NDA/BLA Multi-disciplinary Review and Evaluation

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

Application Type	Supplemental NDA
Application Number(s)	215383-012
Priority or Standard	Priority
Submit Date(s)	November 25, 2024
Received Date(s)	November 25, 2024
PDUFA Goal Date	May 26, 2025
Division/Office	Division of Oncology 2/Office of Oncology Drugs
Review Completion Date	See electronic signature
Established Name	Belzutifan
(Proposed) Trade Name	WELIREG
Pharmacologic Class	Inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α)
Applicant	MERCK
Formulation(s)	Tablets
Dosing Regimen	≥ 40 kg: 120 mg orally once daily ≤ 40 kg : 80 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult and pediatric (12 years and older) patients with advanced, unresectable, or metastatic pheochromocytoma and paraganglioma (PPGL)
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult and pediatric patients 12 years and older with locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma (PPGL)

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

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Glossary

1L	first line
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
APaT	all participants as treated
BICR	blinded independent central review
BLA	biologics license application
BP	blood pressure
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COVID-19	coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template

CSR	clinical study report
CSS	Controlled Substance Staff
DCO	data cutoff
DCR	disease control rate
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EQ-5D-5L VAS	EuroQoL-5 Dimension Questionnaire Visual Analog Scale
EPO	erythropoietin
E-R	exposure response
ERC	Ethics Review Committee
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GIST	gastrointestinal stromal tumor
GLP	good laboratory practice
GM-CSF	granulocyte macrophage colony-stimulating factor
GRMP	good review management practice
HIF-2α	Hypoxia Inducible Factor- 2 alpha subunit
HRQoL	health-related quality of life

HSA	high specific activity
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MIBG	metaiodobenzylguanidine
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NR	not reached
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PHD 1, 2	prolyl hydroxylases 1 and 2
PI	prescribing information

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPGL	pheochromocytoma/paraganglioma
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
Q8W	every 12 weeks
Q12W	every 8 weeks
QD	once daily
RCC	renal cell cacinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SDHB	succinate dehydrogenaseB
SDHx	succinate dehydrogenase gene
SGE	special government employee
SOC	standard of care
SSR	somatostatin receptor
std dev	standard deviation
TEAE	treatment emergent adverse event
TKIs	tyrosine kinase inhibitor
TTR	time to response

US	United States
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor
VHL	von Hippel Lindau
wt	wild-type

1 Executive Summary

1.1 Product Introduction

Belzutifan is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α). HIF-2α is a transcription factor that plays a role in oxygen sensing by regulating genes that promote adaptation to hypoxia. Hypoxic signaling with HIF-2α is thought to be a major driver of tumorigenesis in pheochromocytoma and paraganglioma (PPGL).

Belzutifan is approved for the following indications:

- von Hippel-Lindau (VHL) disease: For the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.
- Advanced Renal Cell Carcinoma (RCC): For the treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

In this supplemental new drug application (sNDA), the Applicant proposed the following indication for belzutifan:

- Adult and pediatric (12 years and older) patients with advanced, unresectable, or metastatic pheochromocytoma and paraganglioma (PPGL)

The recommended belzutifan dosage in adult patients is 120 mg administered orally once daily with or without food. The recommended dosage of belzutifan in pediatric patients 12 years and older is based on bodyweight. For a body weight of $\geq$ 40 kg, the dose is 120 mg orally once daily, and for a body weight of < 40 kg, the dose is 80 mg orally once daily.

The review team recommends traditional approval for adult and pediatric patients 12 years and older with locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma (PPGL).

1.2 Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support the traditional approval of belzutifan for the treatment of adult and pediatric patients 12 years and older with locally advanced, unresectable, or metastatic PPGL. The recommendation for traditional approval is primarily supported by overall response rate (ORR) and duration of response (DOR) results from Cohort A1 of the LITESPARK-015 trial. In this study, belzutifan demonstrated a robust and clinically meaningful effect on ORR that is durable and associated with improvements

in disease-related morbidities including blood pressure control. These factors represent direct clinical benefit to patients and support traditional approval.

LITESPASRK-015 is a multi-center, multi-cohort, single-arm study of belzutifan in patients with advanced PPGL (Cohort A1), pancreatic neuroendocrine tumors (PNET) (Cohort A2), VHL disease-associated tumors (Cohort B1), advanced gastrointestinal stromal tumors (Cohort C), or advanced solid tumors with HIF-2α-related genetic alterations (Cohort D). Cohort A1 included patients with locally advanced or metastatic PPGL that was not amenable to surgery or curative treatment, and adequately controlled blood pressure (defined as BP <150/90 mm Hg, <135/85 mm Hg for adolescents) with no change in antihypertensive medications for patients with concomitant hypertension for at least 2 weeks prior to start of study treatment. Patients with carcinomatous meningitis were excluded. The primary endpoint to demonstrate efficacy of belzutifan for this population was ORR per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by blinded independent central review (BICR). Additional efficacy outcome measures were duration of response (DOR), time to response (TTR), and the proportion of patients who had a reduction in at least one antihypertensive medication by at least 50% maintained for at least six months. Given the morbidity associated with hypertension in this population and the direct contribution of the tumor to hypertension through secretion of catecholamines, a reduction in antihypertensive medications is considered to be a direct measure of clinical benefit.

The primary efficacy population consisted of 72 patients from Cohort A1. The confirmed ORR by BICR was 26% (95% CI: 17, 38). The median DOR was 20.4 (95% CI: 8.3, NR) months. A large proportion of patients, 89% and 53% respectively, maintained their response for at least 6 and 12 months. Among patients who were on antihypertensive medication at baseline and have received at least one dose of study drug, 32% achieved a sustained ≥50% reduction in their total daily dose of at least one antihypertensive medication for at least 6 months.

Given the overall similarity of PPGL in adolescents compared to adult patients, the targeted mechanism of action of belzutifan, the pharmacokinetic data, and safety experience in adolescent patients in Cohorts C and D of LITESPARK-015, the expanded access program and literature review, the review team agrees with the inclusion of patients 12 years of age and older in the proposed indication.

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations.

The evidence submitted meets the statutory evidentiary standard for traditional approval. A durable robust ORR supported by reduction in antihypertensive medication is a measure of direct clinical benefit in this population of patients with a serious, life threatening, and rare disease with no approved available therapy. Given the rarity of PPGL and the associated morbidity in this patient population with no currently available therapies, a randomized trial is not considered feasible. Based on a favorable benefit-risk assessment, the review team recommends traditional

approval of belzutifan for the treatment of adult and pediatric patients 12 years and older with locally advanced, unresectable, or metastatic PPGL.

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors originating in the adrenal medulla (pheochromocytoma) or the extra-adrenal sympathetic and parasympathetic paraganglia (paraganglioma). The incidence of PPGL in the US ranges from 0.04 to 0.95 cases per 100,000 per year. PPGL most commonly presents in adults but can also occur in pediatric patients with an estimated annual incidence of 0.5 cases per million children per year. The survival rates for patients with metastatic PPGL vary and are based on several factors including location of metastasis (range, 20-60% at 5 years). Clinical signs and symptoms are related to catecholamine excess (e.g., headache, palpitations, diaphoresis, or life-threatening hypertensive crisis) with hypertension being the most common sign, observed in more than 95% of patients.

There are currently no approved therapies available for patients with PPGL. Surgical removal is the mainstay of treatment for PPGL when feasible. Systemic treatment includes symptomatic treatment with medications such as octreotide for somatostatin receptor positive tumors, metaiodobenzylguanidine (MIBG) radiation therapy for patients with distant metastasis and systemic chemotherapy such as (e.g. dacarbazine, cyclophosphamide, vincristine or temozolomide). In 2018, the FDA approved iobenguane I 131 (AZEDRA, Progenics Pharmaceuticals, Inc.) for adult and pediatric patients (12 years and older) with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) who require systemic anticancer therapy. However, in 2023, Azedra was withdrawn from the market due to limited usage and manufacturing costs. Control of hypertension is critical in PPGL due to life threatening acute hypertensive emergencies, as well as clinical consequences of long-lasting hypertension, which may result in devastating morbidity to multiple body systems leading to death if untreated.

The primary support for this application is based on safety and efficacy data from Cohort A1 in LITESPARK-015, a multi-center, multi-cohort, single-arm study evaluating the safety and efficacy of belzutifan in patients with PPGL. The primary endpoint was overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by blinded independent central review (BICR). Additional efficacy outcome measures were duration of response (DOR), time to response (TTR), and the proportion of patients who had a reduction in at least one antihypertensive medication by at least 50% maintained for at least six months. Given the morbidity associated with hypertension in this population, and the direct contribution of the tumor to hypertension through secretion of catecholamines, this endpoint of reduction in antihypertensive medications was designed as a measure of clinical benefit.

The primary efficacy population consisted of 72 patients from Cohort A1. The confirmed ORR by BICR was 26% (95% CI: 17, 38). The median DOR was 20.4 (95% CI: 8.3, NR) months. A large proportion of patients, 89% and 53% respectively, maintained their response for at least 6 and

12 months. Among patients who were on antihypertensive medication at baseline and have received at least one dose of study drug, 32% achieved a sustained ≥50% reduction in at least one antihypertensive medication for at least 6 months.

Belzutifan appears to have an acceptable safety profile when assessed in the context of a life-threatening disease. The safety review focused on 72 patients treated with belzutifan as a single agent administered at 120 mg once daily in patients with locally advanced, unresectable, or metastatic PPGL. The most common (≥25%) adverse events (AEs), including laboratory abnormalities were anemia, fatigue, musculoskeletal pain, decreased lymphocytes, increased alanine aminotransferase, increased aspartate aminotransferase, increased calcium, dyspnea, increased potassium, decreased leukocytes, headache, increased alkaline phosphatase, dizziness, and nausea. Serious AEs (SAEs) occurred in 36% of patients. SAEs occurring in >2% of patients were anemia and hypertension (4.2% each) and pyelonephritis, pneumonia, hypoxia, dyspnea and hemorrhage (2.8% each). A total of two patients permanently discontinued study therapy due to increased alanine aminotransferase and paraparesis (one patient each). Dosage interruptions occurred in 40% of patients. AEs which required dosage interruption in >3% of patients were hypoxia, nausea and fatigue (4.2% each). Dose reductions occurred in 14% of patients. The most frequently reported adverse reaction which required dose reduction was hypoxia (4.2%).

No new safety concerns and no new indication-specific AEs were identified. Significant and serious adverse reactions are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in the product labeling. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use. A post-marketing requirement (PMR) will be issued to address safety in adolescents and adults under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

In the opinion of the review team, the submitted evidence meets the statutory evidentiary standard for traditional approval and provides substantial evidence of the effectiveness of belzutifan in adult and adolescent patients with locally advanced, unresectable, or metastatic PPGL. A durable robust ORR supported by reduction in antihypertensive medication is a measure of direct clinical benefit. Given the rarity of PPGL and the associated morbidity in this patient population with no currently available therapy, a randomized trial is not considered feasible. Based on a favorable risk-benefit assessment for this population with a serious, life-threatening disease, rare disease with no FDA-approved therapies, the reviewers recommend traditional approval for the following indication: "Adult and pediatric patients 12 years and older with locally advanced, unresectable, or metastatic pheochromocytoma and paraganglioma (PPGL)."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors originating in the adrenal medulla (pheochromocytoma) or the extra-adrenal sympathetic and parasympathetic paraganglia (paraganglioma) • The incidence of PPGL in the US ranges from 0.04 to 0.95 cases per 100,000 per year. PPGL most commonly present in adults but can also occur in pediatric patients with an estimated annual incidence of 0.5 cases per million children per year. • PPGL typically manifests with clinical signs and symptoms related to catecholamine excess such as headache, palpitations, diaphoresis, or life-threatening hypertensive crisis. • Hypertension is the most common sign, observed in more than 95% of patients with functional tumors. • The survival rates for patients with metastatic PPGL can be heterogeneous and are based on several factors including location of metastasis (range, 20-60% at 5 years)	Locally advanced, unresectable, or metastatic PPGLs are rare, life threatening diseases with poor survival.
Current Treatment Options	• There are no FDA approved therapies available for patients with PPGL. • Surgical removal is the mainstay of treatment for PPGL when feasible. The standard of care for locally advanced unresectable PPGLs includes symptomatic treatment with medications such as octreotide for somatostatin receptor positive tumors, metaiodobenzylguanidine (MIBG) radiation therapy for patients with distant metastasis and systemic chemotherapy such as (e.g. dacarbazine, cyclophosphamide, vincristine or temozolomide). • In 2018, the FDA approved iobenguane I 131 (AZEDRA, Progenics	There is an unmet medical need for patients with locally advanced, unresectable, or metastatic PPGL. There are no FDA approved therapies for this patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Pharmaceuticals, Inc.) for adult and pediatric patients (12 years and older) with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) who require systemic anticancer therapy. However, it was withdrawn from the market in 2023 due to limited usage and manufacturing costs. • Control of hypertension is critical in PPGL due to the high risk of life-threatening acute hypertensive emergencies, as well as the clinical consequences of long-lasting hypertension, which may result in devastating effects on multiple body systems leading to death if untreated.	
Benefit	• The primary support for this NDA is based on safety and efficacy data from Cohort A1 in LITESPARK-015, a multi-center, multi-cohort, single-arm study, to evaluate the safety and efficacy of belzutifan. • The primary endpoint was ORR per RECIST 1.1 by BICR. Additional efficacy outcome measures were duration of response (DOR), time to response (TTR), and the proportion of patients who had a reduction in at least one antihypertensive medication by at least 50% maintained for at least six months. Given the morbidity associated with hypertension in this population, and the direct contribution of the tumor to hypertension through secretion of catecholamines, this endpoint of reduction in antihypertensive medications was designed as a measure of clinical benefit. • The primary efficacy population consisted of 72 patients from Cohort A1. The confirmed ORR by BICR was 26% (95% CI: 17, 38). The median DOR was 20.4 (95% CI: 8.3, NR) months. • A large proportion of patients, 89% and 53%, respectively, maintained	The submitted evidence meets the statutory evidentiary standard for regular approval for the indicated population. A durable robust ORR supported by reduction in antihypertensive medication is a measure of direct clinical benefit in this patient population with no FDA approved therapies. A post-marketing commitment (PMC) will be issued to obtain at least 12 months of DOR from the onset of response for patients in Cohort A1 of LITESPARK-015.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	their response for at least 6 and 12 months. Among patients who were on antihypertensive medication at baseline and received at least one dose of study drug, 32% achieved a sustained ≥50% reduction in at least one antihypertensive medication for at least 6 months. • Of the 19 responders and 42 patients with stable disease, 32% and 31% of patients, respectively, had a decrease in total daily use of at least one antihypertensive which was sustained for at least 6 months.	
Risk and Risk Management	• The primary safety population included 72 patients with advanced, unresectable, or metastatic PPGL in Cohort A1 of LITESPARK-015. • Serious adverse reactions occurred in 36% of patients who received belzutifan. The most frequent serious adverse reactions were anemia and hypertension (4.2% each) and pyelonephritis, pneumonia, hypoxia, dyspnea and hemorrhage (2.8% each). • A total of two patients permanently discontinued study therapy due to increased alanine aminotransferase and paraparesis (one patient each). Dosage interruptions occurred in 40% of patients. AEs which required dosage interruption in >3% of patients were hypoxia, nausea and fatigue (4.2% each). Dose reductions occurred in 14% of patients. The most frequently reported adverse reaction which required dose reduction was hypoxia (4.2%). • The most common (≥25%) adverse reactions, including laboratory abnormalities, that occurred in patients who received belzutifan were anemia, fatigue, musculoskeletal pain, decreased lymphocytes, increased alanine aminotransferase, increased aspartate aminotransferase, increased calcium, dyspnea, increased potassium, decreased leukocytes, headache, increased alkaline phosphatase,	No new safety concerns and no new indication-specific AEs were identified. Significant and serious adverse reactions are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in the product labeling. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use. The observed safety profile is acceptable in the context of the treatment of a life-threatening disease and is overall consistent with the known adverse effects of belzutifan. A PMR will be issued to provide long-term safety data to further characterize the serious risks of anemia and hypoxia with longer-term

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	dizziness, and nausea.	use of belzutifan in pediatric patients.

