 86% and Grade 3 hypoxia was reported. Other vital signs, physical examination and EKG were normal. No treatment for hypoxia was administered. On Day 86, his oxygen saturation was 83%. Belzutifan was interrupted on Day 98 due to hypoxia. On Day 101, he was asymptomatic but was hospitalized for observation. Pulmonary embolism was ruled out. On Day 102, he was discharged. On Day 105, pulmonary function testing showed reduced diffusion capacity (66%). On Day 106, a 6-minute walk test showed normal oxygen saturation (95-99%) and restrictive lung function. Belzutifan was resumed at 80 mg daily. No treatment for hypoxia was reported. Hypoxia resolved on Day 106. His oxygen saturation on Day 112 was 94%. On Day 168, laboratory testing showed Grade 2 anemia which improved to Grade 1 on Day 252. No treatment was reported for anemia. The patient remained on study and receiving belzutifan at data cutoff.

Reviewer's comment: Hypoxia in Patient (b) (6) was asymptomatic and was not treated. It is unclear whether belzutifan could cause the observed pulmonary restrictive pattern and/or reduced diffusion capacity. The positive dechallenge observed (i.e., improvement with dose reduction to 80 mg QD) argues in favor of causality.

In contrast to MK-6482-004 where only one patient experienced hypoxia, all-grade and Grade 3-4 hypoxia was reported in 17 (30.9%) and 9 (15.5%) patients, respectively, in the RCC cohort of MK-6482-001 at 120 mg QD. Comparing these incidences of hypoxia with at earlier dose-escalation cohorts of MK-6482-001, a dose-response relationship is not readily apparent (Table 31).

Table 38. MK-6482-001 TEAEs of Hypoxia by Dosing Cohort

Grade	20 mg QD (N = 6)	40 mg QD (N = 6)	80 mg QD (N = 6)	120 mg QD (N = 58)	160 mg QD (N = 6)	240 mg QD (N = 7)	120 mg BID (N = 27)
Any, n (%)	0 (0.0)	1 (16.7)	1 (16.7)	17 (29.3)	0 (0.0)	3 (42.9)	8 (29.6)
3-4, n (%)	0 (0.0)	1 (16.7)	0 (0.0)	9 (15.5)	0 (0.0)	0 (0.0)	4 (14.8)

Details of the 17 patients in MK-6482-001 who experienced TEAEs of hypoxia are as follows:

- Patient (b) (6) was a 75 year old female with clear cell RCC metastatic to liver, lung and pancreas. Her medical history included hypertension, hypothyroidism. Concurrent medications included aspirin, lisinopril, and levothyroxine. Her pulse oximetry reading at baseline was 99% both at rest and on exertion. On Study Day 43, her oxygen saturation was 85% (baseline not reported). On Day 57, her oxygen saturation was 92%, and she had Grade 2 anemia. On Day 133, she had Grade 3 anemia and was transfused. On Day 253, she experienced Grade 2 hypoxia and Grade 1 dyspnea. No treatment was administered, no action was taken with study drug, and dyspnea resolved the same day. On Day 309, her oxygen saturation was 99%. On Day 421, she discontinued belzutifan because of disease progression.

- Patient (b) (6) was a 75 year old woman with clear cell RCC metastatic to lung. Her medical history included hypothyroidism, salivary gland acinic cell carcinoma, hypertension, gastroesophageal reflux, chronic kidney disease, and anemia. At baseline, her pulse oximetry reading. On Day 1, her oxygen saturation pre-dose was 98% at rest and 100% on exertion, and 6 hours post-dose was and 96% at rest and 84% upon exertion. On Day 7, her oxygen saturation was 98% at rest and 97% on exertion. On Day 15 she was diagnosed with Grade 2 anemia. Iron was started on Day 15, darbepoietin was started on Day 22, and both were continued for the remainder of study treatment. On Day 841 she experienced Grade 2 fatigue and Grade 2 hypoxia (oxygen saturation on exertion 86%). On Day 925, her anemia worsened to Grade 3 (Hb 7.7 g/L) and hypoxia was ongoing (oxygen saturation 86% at rest of 72% on exertion). She remained on study at the time of data cutoff with unresolved anemia, hypoxia, and fatigue.

- Patient (b) (6) was a 63 year old male with RCC metastatic to adrenal gland, bone, lung, and lymph nodes. His medical history included hypercalcemia, dyspnea on exertion, gastroesophageal reflux, hypertension, hyperglycemia, and hypomagnesemia. On Study Day 1, his pre-dose oxygen saturation was 92% at rest and 93% upon exertion. Six hours post-dose, his oxygen saturation was 85% at rest and 84% upon exertion. He was treated with oxygen at 2L/min from Day 1 to Day 7. On Day 59, he developed fever, altered mental status, shortness of breath and generalized weakness. Chest radiography showed infectious or neoplastic disease. Echocardiography showed a left ventricular ejection fraction of 64%. He was hospitalized with Grade 4 sepsis and hypoxic respiratory failure and received antibiotics, fluids, bronchodilators, and oxygen. On Day

64, the events resolved and he was discharged home. No action was taken with belzutifan.

- Patient (b) (6) was a 56 year old man with clear cell RCC metastatic to the chest wall and lungs, previously treated with sunitinib, nivolumab, ipilimumab, cabozantinib, and radiation. His medical history included exertional dyspnea, pneumonitis, pleural effusion, arrhythmia, pericarditis, hypothyroidism, rash, hyperglycaemia, hypoalbuminaemia, and proteinuria. His oxygen saturation at baseline was 98% at rest and 95% on exertion. On Study Day 45, he experienced Grade 2 exertional dyspnea, which improved to Grade 1 on Day 56. On Day 61 he experienced Grade 1 hemoptysis that resolved the same day. On Day 85, exertional dyspnea resolved with no treatment reported and no action was taken with the study medication. On Day 147, he had Grade 2 hemoptysis treated with amoxicillin plus clavulanic acid from Day 148 to Day 151. Hemoptysis worsened to Grade 3 on Day 151, and he was hospitalized with Grade 3 hypoxia. CT angiography showed stable lung metastases and no pulmonary embolism. He underwent bronchoscopic cauterization of bleeding in the left mainstem bronchus, in the area overlying known myocardial metastases. Hypoxia resolved on Day 152 and he was diagnosed with Grade 2 atelectasis. Study medication was interrupted from Day 151 through Day 154. On Day 154 hemoptysis, chest pain, and atelectasis resolved, and the participant was discharged from the hospital. Study medication resumed on Day 155. On Day 197 he experienced Grade 2 exertional dyspnea. On Day 275 exertional dyspnea worsened to Grade 3. Oxygen saturation at home ranged from 70% to 80%. He presented to the emergency department, where his oxygen saturation was 85% on room air. Concurrent AEs were Grade 2 peripheral edema and Grade 2 fatigue. A chest x-ray showed small pleural effusions. The patient was treated with prednisone (2 mg po, daily) and furosemide. On Day 276 study medication was interrupted due to dyspnea and hypoxia. On Day 277 he received 2 L oxygen, hypoxia improved to Grade 2, and dyspnea resolved. On Day 278 he was discharged with oral furosemide. On Day 279, fatigue improved to Grade 1. On Day 281 peripheral edema resolved. Study medication resumed on Day 282 at 80 mg daily. On Day 283 he resumed oxygen therapy, but oxygen saturation remained between 86% and 89% (Grade 2 hypoxia), and belzutifan was discontinued. On Day 288 hypoxia resolved. On Day 289 oxygen saturation improved to 95% on room air. On Day 296 he completed the study with oxygen saturation above 90% without the use of supplemental oxygen; the pleural effusion and fatigue had not resolved.

- Patient (b) (6) was a 74 year old man with clear cell RCC metastatic to lung and adrenal gland. Medical history included hypertension, coronary artery disease, emphysema, chronic kidney disease, peripheral edema, and peripheral neuropathy. On Day -11, a pleural catheter was inserted, and 4.5 liters of pleural fluid was drained. His pulse oximetry reading at baseline was 96% at rest and 91% on exertion. On Day 1 he experienced Grade 2 dyspnea. On Day 4, dyspnea worsened to Grade 3, accompanied

by Grade 3 hypoxia (oxygen saturation 91% on room air) and Grade 3 pleural catheter malfunction. He was treated with alteplase and oxygen. Dyspnea improved to Grade 2 on Day 5. On Day 6 he developed Grade 3 anemia. On Days 7 and 10, he was transfused. A ventilation-perfusion scan showed low probability of pulmonary embolism. Belzutifan was interrupted due to hypoxia, anemia, pneumonia, and atrioventricular block. On Day 13 he was hospitalized with dyspnea, hypoxia, pleural catheter malfunction. On Day 14, computed tomography showed bilateral pleural effusions suggestive of pneumonia, and he received azithromycin, piperacillin plus tazobactam, and vancomycin starting Day 16. Blood and pleural fluid cultures showed no growth. On Day 25 the anemia worsened to Grade 3; he was treated with methylprednisolone. The pleural catheter was removed on Day 29. On Day 31, hypoxia and pneumonia improved to Grade 2, and he was discharged home with prednisone and salbutamol. On Day 32, pneumonia resolved and on Day 36 hypoxia resolved. On Day 45 belzutifan was resumed at the same dose. On Day 52 he experienced Grade 2 hypoxia, hemoglobin 8.0 g/dL, and oxygen saturation 81% on exertion, and he received oxygen and darbepoetin alfa. On Day 53, belzutifan was interrupted. On Day 57, hemoglobin improved to 8.8 g/dL, oxygen saturation on exertion was 86%, and belzutifan was resumed. On Day 66, hemoglobin was 7.9 g/dL. On Day 72, belzutifan was interrupted due to hypoxia. On Day 73, anemia improved to Grade 2. On Day 80, oxygen saturation on exertion was 87%, and belzutifan was resumed at 80 mg daily. On Day 113, anemia worsened to Grade 3 and belzutifan was discontinued due to disease progression.

- Patient (b) (6) was a 75 year old woman with RCC metastatic to lung and lymph nodes previously treated with pazopanib, axitinib, and nivolumab. Medical history included hypertension, pneumonia, and cerebral hemorrhage. Baseline pulse oximetry readings were 99% at rest and 97% on exertion. On Study Day 112, she had Grade 2 anemia treated with darbepoetin. Anemia resolved on Day 140. On Day 224, Grade 2 anemia recurred. On Day 252, she had Grade 2 hypoxia (oxygen saturation on exertion 87%) and received darbepoetin. On Day 279, anemia resolved to Grade 1. On Day 280, Grade 2 hypoxia resolved (oxygen saturation on exertion 95% and at rest 97%). Grade 1 anemia resolved on Day 417. On Day 504, Grade 2 anemia recurred. On Day 562 she received darbepoetin. On Day 588, anemia resolved, and Grade 2 hypoxia recurred (oxygen saturation on exertion 87%). Hypoxia resolved on Day 672 (oxygen saturation at rest 97% and on exertion 98%). On Day 672, Grade 2 anemia recurred, and was treated with darbepoetin. Anemia resolved on Day 756. No action was taken with study medication in response to hypoxia or anemia. The participant remained active in the study as of Day 840.

- Patient (b) (6) was a 43 year old man with clear cell RCC metastatic to lung, bone and lymph nodes previously treated with axitinib, pembrolizumab, and cabozantinib. His medical history included diabetes mellitus, hypertension, hyperlipidaemia, and hypothyroidism. Prior medications included insulin, atorvastatin, amlodipine, carvedilol,

clonidine, repaglinide, glimepiride, linagliptin, and levothyroxine. Baseline oxygen saturation was 98% at rest and 96% on exertion. On Study Day 22, he experienced headache, cough, Grade 1 pyrexia and Grade 2 sinusitis. On Day 24, he was hospitalized with pyrexia, Grade 3 dyspnea and Grade 3 hypoxia (hemoglobin oxygen saturation 83%). Pyrexia resolved the same day. Computed tomography showed disease progression without pulmonary embolism or pneumonia. Treatment included oxygen, levofloxacin, piperacillin plus tazobactam, and vancomycin. No action was taken with study medication. On Day 27, the hypoxia resolved, and the patient was discharged home. On Day 29 the patient was hospitalized due to Grade 2 hypoxia, fatigue, dyspnea, and cough and was treated with methylprednisolone. On Day 32, dyspnea improved to Grade 2, and the patient was discharged home with supplemental oxygen. On Days 30 and 34, he participant experienced Grade 1 hemoptysis. On Day 35, hemoptysis worsened to Grade 3. CT angiography showed numerous pulmonary nodules consistent with metastasis compressing the airway and pulmonary artery to the right upper lobe of the lung. Radiation to the mediastinum started on Day 35. On Day 36, hemoptysis resolved, he was discharged with supplemental oxygen and continued radiation treatment. No action was taken with study medication in response to hemoptysis. On Day 46, he completed the study.

- Patient (b) (6) was a 54 year old man with clear cell RCC metastatic to bone, liver, and pleura previously treated with interferon, interleukins, sorafenib, sunitinib, ipilimumab, nivolumab, bevacizumab, cabozantinib, and radiation. His medical history included melanoma, hypertension, hypothyroidism, and colitis. Baseline pulse oximetry readings were 96% at rest and 93% on exertion. On Study Day 15, he experienced Grade 3 hypoxia that resolved the same day (pre-dose hemoglobin oxygen saturation at rest 86%; 6 hours post-dose resting and exertional levels 93% and 89% respectively). On Day 22, resting and exertional values were 88% and 90%, respectively, no treatment was reported, and no action was taken with study medication. On Day 22 he developed Grade 2 anemia which improved to Grade 1 on Day 29. On Day 43, anemia worsened to Grade 2, and he was transfused on Day 44. On Day 54, disease progression was reported in the liver and study medication was discontinued. On Day 55, he experienced Grade 2 hypoxia (oxygen saturation on exertion was 82%) and Grade 2 dyspnea. On Day 99 the oxygen saturation on exertion was 95%. On Day 99 he completed the study.

- Patient (b) (6) was a 61 year old man with clear cell RCC metastatic to lung, adrenals, and bone previously treated with interleukins, sunitinib, nivolumab, cabozantinib, and radiation. His medical history included cigarette smoking, hypertension, hyperlipidemia, chronic kidney disease, adrenal insufficiency, and myocardial infarction. Baseline oxygen saturation was 100% both at rest and on exertion. On Day 4, he was hospitalized with hypotension, Grade 3 decreased urine output, Grade 1 acute kidney injury, Grade 3 adrenal insufficiency, and a Grade 2 pericardial effusion. A CT scan showed the size of the right adrenal gland nodule had increased. Adrenal insufficiency was treated included

fluids, prednisone and fludrocortisone. No action was taken with belzutifan. On Day 10 he was transfused for Grade 3 anemia; no action was taken with belzutifan. On Day 15, anemia improved to Grade 2, and the hemoglobin oxygen saturation was 86% on exertion and 91% at rest. No action was taken with study medication, and no treatment was reported. On Day 29 he experienced Grade 2 hypoxia (oxygen saturation 99% at rest and 87% on exertion). No action was taken with study medication, and no treatment was reported. On Day 34, he fell at home and was diagnosed with Grade 4 cardiac arrest. Emergency Medical Services performed ACLS and endotracheal intubation. In the emergency department, PO_2 was 212 mm Hg and PCO_2 was 55 mm Hg. Chest radiography showed diffuse bilateral interstitial and airspace opacities. Treatment included a hypothermia protocol, acetylsalicylic acid, amiodarone, calcium carbonate, epinephrine, fentanyl, ketamine, midazolam, mupirocin, norepinephrine, ondansetron, piperacillin plus tazobactam, potassium, and sodium bicarbonate. Study medication was discontinued. On Day 41, he experienced fatal ventricular fibrillation.

- Patient (b) (6) was a 61 year old man with clear cell RCC metastatic to adrenals and liver, previously treated with pazopanib, bevacizumab, sunitinib, nivolumab, cabozantinib, lenvatinib, everolimus, and radiation. Baseline hemoglobin was 10.1 g/dL and pulse oximetry readings were 95% at rest and 94% on exertion. On Day 4, he had Grade 2 dyspnea. On Day 7 he developed Grade 2 pneumonia treated with cefepime, levofloxacin, and methylprednisolone, and belzutifan was held. On Day 8, anemia and dyspnea improved to Grade 1, and on Day 10, belzutifan was resumed. On Day 14, he experienced Grade 1 non-cardiac chest pain and productive cough. On Day 15, anemia worsened to Grade 2, he was transfused, and belzutifan was held until Day 17. Pneumonia and productive cough resolved on Day 18, anemia resolved on Day 22 and non-cardiac chest pain resolved on Day 24. On Day 43 he had Grade 2 anemia, and Grade 2 dyspnea. On Day 57 anemia remained Grade 2, and darbepoetin was administered. From Day 57 to Day 73 he had palliative radiation therapy. On Day 85, anemia improved to Grade 1. On Day 116 anemia worsened to Grade 2. On Day 142, dyspnea resolved. On Day 169, anemia worsened to Grade 2. On Day 189 he was hospitalized with fatigue, weakness, hand tremors, and painless rectal bleeding, and he was diagnosed as having Grade 3 cellulitis, Grade 3 rectal hemorrhage, Grade 1 confusional state, and Grade 2 hypoxia, and Grade 3 anemia (hemoglobin 6.5 g/dL). Chest radiography showed decreased lung volumes. Cranial computed tomography showed no acute process. Chest computed tomography showed a pericardial effusion and masses in the right renal fossa and left liver lobe, consistent with metastatic disease, but no pulmonary emboli or aortic dissection. Treatment included antibiotics, red cell transfusion, and oxygen. On Day 193, CT colonography showed sigmoid diverticulosis. On Day 193, anemia resolved, and on Day 194 hypoxia, rectal hemorrhage, and cellulitis resolved and the patient was discharged home. Confusional state did not resolve. Study medication resumed on Day 198 but was interrupted on Day

200 due the patient not feeling well. Disease progression was reported on Day 211 and the participant completed the study with ongoing Grade 1 anemia.

- Patient (b) (6) was a 66 year old man with clear cell RCC metastatic to bone, adrenals, and lymph nodes previously treated with sunitinib, nivolumab, axitinib, cabozantinib, and radiation. His medical history included diabetes mellitus, hyperlipidemia, hypertension, pulmonary embolism (anticoagulation ongoing), anemia, pneumonia, acute respiratory distress syndrome, renal failure, and cardiac failure. Baseline oxygen saturation was 97% at rest and 93% on exertion. On Day 15, he experienced Grade 3 hypoxia (pre-dose hemoglobin oxygen saturation at rest and on exertion 85% and 93%, respectively; 6 hour post-dose oxygen saturation on exertion 75% and at rest was 84%) treated with oxygen. On Day 22, he developed Grade 2 anemia (hemoglobin 9.9 g/dL), and oxygen saturation on exertion was 99%. On Day 29, hemoglobin was 9.5 g/dL oxygen saturation was 83% at rest and 88% upon exertion. On Day 38, he was hospitalized with Grade 3 hypoxia (oxygen saturation 40% to 50%); treatment included bronchodilators, and belzutifan was interrupted. On Day 41, hypoxia resolved and he was discharged home. Belzutifan was resumed on Day 42. On Day 43 oxygen saturation was 82% at rest and 85% on exertion was 85%. On Day 57 oxygen saturation was 92% at rest was 80% upon exertion. On Day 85 anemia worsened to Grade 3 (hemoglobin 7.9 g/dL), and he was transfused. The last dose of study medication was given on Day 93. On Day 156 the participant completed the study.

- Patient (b) (6) was a 64 year old man with metastatic RCC. His medical history included hypertension and chronic obstructive pulmonary disease. Baseline oxygen saturation was 97% at rest and 96% on exertion. On Study Day 59, he was hospitalized with dyspnea, hypoxia, pain, lower extremity edema, tachycardia, anemia, and inability to swallow. Computed tomography showed pneumonia and widespread disease progression. He was transitioned to comfort measures only with intravenous morphine.

- Patient (b) (6) was a 68 year old man with clear cell RCC metastatic to lymph nodes and lung previously treated with sunitinib and axitinib. His medical history included hypertension, hyperlipidemia, sleep apnea, cigarette smoking, emphysema, gastrooesophageal reflux, and peripheral neuropathy. His medications at screening included budesonide and formoterol for dyspnea. Baseline pulse oximetry readings were 95% at rest and 94% on exertion. On Day 22, belzutifan was interrupted due to Grade 2 increased alanine aminotransferase and was resumed on Day 29. On Day 55 he was diagnosed with Grade 2 pneumonitis and was treated with prednisone and sulfamethoxazole plus trimethoprim. On Day 85, belzutifan was interrupted due to Grade 2 pneumonitis and was resumed on Day 94. On Day 405 he was hospitalized and belzutifan was interrupted because of Grade 2 dyspnea and Grade 3 hypoxia. On Day 412, dyspnea and hypoxia resolved. Study medication was resumed on Day 436.

- Patient (b) (6) was a 66 year old male with clear cell RCC metastatic to adrenals, bladder, bone, chest wall, liver and lymph nodes previously treated with pazopanib, axitinib, nivolumab, and cabozantinib. His medical history included cigarette smoking, and chronic obstructive pulmonary disease. Hemoglobin at screening was 11.5 g/dL. Baseline oxygen saturation was 100% both at rest and on exertion pre-dose and 94% at rest and 93% on exertion 6 hours post dosing of belzutifan. On Day 8, his anemia worsened to Grade 3. On Day 9, he was transfused, and again on Day 15. On Day 28, he was hospitalized for fatigue, headache, Grade 2 productive cough, Grade 2 dyspnea, and Grade 3 hypoxia (oxygen saturation 72% on room air). A chest x-ray showed possible pneumonia, and computed tomography showed no signs of pulmonary embolism. Treatment included oxygen, bronchodilators, and prednisone and antibiotics. On Day 35, anemia worsened to Grade 3, hypoxia improved to Grade 2, and he was discharged home with oxygen and bronchodilators.

- Patient (b) (6) was a 73 year old man with RCC metastatic to lung previously treated with pazopanib. His medical history included congenital heart disease, hypertension, hyperlipidemia, atrial fibrillation, and cigarette smoking. Baseline pulse oximetry readings were 95% at rest and 98% on exertion. On Day 16, he experienced Grade 2 hypoxia. On Day 22, oxygen saturation was 97% at rest and 89% upon exertion. On Day 54, he was diagnosed with Grade 1 pneumonitis. On Day 57, hypoxia worsened to Grade 3 (oxygen saturation 86% at rest and 69% upon exertion), he developed Grade 1 cough, and belzutifan was interrupted. On Day 70 the participant underwent a lung biopsy (results not provided). On Day 72, oxygen saturation at rest was 95%, cough resolved, and study medication resumed. On Day 99, pneumonitis resolved. From Day 114 to Day 226, Grade 2 hypoxia was ongoing. Belzutifan was interrupted from Day 170 to Day 197 due to increased blood creatinine. On Day 225 the last dose of study medication was administered. On Day 251, day of the last contact, Grade 2 hypoxia resolved with an oxygen saturation at rest of 99% and on exertion of 94%, and the participant completed the study.

- Patient (b) (6) was a 46 year old man with clear cell RCC metastatic to lungs and lymph nodes previously treated with interleukin, sunitinib, axitinib, nivolumab, ipilimumab, cabozantinib, and radiation. His medical history included hypertension. Baseline oxygen saturation was 95% at rest and 96% on exertion. On Day 65, he experienced Grade 1 hemoptysis that resolved that day. On Day 86, he was diagnosed with Grade 2 hemoptysis and Grade 2 hypoxia (oxygen saturation 93% at rest and 85% upon exertion). Computed tomography showed progression of lung metastases, and belzutifan was discontinued. On Day 91, he was diagnosed with Grade 3 pulmonary hemorrhage treated with oxygen and transbronchial laser. On Day 92, pulmonary hemorrhage resolved. From Day 92 to Day 98, he received radiation therapy to the mediastinum. On Day 97, he was rehospitalized for Grade 1 pyrexia and recurrent Grade 3 pulmonary hemorrhage that resolved that day. From Day 100 to Day 106, he received

radiation therapy to the mediastinum. On Day 111, he was diagnosed with Grade 1 bilateral pleural effusions. On Day 113, he experienced Grade 2 dehydration, Grade 1 dysphagia, Grade 1 dyspnea, Grade 2 fatigue, Grade 2 muscular weakness, Grade 1 hiccups, Grade 1 hypermagnesemia, Grade 3 nausea, Grade 1 sinus tachycardia, Grade 2 vomiting, and Grade 2 cough, and hypoxia resolved. On Day 113 he discontinued study treatment. Pleural effusion, dehydration, dysphagia, dyspnea, fatigue, muscular weakness, hiccups, hypermagnesemia, nausea, sinus tachycardia, vomiting, and cough were ongoing.

- Patient (b) (6) was a 65 year old man with RCC metastatic to bone, chest wall, lungs, and lymph nodes previously treated with everolimus, pazopanib, axitinib, nivolumab, cabozantinib, and radiation. His medical history included hypertension, coronary artery disease, chronic kidney disease, and pleural effusion. On Day 15, he had Grade 2 hypoxia (oxygen saturation 88% at rest and 90% on exertion pre-dose, and 91% at rest and 89% on exertion 6 hours post-dose). On Day 22, he had Grade 2 anemia (hemoglobin 9.9 g/dL and Grade 1 decreased platelet count. On Day 30, he had Grade 2 dyspnea with oxygen saturation 88% at rest and 83% on exertion, Grade 1 nausea and vomiting and was treated with sodium chloride, ondansetron, and supplemental oxygen. Dyspnea, vomiting, and decreased platelet count resolved that day. The oxygen saturation at rest on Day 42 was 91%. From Day 75 to Day 79, he received radiation to the thoracic spine. On Day 84, his hemoglobin was 9.5 g/dL. On Day 112, he had Grade 2 hypoxia (oxygen saturation 86% at rest), and decreased hemoglobin (8.4 g/dL). The same day progressive disease was reported and the participant discontinued study medication due to progressive disease. On Day 140 hypoxia and anemia resolved (oxygen saturation at rest: 95%; Table), and the patient completed the study.

Reviewer's comments:

1. *Of the 17 patients on MK-6482-001 who experienced hypoxia, 15 (88%) had pre-existing pulmonary conditions predisposing them to hypoxia and thus confounding attribution. These included 12 (71%) patients (Patients (b) (6)) with lung and/or pleural metastases (the narratives and datasets lacked information on sites of metastases for Patients (b) (6)) and 7 (41%) patients with histories of chronic obstructive pulmonary disease (Patients (b) (6)), pneumonitis and/or acute respiratory distress syndrome (Patients (b) (6)) and smoking (Patients (b) (6)).*

2. *Six (35%) patients who developed hypoxia during treatment on MK-6482-001 had concurrent acute pulmonary disorders. These include Patient (b) (6) whose hypoxic respiratory failure appears to have been secondary to sepsis and lung metastases, Patient (b) (6) whose hypoxia appears to have been secondary to pleural effusions and a malfunctioning pleural catheter, Patient (b) (6) who experienced pulmonary and*

mediastinal disease progression, Patient (b) (6) who developed hypoxia concurrently with pneumonia, Patient (b) (6) who experienced hemoptysis and pulmonary hemorrhage, and Patient (b) (6) who experienced multi-organ faire shortly before death.

3. *The clinical courses of 4 (24%) patients who experienced hypoxia (Patients (b) (6)) included positive dechallenges (i.e., resolution of hypoxia following withdrawal of belzutifan), which argues that belzutifan was a causative factor. Three patients (Patients (b) (6)) did not have positive dechallenges but their narratives mention no other persuasive acute precipitant of hypoxia; for these three patients, the reviewer considers belzutifan at least possibly to have been causal. The cause of hypoxia in Patient (b) (6) is unclear, as it resolved despite continued belzutifan treatment and progression of RCC metastatic to lung.*

Hypoxia has been added as a Warning and Precaution to the belzutifan label.

Ocular Toxicity

Investigators reported 17 (28%) patients enrolled on MK-6482-004 as having retinal hemangioblastomas at screening. The IRC assessment of retinal hemangioblastomas was limited to those participants assessed as having retinal hemangioblastomas at screening. The Von Hippel-Lindau Natural History Study, Epidemiology No. EP05047.001, VEAP #: 9038 reports retinal hemangioblastomas in approximately twice as many patients (57%). Caution should be exercised when comparing these prevalence estimates because the estimate in MK-6482-004 describes the percentage of RCC patients with concurrent retinal hemangioblastomas *at a single timepoint* (at screening), whereas the VHL Natural History Study estimated the *lifetime* prevalence of retinal hemangioblastomas (at any prior timepoint) detected during routine clinical care in patients with VHL disease-associated RCC. Despite this caveat, the FDA ophthalmology consultant believed the prevalence of ocular findings in MK-6482-004 was lower than expected, suggesting that the population studied was on the mild end of the disease spectrum.

Treatment emergent AEs within the MedDRA System Organ Class, Eye disorders were reported in 21 (34.4%) of patients in MK-6482-004 and in 11 (19.0%) of patients in MK-6482-001. Investigators considered ocular TEAEs to be at least possibly study drug related in 2 (3.4%) and 10 (16.4%) patients, respectively, in Studies 001 and 004. The pattern of Preferred terms reported suggested that no single pathological process drove these reports (Tables 39 and 40).

Table 39. Treatment Emergent AEs within the System Organ Class Eye Disorders

	MK-6482-004 (N = 61)		MK-6482-001 at 120 mg QD (N = 58)	
	All Grades	**Grade 3-4**	**All Grades**	**Grade 3-4**
Any	21 (34.4%)	1 (1.6%)	11 (19.0%)	0
Vision blurred	9 (14.8%)	0	6 (10.3%)	0
Eye pain[a]	6 (9.8%)	0	2 (3.4%)	0
Visual impairment	4 (6.6%)	0	1 (1.7%)	0
Diplopia	1 (1.6%)	0	0	0
Dry eye	1 (1.6%)	0	2 (3.4%)	0
Lacrimation increased	1 (1.6%)	0	1 (1.7%)	0
Myopia	1 (1.6%)	0	0	0
Periorbital edema	1 (1.6%)	0	0	0
Photophobia	1 (1.6%)	0	0	0
Presbyopia	1 (1.6%)	0	0	0
Retinal detachment	1 (1.6%)	1 (1.6%)	0	0
Retinal vein occlusion	1 (1.6%)	0	0	0
Vitreous floaters	1 (1.6%)	0	0	0
Conjunctival hematoma	0	0	2 (3.4%)	0
Cataract	0	0	1 (1.7%)	0
Eye pruritus	0	0	1 (1.7%)	0
Eye swelling	0	0	1 (1.7%)	0
Swelling of eyelid	0	0	1 (1.7%)	0

[a] includes eye pain, eye irritation, and ocular discomfort

Table 40. Study Drug Related TEAEs within the System Organ Class Eye Disorders (Investigator Attribution)

	MK-6482-004 (N = 61)		MK-6482-001 at 120 mg QD (N = 58)	
	All Grades	**Grade 3-4**	**All Grades**	**Grade 3-4**
Any	2 (3.3%)	0	10 (17.2%)	0
Swelling of eyelid	1 (1.6%)	0	0	0
Vision blurred	1	0	4 (6.9%)	0
Myopia	0	0	1 (1.7%)	0
Dry eye	0	0	1 (1.7%)	0
Periorbital edema	0	0	1 (1.7%)	0
Eye pain	0	0	1 (1.7%)	0
Presbyopia	0	0	1 (1.7%)	0
Visual impairment	0	0	2 (3.4%)	0

Details of two serious and/or high-grade ocular TEAEs are as follows:

- Patient (b) (6), who developed a Grade 4 retinal detachment, is discussed under Serious Adverse Events above.
- Patient (b) (6) was reported as having a central retinal vein occlusion (CVRO). Patient (b) (6) is a 53-year-old female with pre-existing retinal VHL manifestations for which

she received laser treatment in (b) (6). Additional medical history included hypertension treated with ramipril. Approximately 16 months after starting belzutifan, she developed 2 weeks of blurry vision followed by almost complete loss of vision in the right eye (visual acuity not reported). She was diagnosed as having a Grade 2 CVRO approximately 16 months after starting belzutifan. MRI showed diffuse periorbital edema, and laboratory evaluation showed elevated total cholesterol (7.1 mmol/L; ULN 5 mmol/L) and elevated LDL (5.0 mmol/L, ULN 3 mmol/L). Approximately two weeks later, the patient experienced Grade 3 hypertension for which the dose of ramipril was increased from 2.5 mg QD to 7.5 mg QD. Visual acuity did not improve despite treatment with intravitreal aflibercept. At the data cutoff, the patient remained on belzutifan 120 mg QD, and the Grade 2 CRVO was ongoing. The Investigator assessed the CVRO as secondary to hypertension and hypercholesterolemia.

Reviewer's Comments:

1. *CTCAE v.4.03 defines Grade 2 thromboembolic events as "uncomplicated, medical intervention indicated". The CRVO occlusion in Patient (b) (6) caused "almost complete loss of vision in the right eye". The visual acuity was not reported; however, had this CRVO been reported using the MedDRA Preferred term Vision decreased instead of as a thromboembolic event, it would have been classified as Grade 4 if the visual acuity was less than 20/200.*

2. *Toxicities within the MedDRA System Organ Class Eye Disorders were reported in 34.4% and 19.0% of patients, respectively, in Studies 001 and 004. Investigators considered fewer than half of reported ocular TEAEs to be study drug related, and the fact that no single pathological process seemed to drive these reports suggests that ocular toxicities in general were not a direct result of belzutifan.*

3. *In the belzutifan label, ocular toxicity is mentioned in section 6 in the adverse event table under the combined term of visual impairment, which occurred in 21% of patients overall and was Grade 3-4 in 3.3%. This combined the terms of visual impairment, vision blurred, central retinal vein occlusion and retinal detachment.*

Laboratory Findings

Data:

In the MK-6482-004 Safety Dataset, most clinical hematological laboratory values were Grade 0 (80.3% to 100% depending on the parameter) or Grade 1 (0% to 18.0% depending on the parameter) at baseline. Of the 49 participants with normal baseline (ie, Grade 0) hemoglobin values, 3 (4.9%) participants had at least 1 postbaseline Grade 3 abnormal value. One participant (1.6%) with Grade 2 (hypo) hemoglobin levels at baseline shifted to postbaseline Grade 3 abnormal values. No participants with normal baseline value (ie, Grade 0) in leukocytes, lymphocytes, neutrophils, and platelets had postbaseline Grade 3 abnormal values.

One participant (1.6%) with Grade 1 lymphocytes levels at baseline shifted to postbaseline Grade 3 abnormal values.

In the MK-6482-004 Safety Dataset, most clinical serum chemistry laboratory values were Grade 0 (77.7% to 100% depending on the parameter) or Grade 1 (0% to 21.3% depending on the parameter) at baseline. Of the 4 (6.6%) participants with Grade 2 (hyper) glucose levels at baseline, 3 (4.9%) participants had postbaseline Grade 3 abnormal values. Of the 60 (98.4%) participants with normal baseline (ie, Grade 0) phosphate levels, 1 (1.6%) participant had at least 1 postbaseline Grade 3 abnormal value.

In participants with baseline pancreatic lesions in the MK-6482-004 Safety Dataset, no significant abnormalities were noted in serum amylase and lipase levels, per investigator assessment. In participants with baseline pancreatic lesions or adrenal lesions in the MK-6482-004 Safety Dataset, no significant abnormalities were noted in urine metanephrines, per investigator assessment.

No abnormalities were noted from male fertility hormones in the MK-6482-004 Safety Dataset. While a central lab was used for hormone tests, different local andrology labs were used for semen samples. Data from the 12 male subjects in the MK-6482-004 Safety Dataset who were able to provide semen samples at the protocol-specified times at both baseline and at Week 17 were inconclusive. While it is difficult to draw conclusion from the limited semen analysis data, difference over time in semen quality may be explained by specimen-to-specimen variability.

The Applicant's Position:

Laboratory findings are consistent with the known on-target effect of reduction in EPO associated with HIF2α inhibition and corresponding hemoglobin decrease which were mostly mild or moderate. Apart from laboratory changes related to hemoglobin decrease, there were no other significant laboratory findings.

The FDA's Assessment:

The most commonly reported laboratory abnormalities on MK-6482-004 were anemia, hyperglycemia, and elevated serum creatinine.

Table 41. MK-6482-004Laboratory Abnormalities

	Grades 1-4	Grades 3-4
Chemistry		
Increased creatinine	39 (63.9%)	0
Hyperglycemia	21 (34.4%)	3 (4.9%)
Increased ALT	12 (19.7%)	0
Increased AST	10 (16.4%)	0
Hypocalcemia (corrected)	6 (9.8%)	0
Hypophosphatemia	6 (9.8%)	1 (1.6%)
Hyperkalemia	5 (8.2%)	0
Hypokalemia	5 (8.2%)	0

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Hypernatremia	4 (6.6%)	0
Hyponatremia	4 (6.6%)	0
Hyperbilirubinemia	3 (4.9%)	0
Hypoalbuminemia	2 (3.3%)	0
Hypomagnesemia	2 (3.3%)	0
Hypercalcemia (corrected)	1 (1.6%)	0
Hypoglycemia	1 (1.6%)	0
Increased alkaline phosphatase	1 (1.6%)	0
Hyperphosphatemia	0	0
Hematology		
Anemia	57 (93.4%)	4 (6.6%)
Leukopenia	7 (11.5%)	0
Thrombocytopenia	1 (1.6%)	0

Source: Dataset ADLB; variables SUBJID, SAFFL, PARAM, AVAL, BASE, EVLLBFL

Reviewer's comments:

1. *The standard in OOD for analyses reported in the laboratory abnormalities table in product labeling is to use patients with a baseline and at least one post-baseline laboratory evaluation as the denominator for each test. The denominator will vary from test to test. This is to ensure that all patients who had laboratory evaluations done both pre and post-drug exposure for each test are captured. All 61 patients enrolled on MK-6482-004 had a baseline assessment and at least one post-baseline assessment.*
2. *The relatively high incidence of low-grade Increased creatinine in patients on MK-6482-004 is likely in part due to the presence of localized RCC and prior renal procedures.*

Vital Signs

The Applicant's Position:

There were no clinically meaningful findings in the vital sign measurements, physical examination assessments, or other observations related to safety.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. No clinically significant changes over time in mean values for the four vital signs were observed among patients in MK-6482-004 (Figures 16-

19). Further, no patient experienced an abnormal value for any vital sign that was otherwise unexplained and/or associated with clinical sequelae.

Figure 16. MK-6482-004 Pulse Rate Over Time (Safety Population; Applicant's figure)

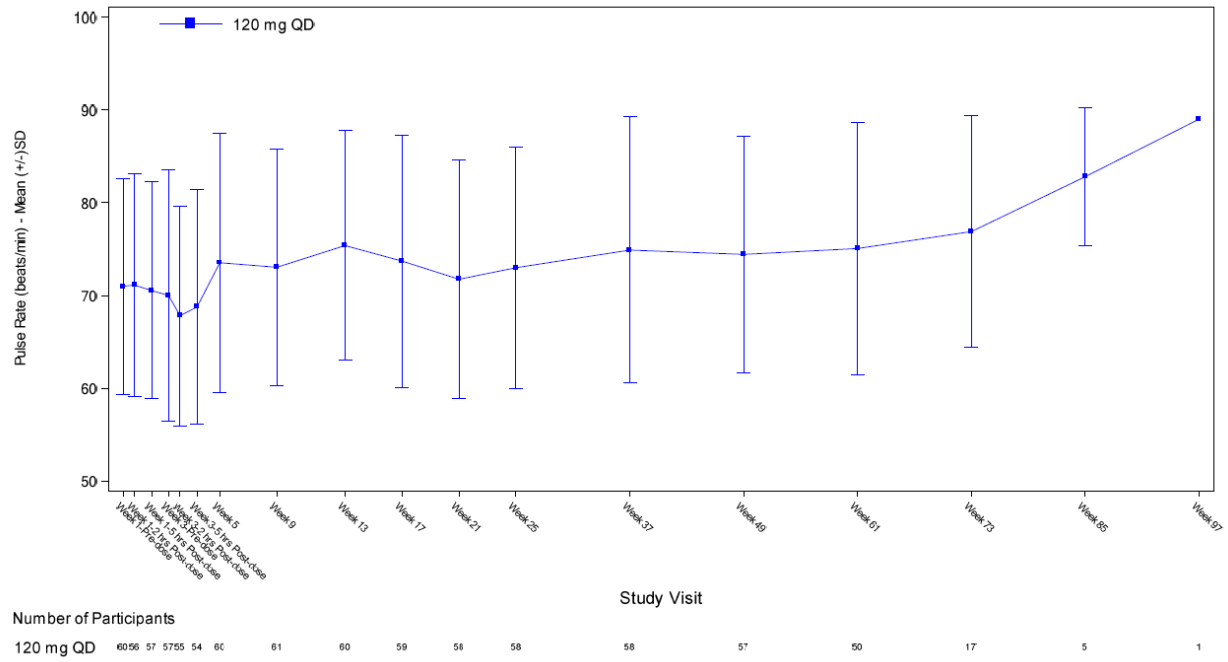

Figure 17 MK-6482-004 Respiratory Rate Over Time (Safety Population; Applicant's figure)

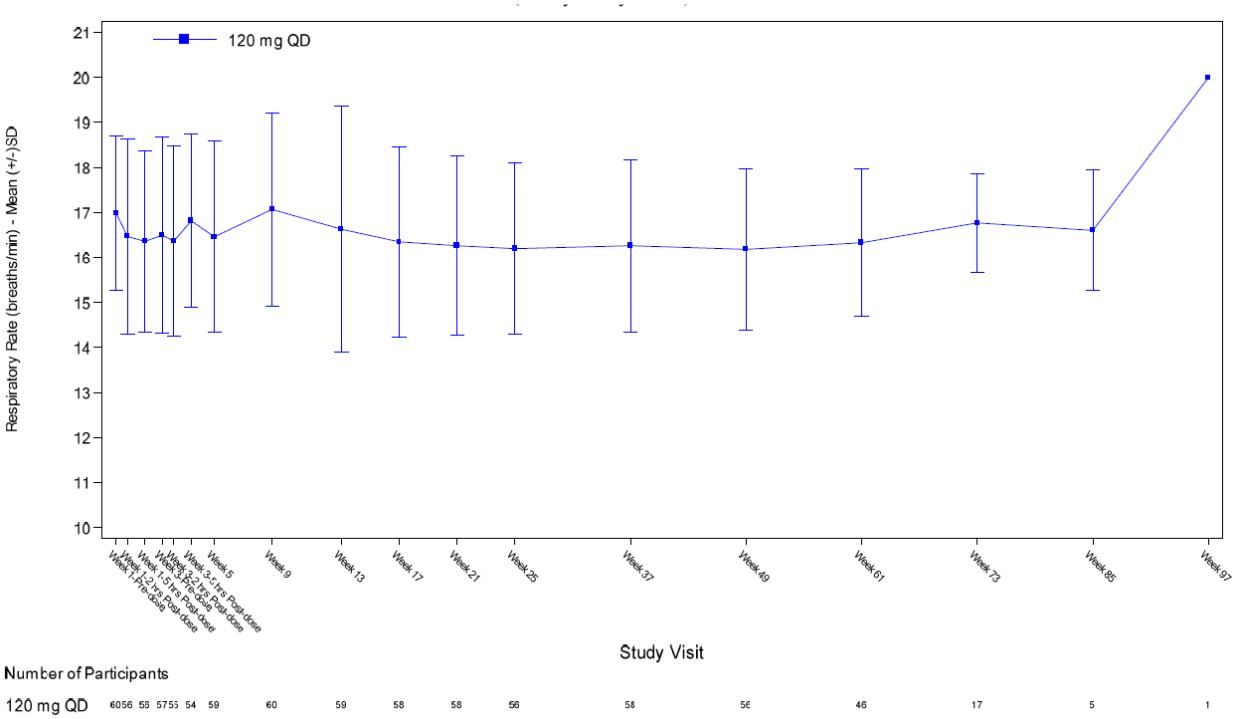

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Figure 18. MK-6482-004 Temperature Over Time (Safety Population; Applicant's figure)