1.4 Patient Experience Data

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

X	The patient experience data that was submitted as part of the application, include:							Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as						Section 8.1.2 Efficacy Results- Secondary or exploratory COA (PRO) endpoints
			X	Patient reported outcome (PRO)				EORTC QLQ-C30 and EQ-5D-5L
			☐	Observer reported outcome (ObsRO)				
			☐	Clinician reported outcome (ClinRO)				
			☐	Performance outcome (PerfO)				
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)						
	☐	Patient-focused drug development or other stakeholder meeting summary reports						[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data						
	☐	Natural history studies						
	☐	Patient preference studies (e.g., submitted studies or scientific publications)						
	☐	Other: (Please specify)						
☐	Patient experience data that was not submitted in the application, but was considered in this review.							

X

Cross-Disciplinary Team Leader
Amy Barone

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:
Pheochromocytoma and paraganglioma (collectively, PPGL) are rare neuroendocrine tumors originating in the adrenal medulla (pheochromocytomas) or the extra-adrenal sympathetic and parasympathetic paraganglia (paragangliomas). Pheochromocytomas account for 80% to 85% of PPGL and paragangliomas account for 15% to 20% [1]. The incidence of PPGL is approximately 2 to 8 individuals per 1 million people each year [2] [3] [4], corresponding to an estimated 659 to 2635 new PPGL cases per year in the US (based on the US population). Most PPGL are diagnosed in adults; approximately 10% to 20% are diagnosed during childhood, mostly at ≥10 years of age [5] [1] [6] [3]. Approximately 15% of PPGL are considered malignant [7]. Common metastatic sites include lymph nodes (80%), skeleton (70%), liver (50%), and lungs (50%) [7], and patients often experience morbidity and mortality associated with catecholamine excess and tumor mass effect, which predisposes them to cardiovascular disease and GI complications [8] [9] [10] [11]. Clinical factors associated with higher risk for malignant/metastatic disease include extra-adrenal location, multifocal presentation, tumor size of >4 cm, pediatric onset, and germline SDHB mutation [12] [13] [14]. Overall, the 5-year relative survival rate for patients with PPGL is 50% to 70% and only 11.8% for patients with distant metastases [15] [16].

Hypoxic (pseudohypoxic) signaling with HIF-2α as one of the major drivers of tumorigenesis has been well documented in PPGL [17]. Mutations in Cluster 1 (hypoxia signaling mutations such as SDHx) are common in PPGL and can lead to increased accumulation of oncometabolites, leading to a pseudohypoxic environment ultimately promoting tumor growth. Approximately 35% to 40% of PPGL result from genetic mutations, with more than 15 predisposing genes identified [18] [19] [20]. Alternatively, mutations in the hypoxia signaling pathway (VHL, HIF-2α, PHD1, PHD2) can directly stabilize HIF-2α, leading to upregulation of the VEGF and related pathways and subsequently leading to tumor growth formation and progression. Novel HIF-2α gain-of-function somatic mutations have been described with the occurrence of paraganglioma, somatostatinoma, and polycythemia [21]. VHL mutations have been observed in PPGL at a frequency ranging from 4% to 17.6% [22] [23] [24] [25].

The FDA's Assessment:
FDA agrees with the Applicant's summary of the epidemiology of PPGL. The median age of initial diagnosis is 13 years of age in pediatric patients and 45 years of age in adult patients. At least 30% of PPGLs are associated with genetic syndromes which include Von Hippel-Lindau (VHL) disease (mutation in VHL), neurofibromatosis (mutation in NF1), multiple endocrine neoplasia (mutation in rearranged during transfection [RET]) and familial paragangliomas (mutation in mitochondrial enzyme succinate dehydrogenase [i.e. SDHx]). Three main PPGL

clusters have been characterized based on germline or somatic PPGL driver genes including pseudohypoxia cluster 1 (e.g., SDHx, VHL, EPAS1), kinase signaling cluster 2 (e.g., RET, NF1), and Wnt signaling cluster 3 (e.g., CSDE1, MAML3). PPGL cluster has been associated with clinical phenotypes and prognosis (Nolting S, et al). Mechanistic pathways support the rationale for HIF-2α inhibition in clusters 1 and 2, with less data for cluster 3 targeting (Fishbein L, et al.).

2.2 Analysis of Current Treatment Options

The Applicant's Position:

There is no universal SOC for metastatic PPGL; available systemic therapies are limited and not curative [26]. Due to the rarity of the disease, very limited clinical data exist on the treatment of pediatric PPGL, and treatment is predominately the same as in adults. The only FDA-approved treatment for metastatic PPGL is HSA iobenguane I-131 MIBG (AZEDRA®), which was approved in 2018 for patients aged ≥12 years with MIBG-positive tumors that are unresectable or not amenable for locoregional treatments. It is a treatment option in ~60% of PPGL patients where MIBG uptake is observed [27] [28] [29]. In the pivotal study (N=68 participants), the ORR was 22%, with 53% of participants with DOR ≥6 months [27]. A total of 25% of patients had reduction of all BP medication by at least 50% for at least 6 months. However, treatment is associated with significant toxicity, including secondary myelodysplastic syndrome and acute leukemia, and with substantial operational limitations [30]. Due to the operational burden and the limited number of patients, manufacture of AZEDRA® has been discontinued and the treatment is no longer available to patients in the US as of 2Q2024 [31].

Other systemic options for the treatment of PPGL include conventional MIBG therapy, ^{177}Lu-dotatate, and chemotherapy [26] [32] [33]. Currently, none of these treatments has received registrational approval for metastatic PPGL. Conventional MIBG therapy is limited to unresectable or metastatic PPGL that is MIBG-positive and is associated with significant hematological toxicity [26] [32] [33]. ^{177}Lu-dotatate is used off-label only for SSR-positive tumors. Systemic chemotherapy with cyclophosphamide, vincristine, and dacarbazine or temozolomide is preferred for patients whose disease is rapidly progressing with predominant skeletal metastases or those with high tumor burden. There is no established optimal chemotherapy regimen. Overall, the ORRs for these systemic treatments range from approximately 13% to 36%; however, data are limited by a lack of rigorous clinical studies and small sample sizes [26] [32] [33].

Recent Phase 2 studies suggest that VEGF TKIs, such as sunitinib and cabozantinib, may be an option for metastatic PPGL [16] [34] [35] [26]. In the Phase 2 FIRSTMAPPP study (the only randomized, placebo-controlled study to date in PPGL), sunitinib showed numerical improvement over placebo in patients with metastatic PPGL (N=78) for the primary endpoint of PFS at 12 months and the secondary endpoints of ORR and median PFS [34]. The ORRs in the sunitinib and placebo arms were 36.1% (95% CI: 20.8, 53.8) and 8.3% (95% CI: 1.8, 22.5), respectively. The 12-month PFS was 35.9% (95% CI: 22.7, 51.6) for the sunitinib group

compared with 18.9% (95% CI: 9.5, 34.1) for the placebo group; median DOR was 12.2 months and not reported, respectively.

While progress has been made, no TKI is approved for treatment of PPGL. In addition, TKIs frequently result in dose reductions, responses can be relatively short lived due to the development of resistance, and the ADR of hypertension for VEGF TKIs can make disease management challenging in this population, particularly for patients with hypertension due to catecholamine excess [36].

The FDA's Assessment:
FDA agrees with the Applicant's position that there are no available treatment options for patients with locally advanced, unresectable, or metastatic PPGL. Surgical removal is the mainstay of treatment for PPGL when feasible. The standard of care for locally advanced unresectable PPGLs includes symptomatic treatment with medications such as octreotide for somatostatin receptor positive tumors, metaiodobenzylguanidine (MIBG) radiation therapy for patients with distant metastasis and systemic chemotherapy such as (e.g. dacarbazine, cyclophosphamide, vincristine or temozolomide) as potential treatment options.

On July 30, 2018, the FDA approved iobenguane I 131 (AZEDRA, Progenics Pharmaceuticals, Inc.) for adult and pediatric patients (12 years and older) with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) who require systemic anticancer therapy based on a reduction in the need for anti-hypertensive medications and overall response rate; however, it was withdrawn from the market in 2023 due to limited usage and manufacturing costs.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:
The current submission includes data from MK-6482-015 (hereafter, LITESPARK-015) Cohorts A1, C, and D to support regular approval of belzutifan monotherapy for the proposed indication: WELIREG® is indicated for treatment of adult and pediatric (12 years and older) patients with advanced, unresectable, or metastatic pheochromocytoma and paraganglioma (PPGL).

Belzutifan was first approved in the US on 13-AUG-2021 under the trade name WELIREG®, based on the results of the MK-6482-004 study (hereafter, LITESPARK-004), an open-label, single arm Phase 2 study of belzutifan monotherapy in participants with VHL-disease associated RCC. Belzutifan was subsequently approved on 14-DEC-2023 for certain patients with advanced RCC based on the results of Study MK-6482-005 (hereafter, LITESPARK-005), an open-label, randomized, Phase 3 study of belzutifan versus everolimus. The global registration status of

WELIREG® is rapidly evolving, and applications are under regulatory agency review worldwide. Currently, belzutifan is approved in the US for the treatment of:

- adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.
- adult patients with advanced renal cell carcinoma (RCC), following a programmed death receptor (PD-1) or programmed death ligand (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF TKI).

The approved dosage of belzutifan is 120 mg QD, administered orally until disease progression or unacceptable toxicity.

The FDA's Assessment:
FDA agrees with the Applicant's description of the relevant US regulatory actions.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
[Table 1] summarizes relevant regulatory correspondence with the Agency for belzutifan under IND 153091 for LITESPARK-015.

Table 1: Applicant − Summary of Key Regulatory-Applicant Interactions During the Belzutifan Clinical Development Program Relevant to LITESPARK-015

Date	Regulatory Activities	Summary of Communication/Outcome
06-OCT-2020	Type B Pre-IND meeting requested	A Pre-IND meeting for LITESPARK-015 was requested.
01-DEC-2020	FDA provided Pre-IND preliminary comments	FDA provided preliminary comments to the Pre-IND meeting. The Applicant determined no further discussion to be necessary and requested to cancel the meeting.
01-MAR-2021	Initial IND submission	Initial IND package was submitted.
30-MAR-2021	IND 153091: study may proceed	FDA issued study may proceed letter.
22-APR-2024	iPSP submission	The Applicant submitted an iPSP for PPGL.
29-AUG-2024	Type B pre-sNDA meeting	Teleconference between Merck and FDA to discuss potential sNDA submission based on LITESPARK-015 Cohort A1.

FDA=US Food and Drug Administration; IND=Investigational New Drug; iPSP=initial Pediatric Study Plan; PPGL=pheochromocytoma and paraganglioma; sNDA=supplemental New Drug Application; US=United States.

The FDA's Assessment:
FDA agrees with the Applicant's description of the relevant regulatory interactions.

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

4.1 Office of Scientific Investigations (OSI)

The Division consulted the Office of Scientific Investigations (OSI) to perform an audit of the imaging Contract Research Organization (CRO). (b) (4) was inspected as part of the review of this NDA supplement. The inspection of (b) (4) did not find significant concerns regarding the conduct of the imaging review, data discrepancies or integrity, Good Clinical Practice (GCP), or regulatory compliance.

Based on this inspection, it appears that the imaging review data generated by the inspected the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication. See Clinical Inspection Summary for full details (uploaded in DARRTS, (b) (4)).

4.2 Product Quality

The Office of Lifecycle Drug Products (OPQ), Division of Post Marketing Activities I recommends approval of this supplement. Please refer to the separate Review of Chemistry, Manufacturing and Controls for further details.

4.3 Clinical Microbiology

No clinical microbiology data were submitted in the supplemental application.

4.4 Devices and Companion Diagnostic Issues

No device or companion diagnostic data were submitted in the supplemental application.

5 Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:
The clinical pharmacology review of this NDA focused on the assessment of acceptability of the proposed dosage of 120 mg once daily (QD) with or without food for the treatment of adult and pediatric (12 years and older) patients with advanced, unresectable, or metastatic pheochromocytoma and paraganglioma (PPGL) and dosage recommendations in patients with moderate hepatic impairment, severe renal impairment, and end stage renal disease (ESRD).

The primary evidence of safety and effectiveness was obtained from adult patients with PPGL who received belzutifan 120 mg QD in Cohort A1 of LITESPARK-015 and three adolescents, one with PPGL and two with advanced gastrointestinal stromal tumor (GIST) (See Section 8).

The recommended dosage of belzutifan is acceptable based evidence below:

- The exposure of belzutifan in pediatric patients who weigh at least 40 kg and adult patients with PPGL at the proposed recommended dosage was comparable to that for previously approved indications for the treatment of renal cell carcinoma and von Hippel-Lindau (VHL) associated RCC.
- There was no clinical data available in pediatric patients weighing less than 40 kg, but simulations predicted that a lower dose of 80 mg would provide exposure in patients who weigh less than 40 kg within the range of that of adults (See Section 19.4).

Based on the available data from dedicated studies and exposure response analyses for safety, dosage recommendations include the following:

- No dosage adjustment is recommended in patients with moderate hepatic impairment or with end stage renal disease requiring dialysis. However, it is recommended to monitor for increased adverse events in patients with moderate hepatic impairment, given that exposure increased 1.5-fold in this population relative to patients with no or mild hepatic impairment and the positive exposure response (ER) trend for safety endpoints, including incidence of grade≥ 3 anemia, grade ≥ 3 hypoxia, based on the integrated safety analysis conducted across studies MK-6482-001, MK-6482-004, MK-6482-005, MK-6482-013, MK-6482-015 (Cohort A1) and MK-6482-018.
- It is also recommended to monitor for increased adverse reactions for patients with renal impairment given the positive ER trend for several safety endpoints and because there are no safety data for patients with severe renal impairment and limited safety data for patients with moderate renal impairment and subjects in ESRD.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in this Efficacy Supplement. This supplement is approvable from a clinical pharmacology perspective provided the Applicant and FDA reach an agreement regarding the labeling language. The key review issues with specific recommendations/comments are summarized below.

Review Issues	Recommendations and Comments
Evidence of effectiveness	The primary evidence of effectiveness comes from 72 adult patients with PPGL who received 120 mg QD in Cohort A1 of LITESPARK-015. The proposed dosing regimen is supported by an overall response rate and comparable safety findings in the PPGL adult population to previously approved indications for the treatment of renal cell carcinoma and von Hippel-Lindau (VHL) associated RCC. The safety population for adolescents includes 3 patients with GIST or PPGL in other cohorts from LITESPARK-015 and one from expanded access program. Refer to Section 8.1 for details.
General Dosing instructions	The recommended dosage in adult patients is 120 mg administered orally once daily and the recommended dosage in pediatric patients 12 years of age and older is based on body weight: (2.1) • ≥ 40 kg: 120 mg orally once daily • < 40 kg: 80 mg orally once daily Continue WELIREG until disease progression or unacceptable toxicity. WELIREG should be taken at the same time each day and may be taken with or without food.

Review Issues	Recommendations and Comments
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No clinically meaningful effect of age (15 to 90 years), sex, race (White [76%], Black [5%], Asian [15%]), ethnicity or body weight (40 to 166 kg). • The exposure of belzutifan in pediatric patients 12 years and older who weigh at least 40 kg is predicted to be within range of exposure observed in adults at the same recommended dose of 120 mg. • The exposure of belzutifan in pediatric patients 12 years and older who weigh less than 40 kg is predicted to be higher following a dose of 120 mg compared to adults at the same dose whereas it is predicted to be within the range of adult exposure following a dose of 120 mg at a lower dosage of 80 mg. • No dosage modification is recommended in patients with renal impairment including patients with end-stage renal disease who require dialysis (eGFR<15 mL). For patients with severe renal impairment, monitor for increased adverse reactions and modify the dosage for adverse reactions as recommended. • No dosage modification is recommended in patients with mild [total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin >1 to 1.5 x ULN and any AST] or moderate (total bilirubin within range of >1.5 x ULN and ≤ 3 x ULN and any AST or Child-Pugh B) hepatic impairment. Belzutifan has not been studied in patients with severe hepatic impairment (total bilirubin >1.5 x ULN and any AST). For patients with moderate and severe hepatic impairment, monitor for increased adverse reactions and modify the dosage for adverse reactions as recommended.
Labeling	Changes were made to subsections 8.4, 8.6, 8.7 and 12.3 to integrate exposure information in pediatric patients and update recommendation for specific populations including patients with ESRD or patients with moderate hepatic impairment.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

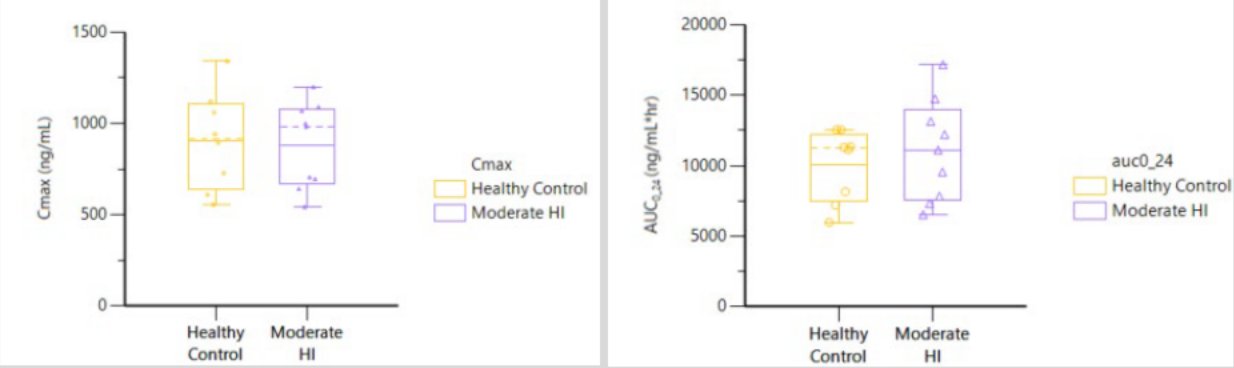
The Applicant's Position:

The updated clinical pharmacology assessment includes data from the 2 dedicated PK studies, MK-6482-020 (Study 020) in participants with moderate hepatic impairment and MK-6482-021 (Study 021) in participants with end-stage renal disease. In addition, the population PK and E-R analysis for safety and efficacy have been updated with data in adult participants with advanced, unresectable, or metastatic PPGL (Cohort A1) and adolescent participants from Cohorts C and D (LITESPARK-015).

The FDA's Assessment:

According to Study MK-6482-020 (Study 020), participants with moderate hepatic impairment (classification based on Child-Pugh criteria) had 1.5-fold higher belzutifan exposure compared to that of participants with normal hepatic function. A similar increase was observed when an exploratory analysis was conducted with hepatic impairment classification based on NCI-ODWG criteria.

Figure 1: Box plots comparing moderate hepatic impairment and normal hepatic function with single belzutifan dosage of 80 mg.

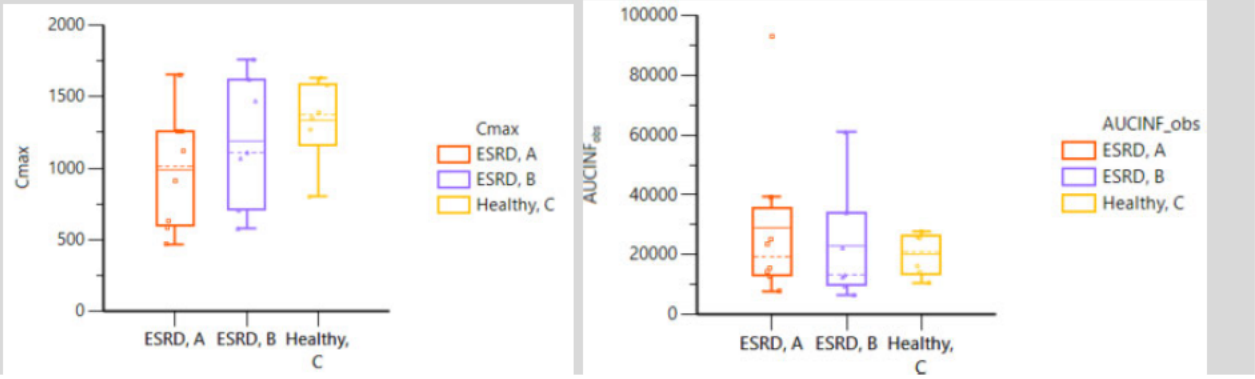


Moderate HI: Moderate Hepatic impairment

Source: Reviewer's analysis based on applicant's data

According to the study MK-6482-021 (Study 021), participants with end stage renal disease (ESRD) had a higher belzutifan exposure (AUC) by 14% before hemodialysis and a lower exposure (AUC) by 14% after hemodialysis compared to participants with normal renal function.

Figure 2: Box plots comparing ESRD and normal renal function with single belzutifan dosage of 120 mg.



ESRD, A: Subjects with ESRD received belzutifan dose at approximately 2 hours prior to hemodialysis; ESRD, B: Subjects with ESRD received belzutifan dose immediately after hemodialysis; Healthy, C: Subjects with normal renal function.

Source: Reviewer's analysis based on applicant's data.

For the population PK and E-R assessment, see section 19.4.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

Previously, a population PK analysis was performed using pooled PK data from the Phase 1 studies (Studies MK-6482-001, MK-6482-002, MK-6482-006, MK-6482-007, MK-6482-010, MK-6482-014, and MK-6482-025) as well as a randomized Phase 2 dose optimization study (MK-6482-013 [hereafter, LITESPARK-013]), the pivotal Phase 2 study in VHL-associated neoplasms (LITESPARK-004), and the pivotal Phase 3 study in advanced RCC patients (LITESPARK-005). In this application, the population PK analysis was updated by including an additional Phase 1 study (Study MK-6482-018) and the pivotal Phase 2 study in adult participants with advanced, unresectable, or metastatic PPGL (Cohort A1) and select participants from Cohorts C and D (including pediatric participants) (LITESPARK-015).

The Applicant's Position:

A total of 109 participants were added to the original analysis dataset of 831. Model parameters were re-estimated after the inclusion of the additional data, and the results were comparable to the previous values. The majority of the distribution of the covariates from the new datasets were within the range of those in the original datasets, and thus no new covariates were identified.

Furthermore, observed belzutifan exposures in adolescent participants in Cohorts C and D of LITESPARK-015 are within the range of belzutifan exposures based on adult data across indications.

Based on the above data, the 120 mg QD dose of belzutifan until disease progression or unacceptable toxicity is appropriate in adults and pediatric (12 years and older) patients with advanced, unresectable, or metastatic PPGL.

The FDA's Assessment:
FDA agrees with the Applicant's position that belzutifan exposure in pediatric patients who weigh at least 40 kg is predicted to be within the range of adults with PPGL given the same recommended dosage of 120 mg once daily; however, belzutifan exposure in pediatric patients 12 years and older and body weight < 40 kg is predicted to be higher than that of adults at the proposed dose of 120 mg. Based on simulations, belzutifan exposure at a lower dose of 80 mg in pediatrics < 40 kg is predicted to be within the range of that observed in adults at the recommended dose of 120 mg.

6.2.2.2. Therapeutic Individualization

Data:
See Sections 6.2.1, 6.2.2.1, and 6.3.1.

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

The FDA's Assessment:
FDA agrees with the Applicant's position, recommends monitoring for a higher rate of adverse reactions and modification of the dosage for adverse reactions as recommended for patients with severe renal impairment or with moderate or severe hepatic impairment.

6.2.2.3. Outstanding Issues

The Applicant's Position:
(b) (4)

The FDA's Assessment:
FDA will assess the adequacy of the proposed change to the protocol when the Applicant submits the revised protocol in a future submission for FDA review.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:
Data from 2 new clinical pharmacology studies in specific populations are available. Study 020 investigated the impact of moderate hepatic impairment on belzutifan PK, and Study 021

investigated the impact of end-stage renal disease on belzutifan PK. PK data from these studies support that no dose adjustment is needed for belzutifan for patients with moderate hepatic impairment or renal impairment including end-stage renal disease.

The FDA's Assessment:
FDA generally agrees with the Applicant's position that the clinical pharmacology data from the two trials support that no dosage adjustment is required for patients with moderate hepatic impairment or patients with ESRD who require dialysis. However, given the exposure increased 1.5-fold in patients with moderate hepatic impairment relative to that observed in patients with no or mild hepatic impairment and the positive ER trend noted for safety endpoints, including incidence of grade≥ 3 anemia and grade ≥ 3 hypoxia from the pooled safety analysis, FDA recommends monitoring for a higher rate of adverse reactions in patients with moderate hepatic impairment.

There are no clinical data available for patients with severe renal impairment; however, some exposure and safety data are available in patients with moderate renal impairment and subjects with ESRD, that shows minimal change in belzutifan exposure for these populations compared to that observed in patients with normal renal function. Additionally, no new safety signals were identified. Therefore, no dosage adjustment is recommended in patients with severe renal impairment or with ESRD; however, FDA recommends monitoring for a higher rate of adverse reactions based on the positive ER trend for safety events.

6.3.2. Clinical Pharmacology Questions

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

Data:
Exploratory E-R analyses for efficacy and safety were performed with the LITESPARK-015 population in advanced, unresectable, or metastatic PPGL.

The Applicant's Position:
The exploratory E-R relationships for efficacy and safety provide supportive evidence of effectiveness for the belzutifan 120 mg QD dose as described in Section 6.3.2.2.

The FDA's Assessment:
The proposed dosing regimen of belzutifan 120 mg QD for adult and pediatric patients (12 years and older) who weigh at least 40 kg appears reasonable based on the PK, efficacy and safety data. The exploratory exposure-safety analysis conducted based on the probability of an event vs binned exposure quartile, identified positive trends for grade ≥3 anemia, grade ≥3 hypoxia and all grade hypoxias. Similarly for efficacy, a positive E-R trend noted for ORR and AUC_{avg}. These E-R relationships with respect to safety and efficacy are generally limited because only one dose was studied in patients with PPGL.

There are no clinical data in adolescent patients who weigh less than 40 kg. A lower dosage of 80 mg QD is recommended based on simulation-based predictions which show that exposures at this dosage are within the range of that observed in adults at a dosage of 120 mg QD. Exposure matching in adolescents who weigh less than 40 kg is supported by positive E-R trends observed with grade ≥3 anemia and grade ≥3 hypoxia.

Also refer to the clinical efficacy data in Section 8.1.

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

Data:
See Section 6.2.2.

The Applicant's Position:
Based on the totality of data, 120 mg QD is the optimal dose for patients with advanced, unresectable, or metastatic PPGL which is supported by the efficacy and safety data from LITESPARK-015 and an overall favorable risk-benefit profile, even taking into account the potential E-R relationship for ORR and safety:

- A positive trend toward more responders with increasing exposure was observed across the range of exposures in the participants with advanced PPGL.
- No relationships were found for efficacy endpoints of PFS or OS.
- In general, E-R analyses for safety do not show significant safety concerns associated with higher belzutifan exposures. Positive associations were observed for ≥Grade 3 anemia but not all grades of anemia, in patients with advanced, unresectable, or metastatic PPGL. No relationships were found for hypoxia due to small numbers of events.

The FDA's Assessment:
FDA agrees with the proposed recommended dosage of 120 mg once daily for adults and pediatric patients (12 years and older, 40 kg and heavier).

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

The Applicant's Position:
Based on updated population PK analysis, no alternative dosing regimen or management strategy is required for subpopulations in patients with advanced, unresectable, or metastatic PPGL.