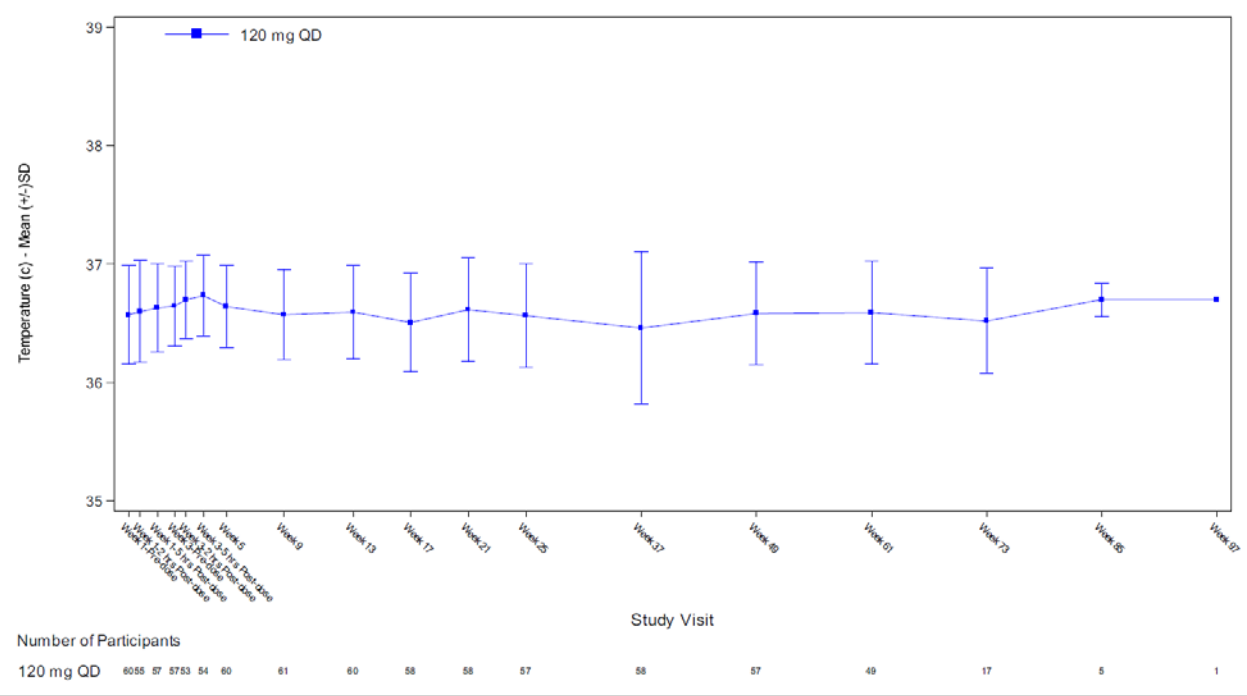
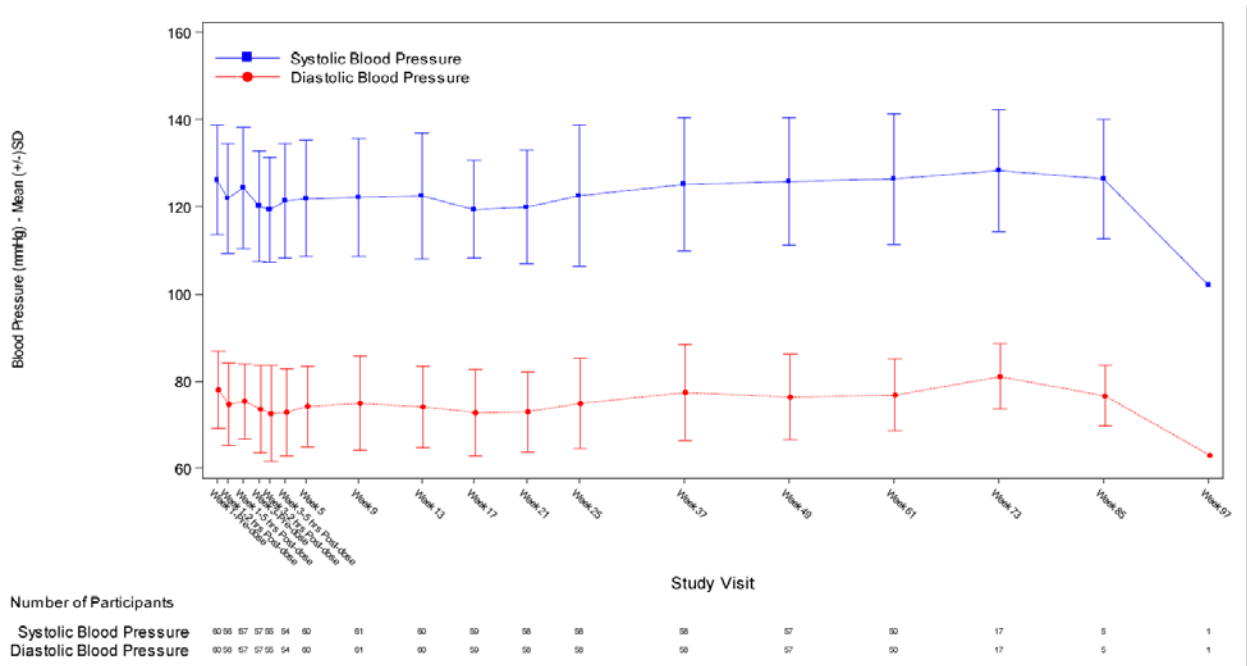


Figure 19. MK-6482-004 Blood Pressure Over Time (Safety Population; Applicant's Figure)



Electrocardiograms (ECGs)

The Applicant's Position:

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

There were no clinically meaningful findings in the ECG measurements.

The FDA's Assessment:

The Applicant analyzed EKG data and plasma levels of belzutifan and its metabolite PT3317 obtained during MK-6482-004 to evaluate the effects of belzutifan on QTcF and other EKG parameters. Cardiac exclusion criteria for MK-6482-004 included any major cardiovascular event within 6 months prior to study drug administration including but not limited to myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic event, pulmonary embolism, clinically significant ventricular arrhythmias (e.g., sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes) or New York Heart Association Class III or IV heart failure, or because of any other cardiac condition which, in the opinion of the investigator or medical monitor, might interfere with participation in the trial or interfere with the interpretation of trial results.

EKGs and plasma samples were collected during MK-6482-004 on the following schedule:

- Screening (single ECG only)
- Week 1 Day 1: triplicate ECGs pre-dose; 2 and 5 hours post-dose
- Week 3: triplicate ECGs pre-dose; 2 and 5 hours post-dose
- Weeks 5, 9, 13: single ECG pre-dose
- Weeks 17, 21, 25 and every 12 weeks thereafter: single ECG without regard to timing of study drug administration

The Applicant concluded:

- Based on the results up to Week 13, once daily dosing with 120 mg PT2977 had no clinically relevant effects on QTc or other ECG parameters.
- Based on the concentration-QTc and by time point analyses, a ΔQTcF effect exceeding 20 ms can be excluded within the observed ranges of PT2977 and PT3317 plasma concentrations.

QT

The Applicant's Position:

No clinically meaningful effects of belzutifan on cardiac QTc interval were identified in the safety analyses.

The FDA's Assessment:

The FDA Interdisciplinary Review Team (IRT) for Cardiac Safety Studies reviewed the Applicant's Cardiac Safety Report as well as nonclinical safety pharmacology assessments, the results of MK-6482-004, and a previous IRT review under IND 132120 dated 14 February 2019. The IRT concluded that at the recommended dose, belzutifan does not cause large mean increases (i.e., > 20 msec) in the QT interval.

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Immunogenicity

The Applicant's Position:

Not applicable as MK-6482 does not induce immune changes or impact the immune system.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

10.2.4 Analysis of Submission-Specific Safety Issues

The Applicant's Position:

No submission-specific safety issues are identified by the Applicant.

The FDA's Assessment:

See above under Treatment Emergent Adverse Events and Adverse Reactions.

10.2.5 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

No COA analyses were performed for MK-6482-004 and MK-6482-001.

The FDA's Assessment:

Not applicable. While patient-reported outcomes (PROs) data may have helped descriptively inform the tolerability profile of belzutifan, no PROs were collected.

10.2.6 Safety Analyses by Demographic Subgroups

The Applicant's Position:

There were no trends suggesting any safety concerns for belzutifan based on the AE profile by age, ECOG PS, region, or sex.

The FDA's Assessment:

Examining the incidences of TEAEs by key demographic subgroup, the FDA notes a numerically higher incidence of Grade 3-4 TEAEs in women compared to men (Table 42).

Table 42. MK-6284-002 Summary of TEAEs by Demographic Subgroup

	All Grades	**Grade 3-4**
Age		
< 65	59/59 (100%)	14/59 (23.7%)
65	2/2 (100%)	0
Sex		
Male	29/29 (100%)	3/29 (10.3%)
Female	32/32 (100%)	11/32 (34.3%)
Region		
US	48/48 (100%	9/48 (18.7%)
Ex-US	13/13 (100%)	5/13 (38.5%)
Race		
White	55/55 (100%)	13/55 (23.6%)
Non-White	6/6(100%)	1/6 (16.7%)
Ethnicity		
Hispanic	7/7 (100%)	2/7 (28.6%)
Not Hispanic or Unknown	54/54 (100%)	12/54 (22.2%)

Source: datasets ADSL and ADAE; variables STUDYID, SUBJID, AGE, SEX, RACE, ETHNIC

Given that the primary mechanism of action of belzutifan is not hormonal, this concentration of Grade 3-4 TEAEs among women was unexpected. An examination of the individual Grade 3-4 TEAEs reported showed this trend to be driven by an imbalance in reports of anemia (Table 43).

Table 43. MK-6482-004 Grade 3-4 TEAEs by Sex

	Females (N = 32)	Males (N = 29)
Anemia	4 (12.5%)	0
Fatigue	3 (9.4%)	0
Anaphylactic reaction	1 (3.1%)	0
Cholecystectomy	1 (3.1%)	0
Coronary artery dissection	1 (3.1%)	0
Dyspnea	1 (3.1%)	0
Hypertension	1 (3.1%)	1 (3.4%)
Hypotension	1 (3.1%)	0
Retinal detachment	1 (3.1%)	0
Hyperglycemia	1 (3.1%)	0
Hypoxia	0	1 (3.4%)
Weight increased	0	1 (3.4%)

Source: datasets ADSL, ADAE; variables STUDYID, SUBJID, SEX, AEDECOD, AETOXGR

Women enrolled on MK-6482-004 may have been at increased risk of Grade 3-4 anemia compared to men because they had lower hemoglobin values at baseline (Table 37). Women of childbearing age in the general US population are at higher risk of anemia compared to men.[1]

Table 44. MK-6482-004 Screening Hemoglobin Values by Sex

	Females (N = 32)	Males (N = 29)
Mean ± SD	131.8 ± 11.7	150.3 ± 12.9
Median (range)	132 (99, 154)	150 (121, 185)

Source: datasets ADSL, ADLB; variables STUDYID, SUBJID, SEX, PARAM, AVAL

10.2.7 Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The FDA agrees that no special safety studies were conducted.

10.2.8 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Not applicable.

The FDA's Assessment:

[1] Le CHH (2016) The Prevalence of Anemia and Moderate-Severe Anemia in the US Population (NHANES 2003-2012). PLoS ONE 11(11): e0166635. doi:10.1371/journal.pone.0166635

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Anemia is a common adverse reaction with belzutifan, and the presumed mechanism of belzutifan-induced anemia suggests that erythropoiesis stimulating agents (ESAs) would be expected to provide effective mitigation. Secondary malignancies are a known adverse effect of ESAs, and patients with VHL disease are already at heightened risk for a variety of new malignancies.

One patient on MK-6482-004(Patient (b) (6)) experienced a secondary malignancy of vulvar cancer on Study Day 109 after having received one dose of darbepoietin on Day 73. In addition, three patients on MK-6482-001 experienced adverse events of progression of their underlying renal cell carcinoma. While these incidences by themselves are too small to be considered potential signals of carcinogenicity, this is not fully reassuring because ESA-induced growth of existing tumors would have likely been obscured by the primary tumor shrinking activity of belzutifan, and ESA-induced secondary malignancies are rare and follow-up time on MK-6482-004 was short.

To mitigate the risk of carcinogenicity, the clinical review team recommends the following:

- The Warning and Precautions for anemia in the product Prescribing Information should contain the following language:

For patients treated with TRADEMARK who develop anemia, the safety and effectiveness for use of erythropoiesis stimulating agents (ESAs) 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.

- As a postmarketing commitment, the Applicant should continue to follow patients enrolled on MK-6482-004, and submit safety updates every 6 months for 3 years to include the use of erythropoiesis stimulating agents and reports of secondary malignancies (see Section 14 of this Assessment Aid for additional details).

Human Reproduction and Pregnancy

The Applicant's Position:

There were no reports of pregnancy in participants in either the MK-6482-004 and MK-6482-001 study populations. There was one pregnancy in a female partner of a male study participant. The pregnancy resulted in a normal healthy baby born at term.

No information is available on the effects of MK-6482 on embryonic or fetal development in humans. Pregnant women were not permitted to enroll in the MK-6482-001 and MK-6482-004 studies. WOCBP were required to use a highly effective (with a failure rate of <1% per year) contraceptive method, with low user dependency, or be abstinent from heterosexual

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intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), during the intervention period and for at least 30 days after the last dose of study intervention.

No information is available on the secretion of MK-6482 in breast milk. Nursing women were not permitted to enroll in the MK-6482-001 and MK-6482-004 studies.

The FDA's Assessment:

Belzutifan was embryofetal toxic in nonclinical studies but was not genotoxic. The embryofetal toxicity seen in nonclinical studies was not markedly greater in incidence or severity than that observed with many oncology drug products approved in recent years; however, the patient population for whom the drug will be indicated is younger than that for many oncology products, and the expected duration of exposure may be longer. The median age of patients enrolled on MK-6482-004 was 42 years (range 19-66) and approximately half of patients were female. In addition, mitigation of the embryofetal toxicity of belzutifan is complicated by the fact that drug-drug interactions with belzutifan can render some hormonal contraceptives ineffective. Because of these considerations, the clinical review team recommends placing Boxed Warning for embryofetal toxicity in the product label and a to convert the Patient Package Insert to a Medication Guide.

Other options which the clinical review team considered for mitigating the risk of embryofetal toxicity with belzutifan included 1) issuing a Postmarketing Requirement for a pregnancy exposure registry or a single-arm pregnancy surveillance study (SPSS; also termed pregnancy exposure registry, or enhanced pregnancy pharmacovigilance) to collect postmarketing real-world data, 2) issuing a Death Healthcare Provider (DHCP) letter, and 3) a risk evaluation and mitigation strategy (REMS). Ultimately, it was determined that a Boxed Warning plus a Warning and Precautions in Section 5 the product label plus a Medication Guide were adequate to mitigate embryofetal risk. This determination took into consideration the fact that recent SPSS's with other oncology drugs (e.g., trastuzumab, pertuzumab, ado-trastuzumab, midostaurin, vismodegib, and sonidegib) ultimately enrolled too few patients to draw inferences to inform labeling.

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. See Section 13 of this Assessment Aid for additional information.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

At the time of the data cutoff, there were no reports of overdose of belzutifan. Potential for drug abuse or dependence is not expected for a HIF2α inhibitor, and no reports of drug abuse with belzutifan have occurred. No withdrawal or rebound effects are expected for drugs in this class, and none have been observed in belzutifan clinical studies to date.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

10.2.9 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable – this is the first marketing submission for belzutifan.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Postmarketing data from the safety reporting database will be routinely reviewed for belzutifan. The Applicant's AE reporting system will contain all data from postmarket sources, including health care providers, consumers, and scientific literature as well as competent authorities worldwide. The Applicant will monitor postmarketing data associated with belzutifan.

There are no specific safety concerns associated with subpopulations not adequately represented in the safety database for belzutifan. There are no differences in the administration of belzutifan in the postmarketing setting expected to affect safety.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. For patients with metastatic RCC, the efficacy of belzutifan has not been evaluated, and its safety profile appears to be worse than in the patient population enrolled in MK-6482-004. Belzutifan is not expected to be used in patients with metastatic RCC as this was not the reviewed population for this approval.

10.2.10 Integrated Assessment of Safety

The Applicant's Position:

Overall, belzutifan 120 mg once daily is generally tolerable in patients with VHL-associated RCC with a low frequency of AEs leading to discontinuation of treatment. In addition, belzutifan has a manageable safety profile as demonstrated by the mostly mild to moderate severity of events. AEs were effectively managed with standard of care protocols and by dose interruption

or dose reduction. There were no drug-related life threatening or fatal events. This safety summary is supported by an analysis of the MK-6482-004 study and the MK-6482-001 study.

The FDA's Assessment:

[F The safety database for belzutifan at the proposed dose in patients with the proposed indication is relatively small, consisting of only 61 patients treated in MK-6482-004 and 58 patients treated in MK-6482-001 with advanced cancer who were treated at the proposed dose of 120 mg daily. However, due to the rarity of the condition treated, i.e. VHL-associated RCC, this was considered acceptable, and patients in MK-6482-004 had an overall long median duration of exposure of 68 weeks.

Among the 61 patients in MK-6482-001:

- Treatment emergent AEs reported in 20% of patients were anemia, fatigue, headache, dizziness, nausea, and upper respiratory tract infection.
- Grade 3-4 treatment emergent AEs reported in 2 patients were anemia, fatigue, and hypertension.
- One (1.6%) death was reported.
- Nine (14.8%) patients experienced SAEs.
- Two patients experienced AEs leading to discontinuation of study drug

Anemia and hypoxia are thought to be on-target adverse effects of belzutifan and are labeled as Warnings and Precautions in belzutifan product labeling. Anemia and hypoxia were observed in 55 (90.2%) and 1 (1.6%) patients, respectively, on MK-6482-004, and in 44 (75.9%) and 17 (29.3%) patients, respectively, on MK-6482-001. Anemia and hypoxia can be especially dangerous should they occur concurrently, as anemia can worsen the clinical manifestations of hypoxia, and hypoxia can worsen the clinical manifestations of anemia. The presumed mechanism of belzutifan-induced anemia suggests that erythropoiesis stimulating agents (ESAs) would be expected to provide mitigation; however, as. secondary malignancies are a known adverse effect of ESAs, and patients with VHL disease are already at heightened risk for a variety of new malignancies. Because of this risk, the use of ESAs in patients who develop anemia while taking belzutifan was discouraged in product labeling for belzutifan. The higher incidence of hypoxia, both all grades and Grade 3-4, in MK-6482-001 than in MK-6482-004 appeared to be due largely to the presence of additional pulmonary comorbidities in patients with metastatic RCC.

No pregnancies were reported in MK-6482-004 or MK-642-001, where precautions to prevent pregnancy were in place. The degree of embryofetal toxicity seen in nonclinical studies was comparable to that observed with many oncology drug products approved in recent years; however, the patient population for whom belzutifan will be indicated is younger than that for many oncology products, and the expected duration of exposure may be longer. Further, drug-drug interactions with belzutifan may render some hormonal contraceptives ineffective.

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Because of these considerations, the clinical review team recommends placing a boxed warning for embryofetal toxicity in the product label in addition to having this appear as a Warning and Precaution, and a to convert the Patient Package Insert to a Medication Guide.

Toxicities within the MedDRA System Organ Class Eye Disorders were reported in 34.4% and 19.0% of patients, respectively, in Studies 001 and 004. Investigators considered fewer than half of reported ocular TEAEs to be study drug related, and the fact that no single pathological process seemed to drive these reports suggests that ocular toxicities in general were not a direct result of belzutifan.

11 SUMMARY AND CONCLUSIONS

11.1 Statistical Issues

The FDA's Assessment:

There are no major statistical review issues with this application. Time-to-event endpoints, such as PFS and time-to-surgery, are not interpretable in single-arm trials.

11.2 Conclusions and Recommendations

The FDA's Assessment:

The review team recommends regular approval for WELIREG 120 mg (three 40 mg tablets) orally once daily. WELIREG is a hypoxia-inducible factor inhibitor indicated for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma, central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

X	X
Primary Statistical Reviewer	Statistical Team Leader
Haley Gittleman	Erik Bloomquist

X	X
Primary Clinical Reviewer	Clinical Team Leader
Jaleh Fallah	Chana Weinstock
Michael Brave	

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12 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

The FDA's Assessment:

An advisory committee meeting was not needed for this application.

A regular government employee (RGE) was retained for advice on this application. He was asked questions about the adequacy of diagnostic methods, endpoints, and efficacy results to support an indication for treatment of VHL-associated RCC, CNS hemangioblastoma and pNET after being provided with a synopsis of efficacy and safety results for belzutifan. According to the RGE's responses, including a telephone discussion, the radiologic diagnostic criteria used in Study 004 in the absence of histologic confirmation is adequate for diagnosis of VHL-associated RCC ; ORR and DoR as primary and key secondary endpoint and RECIST criteria for evaluation of response in VHL-associated RCC is adequate since the decision to treat VHL RCCs with surgery or ablation are decided based on imaging criteria (size and how solid it appears on images); Waxing and waning in RCC measurements observed in Study 004 is not a major concern and the RCC lesion size may decrease slightly but if imaged years later these tumors almost always continue to grow. The RGE generally agreed with the FDA assessment.

13 PEDIATRICS

The Applicant's Position:

Belzutifan has been developed in adult patients. A waiver request of pediatric development for belzutifan was submitted with the NDA submission, and can be granted under the PREA requirements as amended by FDARA.

The Sponsor conducted a Type F pediatric scientific advice meeting on August 5, 2020, to discuss the iPSP preparation under FDARA for MK-6482. In this meeting, FDA and the Sponsor agreed that, given that activity of belzutifan requires the association of VHL mutations, there was no strong rationale for development of belzutifan in the pediatric population. A planned request for waiver in the iPSP was supported.

The FDA's Assessment:

The activity of belzutifan requires the presence of VHL aberrations, and such aberrations are rare in children, which makes pediatric studies highly impracticable to conduct. There is also insufficient evidence of the relevance of the VHL/HIF-2α pathway to the growth or progression of any pediatric cancers to support a potential clinical benefit. Further, HIF-2α is neither on the *Relevant Molecular Target List*, nor on the *Non-Relevant Molecular Target Leading to Waiver List* as determined by the FDA Draft Guidance (Dec 2019), *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* and FDA Draft Guidance (Jan 2020), *Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504 – Questions and Answers*.

Based on these considerations, On November 19, 2020, the FDA issued an Agreed initial Pediatric Study Plan (iPSP) granting a full waiver from the requirements of PREA, as amended by FDARA, for all pediatric age groups.

14 LABELING RECOMMENDATIONS

Applicant Position:

The Applicant has provided proposed labeling separately.

The FDA's Assessment:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
Boxed Warning	None.	FDA added a Boxed Warning for Embryo-Fetal Toxicity to increase the prominence of this risk since beltuzifan will be used for prolonged periods of time in a relatively young patient population.
1. Indications and Usage	TRADEMARK (belzutifan) is indicated for the treatment of patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), not requiring immediate surgery.	FDA revised to: WELIREG is indicated for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma, central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. (1)
2. Dosage and Administration	**2.1 Recommended Dosage** **…**	FDA added "Do not chew, crush, or split WELIREG".
	2.2 Dosage Modifications for Adverse Reactions **…**	FDA added recommended dose level reductions (i.e., first – 80 mg orally once daily, second – 40 mg orally once daily, and third – permanently discontinue). FDA revised Table 1 Dosage Modifications for Adverse Reactions as follows: - Revised the dosage modification criteria for anemia (i.e., withhold and start at lower dose) from (b) (4)

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		to 10 g/dL given safety concerns related to ESA-induced malignancies and the risks of red cell transfusions. - FDA added dosage modification criteria for Grade 2 hypoxia (i.e., consider withholding and resume at same dose or reduced dose). - FDA revised the dosage modification severity grading proposed (e.g., (b) (4)) to align with CTCAE grading definitions. - FDA added permanent discontinuation criteria for recurrent symptomatic hypoxia.
3. Dosage Forms and Strengths	…	FDA added additional tablet description information ("plain on the other side").
5. Warnings and Precautions	**5.1 Anemia**	FDA revised to remove (b) (4) FDA removed (b) (4) Consistent with safety information in approved ESA labeling and available evidence of ESA use in WELIREG, FDA added the following: "The use of erythropoiesis stimulating agents (ESAs) for treatment of anemia is not recommended in patients treated with WELIREG. For patients treated with TRADEMARK who develop anemia, the

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		safety and effectiveness for use of ESAs 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." FDA revised the dose modification and discontinuation criteria for anemia consistent with the revisions made above in Section 2.2 and added advice to transfuse patients as clinically indicated.
5. Warnings and Precautions	**5.2 Hypoxia** **…**	FDA added: "WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization *[see Dosage and Administration (2.2)]*." FDA revised the dose modification and discontinuation criteria for hypoxia consistent with the revisions made above in Section 2.2.
5. Warnings and Precautions	**5.3 Embryo-Fetal Toxicity** …	FDA revised to add "embryo-fetal lethality, reduced fetal body weight, and fetal skeletal malformations at 0.2 times the human exposures" based on FDA Pharmacology/ Toxicology review. FDA revised (b) (4) to "effective non-hormonal contraception". FDA added "since WELIREG can render some hormonal contraceptives ineffective *[see Drug Interactions (7.1)]*."
6. Adverse Reactions	**6.1 Clinical Trials**	FDA revised the proposed serious adverse reactions (SARs) to remove (b) (4)

	Experience …	(b) (4) consistent with FDA Labeling Guidance for Adverse Reactions; and added anaphylaxis reaction, retinal detachment, and central vein occlusion SARs that occurred in patients treated with WELIREG. FDA revised the adverse reactions leading to dose interruption (>2%) to add "decreased hemoglobin, anemia, nausea, abdominal pain, headache, and influenza-like illness". FDA revised the most common adverse reactions statement to include laboratory abnormalities (≥25%), and added decreased hemoglobin, increased creatinine, and increased glucose. To Table 2, Adverse Reactions >10% of Patients Treated with WELIREG, FDA made the following revisions: - Revised (b) (4) to "Visual Impairment (and increased All Grades from (b) (4)% to 21%; and Grade 3-4 from (b) (4)% to 3.3%) to include events of retinal detachment and central retinal vein occlusion. - FDA revised the incidence (increased) of fatigue, headache, dizziness, abdominal pain, and upper respiratory tract infection by including applicable grouped terms identified in the FDA safety review and added these definitions to the table footnotes. FDA added Table 3: Select Laboratory Abnormalities (≥10%) That Worsened from

		Baseline in Patients Who Received WELIREG in Study-004. FDA removed proposed (b) (4) and revised: - To remove (b) (4) information that is potentially misleading and may complicate interpretation of this safety information. - To add other clinically significant adverse reactions observed in patients treated with WELIREG at the recommended dosage and not observed in Study-001 (i.e., edema, cough, musculoskeletal pain, vomiting, diarrhea, and dehydration).
7. Drug Interactions	**7.1 Effects of Other Drugs on WELIREG** **…**	FDA revised as follows: - Added consequences for increases in plasma exposure with UGT2B17 or CYP2C19 inhibitors (i.e., "which may increase the incidence and severity of adverse reactions of WELIREG") - Added advice to monitor for anemia and hypoxia. - Added cross references to required dosage modifications for adverse reactions.
7. Drug Interactions	**7.2 Effects of WELIREG on Other Drugs** **…**	FDA revised as follows: - Added "including hormonal contraceptives" to CYP3A4 substrates.

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		- Added "may reduce the efficacy of these substrates". - Added "Coadministration of WELIREG with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding."
8. Use in Specific Populations	**8.1 Pregnancy** …	FDA revised to add the E-F risks identified above in Section 5.
8. Use in Specific Populations	**8.3 Females and Males of Reproductive Potential** …	FDA revised to add an initial "can cause fetal harm" statement, and added revisions to contraception (*Females and Males*) identified in Sections 5 and 7 above. FDA removed (b) (4) . FDA removed (b) (4) . FDA revised infertility information to include females and added "The reversibility of the effect on fertility is unknown".
8. Use in Specific Populations	**8.5 Geriatric Use** …	FDA revised to remove (b) (4)

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8. Use in Specific Populations	**8.6 Renal Impairment** **…** **8.7 Hepatic Impairment** **…**	FDA revised to add the definitions for mild, moderate, and severe renal impairment and hepatic impairment (respectively).
8. Use in Specific Populations	**None.**	FDA added the subsection **8.8 Dual UGT2B17 and CYP2C19 Poor Metabolizers**.
10. Overdosage	…	FDA revised to remove (b) (4) and clarified that Grade 3 hypoxia and Grade 4 thrombocytopenia occurred in patients treated at approximately twice the recommended dosage of WELIREG.
12. Clinical Pharmacology	**12.1 Mechanism of Action** **…**	FDA revised to remove (b) (4) the established mechanism of action information on the indicated populations and established activity related to the safety or efficacy of belzutifan.
12. Clinical Pharmacology	**12.2 Pharmacodynamics** **…**	FDA revised to add "The incidence of Grade 3 anemia is increased with increased belzutifan exposure in patients with baseline hemoglobin levels < 12 mg/*dL [see Warning and Precautions (5.1)]*." FDA revised *Cardiac Electrophysiology* findings from (b) (4) to "does not cause large mean increases (i.e., >20 msec) in the QT interval" based on FDA QT review and

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		available data.
12. Clinical Pharmacology	**12.3 Pharmacokinetics** **…**	FDA revised as follows: - Removed (b) (4) [redacted] - Added a description of the meal used in the food effect study per FDA Guidance for the Clinical Pharmacology Section of Labeling; and added a statement that had food had "no clinically meaningful effect" on belzutifan Cmax or AUC. - Revised Specific Populations to add "Patients who are poor metabolizers of UGT2B17 and CYP2C19 had higher belzutifan AUC *[see Clinical Pharmacology (12.5)]*"; and added additional detail on race, ethnicity, and renal and hepatic impairment. - Revised the Drug Interactions Studies to remove (b) (4) [redacted] and added clinically relevant information for these and other *Transporter systems.*
12. Clinical Pharmacology	**12.5 Pharmacogenomics** **…**	FDA revised as follows: - To provide accurate increases in exposure for UGT2B17, CYP2C19, or dual UGT2B17 and CYP2C19 poor metabolizers

		- To provide clear definitions and alleles associated with each clinically relevant metabolizer category described in this subsection.
13. Nonclinical Toxicology	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** **…**	FDA revised to add findings from repeat-dose toxicity studies; and removed (b) (4) to include only clinically significant animal data necessary for safe and effective use of belzutifan in humans not incorporated in other sections of labeling.
14. Clinical Studies	…	FDA revised as follows: - Added "Enrolled patients had other VHL-associated tumors including CNS hemangioblastomas and pNET. CNS hemangioblastoma and pNET in these patients were diagnosed based on the presence of at least one measurable solid tumor in brain/spine and pancreas, respectively". - Added "3.3% were Black or African-American, 1.6% were Asian, and 1.6% were Native Hawaiian or other Pacific Islander" to study demographic information. - Deleted (b) (4) - Removed (b) (4)

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		[redacted] (b) (4) - Removed [redacted] (b) (4) - Removed [redacted] (b) (4) - Revised the efficacy results for pNET and CNS hemangioblastomas to reflect FDA review of measurable patients and available evidence. - Removed [redacted] (b) (4) - Added "Decreases in size of CNS hemangioblastoma-associated peri-tumoral cysts and syringes were observed."
16. How Supplied/Storage and Handling	…	FDA added ("plain on the other side") to tablet description, "tablets with child-resistant closure" (bottle description), and "The bottle also contains two desiccant canisters. Do not eat."
17. Patient Counseling Information	…	FDA revised as follows to align with revisions in other sections of labeling: - For anemia, removed [redacted] (b) (4) and added "may require blood

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		transfusions". - For hypoxia, added "severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization". - For embryo-fetal toxicity, revised to advise females to inform their healthcare provider of known or suspected pregnancy, to use effective "non-hormonal" contraception. - For infertility, added "females" to this counseling topic. - Added the entire Lactation counseling topic.

15 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

The FDA's Assessment:

No REMS was required for this application.

16 POSTMARKETING REQUREMENTS AND COMMITMENT

The FDA's Assessment:

BACKGROUND:

On August 5, 2021, the FDA requested the Sponsor provide timeline proposals for three PMRs and three PMCs with respect to the belzutifan original NDA 215383. A response was provided to the Agency on August 6, 2021.

On August 10, 2021, FDA provided additional comments on the timetables related to the PMRs and PMCs. The Agency requested a response by 4 pm on August 10, 2021.

Reference is made to the teleconference between FDA and Merck on August 10, 2021, in which label and PMR/PMC related topics were discussed. FDA clarified that dose modifications for belzutifan should be amended in PMR/PMC-related study protocols which investigate localized VHL disease associated tumors.

AGENCY COMMENT #1:

PMR #1: 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.

Draft Protocol Submission: MM/YYYY
Final Protocol Submission: MM /YYYY
Interim Report Submission #1: MM/YYYY
Interim Report Submission #2: MM/YYYY
Interim Report Submission #3: MM/YYYY
Trial Completion: MM /YYYY
Final Report Submission: MM /YYYY

FDA additional comments dated 10-AUG-2021:

Dose modifications for belzutifan should be amended in all the clinical protocols to be consistent with the label.

These data should be collected proactively, and CRF amended as needed, to specifically capture the elements outlined. Any further enrollment should be based on amended protocol that is consistent with labeling recommendations

FDA additional comments dated 11-AUG-2021:

Ensure dates are accurate. Interim Reports is dated before the final protocol submission.

COMPANY RESPONSE:

Upon FDA's additional comments, the Sponsor proposes the following timetable for PMR#1:

Draft Protocol Submission:	12/2021
Final Protocol Submission:	04/2022
Interim Report Submission #1:	05/2022
Interim Report Submission #2:	05/2023
Interim Report Submission #3:	05/2024
Trial Completion:	06/2026
Final Report Submission:	12/2026

The Sponsor is currently conducting an interim database lock of Study 004 in Q3 2021 and plans to utilize data from this database lock for the interim report submission #1 under the PMR. Future report submissions following the annual interval will be made in January of each year.

Per discussion with the Agency on 10-AUG-2021, the Sponsor will amend PMR/PMC-related study protocols which investigate localized VHL disease associated tumors. Specifically, the Sponsor will amend the Study 004 protocol to include the latest dose modification guidance to be consistent with the approved labeling recommendation. The draft protocol and final protocol submission dates have been updated.

Response to FDA comment dated 11-AUG-2021:
The Sponsor has modified the interim report submission dates to be in May, annually. Please note that PMC #1 interim report milestone dates have been aligned with the latest proposal outlined in PMR #1.

AGENCY COMMENT #2:

PMR #2: Conduct a carcinogenicity study in mice to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

Draft Protocol Submission: MM/YYYY
Final Protocol Submission: MM /YYYY
Study Completion: MM /YYYY
Final Report Submission: MM /YYYY

FDA additional comments dated 10-AUG-2021:

The final report is generally submitted six months after the study has completed. Consider revising the final report submission date to 10/2025 or provide justification for the extension.

COMPANY RESPONSE:

The Sponsor agrees with the PMR description and proposes the following timetable for PMR #2. The detailed justification is provided below.

Draft Protocol Submission: 01/2023
Final Protocol Submission: 04/2023
Study Completion: 04/2025
Final Report Submission: 04/2026

Note: Since the rat carcinogenicity study is rate limiting, the carcinogenicity study in TG rasH2 mice will be conducted within the same time frame as the rat study (see rationale for PMR #3 below).

Detailed justification/explanation:

The sponsor proposes to retain the previously communicated timeline with the requested justification. For clarification, "Study Completion" is defined as the end of the in-life phase of the study. Please note the 2-year rat carcinogenicity study is the largest routine nonclinical safety study conducted with extensive and resource intensive evaluation of ~600 rats. The activities requiring one year to generate the final report for submission will include, but are not limited to, the following:

- Comprehensive histopathology slide preparation (~60 tissues/animal)
- Histopathology primary evaluation
- Pathology peer review

- Statistical analysis
- Quality Assurance review
- Report authoring, review, and finalization

Since the rat carcinogenicity study is rate limiting, the carcinogenicity study in TG rasH2 mice will be conducted within the same time frame as the rat carcinogenicity study.

AGENCY COMMENT #3:

PMR #3: Conduct a carcinogenicity study in rats to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

Draft Protocol Submission: MM/YYYY
Final Protocol Submission: MM /YYYY
Study Completion: MM /YYYY
Final Report Submission: MM /YYYY

FDA additional comments dated 10-AUG-2021:

The final report is generally submitted six months after the study has completed. Consider revising the final report submission date to 10/2025 or provide justification for the extension.

COMPANY RESPONSE:

The Sponsor agrees with the PMR description, and proposes the following timetable for PMR #3. The detailed justification is provided below.

Draft Protocol Submission: 01/2023
Final Protocol Submission: 04/2023
Study Completion: 04/2025
Final Report Submission: 04/2026

Note: Timelines outlined above are predicated on the need to conduct repeat-dose toxicokinetic and dose range finding studies in Wistar Hannover (WH) rats with belzutifan before submitting a carcinogenicity protocol for SPA. The Sponsor plans to use the WH rat strain due to experience in this strain as well as improved survival (thereby reducing animal numbers required) compared to Sprague-Dawley (SD) rat strain [references 1 and 2]. Provided systemic exposure to belzutifan in WH rats is demonstrated to be comparable or higher than in SD rats at the maximum feasible dose, a 3-month toxicity study in WH rats will be conducted prior to the SPA submission.

Detailed justification/explanation:

The sponsor proposes to retain the previously communicated timeline with the requested justification. For clarification, “Study Completion” is defined as the end of the in-life phase of the study. Please note the 2-year rat carcinogenicity study is the largest routine nonclinical safety study conducted with extensive and resource intensive evaluation of ~600 rats. The

activities requiring one year to generate the final report for submission will include, but are not limited to, the following:

- Comprehensive histopathology slide preparation (~60 tissues/animal)
- Histopathology primary evaluation
- Pathology peer review
- Statistical analysis
- Quality Assurance review
- Report authoring, review, and finalization

References:

1. Horn, M. White Paper: The Wistar Hannover rat for carcinogenicity studies - a more effective model. Envigo, September 2018.
2. Weber K. Differences in Types and Incidence of Neoplasms in Wistar Han and Sprague-Dawley Rats. Toxicol Pathol. 2017 Jan;45(1):64-75.

AGENCY COMMENT #4:

PMC #1: Provide an analysis for the overall response rate and duration of response in all patients and in the subgroups of patients with partial or complete VHL gene deletion, CNS hemangioblastoma, and pNET enrolled in Study MK-6482-004 annually for five years. The study reports should include the number of patients who undergo surgical intervention and/or procedures for renal cell carcinoma (RCC) and/or non-RCC tumors and who develop metastatic RCC.

Interim analysis #1: MM/YYYY
Interim Analysis #2: MM/YYYY
Interim Analysis #3: MM/YYYY
Interim Analysis #4: MM/YYYY
Study Completion: MM /YYYY
Final Report Submission: MM /YYYY

Provide the datasets with the final report.

FDA additional comments dated 10-AUG-2021:

Further enrollment should be based on amended protocol that is consistent with labeling recommendations.

COMPANY RESPONSE:

The Sponsor agrees with the PMC description, and proposes the following timetable for the PMC #1:

Interim analysis #1: 01/2022
Interim Analysis #2: 01/2023
Interim Analysis #3: 01/2024
Interim Analysis #4: 01/2025
Trial Completion: 06/2026
Final Report Submission: 12/2026

The Sponsor is currently making an interim database lock of Study 004 in Q3 2021 and plans to utilize data from this database lock for the first interim report #1 under the PMC. Future report submissions following the annual interval will be made in January of each year.

The Study 004 has been fully enrolled. The Sponsor will amend the Study 004 protocol to incorporate the dose modification guidance in the final approved label. In addition, under PMC #2, the Sponsor plans to add another Cohort (B1 - VHL disease associated localized tumors) in

the MK-6482-015 study for which dose modification will be consistent with the approved labeling.

AGENCY COMMENT #5:

PMC #2: Conduct a clinical trial evaluating overall response rate, and duration of response, to further characterize the efficacy and clinical benefit of belzutifan in patients with VHL disease-associated non-RCC tumors, including an adequate number of patients and representation of tumor types, with a minimum of 30 patients in the following subgroups: (1) Pheochromocytoma/paraganglioma and (2) PNET. Characterize response rate and duration of response for at least 24 months from the onset of response.

Draft Protocol Submission: MM/YYYY
Final Protocol Submission: MM /YYYY
Study Completion: MM /YYYY
Final Report Submission: MM /YYYY

Provide the datasets with the final report.

FDA additional comments dated 10-AUG-2021:

Amendments to the protocol are necessary and will need to be reviewed by the Agency. Amendment should include radiologic diagnostic/assessment criteria and review charters for each non-RCC tumor. Patients should be screened appropriately for other concomitant non-RCC tumors at the time of enrollment. Any further enrollment on clinical trials should be based on amended protocol that is consistent with labeling recommendations

COMPANY RESPONSE:

The Sponsor agrees with the PMC description, and proposes the following timetable for the PMC #2. The Sponsor will amend the Study 015 protocol to include specific items as described below.

Draft Protocol Submission: 01/2022
Final Protocol Submission: 05/2022
Trial Completion: 02/2026
Final Report Submission: 08/2026

The Sponsor plans to expand the existing MK-6482-015 study with a localized VHL disease-associated tumor cohort (Cohort B1) to further characterize the efficacy and clinical benefit of belzutifan in localized VHL disease-associated non RCC tumors which will include a minimum of 30 pheochromocytoma/paraganglioma (PPGL) and 30 pancreatic NET (pNET) patients. The new

Cohort B1 under MK-6482-015 serves as the basis for fulfilling PMC #2. The relevant PMC milestones are proposed above.

The amendment will include information on radiologic diagnostic/assessment criteria for non RCC tumors as requested. Patients will be appropriately screened for concurrent non RCC tumors at the time of enrollment. The VHL disease localized tumor cohort (B1) to satisfy PMC#2 will include a dose modification guidance that is consistent with labeling recommendations. Also refer company response to Agency's Comment #6 for ongoing cohorts A1 and A2 (PPGL and pNET) in the advanced/metastatic tumor setting.

AGENCY COMMENT #6:

PMC #3: Submit the final objective response rate and duration of response to further characterize efficacy in the subgroup of patients with VHL disease from the phase II clinical trial of belzutifan for treatment of advanced and metastatic pheochromocytoma/ paraganglioma or pancreatic neuroendocrine tumor (MK-6482-015, NCT04924075).

Final Protocol Submission: MM /YYYY
Study Completion: MM /YYYY
Final Report Submission: MM /YYYY

Provide the datasets with the final report.

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

FDA additional comments dated 10-AUG-2021:

Any further enrollment on clinical trials should be based on amended protocol that is consistent with labeling recommendations. Amendments to the protocol are necessary and will need to be reviewed by the Agency.

COMPANY RESPONSE:

The Sponsor proposed follow timetable for the PMC #3:

Final Protocol Submission: 05/2022
Trial Completion: 02/2026
Final Report Submission: 08/2026

The Sponsor will include a dose modification table that is consistent with approved label for the proposed new cohort B1, namely the VHL disease associated localized tumors to support PMC#2 in MK-6482-015 study as part of an amendment as per the timelines provide above.

As discussed during the labeling teleconference meeting on August 10, 2021 with the FDA, the Sponsor would like to retain the dose modification table as approved for advanced/metastatic PPGL and pNET cohorts (Cohort A1 and A2) in MK-6482-015 study which is consistent with all clinical protocols assessing belzutifan in advanced/metastatic tumors that are ongoing. The Sponsor considers that the risk benefit assessment differs for metastatic cancers in comparison to VHL disease associated localized tumors.

17 DIVISION DIRECTOR (DHOT) (NME ONLY)

X

John K. Leighton

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18 DIVISION DIRECTOR (OCP)

X

Nam Atiqur Rahman, PhD

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19 DIVISION DIRECTOR (OB)

X

Shenghui Tang, PhD

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20 DIVISION DIRECTOR (CLINICAL)

X

Amna Ibrahim, MD

21 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

Julia Beaver, MD

22 APPENDICES

22.1 References

The Applicant's References:

[1] Linehan WM, Zbar B, Klausner DR. The metabolic & molecular bases of inherited disease. 8th ed. Vol. 1. Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, Vogelstein B, editors. New York (NY): McGraw-Hill; c2001. Chapter 41, Renal carcinoma; p. 907-29.

[2] Linehan WM, Lerman MI, Zbar B. Identification of the von Hippel-Lindau (VHL) gene: its role in renal cancer. JAMA. 1995 Feb 15;273(7):564-70.

[3] Clifford SC, Maher ER. von Hippel-Lindau disease: clinical and molecular perspectives. Adv Cancer Res. 2001:85-105.

[4] Maher ER, Kaelin WG Jr. von Hippel-Lindau disease. Medicine. 1997;76(6):381-91.

[5] Kaelin WG Jr. Molecular basis of the VHL hereditary cancer syndrome. Nat Rev Cancer. 2002 Sep;2:673-82.