The FDA's Assessment:
FDA agrees with the Applicant's position. Based on the updated population PK analysis, no dosage adjustment is required because no clinically significant PK differences are expected

across age (15 to 90 years), weight (40 to 166 kg), sex, race (White (76%), Black (5%), Asian (15%), Native American, Pacific Islander), ethnicity (non-Hispanic, Hispanic), mild/moderate hepatic impairment, mild/moderate renal impairment or ESRD requiring dialysis.

UGT2B17 and CYP2C19 genotype
Participants in LITESPARK-015 cohorts A1 (PPGL, n=72), C (GIST, n=2), and D (solid tumors, n=7) were genotyped for CYP2C19 no function (*2, *3, *4, *5, *6, *7, *8, *35), decreased function (*9, *10), and increased function (*17) alleles (Bousman CA, et al.) and UGT2B17 gene deletion (*2), rs59678213, and rs28660525 (https://www.pharmacogenomics.pha.ulaval.ca/wp-content/uploads/2015/04/HAP-UGT2B17.htm; last accessed 2025-03-04) using TaqMan assays. Phenotypes were inferred from genotypes using standard methods (Bousman CA, et al.). Three patients categorized as CYP2C19 ultrarapid metabolizers by the Applicant were recategorized as CYP2C19 rapid metabolizers by the reviewer based on reported CYP2C19*1/*17 genotype. Although eligible, no dual UGT2B17 and CYP2C19 poor metabolizers were enrolled. Among participants with PPGL, there were seven (9.7%) UGT2B17 poor metabolizers, of whom two (2.8%) were also CYP2C19 intermediate metabolizers. There was one (1.4%) CYP2C19 poor metabolizer who was also a UGT2B17 intermediate metabolizer. No clear trends were observed in the reviewer's exploratory analysis of adverse events in UGT2B17 poor metabolizers (n=7) vs non-poor metabolizers (n=65). Of the three participants who had dual UGT2B17 and CYP2C19 phenotypes with reduced or no function, one participant experienced a drug-related SAE of anemia. The population PK model was updated to include additional participants from LITESPARK-015 (see section 19.4.1) and still indicates a higher exposure in dual UGT2B17 and CYP2C19 poor metabolizers. There are insufficient data to evaluate the impact of dual UGT2B17 and CYP2C19 poor metabolizer status on risk of adverse events. Therefore, information in current labeling which indicates a higher exposure and potential increased risk of adverse events in dual UGT2B17 and CYP2C19 poor metabolizers is supported by available data.

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

The Applicant's Position:
No new food-drug or drug-drug interaction studies were conducted.

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

X	X
Primary Reviewer Ritu Chadda	Team Leader Jeanne Fourie Zirkelbach

7 Sources of Clinical Data

7.1 Table of Clinical Studies

Data:

Table 2: Applicant − List of Clinical Trials Relevant to this sNDA

Trial Identity/ NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety							
MK-6482-015/ LITESPARK-015/ NCT04924075 (Cohort A1)	A Phase 2, nonrandomized, open-label study to evaluate the efficacy and safety of belzutifan (MK-6482) monotherapy in participants with advanced PPGL. No stratification based on age, sex, or other characteristics was used in this study.	Belzutifan 120 mg once daily/oral	Primary: OR per RECIST 1.1 by BICR Secondary: DOR, TTR, DC, PFS, OS, AEs, discontinuations due to AEs	Treatment continued until the protocol-defined discontinuation criteria were met (Section 8.1.1). All participants underwent long-term follow-up for OS until death, withdrawal of consent, or the end of study.	72	Advanced, unresectable, or metastatic PPGL	12 countries 31 sites
AE=adverse event; DC= disease control; DOR=duration of response; NCT=National Clinical Trials; NDA=new drug application; OR=objective response; OS=overall survival; PFS=progression-free survival; PPGL=pheochromocytoma/paraganglioma; TTR=time to response.							

The Applicant's Position:
[Table 2] presents details of the pivotal Phase 2 study, LITESPARK-015 (Cohort A1), that supports safety and efficacy for the proposed indication. Supportive pediatric data, including data from Cohorts C and D, are described in Section 10.

The FDA's Assessment:
FDA agrees with the Applicant's summary of the sources of clinical data for this supplemental application. The efficacy and safety dataset comprised of 72 patients in LITESPARK-015 (Cohort A1). Please refer to Section 8.2 regarding FDA's approach to the safety analysis.

8 Statistical and Clinical Evaluation

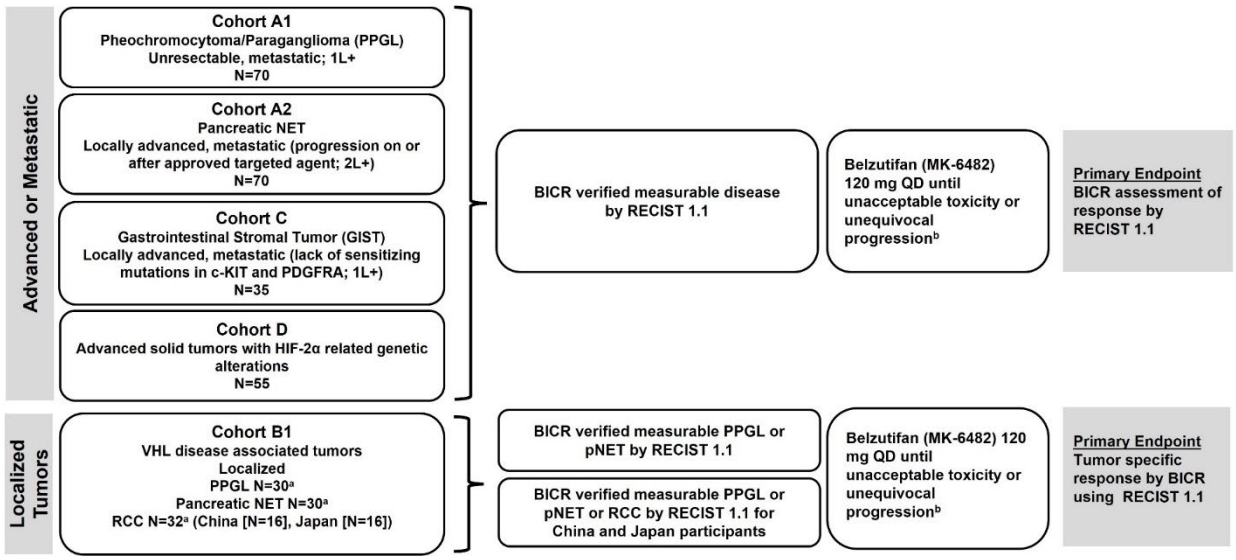
8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. LITESPARK-015 Cohort A1

Trial Design

The Applicant's Description:
LITESPARK-015 is an ongoing, Phase 2, open-label, nonrandomized, multicenter study of belzutifan monotherapy in participants with advanced, unresectable, or metastatic PPGL, advanced pNET, VHL-disease associated tumors, advanced wt GIST, or advanced solid tumors with HIF-2α related genetic alteration [Figure 1]. All participants in Cohort A1 received belzutifan 120 mg QD (oral) until disease progression or unacceptable toxicity.

Figure 3: Applicant – Study Design Schematic for LITESPARK-015



1L+=First-line or greater; 2L+=second-line or greater; BICR=blinded independent central review; GIST=gastrointestinal stromal tumor; HIF-2α=Hypoxia Inducible Factor-2 alpha subunit; PDGFRA=platelet-derived growth factor receptor alpha; pNET=pancreatic neuroendocrine tumor; PPGL=pheochromocytoma/ paraganglioma; QD=once daily; RCC= renal cell carcinoma; RECIST 1.1=response evaluation criteria in solid tumors version 1.1; VHL= von Hippel-Lindau.

Note: Participant population consists of adults and adolescents (age ≥12 years and body weight ≥40 kg) for Cohort A1, A2, C, and D. Cohort B1 was to enroll only adult participants.

Note: Treatment decisions are based on investigator assessment. Belzutifan can be continued beyond radiographic progression for clinical benefit in consultation with the Applicant.

Note: Specific cohort(s) may be terminated early and/or further enrollment stopped (study protocol Section 4.1.1).

[a] One participant can have >1 tumor type and contribute to >1 tumor type for the required sample size.

[b] Or until a treatment discontinuation criterion is met.

Study Location: Clinical investigator study sites for Cohort A1 are located in 12 countries: Canada, Denmark, France, Germany, Hungary, Italy, Russia, Spain, Sweden, Turkiye, United Kingdom, and United States. Across 31 study sites, a total of 72 participants were allocated to Cohort A1; all allocated participants received study intervention.

Dose Selection: Participants were treated with oral belzutifan 120 mg QD until disease progression or unacceptable toxicity. This is the approved dose for belzutifan in the US.

***Assignment to Treatment*:** All participants received belzutifan 120 mg QD until disease progression or unacceptable toxicity. No stratification based on age, sex, or other characteristics

was used in this study.

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

Dose Modification: Toxicity management guidelines for belzutifan, including treatment reduction, interruption, or discontinuation, were managed per protocol.

Administrative Structure: Although the study is open-label, independent radiologist(s) were blinded to clinical data as appropriate when performing the central imaging review.

Procedures and Schedules: After a screening phase of 28 days, each participant received treatment with belzutifan 120 mg QD until disease progression was radiographically documented per RECIST 1.1 (investigator), unacceptable AEs, intercurrent illness that prevented further administration of treatment, investigator's decision to discontinue the participant, or administrative reasons that required cessation of treatment. Participants were evaluated by imaging Q8W from Week 1 Day 1, or more frequently if clinically indicated. After Week 49, participants who remained on study intervention would have imaging performed Q12W. Imaging would continue until disease progression was identified by the investigator, the start of new anticancer treatment, pregnancy, withdrawal of consent, or death, whichever occurred first.

Subject completion, discontinuation, or withdrawal: Treatment beyond disease progression was allowed. After the end of treatment, each participant will be followed for the occurrence of AEs and other reportable safety events. A participant must be discontinued from treatment for any of the following reasons: radiographic disease progression per RECIST 1.1, progression or recurrence of any malignancy which requires active treatment, the start of a new anticancer treatment, unacceptable AEs/toxicity, intercurrent illness that prevents administration of study treatment, medical condition that poses unnecessary risk, withdrawal of consent, death, or loss to follow-up. All participants will be followed for OS until death, withdrawal of consent, or the end of the study.

The FDA's Assessment:
FDA agrees with the Applicant's description of the study design for LITESPARK-015.
Data from Cohort A1 was used to support the efficacy and safety of belzutifan in patients with advanced PPGL. See Sections entitled "*Study Endpoints"* and "*COA (PRO) Endpoints Results"* for a detailed description of the exploratory endpoint of decrease in anti-hypertensive medication.

Eligibility Criteria

The Applicant's Description:
Key Inclusion Criteria: Male or female participants ≥12 years of age with a histopathological

diagnosis (local report) of PPGL, locally advanced or metastatic disease that is not amenable to surgery or curative intent treatment, adequately controlled BP, an ECOG performance status of 0 or 1, and adequate organ function.

Key Exclusion Criteria: History of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years; pulse oximeter reading <92% at rest, required intermittent supplemental oxygen, or required chronic supplemental oxygen; clinically significant cardiac disease; prior therapy (chemotherapy, targeted therapy, biologics, investigational therapy, locoregional therapies or radiation) within the past 4 weeks of first dose of study intervention; MIBG therapy or radiopharmaceutical therapy within 12 weeks from Screening for participants with PPGL; treatment with any HIF-2α inhibitor (including belzutifan); or colony-stimulating factors (eg, G-CSF, GM-CSF, or recombinant EPO) ≤28 days prior to the first dose of study intervention.

The FDA's Assessment:
FDA agrees with the Applicant's description of the eligibility criteria.

Additionally, patients who had received no prior therapy for PPGL were allowed to enroll if a satisfactory treatment option did not exist or if they were not candidates for systemic chemotherapy or had refused such therapy. There was no limit on number of prior systemic therapies. Locoregional therapies or adjuvant/neoadjuvant therapies were not considered a line of prior systemic therapy.

Patients with concomitant hypertension must have had no change in anti-hypertensive medications for at least 2 weeks prior to the start of study treatment to be eligible.

Study Endpoints

The Applicant's Description:
The study endpoints for LITESPARK-015 Cohort A1 are detailed in [Table 3].

Table 3: Applicant – Study Endpoints for LITESPARK-015 Cohort A1

Primary Endpoints	
OR	A confirmed CR or PR per RECIST 1.1 assessed by BICR
Secondary Endpoints	
DOR	The time from first documented evidence of CR or PR until disease progression per RECIST 1.1 assessed by BICR, or death due to any cause, whichever occurs first
TTR	The time from first dose of belzutifan to first documented evidence of CR or PR; per RECIST 1.1 assessed by BICR
DC	A confirmed CR, PR, or SD; per RECIST 1.1 assessed by BICR
PFS	The time from first dose of belzutifan to the first documented PD per RECIST 1.1 assessed by BICR, or death from any cause, whichever occurs first
OS	The time from first dose of belzutifan until death from any cause
Safety	AEs Discontinuations due to AEs
Tertiary/Exploratory Endpoints	
BP medication reduction	Reduction in all BP medication (total daily dose) from baseline and duration
EORTC QLQ-C30 global health status/HRQoL and physical functioning	Change from baseline in EORTC QLQ-C30 global health status/HRQoL (Items 29 and 30) and physical functioning (Items 1-5)
EQ-5D-5L	Change from baseline in EQ-5D-5LVAS
AE=adverse event; BP= blood pressure; CR=complete response; DCR=disease control rate; DOR=duration of response; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; EQ-5D-5L= European Quality of Life Five Dimensions Five Level Questionnaire; OR=objective response; OS=overall survival; PFS=progression-free survival; PR=partial response; QoL=quality of life; SD=stable disease; TTR=time to response; VAS=Visual Analog Scale	

The FDA's Assessment:

FDA agrees with the Applicant's description of the endpoints. In general, durable confirmed ORR is a relevant endpoint to evaluate the treatment effect of belzutifan in this patient population and disease setting. Blood pressure (BP) medication reduction is a clinically meaningful endpoint and was used to support the primary endpoint of ORR and DOR assessed by BICR.

Time-to-event endpoints (such as PFS, TTR and OS) and stable disease are generally not interpretable in a single-arm trial.

Statistical Analysis Plan and Amendments

The Applicant's Description:
[Table 4] summarizes the analysis strategy for LITESPARK-015.