[6] Genetics Home Reference [Internet]. Bethesda (MD): National Library of Medicine (NLM); Von Hippel-Lindau syndrome; 2020 Jan 21 [cited 2020 Jan 22]; [about 8 screens]. Available from: https://ghr.nlm.nih.gov/condition/von-hippel-lindau-syndrome.

[7] Duffey BG, Choyke PL, Glenn G, Grubb RL, Venzon D, Linehan WM, et al. The relationship between renal tumor size and metastases in patients with von Hippel-Lindau disease. J Urol. 2004 Jul;172:63-5.

[8] Li M, Kim WY. Two sides to every story: the HIF-dependent and HIF-independent functions of pVHL. J Cell Mol Med. 2011;15(2):187-95.

[9] Walther MM, Choyke PL, Weiss G, Manolatos C, Long J, Reiter R, et al. Parenchymal sparing surgery in patients with hereditary renal cell carcinoma. J Urol. 1995 Mar;153:913-6.

[10] Kwon T, Jeong IG, Pak S, You D, Song C, Hong JH, et al. Renal tumor size is an independent prognostic factor for overall survival in von Hippel-Lindau disease. J Cancer Res Clin Oncol. 2014;140:1171-7.

[11] Herring JC, Enquist EG, Chernoff A, Linehan WM, Choyke PL, Walther MM. Parenchymal sparing surgery in patients with hereditary renal cell carcinoma: 10-year experience. J Urol. 2001 Mar;165:777-81.

[12] Ploussard G, Droupy S, Ferlicot S, Ples R, Rocher L, Richard S, et al. Local recurrence after nephron-sparing surgery in von Hippel-Lindau disease. Urology. 2007;70(3):435-9.

[13] Reed AB, Parekh DJ. Surgical management of von Hippel - Lindau disease: urologic considerations. Surg Oncol Clin N Am. 2008;18:157-74.

[14] van Leeuwaarde RS, Ahmad S, Links TP, Giles RH. GeneReviews [Internet]. Adam MP, Ardinger HH, Pagon RA, editors. Seattle (WA): University of Washington; c1993-2020. Von Hippel-Lindau syndrome; 2000 May 17 [updated 2018 Sep 6; cited on 2020 Jan 27]; 32 p. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1463/.

[15] Johnson A, Sudarshan S, Liu J, Linehan WM, Pinto PA, Bratslavsky G. Feasibility and outcomes of repeat partial nephrectomy. J Urol. 2008 Jul;180:89-93.

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[16] Jonasch E, McCutcheon IE, Waguespack SG, Wen S, Davis DW, Smith LA, et al. Pilot trial of sunitinib therapy in patients with von Hippel-Lindau disease. Ann Oncol. 2011 Dec;22(12):2661-6.

[17] Stamatakis L, Shuch B, Singer EA, Nix J, Truong H, Friend JC, et al. Phase II trial of vandetanib in Von Hippel-Lindau-associated renal cell carcinoma [abstract]. Presented at: 2013 American Society of Clinical Oncology (ASCO) Annual Meeting; 2013 May 31-Jun 4; Chicago, IL. J Clin Oncol. 2013;31(15 suppl). Abstract no. 4584.

[18] Jonasch E, McCutcheon IE, Gombos DS, Ahrar K, Perrier ND, Liu D, et al. Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, phase 2 trial. Lancet Oncol. 2018 Oct;19:1351-9.

[19] Keutgen XM, Hammel P, Choyke PL, Libutti SK, Jonasch E, Kebebew E. Evaluation and management of pancreatic lesions in patients with von Hippel-Lindau disease. Nat Rev Clin Oncol. 2016 Sep;13:537-49.

[20] Lonser RR, Butman JA, Huntoon K, Asthagiri AR, Wu T, Bakhtian KD, et al. Prospective natural history study of central nervous system hemangioblastomas in von Hippel-Lindau disease. J Neurosurg. 2014 May;120:1055-62.

[21] Hajjaj A, van Overdam KA, Oldenburg RA, Koopmans AE, van den Ouweland AMW, de Klein A, et al. Retinal haemangioblastomas in von Hippel-Lindau germline mutation carriers: progression, complications and treatment outcome. Acta Ophthalmol. In press 2020.

[22] Haase VH. Regulation of erythropoiesis by hypoxia-inducible factors. Blood Rev. 2013;27:41-53.

[23] Ball MW, An JY, Gomella PT, Gautam R, Ricketts CJ, Vocke CD, et al. Growth rates of genetically defined renal tumors: implications for active surveillance and intervention. J Clin Oncol. 2020;38(11):1146-53.

[24] Peng X, Chen J, Wang J, Peng S, Liu S, Ma K, et al. Natural history of renal tumours in von Hippel-Lindau disease: a large retrospective study of Chinese patients. J Med Genet. 2019;56:380-7.

[25] Schuhmacher P, Kim E, Hahn F, Sekula P, Jilg CA, Leiber C, et al. Growth characteristics and therapeutic decision markers in von Hippel-Lindau disease patients with renal cell carcinoma. Orphanet J Rare Dis. 2019;14:235.

[26] Jilg CA, Neumann HP, Glasker S, Schafer O, Ardelt PU, Schwardt M, et al. Growth kinetics in von Hippel-Lindau-associated renal cell carcinoma. Urol Int. 2012;88:71-8.

[27] Liumbruno GM, Bennardello F, Lattanzio A, Piccoli P, Rossetti G. Recommendations for the transfusion management of patients in the peri-operative period. II. The intra-operative period. Blood Transfus. 2011;9:189-217.

[28] Fadahunsi AT, Sanford T, Linehan WM, Pinto PA, Bratslavsky G. Feasibility and outcomes of partial nephrectomy for resection of at least 20 tumors in a single renal unit. J Urol. 2011 Jan;185:49-53.

[29] Liu NW, Khurana K, Sudarshan S, Pinto PA, Linehan WM, Bratslavsky G. Repeat partial nephrectomy on the solitary kidney: surgical, functional and oncological outcomes. J Urol. 2010 May;183:1719-24.

The FDA's References:

Lonser RR, Glenn GM, Walther M, Chew EY, Libutti SK, Linehan WM, Oldfield EH. von Hippel-Lindau disease. Lancet. 2003;361(9374):2059-67.

Carrion, D. M., Linares-Espinós, E., Ríos González, E., Bazán, A. A., Alvarez-Maestro, M., & Martinez-Pineiro, L. Invasive management of renal cell carcinoma in von Hippel-Lindau disease. Central European journal of urology. 2020; 73(2), 167–172.

Gruber M, Hu CJ, Johnson RS, Brown EJ, Keith B, Simon MC. Acute postnatal ablation of Hif-2alpha results in anemia. Proc Natl Acad Sci USA. 2007;104:2301–6.

Peng J, Zhang L, Drysdale L, Fong GH. The transcription factor EPAS-1/hypoxia-inducible factor 2α plays an important role in vascular remodeling. Proc Natl Acad Sci USA. 2000;97:8386-8391.

Tian H, Hammer RE, Matsumoto AM, Russell DW, McKnight SL. The hypoxia-responsive transcription factor EPAS1 is essential for catecholamine homeostasis and protection against heart failure during embryonic development. Genes Dev. 1998;12:3320-3324.

Compernolle V, Brusselmans K, Acker T, Hoet P, Tjwa M, Beck H, Plaisance S, Dor Y, Keshet E, Lupu F, et al. Loss of HIF-2α and inhibition of VEGF impair fetal lung maturation, whereas treatment with VEGF prevent fatal respiratory distress in premature mice. Nat Med. 2002;8:702-710.

Tarade D, Ohh M. The HIF and other quandaries in VHL disease. Oncogene. 2018 Jan 11;37(2):139-147.

22.2 Financial Disclosure

The Applicant's Position:

Disclosure of financial interests of the investigators who conducted the MK-6482-001 and MK-6482-004 studies are described in the current submission, including statements of due diligence (FDA forms 3454) in cases where the Applicant was unable to obtain a signed form from the investigator.

The FDA's Assessment:

Covered Clinical Study (Name and/or Number):* MK-6482-001 and MK-6482-004

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 227		

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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): 3		
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: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: Merck		
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 reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the Applicant, and confirmed/edited by the FDA.

22.3 Nonclinical Pharmacology/Toxicology

The Applicant's Position:

All nonclinical pharmacology/toxicology information is included in Section 5 above.

22.4 OCP Appendices (Technical Documents Supporting OCP Recommendations)

22.4.1 Pharmacometrics Review focusing on Population Pharmacokinetics

Review Summary

In general, the Applicant's population PK analysis is considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. Specifically, the developed model was used to support the current submission as outlined in Table 45.

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Table 45: Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	(b) (4)	The statements are acceptable in general. The following is recommended: There was no clinically significant differences in the pharmacokinetics of betzutifan based on age (19 to 84 years(, sex, ethnicity (non-Hispanic, Hispanic), race (White, Black, Asian, Pacific Islander), body weight (42 to 166 kg), mild to moderate renal impairment, or mild hepatic impairment (total bilirubin ≤ULN with AST>ULN or total bilirubin > ULN to 1.5 times ULN with any AST). The effect of severe renal impairment and moderate to severe hepatic impairment (total bilirubin >1.5 times ULN and any AST) have not been studied.

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		(b) (4)	
	Extrinsic factor	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.	Generally acceptable.
Derive exposure metrics for Exposure-response analyses	AUCss		Model predicted.
Predict exposures at alternative dosing regimen	NA		NA

Aim

1) estimate the population PK parameters that define the exposure of oral MK-6482 in healthy subjects and patients with renal cell carcinoma (RCC), Von Hippel-Lindau disease associated RCC (VHL-RCC), or solid tumor (ST);
2) evaluate the impact of intrinsic/extrinsic factors on PK characteristics of MK-6482;
3) explore the E-R relationship between MK-6482 exposure and selected efficacy endpoints based on data from all patients from Study MK-6482-004 and patients with RCC (from all dose levels) from Study MK-6482-001 (other ST types were excluded), for whom exposure could be estimated; and
4) explore the E-R relationship between MK-6482 exposure and selected safety endpoints based on data from Study MK-6482-004 and Study MK-6482-001, for whom exposure could be estimated.

Data

The population PK analysis dataset included 5291 measurable PK observations from 239 subjects. Seven continuous covariates (age, body weight, BMI, height, eGFR, AST and ALT) and ten categorical covariates (sex, race, ethnicity, disease state, Food, formulation, CYP2C19 phenotype, UGT2B17 phenotype, hepatic dysfunction (NCI) and renal impairment) were considered for the population PK analysis. Baseline values of continuous and categorical covariates are summarized in Table 46 and Table 47.

Model

The plasma concentration of MK-6482 following oral administration was well-characterized by a 2-compartment model with first order absorption and elimination. Body weight had a significant impact on MK-6482 clearances and volumes. CL/F and Q/F were scaled by the same exponent, as were V2/F and V3/F. Body weight, as well as a food effect on KA, had to be included in the base model as structural covariates. Additional covariates including UGT2B17 polymorphism, CYP2C19 polymorphism, age, and formulation were selected in the final population PK model. The final model parameter estimates are shown in Table 48. The final model was further assessed via goodness-of-fit indicators and prediction performance (e.g., plots, see Figure 20). Body weight at the 5th and 95th percentiles (48 and 118 kg) of the observed range positively correlated with a -24% to +36% change in apparent clearances and a -37% to +65% change in apparent volumes at the 5th and 95th percentiles compared to subjects with median weight. Age at the 5th and 95th percentiles (26 and 74 years) of the observed range negatively correlated with a +31% to -10% change of CL/F and a +16% to -6% of V2/F. Food led to a reduction of KA of 88%. Formulation B (FMF) led to a 47% lower KA. For the UGT2B17 effect on F, only 2 categories could be distinguished: intermediate/extensive (pooled) vs poor metabolizers. Poor metabolizers had an 11% higher F than intermediate/extensive metabolizers. CYP2C19 poor metabolizers had a 36% lower CL/F than the other categories (which were pooled since their effect on CL/F could not be distinguished based on available data).

Simulations

First, simulations were performed to derive PK parameters. These simulations of SS profiles with a 120-mg QD dosing regimen were based on the demographics of the 61 VHL-RCC patients included in Study 4. The resulting geometric mean values and geometric CV, as well as medians and CV, are presented in Table 49. Second, the effects of each covariate on exposure after treatment with 120 mg QD were calculated individually, with all other covariates fixed to their typical values (as estimated for the reference subject). Continuous covariates were evaluated at the 5th and 95th percentiles of the Study 4 population. Categorical covariate effects were

evaluated for each level. A CYP2C19 poor metabolizer had a 56% higher exposure than a subject in the "extensive" category (pooled category including intermediate, extensive, rapid and ultrarapid metabolizers). A poor UGT2B17 poor metabolizer had a 46% higher exposure than an intermediate or extensive metabolizer. Body weight resulted in +25% and -30% changes in MK-6482 AUCss at the 5th and 95th percentiles of the body weight distribution in all patients enrolled in Study 4. Age resulted in -20% and +17% changes in exposure at the 5th and 95th percentiles of the age distribution. Formulation and food only affected the absorption rate of MK-6482 and thus did not influence exposure at steady state. Third, simulations were performed to assess the impact of missed or delayed doses on MK-6482 exposure. 72-hour concentration-time profiles were simulated with observations at the following time points: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 18, 24 hours after each dose, and thereafter every 6 hours until the next dose was given. The covariates from the Study 4 population (61 patients) were used 10 times to generate 610 virtual patients. The following dosing scenarios were evaluated:

- Scenario 1: doses at 0 (SS assumed), 24 and 48 hours
- Scenario 2: doses at 0 (SS assumed) and 48 hours; second dose missed
- Scenario 3: doses at 0 (SS assumed), 36 and 48 hours; second dose 12 hours delayed.
- Scenario 4: doses at 0 (SS assumed), 40 and 48 hours; second dose 16 hours delayed
- Scenario 5: doses at 0 (SS assumed), 42 and 48 hours; second dose 18 hours delayed
- Scenario 6: doses at 0 (SS assumed), 45 and 48 hours; second dose 21 hours delayed

AUC, Cmax and Cmin by scenario are shown in Table 50. Based on these simulations, with a single missed dose over a period of 3 days, the average daily exposure (AUC0-24h) over a 3-day duration is reduced by 30% compared to the scenario without a missed dose (11.6 vs 16.5 µg*h/mL). The impact of any delayed second (make-up) dose on average AUC0-24h over 3 days appears small; however, Cmax is almost 50% higher in scenario 6 compared to QD dosing (scenario 1), and Cmin of scenario 6 is approximately 1/3rd of the steady-state Cmin with QD dosing (scenario 1).

Table 46: Summary of Baseline Continuous Covariates.

Covariate	Study	Mean	Stdev	Q1	Median	Q3	Range	N	Missing
Age (years)	All	52.3	14.5	43	55	62.5	19 - 84	239	0
	1	61.5	11.6	56	62	72	27 - 84	95	0
	2	35.2	7.3	31.5	35	42	22 - 44	16	0
	4	41	13.5	29	41	51	19 - 66	61	0
	6	42.2	7.5	36.5	45.5	47	27 - 51	18	0
	7	57.9	3.8	56	58	60	50 - 65	49	0
Body weight (kg)	All	77.6	22.9	61.5	73.6	90.2	42.1 - 165.8	239	0
	1	88.7	22.8	73	86.6	100.3	42.1 - 165.8	95	0
	2	70.4	10.4	64.9	67.6	77.1	55.1 - 90.1	16	0
	4	79.7	23.4	63.7	74.4	89.4	47.7 - 147.6	61	0
	6	76.8	11.4	67	77.7	83.6	57.8 - 102	18	0
	7	56.1	9	49	54.1	62.4	43.1 - 76.9	49	0
BMI (kg/m^2)	All	27.1	6.1	22.7	26.4	30	15.4 - 52	239	2
	1	29.1	6.1	25.2	28.4	32.8	15.4 - 51.7	95	0
	2	25.9	3.5	23	25.4	28.6	21.3 - 31.7	16	0
	4	27.8	7.4	23	26.3	30.4	17.2 - 52	61	2
	6	28.4	2.3	27.1	29	29.6	21.9 - 31.7	18	0
	7	22.4	2.8	20.5	21.9	24	17.8 - 29.4	49	0
Height (cm)	All	168.2	11.2	159	167.6	176	143.5 - 196.5	239	2
	1	173.9	10.1	168.3	175.3	180.3	143.5 - 196.5	95	0
	2	164.9	8	158.2	166.5	168.6	153.5 - 182	16	0
	4	169.5	11	160.7	169	176.1	148 - 195	61	2
	6	163.7	9.7	155	162.2	169.6	150 - 186	18	0
	7	158.2	5.7	154.8	158.2	162.2	146 - 171	49	0
eGFR ($mL/min/1.73\ m^2$)	All	77.2	26.5	56.6	77.5	92.8	19.6 - 171.2	239	0
	1	65.5	26.9	44.8	59	78.3	19.6 - 171.2	95	0
	2	97.5	14.5	91.2	99.5	106.6	71.8 - 125.8	16	0
	4	79	29.5	52.4	82.8	96	30.5 - 163	61	0
	6	100.4	16.3	87.6	100.3	111.5	77.1 - 130.2	18	0
	7	82.3	13.6	73.7	81.1	89.8	56.8 - 119.8	49	0
AST (U/L)	All	20.7	9.7	15	18	24	5 - 85	239	0
	1	25.2	12.5	18	22	30	5 - 85	95	0
	2	16.3	4.6	13.8	15	18.2	11 - 29	16	0
	4	16.7	6.6	12	15	20	5 - 40	61	0
	6	16.2	4	14	15	17.5	11 - 28	18	0
	7	20.1	4.1	17	19	22	15 - 31	49	0
ALT (U/L)	All	22.1	16.1	12	17	26	5 - 138	239	0
	1	30.5	20	21	26	35	5 - 138	95	0
	2	11.5	3.1	8.8	11	14	7 - 17	16	0
	4	18.6	12.8	11	15	24	5 - 84	61	0
	6	16	7.4	12	13.5	20.2	8 - 39	18	0
	7	16.1	5.2	12	15	17	9 - 34	49	0

Source: 2020-10-27-covariate-statistics.r

Abbreviations: ALT=alanine aminotransaminase; AST=aspartate aminotransaminase; BMI=body mass index; eGFR=estimated glomerular filtration rate; Q=quartile;

Source: Table 5 in the PopPK and ER report 05mssh.

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

Table 47: Summary of Baseline Categorical Covariates.

Covariate	Level	All Studies	Study 1	Study 2	Study 4	Study 6	Study 7
Sex	Male	105 (43.9%)	70 (73.7%)	0 (0%)	32 (52.5%)	3 (16.7%)	0 (0%)
	Female	134 (56.1%)	25 (26.3%)	16 (100%)	29 (47.5%)	15 (83.3%)	49 (100%)
Race	White	171 (71.5%)	86 (90.5%)	9 (56.2%)	55 (90.2%)	8 (44.4%)	13 (26.5%)
	Black	23 (9.6%)	6 (6.3%)	7 (43.8%)	2 (3.3%)	8 (44.4%)	0 (0%)
	Asian	38 (15.9%)	0 (0%)	0 (0%)	1 (1.6%)	1 (5.6%)	36 (73.5%)
	Pacific Islander	1 (0.4%)	0 (0%)	0 (0%)	1 (1.6%)	0 (0%)	0 (0%)
	Multiple/Other	4 (1.7%)	3 (3.2%)	0 (0%)	0 (0%)	1 (5.6%)	0 (0%)
	Missing	2 (0.8%)	0 (0%)	0 (0%)	2 (3.3%)	0 (0%)	0 (0%)
Ethnicity	Not Hispanic	202 (84.5%)	73 (76.8%)	14 (87.5%)	54 (88.5%)	13 (72.2%)	48 (98%)
	Hispanic	34 (14.2%)	20 (21.1%)	2 (12.5%)	6 (9.8%)	5 (27.8%)	1 (2%)
	Missing	3 (1.3%)	2 (2.1%)	0 (0%)	1 (1.6%)	0 (0%)	0 (0%)
Disease State	HV	83 (34.7%)	0 (0%)	16 (100%)	0 (0%)	18 (100%)	49 (100%)
	RCC	74 (31.0%)	74 (77.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	ST	21 (8.8%)	21 (22.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	VHL-RCC	61 (25.5%)	0 (0%)	0 (0%)	61 (100%)	0 (0%)	0 (0%)
Food[1]	Fasted	239 (100%)	95 (100%)	16 (100%)	61 (100%)	18 (100%)	49 (100%)
	Fed	15 (6.3%)	0 (0%)	15 (93.8%)	0 (0%)	0 (0%)	0 (0%)
Formulation[1]	Formulation A (FFP)	190 (79.5%)	95 (100%)	16 (100%)	61 (100%)	18 (100%)	0 (0%)
	Formulation B (FMF)	67 (28.0%)	0 (0%)	0 (0%)	0 (0%)	18 (100%)	49 (100%)
CYP2C19 Phenotype[2]	Poor	19 (7.9%)	3 (3.2%)	1 (6.2%)	1 (1.6%)	1 (5.6%)	13 (26.5%)
	Intermediate	65 (27.2%)	25 (26.3%)	3 (18.8%)	18 (29.5%)	5 (27.8%)	14 (28.6%)
	Extensive	96 (40.2%)	43 (45.3%)	4 (25.0%)	21 (34.4%)	10 (55.6%)	18 (36.7%)

Covariate	Level	All Studies	Study 1	Study 2	Study 4	Study 6	Study 7
	Rapid	42 (17.6%)	17 (17.9%)	4 (25.0%)	15 (24.6%)	2 (11.1%)	4 (8.2%)
	Ultrarapid	6 (2.5%)	3 (3.2%)	1 (6.2%)	2 (3.3%)	0 (0%)	0 (0%)
	Missing	11 (4.6%)	4 (4.2%)	3 (18.8%)	4 (6.6%)	0 (0%)	0 (0%)
UGT2B17 Phenotype[2]	Poor	46 (19.2%)	5 (5.3%)	1 (6.2%)	5 (8.2%)	2 (11.1%)	33 (67.3%)
	Intermediate	98 (41.0%)	44 (46.3%)	5 (31.2%)	27 (44.3%)	10 (55.6%)	12 (24.5%)
	Extensive	84 (35.1%)	42 (44.2%)	7 (43.8%)	25 (41.0%)	6 (33.3%)	4 (8.2%)
	Missing	11 (4.6%)	4 (4.2%)	3 (18.8%)	4 (6.6%)	0 (0%)	0 (0%)
Hepatic Dysfunction (NCI-ODWG)	Normal	226 (94.6%)	89 (93.7%)	15 (93.8%)	57 (93.4%)	18 (100%)	47 (95.9%)
	Mild	12 (5.0%)	5 (5.3%)	1 (6.2%)	4 (6.6%)	0 (0%)	2 (4.1%)
	Moderate	1 (0.4%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal Impairment	Normal	80 (33.5%)	22 (23.2%)	10 (62.5%)	29 (47.5%)	12 (66.7%)	7 (14.3%)
	Mild	104 (43.5%)	42 (44.2%)	6 (37.5%)	16 (26.2%)	6 (33.3%)	34 (69.4%)
	Moderate	52 (21.8%)	30 (31.6%)	0 (0%)	14 (23.0%)	0 (0%)	8 (16.3%)
	Severe	1 (0.4%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Missing	2 (0.8%)	0 (0%)	0 (0%)	2 (3.3%)	0 (0%)	0 (0%)

Source: Source: 2020-10-27-covariate-statistics.r
[1] Information on food and formulation effect was obtained in crossover studies. Therefore, numbers of patients by category can add up to more than the total number of patients, and percentages to more than 100%.
[2] The data included 10 subjects with UGT2B17/CYP2C19 dual PM (poor metabolizer phenotype for both enzymes). All 10 were from Study 7. There were no subjects with dual PM phenotype in patient studies (Study 1 and Study 4).
Abbreviations: FFP=fit-for-purpose formulation; FMF=final market formulation; HV=healthy volunteer; NCI=national cancer institute; ODWG=organ dysfunction working group; RCC=(advanced) renal cell carcinoma; ST=solid tumor (advanced, besides RCC); VHL=Von Hippel-Lindau; VHL-RCC=VHL disease-associated RCC
Note: Details on the levels of categorical covariates, including definition of renal and hepatic impairment (NCI index) categories, can be found in Table 58.