Table 4: Applicant – Summary of the Statistical Analysis Plan for LITESPARK-015 Cohort A1

Study Design Overview	Phase 2 study to evaluate the efficacy and safety of belzutifan monotherapy in participants with PPGL, pNET, VHL disease associated tumors, wt GIST, or advanced solid tumors with HIF-2α related genetic alterations
Treatment Assignment	Belzutifan 120 mg QD, single treatment arm, open-label
Analysis Populations	Efficacy and safety: APaT
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	For ORR, the point estimate and exact Clopper-Pearson CI were to be provided.
Statistical Methods for Key Safety Analyses	Safety was to be evaluated using descriptive statistics.
Interim Analyses	Efficacy and safety data were to be monitored regularly throughout the study. The Applicant was to review results. Based on the review, the study enrollment may be discontinued at the discretion of the Applicant if a clinically meaningful response was not observed, or a safety concern was identified. Interim analyses were to be conducted after participants were followed up for approximately 6 months or longer.
Multiplicity	No multiplicity adjustment was planned.
Sample Size and Power	Cohort A1: Approximately 70 participants were planned to be enrolled in Cohort A1.

APaT=all participants as treated; CI=confidence interval; HIF-2α=hypoxia inducible factor-2 alpha; ORR=objective response rate; pNET=pancreatic neuroendocrine tumors; PPGL= pheochromocytoma and paraganglioma; QD=once daily; VHL=von Hippel-Lindau.

The FDA's Assessment:
FDA agrees with the Applicant's summary of the SAP for Cohort A1. All efficacy and safety analyses were conducted in the All Participants as Treated (APaT) population, defined as all patients who received at least one dose of study drug. For BP medication related endpoints, the analyses were conducted in the BP medication Full Analysis Set (FAS) population, defined as patients who were on antihypertensive medication at baseline and have received at least one dose of study drug.

The Applicant submitted 90-day efficacy and safety updates based on a data cutoff (DCO) date of October 23, 2024. Compared to the original DCO of May 23, 2024, the updated data provided an additional 5 months of follow-up for patients in LITESPARK-015 Cohort A1 and were used for the primary efficacy evaluation.

No hypothesis testing was planned. Sample size calculation was based on the desired precision of ORR estimates. ORR and its exact 95% CI were calculated using Clopper-Pearson method. Patients with no post-baseline assessments were considered non-responders. The median DOR was summarized using the Kaplan-Meier method.

The last update of Supplemental SAP Amendment 03 was completed on February 6, 2024, prior to the database lock on June 20, 2024. The updates and changes in the SAP were aligned with those in the protocol amendments.

Protocol Amendments

The Applicant's Description:
The original protocol was finalized on 19-FEB-2021 and amended 5 times [Table 5].

Table 5: Applicant − Protocol Amendments for LITESPARK-015

Document	Date of Issue	Overall Rationale
Amendment 05	06-FEB-2024	To align dose modification guidelines with the USPI, which was updated based on the availability of new data (12/2023).
Amendment 04	09-NOV-2023	The primary reason for this amendment is to address country-specific regulatory guidance (b) (4)
Amendment 03	29-MAR-2023	Corrected Exclusion Criterion Number 8 to include criterion timeframe relative to first dose of study intervention.
Amendment 02	28-FEB-2023	Updated to include advanced wt GIST cohort (Cohort C) and advanced solid tumors with HIF-2α related genetic alterations cohort (Cohort D).
Amendment 01	17-MAY-2022	Added VHL disease-associated tumors cohort (Cohort B1) to satisfy US FDA postmarketing commitments and study the safety and efficacy in (b) (4) participants for regional regulatory requirements.
Original Protocol	19-FEB-2021	Not applicable.

FDA=US Food and Drug Administration; GIST=gastrointestinal stromal tumor; HIF-2α=hypoxia-inducible factor 2a; US=United States; USPI=US Prescribing Information; VHL=von Hippel-Lindau; wt=wild type.

The FDA's Assessment:
FDA agrees with the Applicant's description of protocol amendments.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:
LITESPARK-015 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 that LITESPARK-015 was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Financial Disclosure

The Applicant's Position:
A financial disclosure review of LITESPARK-015 has been conducted.

The FDA's Assessment:
In accordance with 21 CFR Part 54, the Applicant submitted Form FDA 3454 (Financial Interests and Arrangements of Clinical Investigators) certifying that as the Sponsor of the submitted studies, they did not enter into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. All investigators were assessed for equity interest, significant payments of other sorts, and other compensation by the sponsor or proprietary interest.

The Applicant certified that none of the financial interests or arrangements described in 21 CFR Part 54 existed for any of the investigators who participated in Cohort A1 of LITESPARK-015. The Applicant provided a list of all investigators for Cohort A1 LITESPARK-015 in the Financial Disclosure form and in Appendices 16.1.4.

FDA reviewed the financial disclosure information provided by the Applicant (see Appendix 18.2) and agrees that the integrity of the study data was not affected by the financial interest of the investigators.

Patient Disposition

Data:

Table 6: Applicant – Disposition of Participants (Cohort A1; APaT Population)

	Belzutifan 120 mg QD

	n	(%)
Participant in population	72	
Status for Trial		
Discontinued	18	(25.0)
Death	18	(25.0)
Ongoing	54	(75.0)
Status for Study Medication in Trial		
Started	72	
Discontinued	35	(48.6)
Adverse Event	2	(2.8)
Clinical Progression	3	(4.2)
Non-Study Anti-Cancer Therapy	1	(1.4)
Physician Decision	1	(1.4)
Progressive Disease	28	(38.9)
Ongoing	37	(51.4)

If the overall count of participant is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participant in population is used as the denominator for the percentage calculation.

Database Cutoff Date: 23MAY2024.

Source: [P015V02MK6482: adam-adsl]

The Applicant's Position:
A total of 72 participants were allocated to Cohort A1 [Table 6]. As of the DCO (23-MAY-2024), 48.6% of participants had discontinued study intervention, primarily due to PD, and 51.4% of participants were continuing to receive study intervention. A total of 25.0% of participants discontinued the study due to death. The median duration of follow-up was 23.6 months (range: 2.1 to 32.5 months).

The FDA's Assessment:
FDA agrees with the Applicant's assessment of patient disposition at the original DCO of May 23, 2024. At the updated DCO (October 23, 2024), the estimated median duration of follow-up using reversed Kaplan-Meier method was 30.8 months (95% CI: 27.0, 33.1).

Protocol Violations/Deviations

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

Important protocol deviations were reported for 32 participants in LITESPARK-015 Cohort A1; none of the important protocol deviations were considered to be clinically important.

No participant's data were excluded from analyses for LITESPARK-015 due to a protocol deviation; no important protocol deviations were classified as a serious GCP compliance issue for this study.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of protocol deviations. There were no significant protocol deviations identified that would likely lead to an alternative interpretation of LITESPARK-015 trial results.

Table of Demographic Characteristics

Data:

Table 7: Applicant –Participant Characteristics (Cohort A1; APaT Population)

	Belzutifan 120 mg QD	
	n	(%)
Participants in population	72	
Sex		
Male	42	(58.3)
Female	30	(41.7)
Age (Years)		
<18	0	(0.0)
>= 18 - < 65	63	(87.5)
>= 65	9	(12.5)
Mean	51.1	
SD	12.5	
Median	51.5	
Range	22 to 77	
Race		
Asian	1	(1.4)
Black Or African American	3	(4.2)
Multiple	1	(1.4)
White,asian	1	(1.4)
White	67	(93.1)
Ethnicity		
Hispanic Or Latino	4	(5.6)
Not Hispanic Or Latino	67	(93.1)
Unknown	1	(1.4)
Region		
North America	21	(29.2)
Western Europe	46	(63.9)
Rest of the World	5	(6.9)
ECOG		
0	39	(54.2)

	Belzutifan 120 mg QD	
	n	(%)
1	33	(45.8)
Number of Prior Lines of Therapy[a]		
0	18	(25.0)
1	20	(27.8)
2	11	(15.3)
>=3	23	(31.9)
Genetic Syndrome History		
Yes	28	(38.9)
FAMILIAL PARAGANGLIOMA TYPE 1 (SDHD)	2	(2.8)
FAMILIAL PARAGANGLIOMA TYPE 4 (SDHB)	24	(33.3)
SDHA MUTATION	2	(2.8)
No	20	(27.8)
Unknown	24	(33.3)
VHL Disease History		
No	48	(66.7)
Unknown	24	(33.3)
Functional Syndrome		
Yes	43	(59.7)
No	14	(19.4)
Unknown	15	(20.8)
Disease Presentation Type		
LOCALLY ADVANCED	2	(2.8)
METASTATIC CANCER	70	(97.2)
Prior Surgery		
Yes	60	(83.3)
No	12	(16.7)
Medical History of Hypertension		
Yes	60	(83.3)
No	12	(16.7)
Paraganglioma Diagnosis		
Yes	45	(62.5)
No	27	(37.5)
Pheochromocytoma Diagnosis		
Yes	24	(33.3)
No	48	(66.7)
Both Paraganglioma and Pheochromocytoma Diagnosis		
Yes	3	(4.2)
No	69	(95.8)

[a]0 means no prior systemic therapy or the prior therapies do not fulfill the definition of prior lines of therapy.
Database Cutoff Date: 23MAY2024.

Source: [P015V02MK6482: adam-adsl]

The Applicant's Position:

Demographic and baseline characteristics are provided in [Table 7]. The demographics and baseline characteristics of participants in Cohort A1 were generally representative of the patient population with advanced, unresectable, or metastatic PPGL.

The FDA's Assessment:
FDA generally agrees with the Applicant's summary of patient demographics and baseline characteristics. While LITESPARK-015 (Cohort A1) did allow enrollment as young as 12 years of age, no patients less than 18 years old enrolled into cohort A1. The median age was 52 years (range: 22 to 77). Enrollment consisted largely of patients outside of the US, with most patients being enrolled in Western European countries such as France, Italy and Sweden. Regarding disease characteristics, a similar proportion of patients had ECOG score of 0 and 1, with slightly more having ECOG of 1 (54%). There were more patients with a diagnosis of paraganglioma (63%) than pheochromocytoma (33%) and majority of patients received at least one prior line of therapy. Notably most patients (83%) had a history of hypertension.

FDA notes that some demographics may be under-represented based on the incidence reported for the US patient population (e.g. race, Hispanic ethnicity); however, these demographics are not well characterized for patients with PPGL. In the context of a rare disease, the baseline disease characteristics of the enrolled patients appear to be representative of the disease in the US population.

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

The Applicant's Position:
The majority of participants in Cohort A1 were White, not Hispanic or Latino, and from North America or Western Europe. Slightly more than half of participants were male (58.3%) and had an ECOG PS of 0 (54.2%). The median age was 51.5 years (range: 22 to 77 years); no participant under 18 years was enrolled. The majority of participants had metastatic disease (97.2%) at baseline, had prior surgery (83.3%), and had received 1 or more prior lines of therapy (75%). The study population included participants who identified as multiple races. Diversity in clinical trials has been and continues to be a priority for the Applicant, as an integral component of the Applicant's broader Diversity and Inclusion strategy and commitments, and in recognition of the clinical value of continued focus on the diversity of our studies.

The FDA's Assessment:
FDA agrees with the Applicant's summary of baseline disease characteristics. Please see the section above for further details.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:
***Treatment compliance*:** Study intervention was dispensed to participants for oral administration,

and the number of tablets returned at a visit was used to assess compliance. Median treatment compliance was 99.6%, with 97.2% of participants having compliance >80%.

Concomitant Medications and Subsequent Oncological Therapies: Overall, the concomitant treatments administered were representative of those commonly prescribed for patients of the target population and were not considered to have impacted the study results. The most commonly reported prior and concomitant medications were chemotherapy (50.0%), radiopharmaceutical (44.4%), and VEGF TKI (25.0%).

A total of 26.4% of participants received subsequent systemic oncologic therapies, and the most frequently reported (≥5% of participants) were lutetium (^{177}LU) dotatate (9.7%), dacarbazine (6.9%), and temozolomide (6.9%).

The FDA's Assessment:

FDA agrees with the Applicant's description of concomitant and subsequent therapies; however, chemotherapy, radiopharmaceutical therapy, and VEGF TKIs were prior therapies received by some patients. No patients received concomitant disease-modifying therapy while receiving study therapy with belzutifan.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

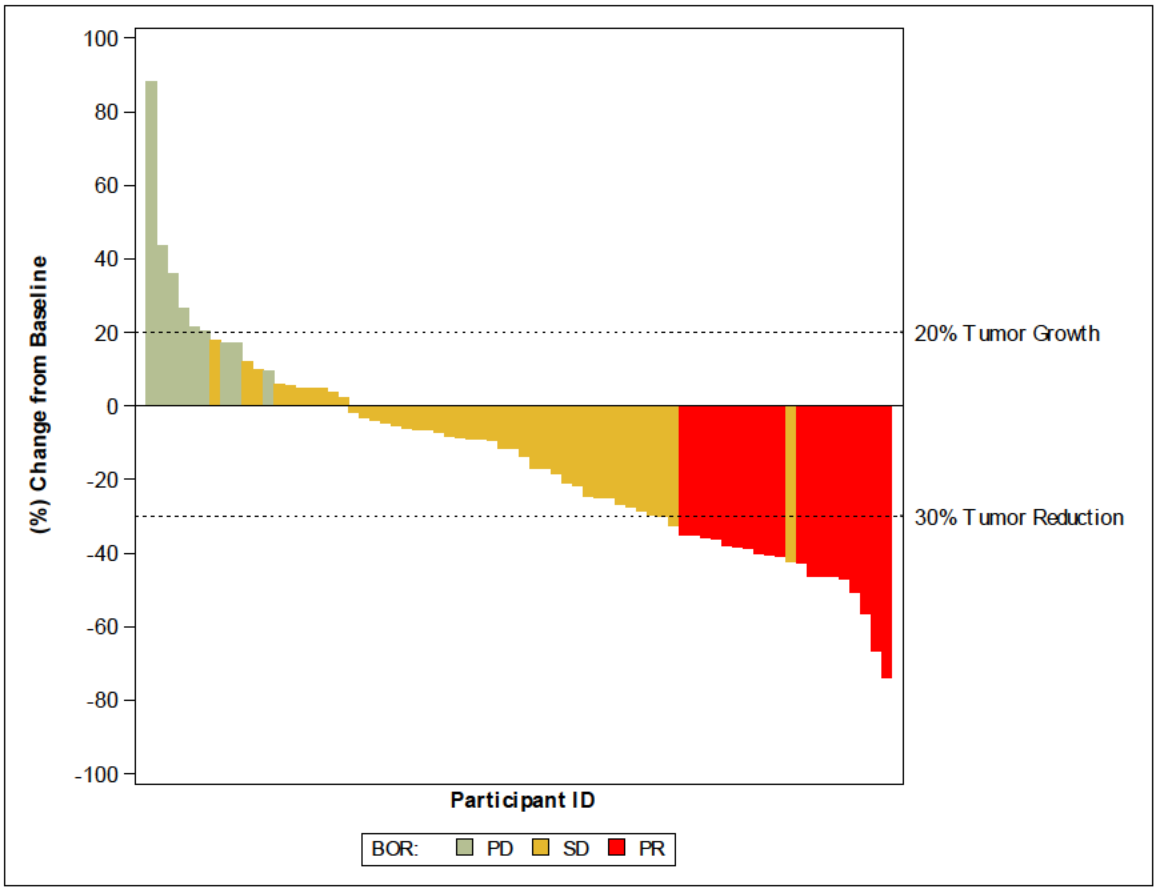
Table 8: **Applicant – Summary of Best Overall Response (Confirmed) Based on BICR per RECIST 1.1 (Cohort A1; APaT Population)**

Response Evaluation	Belzutifan 120 mg QD		
	n	%	95% CI[a]
Participants in population	72		
Complete Response (CR)	0	0.0	(0.0, 5.0)
Partial Response (PR)	19	26.4	(16.7, 38.1)
Objective Response (CR+PR)	**19**	**26.4**	**(16.7, 38.1)**
Stable Disease (SD)	42	58.3	(46.1, 69.8)
Disease Control (CR+PR+SD)	**61**	**84.7**	**(74.3, 92.1)**
Progressive Disease (PD)	10	13.9	(6.9, 24.1)
No Assessment	1	1.4	(0.0, 7.5)

[a] Based on the exact method for binomial data.
Database Cutoff Date: 23MAY2024.