Source: Table 6 in the PopPK and ER report 05mssh.

Table 48: The Final Model Parameter Estimates.

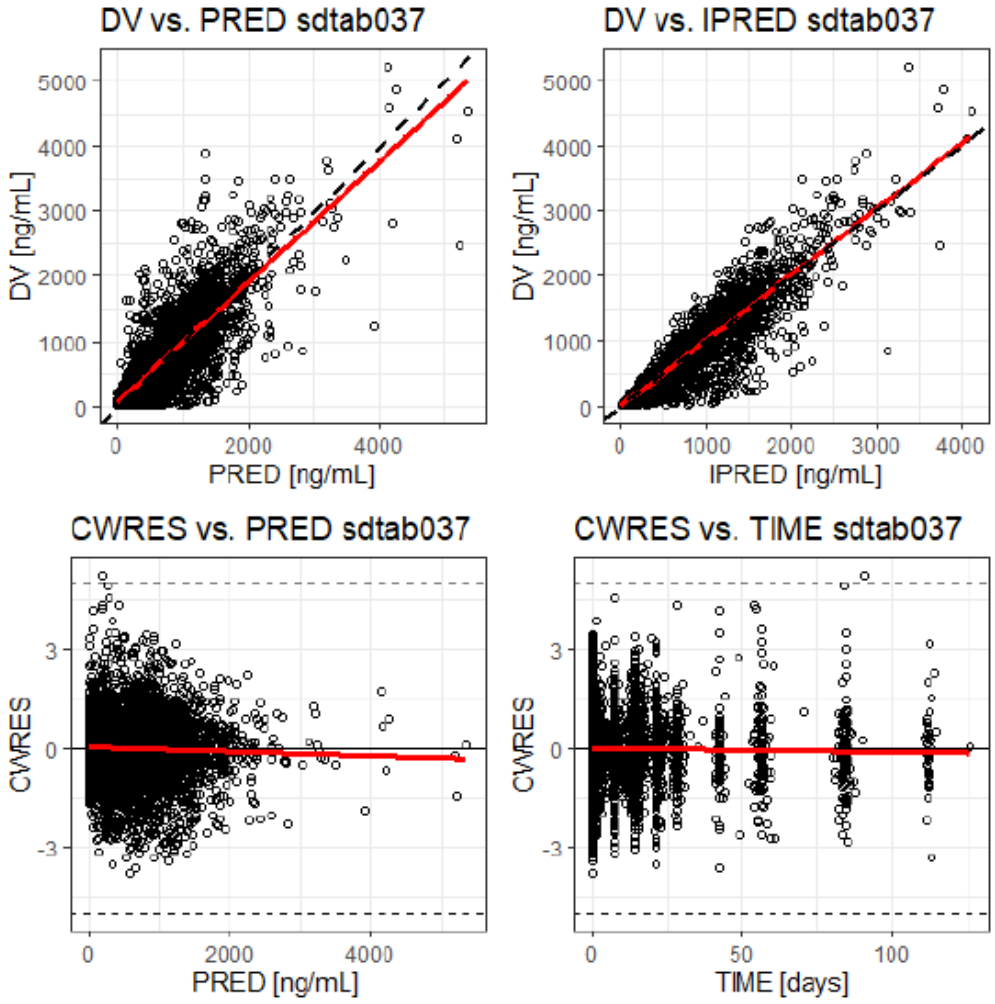
Parameter	Estimate	% Relative S.E.	Asymptotic 95% CI	% Shrinkage
Fixed Effects				
CL/F (L/h)	5.628	3.402	5.253;6.003	--
V2/F (L)	85.4	2.9	80.55;90.26	--
Q/F (L/h)	5.368	14.07	3.888;6.848	--
V3/F (L)	30.38	6.648	26.42;34.34	--
KA (/h)	2.398	7.704	2.036;2.76	--
ALAG (h)	0.164	1.501	0.1592;0.1688	--
KA-FED	-0.8761	7.195	-0.9996;-0.7525	--
CL-WT	0.6453	15.55	0.4486;0.8419	--
V-WT	1.058	3.994	0.9756;1.141	--
CL-UGT2B17 extensive metabolizers	0.3908	19.17	0.244;0.5376	--
CL-UGT2B17 poor metabolizers	-0.2422	19.54	-0.335;-0.1495	--
CL-CYP2C19 poor metabolizers	-0.3601	14.96	-0.4657;-0.2546	--
F-UGT2B17 poor metabolizers	0.1102	22.78	0.06102;0.1595	--
KA-FORM	-0.4739	34.48	-0.7941;-0.1537	--
V-AGE	-0.205	23.82	-0.3007;-0.1093	--
CL-AGE	-0.3606	22.57	-0.52;-0.2011	--
Random Effects				
IIV on CL/F	0.1468	11.43	0.1139;0.1797	1.6
IIV on V2/F	0.01258	24.92	0.006436;0.01873	34
IIV on V3/F	0.1918	37.21	0.05192;0.3317	32
IIV on KA	1.148	16.38	0.7797;1.517	18
Residual Error				
RES HV	0.2597	4.771	0.2354;0.284	--
RES PAT	0.2916	3.287	0.2728;0.3104	--
EPS	1 FIX	0	-	5.2

Source: run-mk6482-ppk-037.html
Abbreviations: ALAG=lag time; CI=confidence interval; CL=clearance; CL-AGE=age effect on CL (exponent); CL/F=apparent clearance; CL-CYP2C19=CYP2C19 phenotype effect on CL (coefficient); CL-UGT2B17=UGT2B17 phenotype effect on CL (coefficient); CL-WT=body weight effect on clearances (exponent); CV=coefficient of variation; EPS=ε (random error); F=bioavailability; F-UGT2B17=UGT2B17 phenotype effect on F (coefficient); HV=healthy volunteer; IIV=inter-individual variability; KA=absorption rate constant; KA-FED=food effect on KA (coefficient); KA-FORM: formulation effect on KA (coefficient); PAT=patient; Q/F=apparent inter-compartmental clearance; RES=proportional residual error; SE=standard error; V2/F=apparent central volume of distribution; V3/F=apparent peripheral volume of distribution; V-AGE=age effect on central volume of distribution (exponent); V-WT: body weight effect on distribution volumes (exponent); WT=body weight; η=difference between population and individual parameter
Note: The following η-correlations were estimated: CL/F-V2/F: 0.40; CL/F-V3/F: 0.54; V2/F-V3/F: 0.38
Equations for the PK parameters were as follows:
CL/F=CL/Fpop * (WT/73.64)^CL-WT * (1+CL-UGT2B17P) * (1+CL-CYP2C19P) * (AGE/55)^CL-AGE * η1
V2/F=V2/Fpop * (WT/73.64)^V-WT * (AGE/55)^V-AGE * η2
Q/F=Q/Fpop * (WT/73.64)^CL-WT
V3/F=V3/Fpop * (WT/73.64)^V-WT * η3
F=1 * (1+F-UGT2B17P)
KA=KApop * (1+ KA-FED) * (1+KA-FORM) * η4

Note that subject (b) (6) was removed from the PopPK analysis due to time of first dose missing.

Source: Table 10 in the PopPK and ER report 05mssh.

Figure 20: Goodness of Fit Plots for the Final Model.



Source: 2020-10-19-gof-plots-mk6482-ppk.r
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.
Abbreviations: CWRES=conditional weighted residuals; DV=dependent variable (usually observation); GOF=goodness of fit; IPRED=individual predictions; PRED=population predictions

Source: Figure 5 in the PopPK and ER Report 05mssh.

Table 49: Derived Population PK parameters for VHL-RCC Patients (120 mg QD)

Parameter	Formulation	Geometric Mean	Geometric CV%	Arithmetic Mean	Standard Deviation
CL/F (L/h)	FFP, FMF	7.25	51.36	8.15	4.17
Vd/F (L)	FFP, FMF	129.5	35.18	137.62	51.45
KA (1/h)	FFP	2.51	145.43	4.40	5.83
	FMF	1.32	145.43	2.32	3.06
AUC0-24h (µg.hr/mL)	FFP, FMF	16.71	52.34	18.86	9.89
Cmin (ng/mL)	FFP	306.66	92.3	406.24	321.82
	FMF	318.18	91.12	418.7	326.31
Cmax (ng/mL)	FFP	1362.54	39.77	1463.81	564.83
	FMF	1263.72	42.2	1368.93	559.18
Tmax (h)	FFP	1.42	69.72	1.73	1.15
	FMF	2.05	69.56	2.48	1.57
t1/2 alpha (h)	FFP, FMF	2.60	37.28	2.77	0.99
t1/2 beta (h)	FFP, FMF	14.34	36.82	15.29	5.68
t1/2 eff (h)	FFP, FMF	12.39	41.61	13.42	5.59
t1/2 abs (h)	FFP	0.28	145.43	0.48	0.60
	FMF	0.52	145.43	0.91	1.15

Source: 2020-10-20-cmax-tmax-simulations.r, 2020-12-15-cmax-tmax-simulations-new-formulation.r
Abbreviations: AUC0-24h=area under the concentration vs time curve for a 24-hour interval, CL=clearance; CL/F=apparent clearance; Cmax=peak plasma concentration, Cmin=trough concentration; CV=coefficient of variation, F=bioavailability; FFP=fit-for-purpose formulation; FMF=final market formulation; KA=absorption rate constant; PK=pharmacokinetic; t1/2=half-life; t1/2 abs=absorption half-life; t1/2 alpha=initial elimination half-life;

Source: Table 15 in the PopPK and ER report 05mssh.

Table 50: Exposure Comparison between Missed and Delayed Dosing Scenarios.

Scenario	Dosing Times [h]	AUC0-72h [µg*h/mL] median	AUC0-72h [µg*h/mL] p5-p95	Average AUC0-24h [µg*h/mL] median	Average AUC0-24h [µg*h/mL] p5-p95	Cmax [ng/mL] median	Cmax [ng/mL] p5-p95	Cmin [ng/mL] median	Cmin [ng/mL] p5-p95
#1: Regular QD dosing	0, 24, 48 h	49.5	21.1 - 107.1	16.5	7.0 - 35.7	1290.1	663.2 - 2271.7	306.2	84.7 - 955.3
#2: Missed dose	0, 48 h	34.9	13.2 - 85.0	11.6	4.4 - 28.3	1093.1	550.4 - 1875.9	96.0	11.0 - 531.2
#3: Delayed 2nd dose (by 12 h)	0, 36, 48 h	48.3	20.8 - 103.8	16.1	6.9 - 34.6	1496.0	783.2 - 2532.4	163.8	36.4 - 644.2
#4: Delayed 2nd dose (by 16 h)	0, 40, 48 h	47.8	20.5 - 102.4	15.9	6.8 - 34.1	1633.6	860.1 – 2689.0	133.0	26.2 - 565.6
#5: Delayed 2nd dose (by 18 h)	0, 42, 48 h	47.4	20.9 - 113.3	15.8	7.0 - 37.8	1674.8	905.0 - 2943.7	127.4	20.4 - 613.1
#6: Delayed 2nd dose (by 21 h)	0, 45, 48 h	47.1	19.7 - 103.2	15.7	6.6 - 34.4	1900.0	1033.1 - 3089.7	106.0	14.2 - 511.4

Source: 2020-10-30-derived-pk-parameter-calculation.r
Abbreviations: AUC=area under the plasma concentration-time curve, AUC0-72h=area under the plasma concentration-time curve over 72 hours; AUC0-24h=area under the plasma concentration-time curve over 24 hours; Cmax=maximum plasma concentration, Cmin=minimum plasma concentration, h=hour; p=percentile, QD=once daily
Note: Since steady-state no longer applies in all scenarios except scenario 1, AUCs were calculated by trapezoidal rule.

Source: Table 17 in the PopPK and ER report 05mssh.

Exposure-Response Analyses

Data

The pooled source analysis datasets from studies 1 and 4 contained 155 and 133 patients were available for safety and efficacy ER analysis, respectively. Steady-state exposures were generated to investigate the extent of correlation between AUC, Cmax, and Cmin at steady state based on the nominal dose and to guide the selection of the exposure metric to be used for the E-R analyses. The post hoc estimated exposures were strongly correlated in both the exposure-safety analysis population and the exposure-efficacy analysis population for AUC and Cmax and for AUC and Cmin. Due to the high degree of correlation between the post hoc exposure estimates, there was no preference from a mechanistic perspective for AUCss or Cmin as the exposure parameter for the exposure-efficacy analysis, or for AUCss or Cmax for the exposure-safety analysis, as both exposure parameters would result in similar E-R relationships. AUC is generally less sensitive to variability in concentration values at specific time points and was therefore used for both the exposure-efficacy and exposure-safety analyses. To account for dose reductions and interruptions, the following AUC exposure metrics at steady state were investigated:

- Steady-state AUCss based on average dose intensity up to the event (or censored to end of treatment or data cutoff date in case no event) [AUCavg]
- Steady-state AUCss based on average dose intensity until end of treatment or data cutoff date [AUCavgeot]
- Steady-state AUCss based on average dose intensity up to Day 1 of Week 3 [AUCwk3]

All patients from Study 4 were treated with 120 mg QD. The majority of patients (54 out of 72) from Study 1 were treated with 120 mg QD (See Table 51). This is one of the limitations of the analysis. Due to possible confounding issues, results of these analyses would need to be interpreted with caution to avoid mis- or over-interpretation of the results.

E-R Efficacy Analyses

Various efficacy endpoints including overall response rate (ORR), disease control rate (DCR), progression free survival (PFS), best overall response rate (BOR), time to response (TTR), duration of response (DOR) were investigated. For binary endpoints, univariate logistic regression analyses were performed. For time-to-event endpoints, Kaplan-Meier curves were plotted. Summary statistics by exposure quartiles were also provided. The relationship between exposure (AUC) and various efficacy endpoints (ORR, DCR, PFS, BOR, TTR, DOR) generally appeared to be flat within the observed exposure range for patients with VHL-RCC (Study 4) or RCC (Study 1). In addition, there was a tendency toward higher ORR with exposure for RCC lesions in Study 4. The relationship between exposure (AUC) and ORR for CNS lesions in Study 4 generally appeared to be flat within the observed exposure range. A slight positive trend was observed for DCR for RCC lesions in Study 1. While no similar trend for DCR for RCC lesions could be discerned in Study 4, a slight trend for improvement in BOR for RCC lesions was observed in this study. Given the relatively long TTR for patients with VHL-RCC treated with MK-6482 in Study 4, the E-R analyses

described in this report may not yet fully reflect potential underlying relationship for ORR and DCR for RCC lesions.

Table 51: Number of Patients for Each Efficacy Endpoint by Study and Dose Level included in the ER analyses.

Efficacy Endpoint, n	MK-6482 Dose Level							
	20 mg QD	40 mg QD	80 mg QD	120 mg QD	160 mg QD	240 mg QD	120 mg BID	Total
PFS, ORR, DCR								
Study 1	2	1	2	54	3	5	5	72
Study 4	0	0	0	61	0	0	0	61
BOR								
Study 1	2	0	1	51	3	4	5	66
Study 4	0	0	0	60	0	0	0	60
TTR, DOR								
Study 1	0	0	0	14	1	2	1	18
Study 4	0	0	0	22	0	0	0	22

Source: ER-analysis.r
Abbreviations: BID=twice daily; BOR= Best overall tumor size response; DCR=disease control rate; E-R=exposure-response; ORR=overall response rate; PFS=progression-free survival; QD=once daily; TTR=time to response

Source: Table 20 in PopPK and ER analyses report 05mssh.

ER Biomarker Analyses

ER analyses for Erythropoietin (EPO) and hemoglobin (Hgb) change of baseline at Day 1 of Week 3 for 139 patients from study 1 and 150 patients from study 4 were conducted. All patients from Study 4 were treated with 120 mg QD and the majority of patients from Study 1 were treated with 120 mg QD (See Table 52). EPO levels decreased upon treatment with MK-6482; the mean percentage change from baseline was -63.9% and -60.2% for Study 1 and Study 4, respectively. In both studies, a consistent trend of a larger change from baseline with higher exposure was observed. In Study 4, the mean percent change from baseline was -50.7% in the exposure quartile 1, compared to -64.1% in exposure quartile 4. The relationship of exposure dependent decrease in EPO seemed to plateau at higher exposures.
Hgb levels decrease upon treatment with MK-6482; the mean percentage change from baseline was -9.77% and -6.98% for Study 1 and Study 4, respectively. In both studies, a consistent trend of a larger percentage change from baseline with higher exposure was observed. In Study 4, the mean percentage change from baseline increased was -5.90% in the exposure quartile 1, compared to -8.39% in exposure quartile 4. Hgb decreased by approximately 3 g/dL in Study 4, compared to approximately 2 g/dL in Study 1. However, this difference, may be explained by the difference in baseline Hgb between the studies; mean baseline Hgb in Study 1 (based on patients included in expansion part) and Study 4 was 12.1 g/dL and 13.8 g/dL. The median baseline Hgb in advanced RCC expansion cohort (MK-6482-001; N=48) and VHL-RCC (MK-6482-004; N=60) were 11.8 and 14.0 g/dL, respectively, and the 120-mg QD dosing in these cohorts resulted in median change from baseline in Hgb of -1.05 and -0.85 g/dL at Week 3.

Table 52: Number of Patients for Each Biomarker Endpoints by Study and Dose Level included in the ER analyses.

	MK-6482 Dose Level							
Biomarker, n	20 mg QD	40 mg QD	80 mg QD	120 mg QD	160 mg QD	240 mg QD	120 mg BID	Total
EPO								
Total	5	6	6	105	5	7	5	139
Study 1	5	6	6	53	5	7	5	87
Study 4	0	0	0	52	0	0	0	52
Hgb								
Total	6	6	6	114	6	7	5	150
Study 1	6	6	6	54	6	7	5	90
Study 4	0	0	0	60	0	0	0	60

Source: ER-analysis.r
Abbreviations: EPO=Erythropoietin; E-R=exposure-response; Hgb=hemoglobin; QD=daily

Source: Table 43 in PopPK and ER analyses report 05mssh.

ER Safety Analyses

Table 53 summarizes the data used in the analyses. Logistic regression was performed on pooled data from both studies on anemia ≥ grade 3 incidence, including both exposure, AUCavg and baseline Hgb as predictors. Parameter estimates are presented in Table 54. Model-based simulations illustrating the anemia ≥ grade 3 incidence vs AUCavg in case of a baseline Hgb of 10, 12 and 14 mg are shown in Figure 21. The result indicated that exposure effects were more predominant in the low baseline Hgb range (e.g. 10 g/dL) and were largely absent in case of a higher baseline Hgb (14 g/dL); the latter is close to the mean baseline Hgb value in Study 4.

No exposure dependency for hypoxia ≥ grade 3 was found in Study 1 and it was not assessed in Study 4 due to the limited number of events.

Table 53: Number of Patients and Incidence of Safety Endpoints by Dose Level Included in the E-R analyses.

	MK-6482 Dose Level							
Safety Endpoint, n (%)	20 mg QD N = 6 N1=6/N4=0	40 mg QD N = 6 N1=6/N4=0	80 mg QD N = 6 N1=6/N4=0	120 mg QD N = 118 N1=57/N4=61	160 mg QD N = 6 N1=6/N4=0	240 mg QD N = 7 N1=7/N4=0	120 mg BID N = 6 N1=6/N4=0	Total N=155 N1=94/N4=61
Anemia ≥ grade 3								
Total	0 (0)	0 (0)	2 (33.3)	20 (16.9)	1 (16.7)	1 (14.3)	1 (16.7)	25 (16.1)
Study 1	0 (0)	0 (0)	2 (33.3)	16 (28.1)	1 (16.7)	1 (14.3)	1 (16.7)	21 (22.3)
Study 4	-	-	-	4 (6.6)	-	-	-	4 (6.6)
Hypoxia ≥ grade 3								
Total	0 (0)	1 (16.7)	0 (0)	10 (8.5)	0 (0)	0 (0)	1 (16.7)	12 (7.7)
Study 1	0 (0)	1 (16.7)	0 (0)	9 (15.8)	0 (0)	0 (0)	1 (16.7)	11 (11.7)
Study 4	-	-	-	1 (1.6)	-	-	-	1 (1.6)

Source: ER-analysis.r
Abbreviations: E-R=exposure-response; N1=number of patients in Study 1; N4=number of patients in Study 4; QD=daily

Source: Table 51 in PopPK and ER analyses report 05mssh.

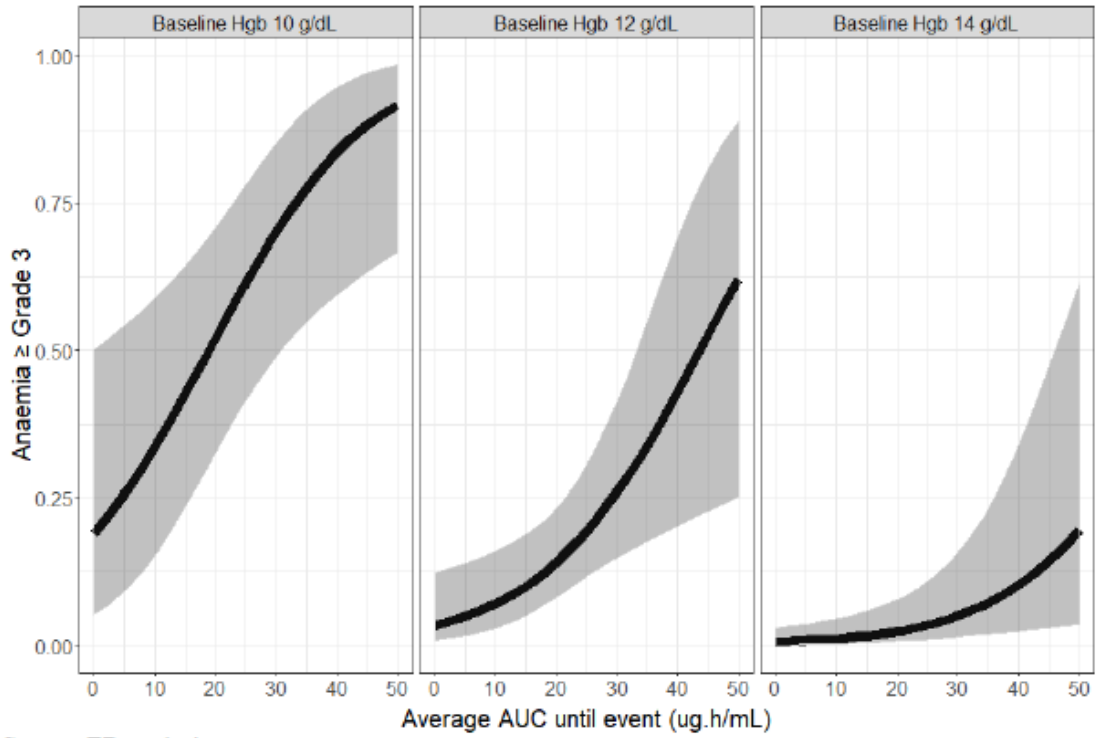
Table 54: Parameter Estimates of the Logistic Regression Model for Incidence of Anemia ≥ Grade 3 Including AUCavg and Baseline Hgb as Predictors Based on Study 1 and Study 4

Parameter	Estimate	Standard Error	*P* value
Intercept	8.073	2.52	0.001356
AUCavg	0.07715	0.02787	0.005627
Baseline Hgb	-0.9529	0.2154	9.645e-06

Source: ER-analysis.r
Abbreviations: AUCavg=steady-state AUCss based on average dose intensity up to the event; Hgb=hemoglobin

Source: Table 54 in PopPK and ER analyses report 05mssh.

Figure 21: Model-Predicted Incidence of Anemia ≥ Grade 3 vs AUCavg Based on Linear Logistic Regression Model including AUCavg and Baseline Hgb as Predictors for 3 Baseline Hgb Scenarios (10, 12 and 14 g/dL)



Source: ER-analysis.r
Notes: Solid lines and shaded areas represent model predicted incidence and 95% CI based on the logistic regression fit of the form logit(prob[event]) AUC × slopeAUC + Baseline Hgb × slopeHgb + intercept.
Abbreviations: AUCavg=steady-state AUCss based on average dose intensity up to the event; Hgb=hemoglobin

Source: Figure 43 in PopPK and ER analyses report 05mssh.

Exposure Response Analyses on Time to First Dose Reduction, Interruption and Discontinuation

The time to first dose reduction, time of first dose interruption and time to dose discontinuation was evaluated in a total of 61 patients from Study 4, who received 120 mg QD as a starting dose. There were 6 patients with a dose reduction due to drug-related AEs. There were 14 patients with a dose interruption due to drug-related AEs. There was 1 patient that discontinued treatment due to drug-

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related AEs. As a result, no E-R analysis was performed for dose discontinuation because of data limitations.

22.4.2 Physiologically Based Pharmacokinetic Modeling Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses report (#05kp6f) entitled "*Physiologically Based Pharmacokinetic Model (PBPK) of MK-6482 to evaluate the impact of CYP2C19 and UGT2B17 polymorphisms on pharmacokinetic variability and CYP3A4 mediated perpetrator drug-drug interaction potential*" to support the label recommendation based on the predicted DDI potential.

The Division of Pharmacometrics has reviewed the original PBPK report, the addendum to the report, supporting modeling files, the Applicant's response to Clinical Pharmacology Information Requests (IRs) received dated April 14, July 09, and July 16, 2021, and concluded that:

- The belzutifan PBPK model is adequate to predict the PK in subjects who are dual CYP2C19 and UGT2B17 poor metabolizers (PMs) . The model predicted that belzutifan exposure (AUC) could be increased approximately by 4-fold in subjects who is a dual PM of CYP2C19 and UGT2B17 compared to that in a non-PM.
- The PBPK analysis is adequate to predict the effect of belzutifan on the exposure of a sensitive CYP3A subtract, such as midazolam (MDZ). The model predicted that coadministration of belzutifan 120 mg once daily decreased the midazolam AUC by up to 70% in subjects with higher belzutifan concentrations.

Background

Belzutifan (MK-6482) is developed to patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), not requiring immediate surgery. The proposed dosing of belzutifan is 120 mg orally once daily (QD) with or without food. The Applicant reported that the maximum tolerated dose (MTD) was not reached in the clinical studies where belzutifan doses were ranging from 20 to 240 mg (including 120 mg BID).

Cmax and AUC increase proportionally following multiple doses in patients over a dose range of 20 mg 200 mg daily. The median time to reach maximum observed plasma concentration (Tmax) is around 1 to 2 hours. Human mass balance study (study#008) is currently ongoing. In animals (dog and monkey), less than 1% of total oral dose was excreted unchanged in urine. The glucuronide metabolite of belzutifan, PT3317, was quantified in clinical studies and circulates in plasma at ~ 32% of belzutifan exposures. Effect of hepatic impairment (mild) and renal impairment (mild and moderate) on PK of belzutifan were evaluated in clinical studies 001 and 004. Population PK analysis suggested no clinically

significant effects of mild hepatic impairment and mild to moderate renal impairment on MK-6482 exposures.

Studies with human liver microsomes and recombinant enzymes demonstrated that belzutifan is metabolized by glucuronidation catalyzed by UGT2B17 and by oxidative metabolism, catalyzed by CYP2C19, and to a lesser extent by CYP3A4. belzutifan and its metabolite, PT3317, demonstrated low potential to inhibit major CYP (expect CYP3A4) or UGT enzymes and major drug transporters. Clinical DDI study (#009) showed a 40% and 34% reduction in AUC and Cmax of midazolam, respectively, following 120mg oral QD dosing of MK-6482 in the fasted state for 7 days and a single oral dose of 2 mg midazolam on day 7, relative to midazolam exposures when administered alone.

UGT2B17 and CYP2C19 phenotype were identified as important intrinsic factors impacting MK-6482 PK. The Applicant conducted pop-PK analysis (study # 05MSSH) and pharmacogenetic pharmacokinetic (PGx-PK) analysis (study # 05nhzl) to evaluate the PK difference in subjects with different phenotypes. The pop-PK analysis is a non-linear mixed effects model that incorporates clinical PK data collected across MK-6482 studies with both sparse and intensive PK sampling (MK-6482-001, 002, 004, 006, and 007). Compared to popPK analysis, the pharmacogenetic analysis (study # 05nhzl) is considered more exploratory by the Applicant. The PGx-PK model in study # 05nhzl is a linear mixed effects model that incorporates PK parameters derived from noncompartmental PK analysis from studies with intensive PK sampling only. Table 55 compared the estimated steady state belzutifan AUC for a 74 kg subject receiving 120 mg belzutifan with different phenotypes.

Table 55: Comparison of the estimated steady state belzutifan AUC for a 74 kg subject receiving 120 mg belzutifan with different phenotypes

Metabolizer Phenotype		Model Estimates (h*µg/mL) [95% CI] (Fold Change)	
CYP2C19	UGT2B17	Pop-PK*	PGx-PK[$]
IM/EM/RM/UM	EM	13.7 (1.0)	13.9 [12.5, 15.4] (1.00)
IM/EM/RM/UM	IM	19.0 (1.4)	21.3 [19.4, 23.4] (1.53)
IM/EM/RM/UM	PM	27.9 (2.0)	31.4 [27.1, 36.5] (2.27)
PM	EM	21.4 (1.6)	18.8 [12.9, 27.4] (1.36)
PM	IM	29.8 (2.2)	31.8 [23.7, 42.5] (2.29)
PM	PM	43.6 (3.2)	63.8 [51.0, 79.8] (4.60)

*Pop-PK estimates from [Table 2.7.2-vhlrcc1: 29] and an additional new simulation result for CYP2C19 PM, UGT2B17 EM
[$]PGx-PK estimates generated as weighted marginal means from combined relevant CYP2C19 phenotype groups for formulation B
Fold changes are relative to CYP2C19 IM/EM/RM/UM, UGT2B17 EM
PM: poor metabolizer; IM: intermediate metabolizer; EM: extensive metabolizer; RM: rapid metabolizer; UM: ultra-rapid metabolizer

Source: Response to FDA information request received on April 14, 2021.

The Applicant developed a PBPK model to evaluate the impact of population differences in MK-6482 exposure on CYP3A4 induction mediated drug-drug interaction (DDI) with midazolam. DDI effects of belzutifan on midazolam exposure in subjects with higher belzutifan exposure was predicted based on the simulation results.

Methods

PBPK model structure and development

The PBPK model of belzutifan was developed based on in vitro studies, physicochemical properties, clinical single oral dose PK data, and PGx-PK analysis (Study# 05nhzl) in Simcyp (Certara, Version 19). In summary, a first order oral absorption and a minimal PBPK model was used to describe the distribution and PK of belzutifan. The fraction of unbound drug in plasma (fu) was measured using equilibrium dialysis. The average unbound fraction of belzutifan in plasma was 55% (study PK018) and the blood to plasma concentration ratio (B/P) was 0.88 (study PK017).

The apparent permeability (Papp) of MK-6482 was high in both LLC-PK1 and MDCKII cells (29.2-29.4 x 10^-6 cm/s and 24.4-25.7 x 10^-6 cm/s, respectively). The basolateral to apical/apical to basolateral efflux ratio of MK-6482 in MDCKII cells is 1.5. The compound exhibits a constant

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solubility of approximately 10 μg/mL across the physiological pH range (Applicant's BioPharSummary Sec 1.1).
Retrograde method was used to calculate total hepatic intrinsic clearance (CLint) based on the oral clearance (8.62 L/hr) derived from the PGx-PK analysis for a subject who is a dual extensive metabolizer (EM) of CYP2C19 and UGT2B17. The contributions of CYP2C19 and UGT2B17 to the total clearance in EM/EM subjects were based on results of PGx-PK analysis (Study# 05nhzl, Section 6). The contributions of CYP2C19, UGT2B17 and another pathway were 25.3%, 55.0% and 19.7%, respectively, to the overall clearance.
For the population PBPK simulation, the Applicant modified the enzyme phenotype frequencies and relative enzyme abundance in the default NEurCaucasian and Japanese populations in the Simcyp library according to the results obtained from the PGx-PK analysis. CYP2C19 and UGT2B17 frequencies and phenotype definitions used in PGx-PK analysis were adapted from public literature and database such as PharmGKB[2]. The relative activity/abundance in intermediate metabolizers (IMs) and ultra-rapid metabolizers (UMs) was estimated by the Applicant from the shift in exposure compared to that in the EMs (Study# 05nhzl). Table 56 summarized the modified enzyme phenotype frequencies and relative enzyme abundance in the default population library files.

[2] https://www.pharmgkb.org/page/cyp2c19RefMaterials

Table 56: Summary of modifications to enzyme phenotype frequencies and relative enzyme abundance and activity in population library files.

Population	Parameter	Simcyp Value	Modified Value
NEurCaucasian	CYP2C19 PM frequency	0.092	0.0240
	CYP2C19 IM frequency	0	~~0.2416~~ **0.26**
	CYP2C19 EM frequency	0.59	0.3956
	CYP2C19 UM frequency	0.318	0.3190
	UGT2B17 PM frequency	0.09	0.1451
	UGT2B17 IM frequency	0.36	0.4452
	UGT2B17 EM frequency	0.55	0.4097
Japanese	CYP2C19 PM frequency	0.172	0.1919
	CYP2C19 IM frequency	0	0.484
	CYP2C19 EM frequency	0.817	0.3241
	CYP2C19 UM frequency	0.011	0
	UGT2B17 PM frequency	0.83	0.7700
	UGT2B17 IM frequency	0	0.2099
	UGT2B17 EM frequency	0.17	0.0201
NEurCaucasian & Japanese	CYP2C19 IM hepatic abundance (CV%)	0 (0)	3.6 (26)
	CYP2C19 UM hepatic abundance (CV%)	8.7 (71)	7.1 (56)
	CYP2C19 IM intestinal abundance (CV%)	0 (0)	1.6 (26)
	CYP2C19 UM intestinal abundance (CV%)	4 (77)	3.2 (56)
	UGT2B17 PM hepatic relative activity (CV%)	0.08 (40)	0 (0)
	UGT2B17 IM hepatic relative activity (CV%)	0.16 (30)	0.37 (27)
	UGT2B17 PM intestinal relative activity (CV%)	0.08 (60)	0 (0)
	UGT2B17 IM intestinal relative activity (CV%)	0.16 (60)	0.37 (27)

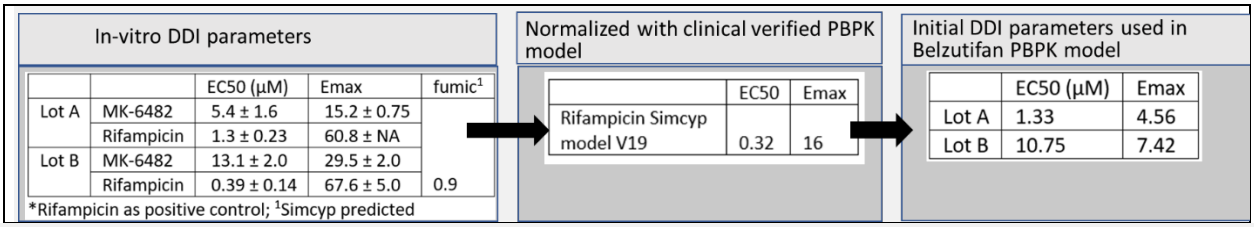
Source: Table 2 in the PBPK report; enzyme abundance in the unit of pmol/mg protein.

Reviewer's comments:
Four phase I studies (MK-6482-001, 002, 006, 007) were included in the PGx-PK analysis. For subjects included in PGx-PK analysis, MK-6482 exposure in individuals with reduced UGT2B17 activity (UGT2B17 PMs) were 2.4-fold higher than that in UGT2B17 EMs after accounting for differences in body weight and CYP2C19 phenotype. MK-6482 exposure in individuals with reduced CYP2C19 activity (CYP2C19 PMs) were 1.7-fold higher than that in CYP2C19 EMs after accounting for differences in body weight and UGT2B17 phenotype. The derived fm values of 0.55 and 0.25 for UGT2B17 and CYP2C19, respective, in EM/EM subject seem reasonable.

Belzutifan is a CYP3A inducer. Induction of CYP3A4 mRNA by belzutifan was measured in vitro from two lots of human hepatocytes prepared from one individual donor each. The corresponding EC50 and Emax values of belzutifan were obtained by fitting the changes in

mRNA with an Emax model. In-vitro CYP3A induction parameters of belzutifan were further calibrated with data collected for the positive control (i.e., rifampicin) and used in belzutifan PBPK model as illustrated in *Figure 22.* CYP3A5 induction by belzutifan was not studied in vitro.

Figure 22: In vitro to in vivo extrapolation of in-vitro CYP3A induction parameters of belzutifan in PBPK model



		EC50 (μM)	Emax	fumic[1]
Lot A	MK-6482	5.4 ± 1.6	15.2 ± 0.75	
	Rifampicin	1.3 ± 0.23	60.8 ± NA	
Lot B	MK-6482	13.1 ± 2.0	29.5 ± 2.0	
	Rifampicin	0.39 ± 0.14	67.6 ± 5.0	0.9

*Rifampicin as positive control; [1]Simcyp predicted

	EC50	Emax
Rifampicin Simcyp model V19	0.32	16

	EC50 (μM)	Emax
Lot A	1.33	4.56
Lot B	10.75	7.42

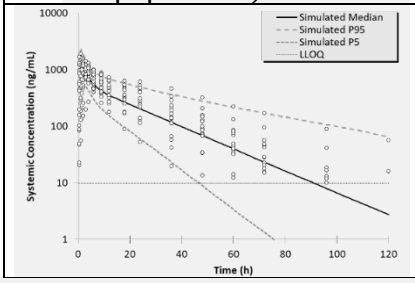
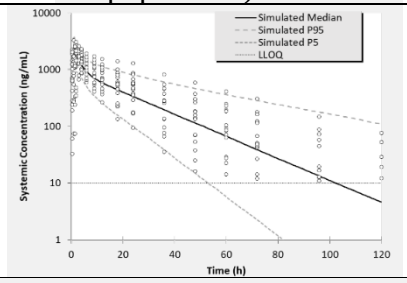
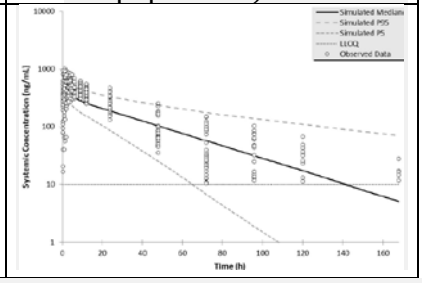
Source: Summarize by Reviewer

Reviewer's comments: The calibration approach used by the Applicant is acceptable. Reviewer noted that different Emax values (ranges 8-30) have been proposed for the rifampin PBPK model (Almond LM et al. DMD 44:821-832, 2016). Thus, the calibrated Emax values of belzutifan is dependent on the selected rifampin model. In addition, approximately two-fold difference was observed in the in-vitro data based on two individuals, thus the effects of parameter variabilities *on the simulated DDI of belzutifan should be considered. Reviewer noted that literature[3,4] suggested that rifampicin exhibited high selectivity for CYP3A4 induction but showed minimal induction effect on CYP3A5.*

Model verification

The Applicant evaluated the performance of belzutifan PBPK model by comparing the simulated and observed clinical PK data following single dose administration of 40, 120 or 200 mg belzutifan in Caucasian and Japanese populations as shown in Figure 23.

Figure 23: Observed and simulated concentration-time profiles following a single oral (a) 120 mg (b) 200 mg dose of belzutifan in Caucasians, and (c) 40 mg belzutifan in Japanese

(a) 120 mg (Caucasian population)	(b) 200 mg (Caucasian population)	(c) 40 mg (Japanese population)
		

Source: the Applicant's PBPK report Figure 3, 4 and 5. Observed data: MK-6482 P006 for (a) and (b); MK-6482 P007; Japanese only for (c).

[3] https://www.jbc.org/article/S0021-9258(20)72880-2/fulltext

[4] www.corning.com/catalog/cls/documents/posters/poster_2015_ISSX_P119_Effect_of_Fifteen_Inducer.pdf

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Table 57 showed the comparison between the observed and simulated belzutifan AUCss receiving 120 mg belzutifan by CYP2C19/ UGT2B17 phenotype to the estimates from pop-PK and PGx analysis

Table 57: Comparison of the estimated steady state AUC using different modeling and analysis for different phenotypes

	AUCss(µg/mL.hr) following 120 mg QD			
	PBPK-Caucasian	**PBPK-Japanese**	**PGx-PK**	**pop-PK**
CYP2C19EM + UGT2B17EM	13.1	14.8	13.8	13.7
CYP2C19EM + UGT2B17PM	32.5	36.8	32.1	27.9
CYP2C19PM + UGT2B17EM	17.5	19.5	19.0	21.4
CYP2C19PM + UGT2B17PM	63.9	71.9	63.4	43.6

Data: PBPK results were simulated by reviewer using Applicant's workspace files. PGx-PK and pop-PK results were obtained from Table 9-12 in Applicant's response to Clinical Pharmacology Information Request received on 4/15/2021. Note CYP2C19 EM were pooled CYP2C19 IM/EM/RM (rapid metabolizer)/UM phenotypes

Reviewer's comments:
The simulated PK were similar among three modeling approaches for different phenotype groups except PM/PM. It is expected that PBPK simulation would be similar to PGx-PK results as the same dataset were used in both analyses. Since there is no clinical data for PM/PM subjects, the difference between the simulated results for PM/PM reflecting the differences in methodology. Reviewer considered the differences in belzutifan exposure (AUCss) among three modeling approaches (43.6 -63.9 µg/mL.hr) are reasonable.
The reviewer also compared the simulated belzutifan PK following a single oral 40 mg dose of belzutifan in Japanese using the original and refined population database (Table 58). As shown in Table 58, the simulated PK using the refined population is in a better agreement with the observes data.

Table 58: Observed and simulated AUCinf and Cmax following a single oral 40 mg dose of belzutifan in Japanese

		Predicted Median Trial GM (95% PI)		**Predicted / Observed**	
	Observed GM (95% CI)	Default Simcyp library file	Refined PGx database	Default Simcyp library file	Refined PGx database
AUCinf (µg/mL.hr)	15.0 (13.3,16.9)	12.5 (10.2-14.8)	15.1 (12.6, 18.2)	0.83	1.01

Cmax (ng/mL)	665 (616, 717)	521.9 (457.7-596.6)	543 (471, 613)	0.78	0.82

Data: Reviewer's analysis and the Applicant's PBPK table 5

In the original PBPK analysis report (dated January 2021), the Applicant verified the PBPK model of belzutifan using clinical single oral dose PK data. The Applicant later compared the simulated belzutifan PK with clinical data in steady state in response to the FDA's request (Response to Clinical Pharmacology Information Request submitted on July 09 and July 16, 2021). Table 59 compares the simulated and observed AUCt for 120 mg QD dose. As shown in Table 59, belzutifan PBPK model reasonably described belzutifan PK following multiple dose of belzutifan 120 mg QD in patients.