Source: [P015V02MK6482: adam-adsl; adrs]

Figure 4: Applicant – Waterfall Plot of Best Tumor Change from Baseline Based on RECIST 1.1 Assessed by BICR with Confirmed Response (Cohort A1; APaT Population)



Database cutoff date: 23MAY2024

Source: [P015V02MK6482: adam-adsl; adrs; adtl]

The Applicant's Position:

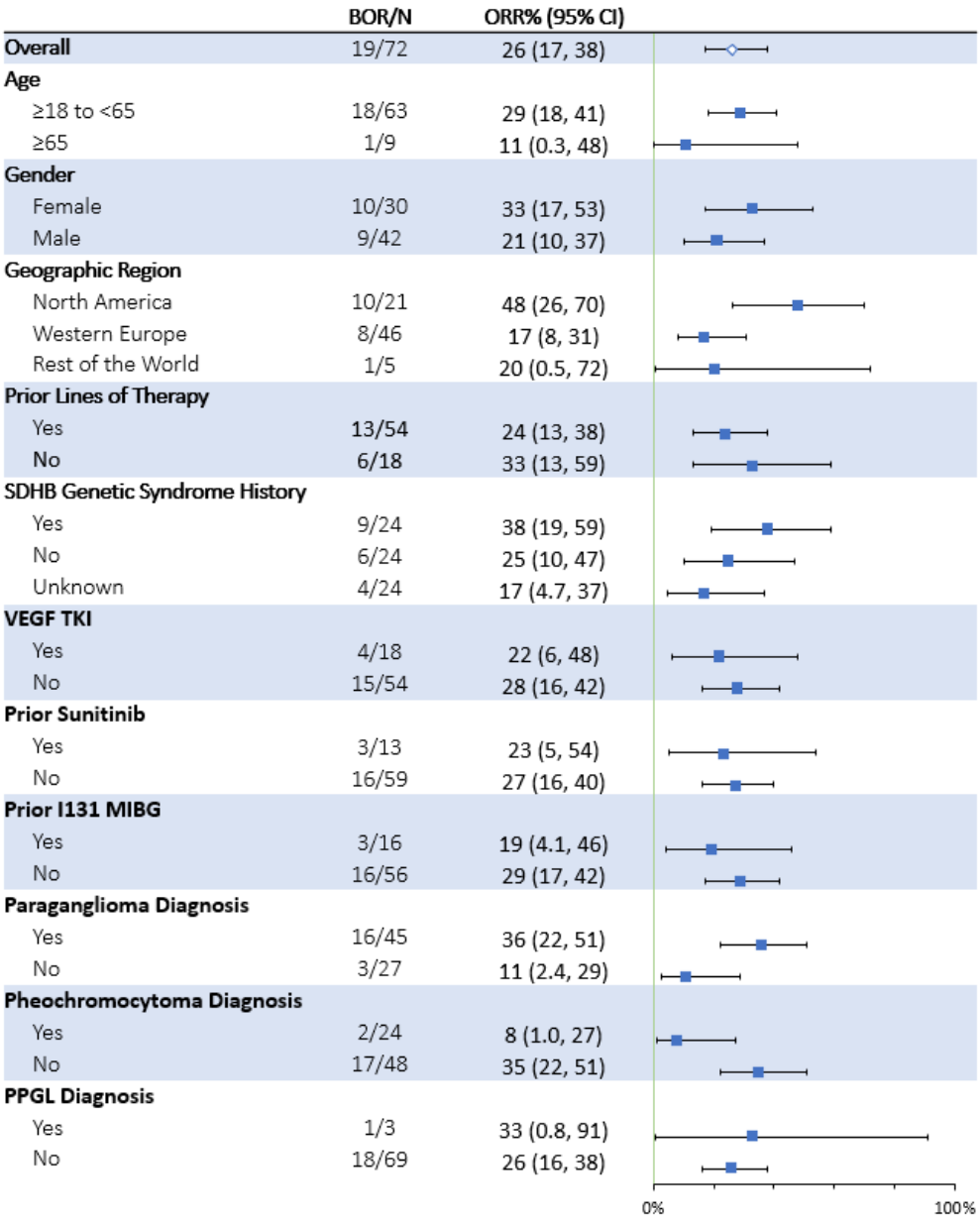
Belzutifan monotherapy provided a clinically meaningful benefit in ORR for participants with advanced, unresectable, or metastatic PPGL in Cohort A1. Based on BICR assessment per RECIST 1.1:

- The confirmed ORR was 26.4% (95% CI: 16.7, 38.1); 19 participants demonstrated a PR [Table 8].
- A waterfall plot of best tumor change from baseline by BICR per RECIST 1.1 for participants with confirmed responses is presented in [Figure 2].
- Results for confirmed ORR were generally consistent across prespecified subgroups. Results should be interpreted with caution due to small sample sizes in selected subgroups.
- ORR by investigator assessment per RECIST 1.1 was consistent with assessment by BICR.

The FDA's Assessment:
FDA agrees with the Applicant's efficacy results for the primary endpoint of confirmed ORR per RECIST v1.1 assessed by BICR at the original DCO of May 23, 2024.

At the updated DCO, the ORR by BICR remained the same whereas the actual responder set changed as a result of revised response assessments. Specifically, one patient became a responder because additional new scans confirmed initial earlier response; a second patient had their response status changed from PR to SD as a result of a change in adjudicator responsible for interpretation of that patient's imaging assessments. The investigator-assessed ORR remained unchanged, which was 22% (95% CI: 13, 34), with no confirmed CR and 16 patients having confirmed PR, consistent with the primary results assessed by BICR. In both analyses of ORR by BICR and investigator, one patient who had no post-baseline assessment was included as a non-responder. Subgroup analyses of ORR were generally consistent across key prespecified subgroups, though the small numbers of patients in each subgroup precludes precise estimation of the ORR. Of note, only 2 of 24 patients (8%) with pheochromocytoma had a response, though this observation should be considered in the context of the small subgroup size (Figure 5). Furthermore, 6 of 24 patients (25%) with pheochromocytoma had a reduction in BP medications by ≥ 50% for at least 6 months, indicating that therapy with belzutifan provided clinical benefit despite the relatively low ORR in this subgroup.

Figure 5. Subgroup Analyses of ORR by BICR, Cohort A1 APaT Population



DCO date: October 23, 2024
Source: FDA reviewer's analyses

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 conducted in accordance with GCP guidelines. Merck Research Laboratory Quality Assurance 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.

Part of this study was conducted during the COVID-19 pandemic. There were no changes in the planned conduct of the study or planned analyses due to the COVID-19 pandemic. No serious GCP compliance issues were identified for this study. Audit information is available on request. No issues were reported concerning the submitted data quality or integrity that raise questions about the reported efficacy results.

The FDA's Assessment:
FDA generally agrees with the Applicant that the data quality and integrity for this application did not raise major concerns.

In response to an information request sent on March 28, 2025 for clarification regarding the derivation of overall survival (OS) data, the Applicant stated that the uncut last known alive date (UCLKADT) in ADTTE dataset was not updated to maintain the consistency with that in ADSL dataset. Therefore, the variable UCLKADT was updated in a revised and re-submitted ADTTE dataset to reflect the actual survival follow-up. Since this only impacted OS derivation and median follow-up estimation in 3 patients, the change is considered minimal, and the overall conclusions remain the same.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:
Duration of Response and Time To Response

Based on BICR assessment per RECIST 1.1:

- The median DOR in responders was NR (95% CI: 11.1, NR); the range was 2.7+ to 24.0+ months [Table 9].
- By KM estimation, 100% of responders showed extended response duration ≥6 months, and 65.7% of responders showed extended response duration ≥12 months [Table 9]. The DOR KM curve showed prolonged response for confirmed responders [Figure 3].
- The median TTR was 9.0 months (range: 1.7 to 24.8 months) [Table 9].
- The median follow-up duration among the 19 participants with confirmed response was 16.2 months (range: 3.3 to 24.6 months). Of the 19 participants with a confirmed response, 17 (89.5%) had a duration of follow-up ≥6 months from the time of onset of response.

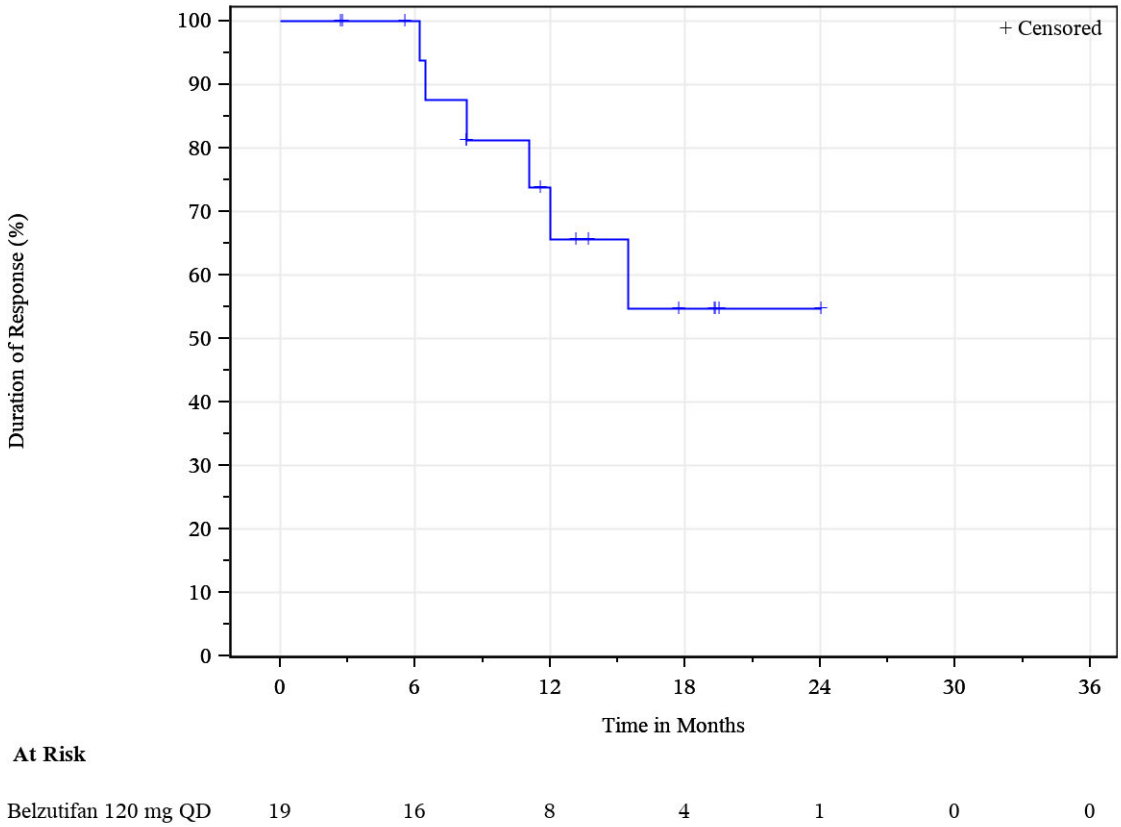
Table 9: Applicant − Summary of Time to Response and Duration of Response Based on RECIST 1.1 Assessed by BICR in Participants with Confirmed Response (Cohort A1; APaT Population)

	Belzutifan 120 mg QD (N=72)
Number of participants with response[a]	19
Time to Response (months)	
Mean (SD)	10.0 (6.7)
Median (Range)	9.0 (1.7 to 24.8)
Response Duration[b] (months)	
Median (95% CI)	NR (11.1, NR)
Range	2.7+ to 24.0+
Number (%[b]) of Participants with Extended Response Duration	
≥3 months	17 (100.0)
≥6 months	16 (100.0)
≥9 months	11 (81.3)
≥12 months	8 (65.7)
≥15 months	6 (65.7)
≥18 months	4 (54.7)
≥21 months	1 (54.7)
≥24 months	1 (54.7)

[a] Includes participants with complete response or partial response.
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 23MAY2024

Source: [P015V02MK6482: adam-adsl; adtte]

Figure 6: Applicant – Kaplan-Meier Estimates of Duration of Response (DOR) Based on RECIST 1.1 Assessed by BICR with Confirmed Response (Cohort A1; APaT Population)



Database Cutoff Date: 23MAY2024.

Source: [P015V02MK6482: adam-adsl; adtte]

Disease Control Rate

Based on BICR assessment per RECIST 1.1, the DCR was 84.7% (95% CI: 74.3, 92.1).

Progression-Free Survival

Based on BICR assessment per RECIST 1.1:

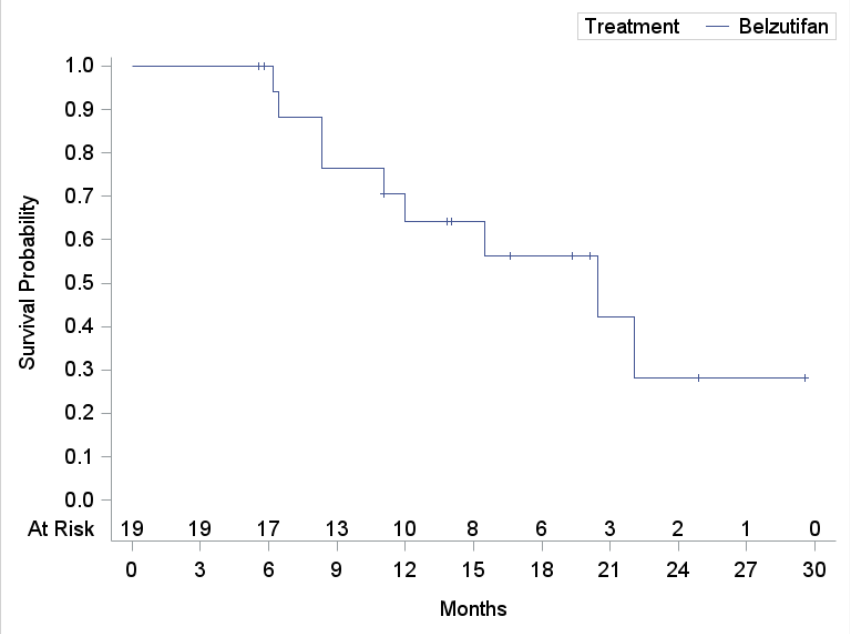
- By KM estimation, the median PFS was 22.0 months (95% CI: 13.8, NR).
- PFS rates at 12 and 24 months by KM estimation were 66.2% (95% CI: 53.7, 76.1) and 49.4% (95% CI: 36.4, 61.0), respectively.

Overall Survival

By KM estimation, the median OS was NR. The OS rates at 12 and 24 months were 88.9% (95% CI: 79.0, 94.3) and 75.5% (95% CI: 63.4, 84.1), respectively.

The FDA's Assessment:
At the original DCO, the median DOR was not reached. Among the 19 responders in Figure 6, 3 (16%) patients were censored within 6 months from the time of initial response. With the 90-day updated data (Figure 7), the responders had an additional 5 months of follow up with a median DOR of 20.4 months (95% CI: 8.3, NR). Among the 19 responders, 2 (11%) patients were censored with a follow-up less than 6 months from the time of onset of response; 8 (42%) patients were censored before reaching the median and all due to ongoing response. An additional 12 months of follow-up data for DOR will be collected as part of a postmarketing commitment (PMC). Furthermore, the Applicant calculated the proportion of patients with a response maintained beyond specific landmark time points using Kaplan-Meier estimates. However, this approach may overestimate the proportions given early censoring. FDA also considered DOR estimates based on observed time which reflects a more conservative estimate (Table 10). As shown in Table 10, at least 89% of the patients had a confirmed tumor response maintained for 6 months or longer.

Figure 7. Kaplan-Meier Plot of DOR by BICR, 90-Day Update



DCO date: October 23, 2024
Source: FDA reviewer's analyses

Table 10. Proportion of Responders with Maintained Response by Observed DOR

DOR, %	Belzutifan N=19*
≥6 months	89
≥12 months	53
≥18 months	32
≥24 months	11

* Proportions calculated based on the number of responders in APaT Population.
DCO date: October 23, 2024
Source: FDA reviewer's analyses

FDA did not independently verify the results for TTR, PFS and OS given that time-to-event endpoints are not interpretable in a single-arm setting.

Dose/Dose Response

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

The FDA's Assessment:
See section 6.2.2.1 for clinical pharmacology's assessment regarding dosing.

Durability of Response

The Applicant's Position:
DOR is discussed in the secondary efficacy endpoints Section 8.1.2 (Efficacy Results – Secondary and other relevant endpoints).

The FDA's Assessment:
FDA agrees with the Applicant's position, noting that with the 90-day update 89% of responders had a response of at least 6 months and 53% had ongoing response of at least 12 months.

Persistence of Effect

The Applicant's Position:
DOR results for LITESPARK-015 are discussed in the secondary efficacy endpoints Section 8.1.2. No additional data on persistence of efficacy are provided.

The FDA's Assessment:
FDA generally agrees with the Applicant's position, noting that 39% of patients have discontinued treatment due to disease progression and 25% of patients have discontinued the trial due to death.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Blood Pressure Control

Participants in Cohort A1 showed sustained reduction in use of BP medication. Sixty participants were on treatment with BP medications at the time of study enrollment.

- The percentages of participants that showed ≥50% reduction in at least 1 BP medication for ≥3 and ≥6 months were 35.0% and 30.0%, respectively.
- The percentages of participants that showed ≥50% reduction in all BP medications for ≥3 and ≥6 months were 16.7% for both.

Patient-reported Outcomes

PRO assessments in this study included EORTC QLQ-C30 and EQ-5D-5L conducted in the PRO FAS population, defined as participants who had PRO assessments available at both baseline and the specified postbaseline timepoint for the specific endpoint and had received at least 1 dose of study intervention.

Week 73 was selected as the time point for change from baseline meeting the prespecified criteria for completion and compliance rates (completion rate ≥60% and compliance rate ≥80%).

EORTC QLQ-C30

Analyses of EORTC QLQ-C30 change scores from baseline to Week 73 show that HRQoL was maintained during treatment with belzutifan monotherapy:

- GHS/QoL score improved or remained stable in the majority of participants (21.7% improved and 52.2% stable).
- Physical functioning scores improved or remained stable in the majority of participants (20.3% improved and 58.0% stable).

The empirical mean changes from baseline to Week 73 were positive, indicating improvement, for all but 1 of the functional scales. The empirical mean changes from baseline to Week 73 were negative, indicating improvement, for most of the symptom scales/items.

EQ-5D-5L VAS

EQ-5D-5L VAS scores showed a numerical improvement from baseline to Week 73, with an empirical mean change of 4.11 (95% CI: -1.88, 10.11).

The FDA's Assessment:
The proportions of patients who achieved a reduction of at least 25% and 50% in at least one BP

medication, maintained for at least 3 and 6 consecutive months from baseline, were calculated and used to support the efficacy evaluation (Table 11).

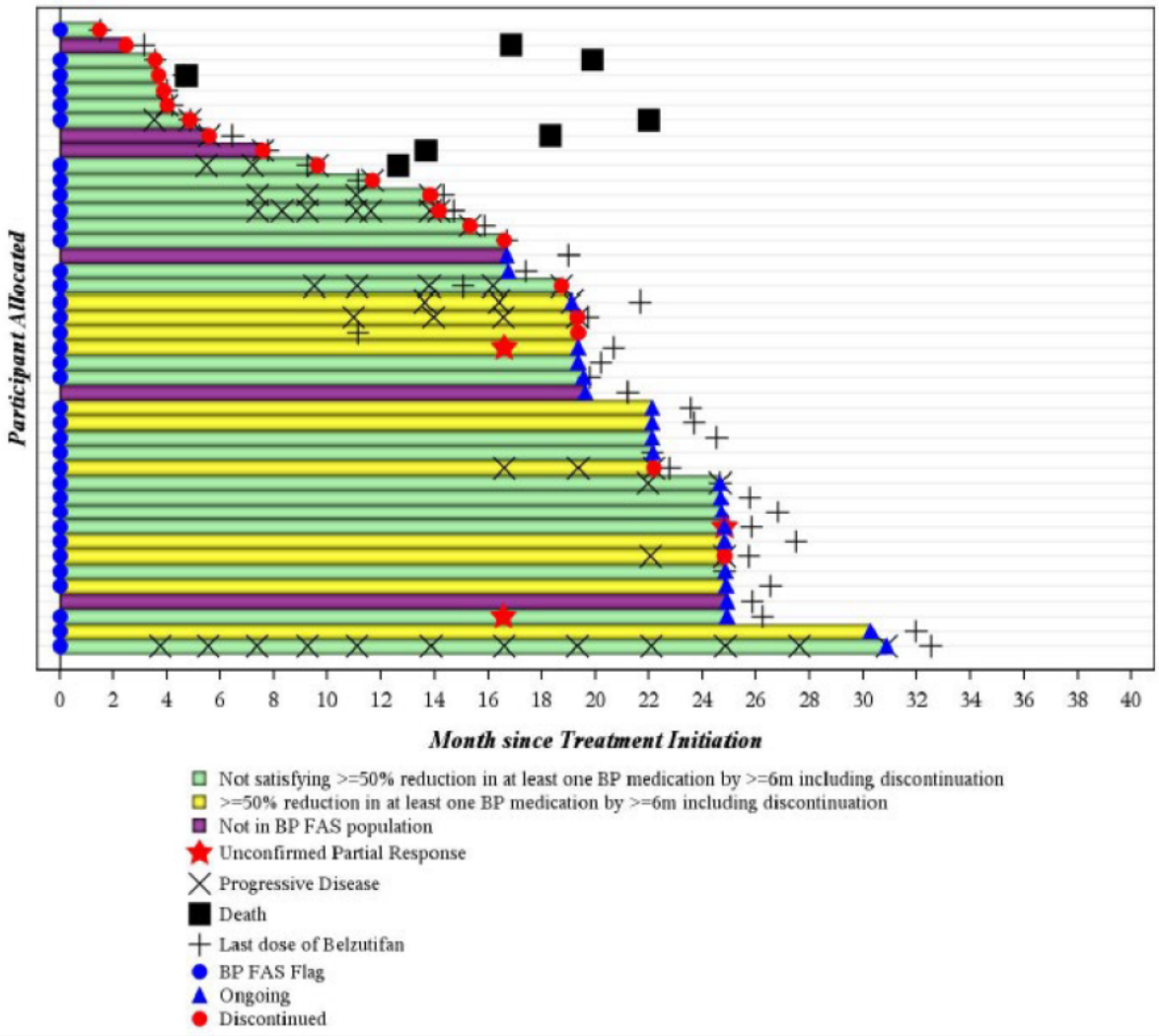
Table 11. Blood Pressure Medication Reduction from Baseline

Reduction in at least one BP medication, n (%)	Belzutifan N = 60
≥ 25% for ≥ 3 months	23 (38)
≥ 25% for ≥ 6 months	20 (33)
≥ 50% for ≥ 3 months	21 (35)
≥ 50% for ≥ 6 months	19 (32)

DCO date: October 23, 2024
Source: FDA reviewer's analyses

Of the 19 responders and 42 patients with stable disease, 6 (32%) patients and 13 (31%) had a 50% decrease in total daily use of at least one BP medication which was sustained for 6 months or more, respectively (see Swimmers Plot below for summary of patients with stable disease).

Figure 8 Swimmer Plot of Participants Of Time to Response and Time to Progression Based RECIST 1.1. Assessed by BICR for Participants with BOR = SD and BP Medication Reduction Status (Cohort A1; APaT Population)



Source: Applicant response to FDA IR issued April 25, 2025

Among patients with greater than 25% reduction in BP medication (n=23) for at least 3 months, the best response was partial response in 7 patients, stable disease in 15 patients and progressive disease in 1 patient.

A potential limitation to the interpretation of the exploratory endpoint of reduction in blood pressure medication is that the protocol did not include guidelines on when and how to reduce the dose of blood pressure medication(s). The reason for reduction in dose was not captured in the study and is not available. In response to an FDA request for additional information, the Applicant provided blood pressure values (diastolic and systolic) captured before and after each

BP medication change for all patients who received at least one dose of BP medication at baseline and at least one dose of belzutifan (n=60). The Applicant provided a tabular listing of all patients, including responders, who had ≥25% reduction in at least one blood pressure medication from baseline and the blood pressure measurements. The focus of the assessment of the data provided was on the 9 responders who also had a reduction in total daily dose of their BP medication.

- 4 patients maintained low BP values after a reduction in their total daily dose of their BP medications was made.
- 4 patients had similar BP values, with no major changes in systolic or diastolic levels after a reduction in their total daily dose of their BP medication was made.
- 1 patient experienced a mild increase in their BP values after the total daily dose of their BP medication was reduced.

Only one patient in LITESPARK-015 Cohort A1 experienced hypertensive crisis leading to hospitalization (Subject ID (b) (6)). This patient initiated belzutifan and experienced Grade 2 nonserious hypotension on Day 2, and thereafter had reduction and discontinuation of all baseline antihypertensive medication. On Day 18, the patient was admitted for Grade 4 hypertensive crisis; resuming antihypertensives resulted in resolution of the AE. Hypertensive crisis resolved within 23 hours. The dose of belzutifan was reduce to 80 mg daily in response to this event. Patient was discharged on Day 22. The patient had a best response of PR which was maintained for 11 months and was also able to decrease blood pressure medication by ≥50%, maintained for ≥ 6 months. Patient discontinued belzutifan on Day 547 due to progressive disease.

Given that PPGLs are neuroendocrine tumors which commonly manifest with clinical signs and symptoms related to catecholamine excess and with hypertension being the most common sign observed in more than 95% of patients, control of hypertension is critical. Therefore, both the improvement in blood pressure values and the reduction in total daily dose of BP medication is a meaningful benefit to patients.

FDA did not independently verify the results for PRO endpoints. FDA generally considers PRO endpoints to be descriptive and exploratory in the context of a single-arm setting due to the lack of randomized comparator to establish clinically meaningful evidence of benefit or tolerance. FDA agrees that the data appear to support a trend towards improvement in symptoms related to autonomic dysfunction such as constipation and improvement in appetite.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
The efficacy results of LITESPARK-015 Study Cohort A1 demonstrated clinically meaningful and durable responses of belzutifan in patients with advanced, unresectable, or metastatic PPGL. The confirmed ORR per RECIST v1.1 by BICR was 26% (95% CI: 17, 38). Subgroup analyses of ORR were generally consistent across key prespecified subgroups. With a median duration of follow-up of 30.8 months (Kaplan-Meier estimate), median DOR was 20.4 (95% CI: 8.3, NR) by the data cutoff date (October 23, 2024). DOR ranged from 5.6+ to 29.6+ months, where "+" denotes ongoing response and 89% of responders had DOR ≥ 6 months. Among the 19 responders, 2 (11%) patients had a duration of follow-up less than 6 months from the time of onset of response. Therefore, additional 12 months of follow-up data for DOR will be collected as part of the traditional approval PMC.

A sustained reduction in total daily dose of blood pressure medication from baseline was an important exploratory endpoint with clinical implications assessed on the study. The proportions of patients who had a reduction of at least 25% and 50% in at least one BP medication and maintained for at least 6 months from baseline, were 33% and 32%, respectively.

Due to the single-arm setting, FDA considers time-to-event and PRO endpoints to be uninterpretable to assess treatment effect and are considered descriptive only. Additionally, results from subgroup analyses are considered exploratory and should be interpreted with caution, particularly those with small sample sizes.