Table 59: Observed and simulated AUCss following multiple-dose of belzutifan 120 mg QD in patients

	Geometric mean of AUC0-24 (µg.hr/mL)							
120 mg QD	**PBPK simulation N = 1200**		**Study 001[b] N =52**		**Study 009[c] N =14**		**PopPK simulation[d] (study 05mssh)**	
	Day 1	**Day 7[a]**	**Day 1**	**Day 15**	**Day 1**	**Day 7[a]**	**Day 1**	**Steady-State**
NEurCaucasian	**11.1**	**16.9**	**12.9**	**18.1**	**16.0**	**23.4**	**11.5 – 14.0**	**14.1 – 19.6**
Caucasian PM/PM	**19.5**	**58.3**					**20.9**	**44.7**
Japanese PM/PM	**24.4**	**70.6**					**26.8**	**53.9**

[a] A 7 day dosing regimen was conducted in P009 and simulated in our PBPK analysis. Study day 8 reflects the 7th day of belzutifan dosing, with belzutifan dosing starting on study day 2
[b] Data from 120 mg QD dose expansion cohort (N=52) in MK-6482-001 which had predominantly Whites (94.2%) and no Asians [Ref. 5.3.5.2: P001V01MK6482: Table 10-4, Table 14.4.1.2.1]
[c] Data from MK-6482-009, which had predominantly White (71.4%) and the rest Black or African American and no Asians [Ref: 5.3.3.4: P009MK6482: Table 10-2, Table 11-4]
[d] Data from [Table 3] . Refer to [Table 3] for additional context.

Source: the Applicant's response to Clinical Pharmacology Information Request received on 7/16/2021.

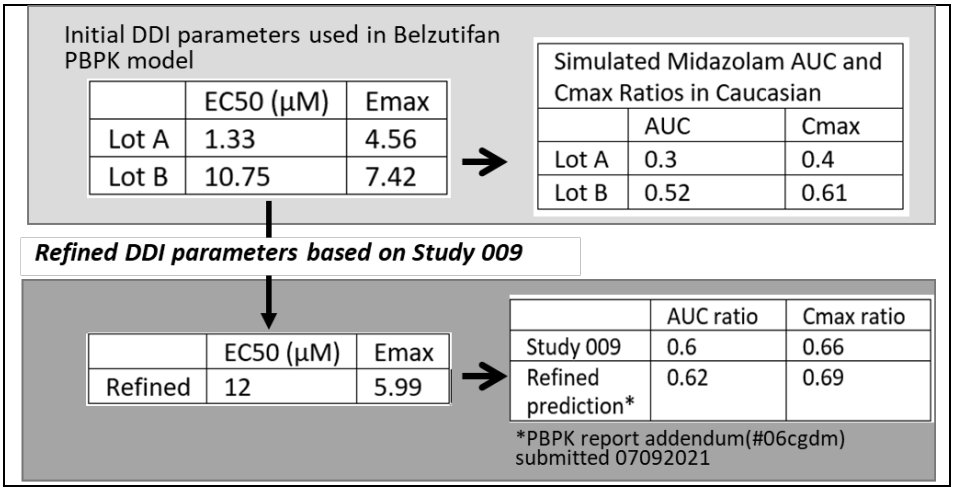
Reviewer's comments:
The belzutifan PBPK model is adequate to predict the PK in subjects with different CYP2C19 and UGT2B17 phenotypes.

Model application

The Applicant used the PBPK modeling and in-vitro induction parameters to predict the effect of 120 mg QD of belzutifan on the PK of midazolam. The model prospectively predicted a reduction of 70% and 48% in midazolam AUC using two sets of induction parameters, Lot A and Lot B, respectively following co-administration with 120 mg QD dose of belzutifan for 7 Days

compared to midazolam alone in Caucasian Population. Figure 24 illustrates the refinement process of using PBPK modeling to evaluate the DDI potential of belzutifan on midazolam PK.

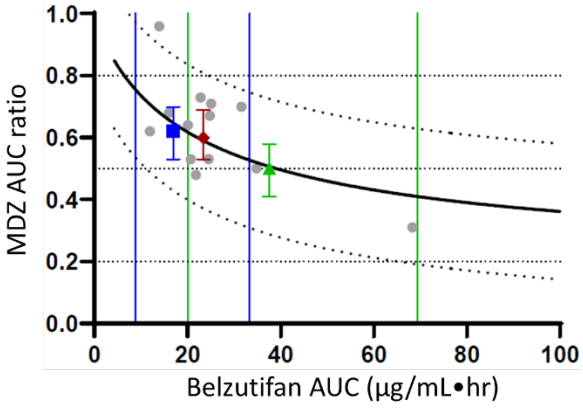
Figure 24: Model refinement process evaluating the DDI potential of belzutifan on the PK of a CYP3A substrate



Source: Summarized by the Reviewer

The Applicant submitted results of clinical DDI study with midazolam (Study 009) under IND 132120 on April 28, 2021. FDA issued an information request on July 02, 2021 for a revised belzutifan PBPK modeling analysis considering the clinical midazolam DDI data. Reviewer requested the Applicant to estimate the DDI effect of belzutifan on midazolam PK in subjects with higher belzutifan concentrations such as UGT2B17/CYP2C19 PM/PM. Applicant submitted "*MK-6482 PBPK MODELING & SIMULATION REPORT ADDENDUM*" on July 09, 2021. The revised CYP3A induction parameters, Emax and EC50, were 5.99 and 12 µM respectively. The Emax value of 5.99 was based on the average of two Emax values (Lot A and B), EC50 value was then optimized to fit observed data. The PBPK simulations with the updated EC50 and Emax parameters suggested a 50% and 38% reduction in midazolam AUC with concomitant administration of 120mg QD dose of belzutifan. Applicant did not report simulate the DDI effects of belzutifan on midazolam for population with different phenotypes such as Caucasian and Japanese PM/PM. Instead, the Applicant generated an exposure-response relationship between belzutifan AUC and midazolam AUC ratio using PBPK simulation results for Caucasian and Japanese populations. Then, based on the simulated belzutifan AUC for different population, midazolam AUC ratio were estimated using the exposure-response relationship. Figure 25 presents the overlay of the PBPK simulated belzutifan AUC vs. midazolam AUC ratio relationship and observed individual data in Study 009. Table 60 presented the projected midazolam AUC ratios based on the simulated belzutifan AUC in different populations and the belzutifan AUC vs. midazolam AUC ratio relationship (Figure 25).

Figure 25: Overlay of simulated relationship between the belzutifan AUC and midazolam AUC Ratio and observed midazolam AUCR (study P009)



PBPK Simulated (90% PI)
Caucasian Population Predicted (AUCR = 0.62 [90% CI: 0.53, 0.70])
Japanese Population Predicted (AUCR = 0.50 [90% CI: 0.41, 0.58])
Individual AUCR Observed in P009
Overall Observed in P009 (AUCR = 0.60 [90% CI: 0.53, 0.69])

Blue and Green vertical lines show the 10th-90th percentile of predicted steady state AUC values for Caucasian and Japanese populations, respectively, with 120 mg QD dosing in patients with VHL-RCC

Source: Figure 1 of 'Response to Clinical Pharmacology Information Request submitted on July 09'

Table 60: Projected midazolam AUC ratio based on the belzutifan AUC vs. midazolam AUC Ratio relationship

Population	UGT2B17 Phenotype	CYP2C19 Phenotype	Belzutifan exposure* (µg/mL*hr)	Projected Midazolam AUC ratio[e]	Interaction level
HV Caucasian	PM	PM	69.9[b]	0.41	Moderate
HV Japanese	PM	PM	80.1[c]	0.39	Moderate
VHL-RCC[†]	EM	IM/EM/RM/UM	13.7[a]	0.68	Weak
	Mixed	Mixed	16.7[d]	0.65	Weak
	PM	Mixed	27.9[a]	0.56	Weak
	PM	PM	43.6[a]	0.48	Moderate

HV= Healthy volunteers, VHL-RCC= Von Hippel Lindau disease associated renal cell carcinoma
* AUC0-inf after a single 120 mg oral dose of Belzutifan. Based on the observed linear PK relationship, this projects to be equivalent to AUC0-24hr at steady state.
[a] Pop-PK estimates from [Table 2.7.2-vhlrcc1: 29]
[b] Simcyp predicted values as Median of Trial Geometric Mean (95% PI) using Caucasian population background [Ref. 5.3.3.5: 05PFJ7: Table 6].
[c] Simcyp predicted values as Median of Trial Geometric Mean (95% PI) using Japanese population background [Ref. 5.3.3.5: 05PFJ7: Table 7].
[d] Pop-PK estimates from [Table 2.7.2-vhlrcc1: 27]
[e] Projected ratio of midazolam AUC following administration of 120mg QD Dose of belzutifan for 7 Days compared to Midazolam alone
† Based on the population in MK-6482-004 which was predominantly Caucasian [Ref. 5.3.3.5: 05MSSH: Table 6]

Source: Table 5 of 'Response to Clinical Pharmacology Information Request submitted on July 09'

Reviewer's comments
The change in midazolam exposure when it is co-administered with belzutifan is determined by two factors: the belzutifan exposure and the involvement of CYP3A5-mediated DDI. Midazolam is metabolized via the CYP3A4/5 pathway. The CYP3A4/5 abundance is different between the NEurCaucasian and Japanese populations (Simcyp library files) and the interaction of belzutifan

in the Applicant's analysis is only modeled via the CYP3A4 pathway. The impact of the CYP3A5-mediated interaction on the on the belzutifan-midazolam DDI prediction is being explored by the reviewer and discussed below.

1. *As shown in Table 61 Scenario A, the midazolam AUC ratio (0.38) simulated for Japanese PM/PM population is slightly higher than those simulated for NEurCaucasian PM/PM population (AUC ratio 0.37). This result is not expected, given the belzutifan AUCss is much higher in Japanese PM/PM population (58.3-vs-70.6 µg/mL-hr, Table 61). One explanation is the difference in the contribution of CYP3A5-mediated clearance in Simcyp's midazolam PBPK model in Japanese and NEurCaucasian. Consequently, the simulated relationships between belzutifan AUC and midazolam AUC Ratio are different in the NEurCaucasian and Japanese PM/PM populations (*Figure 21*).*

Table 61: Comparison of the simulated DDI effect of belzutifan on midazolam PK in NEurCaucasian and Japanese subjects who are dual PMs of CYP2C19 and UGT2B17

	Scenario A[1] Simulated DDI effect of belzutifan on MDZ: Applicant's belzutifan model G.M (5%-95%)			Scenario B[2] Simulated DDI effect of belzutifan on MDZ: Add CYP3A5 induction in belzutifan model* G.M (5%-95%)		
	belzutifan AUC ss µg/mL-hr	Midazolam		belzutifan AUC ss µg/mL-hr	Midazolam	
		AUC ratio	Cmax Ratio		AUC ratio	Cmax Ratio
NEurCaucasian PM/PM	58.3	0.37 (0.36-0.37)	0.46 (0.45-0.46)	58.3	0.34 (0.33-0.34)	0.42 (0.42-0.43)
Japanese PM/PM	70.6	0.38 (0.37-0.39)	0.47 (0.47-0.48)	70.6	0.30 (0.30-0.31)	0.38 (0.37-0.39)

[1]Data were extracted from the model output submitted in the Applicant's response to FDA IR submitted on July 16, 2021; [2]Data were simulated using the Applicant's workspace files with the revised DDI parameters listed in Table 62.

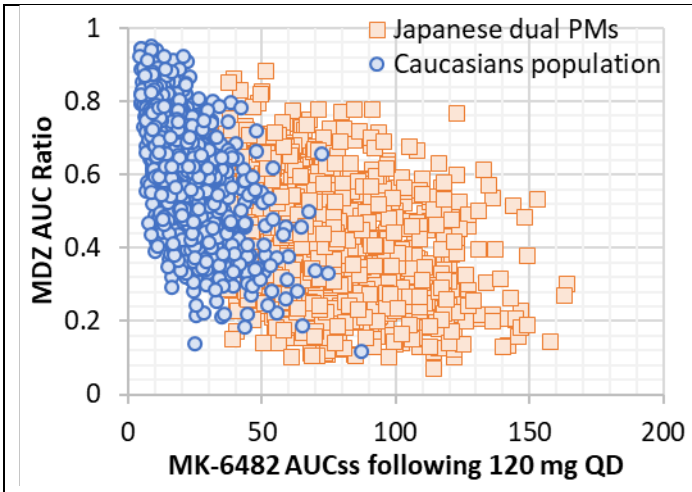
Table 62: Induction parameters used in the two belzutifan model in the Table 1

Applicant's model[1]				Revised model[2]			
CYP3A4		CYP3A5		CYP3A4		CYP3A5	
Emax	EC50	Emax	EC50	Emax	EC50	Emax	EC50
5.99	12	0	0	5.99	12	5.99	12

[1]model was used to simulate the results presented in Table 61 Scenario A.
[2]model was used to simulate the results presented in Table 61 Scenario B.

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

Figure 26: Comparison of exposure-response relationship between NEurCaucasian population and Japanese PM/PM population



Blue circles and orange squares represent the simulated individual data for NEurCaucasian and Japanese PM/PM, respectively. These data were obtained from the workspace file submitted by the Applicant.

2. *As shown in Table 63, the CYP3A5-mediated pathway contributed 35% of midazolam clearance in the Japanese population in Simcyp's midazolam PBPK model. In other word, if only accounting for CYP3A4 induction, 35% of midazolam pathway would not be induced in the Japanese PM/PM population when concomitantly administration with belzutifan. Thus, the PBPK modeling predicted a lower DDI effect for Japanese PM/PM compared to NEurCaucasian PM/PM using the Applicant's model which considered the CYP3A4 induction only (Table 61 Scenario A). Reviewer noted that CYP3A5 induction by belzutifan was not studied in vitro (see discussion regarding induction data in-vitro).*

Table 63: Contribution of CYP3A5 pathway in midazolam clearance in midazolam PBPK model for different virtual population.

	Simulated midazolam Oral Clearance (L/hr) geometric mean (5%-95% CI)		% contribution of CYP3A5 pathway in overall clearance
	Default midazolam model	Turn-off CYP3A5 mediated clearance in midazolam model	
NEurCaucasian	89.8 (80.8-99.8)	79.0 (72.0-85.7)	12%
Japanese	70.3 (60.8-81.3)	45.7 (40.5-51.5)	35%

Note: Simcyp default population libraries were used. Sample size 100; age 20-50, 50% female

3. *Although CYP3A5 mediated clearance is evident in the in-vitro data for midazolam[5], there are several publications suggesting that midazolam metabolism in vivo is not associated with CYP3A genotypes (such as Miao et al[6] and Shih et al[7]). Van Dyk et al[8] conducted midazolam DDI studies in subjects with Caucasian and South Asian ancestries following 300 mg rifampicin QD for 7 day and a single 5 mg midazolam on day 7. In this study, 45% of South Asian subjects have functional CYP3A5 genotype compared to 11% in Caucasian subjects. Results of clinical DDI studies showed the magnitude of effect of rifampin on midazolam PK are similar in Caucasian and South Asian subjects. A 75% and 80% reduction in midazolam AUC was reported in Caucasian and South Asian subjects respectively, following 300 mg rifampicin QD for 7 day.*
4. *Assuming the induction potential on CYP3A4 pathway can be applied to the CYP3A5-mediated clearance for midazolam, Reviewer included the induction parameters for CYP3A5 pathway in the belzutifan PBPK model (Table 62). As shown in Table 61 Scenario B, the simulated midazolam AUC ratio was 0.30 and 0.34 for Japanese PM/PM and NEurCaucasian PM/PM populations, respectively.*

Conclusion:

- The belzutifan PBPK model is adequate to predict the PK in subjects with different CYP2C19 and UGT2B17 phenotypes. The model predicted that belzutifan exposure (AUC) could be increased approximately by 4-fold in subjects who is a dual PM of CYP2C19 and UGT2B17 compared to that in non-PMs.
- The PBPK analysis is adequate to predict the effect of belzutifan on the exposure of a sensitive CYP3A subtract such as midazolam. The model predicted that coadministration of belzutifan 120 mg once daily decreased the midazolam AUC by up to 70% in subjects with higher belzutifan concentrations such as dual poor metabolizers of CYP2C19 and UGT2B17 pathway.

[5] Simcyp V19 midazolam PBPK model verification report

[6] *Miao et al., Pharmacogenomics J. 2009:* https://pubmed ncbi.nlm nih.gov/19506580/

[7] *Shih et al., Drug Metab Dispos. 2002*: https://pubmed ncbi nlm nih.gov/12433824/

[8] *Van Dyk et al., Eur J Clin Pharmacol. 2018* https://pubmed ncbi nlm nih.gov/29572563/

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Non-Clinical/ Toxicology	Claudia Miller, PhD	DHOT	Sections: 7	**Select one:** x Authored x Approved
	Signature: Claudia Miller -S Digitally signed by Claudia Miller -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Claudia Miller -S, 0.9.2342.19200300.100.1.1=2002180206 Date: 2021.08.10 10:05 54 -04'00'			
Non-Clinical/ Toxicology	Tiffany Ricks, PhD	DHOT	Sections: 7	**Select one:** x Authored x Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000497170, cn=Tiffany K. Ricks -S Date: 2021.08.05 11:48:51 -04'00'			
Clinical Pharmacology	Salaheldin Hamed, PhD	DCPI	Sections: 8, 22.4	**Select one:** x Authored ____ Approved
	Signature: Salaheldin S. Hamed -S Digitally signed by Salaheldin S. Hamed -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000952138, cn=Salaheldin S. Hamed -S Date: 2021.08.10 09:30:57 -04'00'			
Pharmacometrics	Junshan Qiu, PhD	OCP/DPM	Sections: 22.4.1	**Select one:** x Authored ____ Approved
	Signature: Junshan Qiu -S Digitally signed by Junshan Qiu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Junshan Qiu -S, 0.9.2342.19200300.100.1.1=2000348577 Date: 2021.08.05 11:27:19 -04'00'			
Pharmacometrics (TL)	Jingyu Yu, PhD	OCP/DPM	Sections: 22.4.1	**Select one:** x Authored x Approved
	Signature: Jingyu Yu -S Digitally signed by Jingyu Yu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jingyu Yu -S, 0.9.2342.19200300.100.1.1=2000794699 Date: 2021.08.09 12:01:13 -04'00'			
PBPK/ Division of Pharmacometrics	Yuching Yang, PhD	OCP/DPM	Sections: 22.4.2	**Select one:** x Authored ____ Approved
	Signature: Yuching Yang -S Digitally signed by Yuching Yang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuching Yang -S, 0.9.2342.19200300.100.1.1=2000846164 Date: 2021.08.05 11:37:09 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
PBPK/ Division of Pharmacometrics (TL)	Xinyuan Zhang, PhD	OCP/DPM	Sections: 22.4.2	**Select one:** ___ Authored x Approved
	Signature: Xinyuan Zhang -S Digitally signed by Xinyuan Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xinyuan Zhang -S, 0.9.2342.19200300.100.1.1=2000431943 Date: 2021.08.05 11:00:42 -04'00'			
Genomics	Sarah Dorff, PhD	OCP/DTPM	Sections: 8	**Select one:** X Authored _____ Approved
	Signature: Sarah E. Dorff -S Digitally signed by Sarah E. Dorff -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sarah E. Dorff -S, 0.9.2342.19200300.100.1.1=2001211253 Date: 2021.08.05 11:04:52 -04'00'			
Genomics (TL)	Rosane Charlab Orbach, PhD	OCP/DTPM	Sections: 8	**Select one:** X Authored X Approved
	Rosane Charlaborbach -S Digitally signed by Rosane Charlaborbach -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300436672, cn=Rosane Charlaborbach -S Date: 2021.08.05 15:06:01 -04'00'			
Biometrics	Haley Gittleman, PhD	OB/DBV	Sections: 3, 10, 11	**Select one:** X Authored ___ Approved
	Signature: Haley R. Gittleman -S Digitally signed by Haley R. Gittleman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2003042602, cn=Haley R. Gittleman -S Date: 2021.08.05 13:10:53 -04'00'			
Biometrics (TL)	Erik Bloomquist, PhD	OB/DBV	Sections: 3, 10, 11	**Select one:** X Authored X Approved
	Signature: Erik W. Bloomquist -S Digitally signed by Erik W. Bloomquist -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000477083, cn=Erik W. Bloomquist -S Date: 2021.08.05 13:07:28 -04'00'			
Clinical	Michael Brave, MD	DO1	Sections: 10	**Select one:** X Authored _____ Approved
	Signature: Michael H. Brave -S Digitally signed by Michael H. Brave -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300221205, cn=Michael H. Brave -S Date: 2021.08.06 10:07:16 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical	Jaleh Fallah, MD	DO1	Sections: 3, 4, 5, 6, 9, 10, 11, 12	**Select one:** X Authored ____ Approved
	Signature: Jaleh Fallah -S Digitally signed by Jaleh Fallah -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jaleh Fallah -S, 0.9.2342.19200300.100.1.1=2003008737 Date: 2021.08.05 10:54:35 -04'00'			
Associate Director for Labeling	William Pierce, PharmD, MPH	OOD	Sections: 14, Prescribing Information, Medication Guide	**Select one:** X Authored X Approved
	Signature: William F. Pierce -S5 Digitally signed by William F. Pierce -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5 Date: 2021.08.06 12:59:03 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Chana Weinstock, MD	DO1	Sections: 3, all	**Select one:** x Authored x Approved
	Signature: Chana Weinstock -S Digitally signed by Chana Weinstock -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001659606, cn=Chana Weinstock -S Date: 2021.08.10 13:25:47 -04'00'			
Division Director – DHOT	John K. Leighton, PhD	DHOT	Sections: 7	**Select one:** ____ Authored x Approved
	Signature: John K. Leighton -S Dig tally signed by John K. Leighton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S Date: 2021.08.05 12:35:42 -04'00'			
Division Director - OCP	Nam Atiqur Rahman, PhD	DCP	Sections: 8, 22.4	**Select one:** ____ Authored X Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2021.08.05 10:57:42 -04'00'			
Division Director - OB	Shenghui Tang	OB/DBV	Sections: 3, 10, 11	**Select one:** ____ Authored X Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Director – DO1	Amna Ibrahim	DO1	Sections: All	**Select one:** ___ Authored _X_ Approved
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Deputy Office Director (Acting)	Julia Beaver	OOD	Sections: All	**Select one:** ___ Authored _X_ Approved
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JULIA A BEAVER
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