Additional Efficacy Considerations

Inclusion of adolescent patients in indicated population

The eligibility criteria for LITESPARK -015 allowed for enrollment of patients 12 years of age and older, however no patients less than 18 years old enrolled into Cohort A1. Therefore, the inclusion of patients 12 years of age and older in the indicated population is primarily based on extrapolation of the effectiveness of belzutifan observed in LITESPARK-015 (Cohort A1) given FDA's consideration that PPGL is similar in adolescents compared to adult patients, supported by the targeted mechanism of action of belzutifan, available PK data and weight-based modeling (Refer to Section 6), and reported clinical safety experience through the expanded access program, literature reports and adolescent patients enrolled in Cohorts C and D of LITESPARK-015.

Summary of patients in Cohort A1 of LITESPARK-015 initially diagnosed with PPG at less than 18 years of age

Through an IR issued on March 11, 2025, FDA obtained data on patients enrolled on Cohort A1 who were initially diagnosed with PPGL at less than 18 years of age (n=4); of these patients, 3 had responses (see Table 12 below). These data further support the anti-tumor activity of belzutifan in PPGLs occurring in adolescent patients.

Table 12 Adult Patients with PPGL in Cohort A1 of LITESPARK-015 initially diagnosed at less than 18 years of age

Patient Identifier	Age at enrollment (in years)	Age at initial diagnosis (in years)	Responder (Y/N)	BP medication at Baseline(Y/N)	BP medication reduction ≥25%(Y/N)
(b) (6)	37	9	Y	Y	Y
	26	17	Y	Y	N
	30	13	N	N	NA
	33	16	Y	N	NA

Y=Yes, N=No

Summary of select safety from adolescent patients in LITESPARK-015

To support safety, the Applicant also provided data from three adolescent patients ages 15-16 enrolled in LITESPARK 015 Cohorts C and D (2 with wild-type gastrointestinal stromal tumor, 1 with paraganglioma). All AEs were Grade 1 and 2 with the most common being anemia (See Table below).

Table 13 Select Pediatric Data from LITESPARK012 Cohorts C and D

Patient (Cohort)	Treatment Duration	Best Response by BICR per RECIST 1.1	Duration of Response by BICR per RECIST 1.1	Safety Results
(b) (6) (Cohort C)	28 days	No assessment	No assessment	Nausea, vomiting, peripheral edema, and anemia
(b) (6) (Cohort C)	461 days	SD	N/A	Asthenia, Increased bilirubin, diarrhea, anemia, decreased appetite, peripheral edema, hypothyroidism, coccydynia,
(b) (6) (Cohort D)	241 days	SD	N/A	Nasal congestion, asthenia, vomiting, anemia and upper abdominal pain

Source: Submitted by Applicant in response to an IR 0n 3/19/2025
Data Cutoff Date: OCT 232024

Summary of safety as reported in literature

Table 14 below summarizes a case series of 5 patients (age range 10-17 years) with VHL-associated hemangioblastomas treated with belzutifan (Duan et al.) All reported AEs were Grade 1 or 2, with anemia being the most common. Three patients had improvement in hemangioblastoma size and visual acuity and two patients with intracranial lesions had an improvement in neurologic symptoms and hemangioblastoma size.

Table 14 Summary of Treatment Duration, Response, Response Duration, and Safety Case Reports (Duan et al.)

Patient	Treatment Duration	Summary of Response	Safety Results
11-year-old female with VHL disease with retinal and cerebellar hemangioblastoma	29 months, 40 mg QD	Improvement in vision, partial regression of feeder vessel at 2 months. Further improvement 6 to 12 months	Grade 1–2 Anemia Fatigue Dizziness
17-year-old male with VHL disease with retinal and intracranial	32 months, 120 mg QD	Significant improvement in right eye macular edema by 1 month and 20/20 visual acuity by 5 months. CR of central fovea	Grade 1 Anemia Fatigue

Patient	Treatment Duration	Summary of Response	Safety Results
hemangioblastomas and pancreatic cyst		edema and improvement in CNS lesions by MRI by 18 months.	
10-year-old male with VHL disease with retinal hemangioblastoma	28 months, 80 mg QD	Tumor regression by 5 months, further regression and decreased fibrosis by 16 months.	Grade 1–2 Anemia
16-year-old female with VHL disease with orbital and intracranial hemangioblastomas and pancreatic cysts	30 months, 80-120 mg QD	Tumor size reduction starting at 1 month with greatest improvement by 10 months. Stable at 15 months.	Grade 1–2 Anemia Nausea Emesis
16-year-old male with VHL disease with retinal and intracranial hemangioblastomas	14 months, 60-80 mg QD	Tumor size reduction at 2 months.	Fatigue Dizziness Headaches (Grades not provided)

Source: Duan et al. Pediatr Blood Cancer. 2025 Jan;72(1). Submitted by Applicant in response to an IR 0n 3/19/2025

Two additional publications were identified after the original sNDA submission and were provided in a response to an FDA IR issued March 19, 2025.

- Aykut et al. (Dec 2024) Case report of a 15-year-old female patient with retinal capillary hemangioblastoma (RCH) tumors with localized exudative and tractional retinal detachment, hard exudates, and subretinal fluid (SRF), and VHL pathogenic variant identified during genetic testing. Belzutifan therapy was started at 120 mg QD. At 1 month after initiation of treatment, SRF started to resolve, and at 1 year, tortuosity of feeder vessels and intrinsic vascularity of small RCH in the right eye had improved. In the left eye, SRF and exudative and tractional retinal detachment were resolved with subretinal fibrosis, and tortuosity of feeder vessels and intrinsic vascularity of RCH improved. Right vision remained stable, although left vision decreased. The only side effect was mild fatigue.
- Brandt et al. (Abstract, Jun 2024) Case report of a 15-year-old male patient with VHL with left craniocervical junction lesion consistent with hemangioblastoma identified by MRI. Patient was treated with belzutifan 120 mg QD. At 3 months post- initiation of treatment, major radiologic response by RANO was noted, and at 11 months post-initiation of treatment, further reduction in size of the target lesion was observed. Treatment was well tolerated, with toxicities limited to Grade 1 fatigue and Grade 2 anemia (CTCAE version 5.0).

The Applicant also provided an updated summary of case reports from the post-marketing safety database.

Table 15 Summary of Case Reports from Postmarketing Safety Database as of 13-MAR-2025

Patient	Treatment Duration	Response Duration of Response	Safety Results
(b) (6) (15 years old)	The patient remained on therapy and had completed 11 months of treatment with further reduction in the size of the target lesion.	The first MRI on therapy (3 months after treatment started) demonstrated a major radiologic response.	Fatigue G1 Anemia G2 Off label use in unapproved age group
(b) (6) (10 years old)	Unknown	On an unknown date (also reported as within 5 months of belzutifan therapy), the tumor demonstrated evidence of regression and decreased exudate. On an unspecified date (also reported as at 16 months of belzutifan treatment), there was further tumor regression and decreased fibrosis and ultrasonography of an left eye B-scan showed a decrease in apical tumor height from 3 to 2.5 mm. Given the disease improvement, bevacizumab injections were discontinued at that point and the patient continued on belzutifan monotherapy.	Anemia G1-2 Off label use in unapproved age group
(b) (6) (16 years old)	Unknown	On an unspecified date (also reported as approximately 10 months of belzutifan therapy), magnetic resonance imaging (MRI) showed interval improvements in the size of her cervico-medullary hemangioblastoma as early as month 1 of therapy, with the greatest improvement occurring, at which point the cervico-medullary lesion decreased from 14 x 14 x 17 to 8 x 8 x 11 mm and the cerebellar lesion decreased from 4 to 2 mm. On an unspecified date (also reported as at 15 months of therapy), imaging showed mild growth of the cervico-medullary hemangioblastoma, but the patient has	Anemia G1-2 Nausea Emesis Off label use in unapproved age group

Patient	Treatment Duration	Response Duration of Response	Safety Results
		remained neurologically asymptomatic.	
(b) (6) (16 years old)	Unknown	On an unspecified date (also reported as after 2 months of belzutifan), radiographic examination showed that cervico-medullary junction lesion decreased from 14 to 10 mm in the cystic component and from 5 to 3 mm in the dorsal nodule. There was a similar decrease from 10 to 8mm in the lesion along the left cerebellum.	Fatigue Dizziness Headache Off label use in unapproved age group
(b) (6) (17 years old)	24 months, 120 mg QD	Decrease in adrenal mass at 17 days post-initiation of belzutifan and shrinkage in all lesions at Day 56 post- initiation of treatment. MRI on day 696 showed further reduction of adrenal mass; patient was still responding at data cutoff.	Grade 1: decreased white cell and neutrophil counts, eosinophilia, maculopapular rash, dry skin, QTc prolongation, hypertension (intermittent), hypotension, hyperkalemia, sinus tachycardia, proteinuria, and hematuria Grade 2: anemia, weight gain, decrease lymphocyte count
(b) (6) (11 years old)	120 mg QD for 2 months, reduced to 80 mg QD for 6 months	Improvement of engorgement and tortuosity in feeding arterioles and draining veins, decreased extent of exudative retinal detachment, and decreased lesion elevation with fibrosis. Patient response was observed at 6 months post-initiation of 80 mg QD.	Anemia resulting in dose reduction
(b) (6) (Pediatric patient of unknown age)	80 mg QD adjusted to 40 mg 5x per week for 12 months	Involution; resolution of ocular tumors after initial dose with reoccurrence when dose was reduced to 40 mg 3x per week. On readjustment to 40 mg 5x per week, involution was again noted.	Fatigue Lightheadedness
(b) (6) (11 years old)	Unknown	On an unknown date (also reported as after 2 months on belzutifan), improvement in her right eye vision from pretreatment 20/30 vision to 20/25 and partial regression of feeder vessels was observed. On an unspecified date (also reported as between 6 months and 1 year of therapy), there was further improvement in feeder vessel atrophy,	Off label use in unapproved age group Anemia G1-2 Intermittent Fatigue & dizziness

Patient	Treatment Duration	Response Duration of Response	Safety Results
		hemangioblastoma size and macular peripheral changes from tumor fluid transudation.	
(b) (6) (16 years old)	Unknown	Unknown	Anemia Off label use

Source: Submitted by Applicant in response to an IR 0n 3/19/2025

Lastly, a 17-year-old patient diagnosed with Pacak–Zhuang syndrome with polycythemia and paragangliomas was treated with belzutifan 120 mg once daily under the expanded access program. The publication reported the duration of treatment was 24 months and led to rapid and sustained tumor response, as well as symptom (hypertension, headache, and polycythemia) resolution. The reported side effects were minimal (Grade 1 or 2) and consistent with the established safety profile of belzutifan (Kamihara, et al.)

Conclusion
Overall, although there are limited adolescent safety data from LITESPARK-015, supportive PK data, along with notable similarities between adolescent and adult PPGL disease presentation and the magnitude of clinical benefit observed in Cohort A1 of LITESPARK-015, FDA considers it appropriate to include adolescent patients 12 years of age and older in the indicated population. The safety experience outlined above is consistent with the current adult safety that is reported in the current USPI; however, a Food and Drug Administration Amendments Act of 2007 (FDAAA) post-marketing requirement (PMR) will be issued to further characterize safety in a larger pediatric population. See PMR Section 13.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

Not applicable.

The FDA's Assessment:
See Section 8.1.3

8.2 Review of Safety

The Applicant's Position:
Safety results from Cohort A1 of LITESPARK-015 show that belzutifan 120 mg administered orally QD until disease progression or unacceptable toxicity to participants with locally advanced, unresectable, or metastatic PPGL had a generally manageable and tolerable safety profile, which was consistent with the known safety profile of belzutifan monotherapy for the approved indications. The proportion of participants who experienced all categories of AEs was generally consistent with the previously observed safety profile of belzutifan. No fatal AEs were reported. Anemia and hypoxia, clinically important ADRs for belzutifan, were manageable with standard medical practice; no study intervention discontinuations due to anemia or hypoxia were reported.

The FDA's Assessment:
FDA agrees with the Applicant's position. The overall safety population includes all patients in Cohort A1 of LITESPARK-015 who received at least 1 dose of belzutifan (n=72). Overall, the adverse events (AE) observed in Cohort A1 are consistent with the adverse reactions (ARs) in the current United States Prescribing Information (USPI) of belzutifan.

8.2.1. Safety Review Approach

The Applicant's Position:
Safety results are presented for participants in Cohort A1 of LITESPARK-015 based on data from the APaT population (N=72) with a DCO date of 23-MAY-2024.

The FDA's Assessment:
FDA agrees with the Applicant's safety review approach. FDA independently reviewed exposure and safety data for Cohort A1 of LITESPARK-015 to support the safety profile for the proposed indication. FDA also reviewed data from the 90-day safety update (DCO October 23, 2024); no new safety signals were identified with 5 months of additional follow-up.

8.2.2. Review of the Safety Database

Overall Exposure

Data:
Table 16: Applicant – Summary of Drug Exposure (Cohort A1; APaT Population)

	Belzutifan 120 mg QD (N=72)

Duration on Therapy[a] (months)	
n	72
Mean (SD)	17.2 (9.6)
Median	20
Range	0.3 to 32.5
Number of Days on Drug[b]	
n	72
Mean (SD)	513.4 (290)
Median	596
Range	5 to 978

[a] Duration on Therapy is calculated as the days between first dose date and last dose date in each treatment arm.
[b] 'Number of Days on Drug' for a participant is the total number of days when the participant took non-zero doses.
Database Cutoff Date: 23MAY2024.

Source: [P015V02MK6482: adam-adsl; adexsum]

Table 17: Applicant – Drug Exposure by Duration (Cohort A1; APaT Population)

	Belzutifan 120 mg QD (N=72)		
	n	(%)	Person-years
Duration of Exposure			
> 0 m	72	(100.0)	103.3
>= 1 m	70	(97.2)	103.2
>=3 m	63	(87.5)	101.9
>=6 m	55	(76.4)	99.3
>=12 m	50	(69.4)	95.4
>=18 m	40	(55.6)	82.2
>=24 m	22	(30.6)	49.7

Each participant is counted once on each applicable duration category row.
Duration of exposure is the time from the first dose date to the last dose date.
Database Cutoff Date: 23MAY2024.

Source: [P015V02MK6482: adam-adsl; adexsum]

The Applicant's Position:

The median duration of exposure to belzutifan was 20 months (range: 0.3 to 32.5 months) [Table 10]. A total of 30.6% of participants were exposed to belzutifan ≥24 months [Table 11].

The FDA's Assessment:

FDA agrees with the Applicant's presentation of exposure data. The overall exposure to belzutifan in Cohort A1 of LITESPARK-015 is adequate to evaluate the safety profile of belzutifan as single-agent treatment in patients with PPGL.

Relevant characteristics of the safety population:

Data:
See [Table 7].

The Applicant's Position:
Demographic and other baseline characteristics of study participants in Cohort A1 of LITESPARK-015 were representative of a population with advanced PPGL and are described in Section 8.1.2.

The FDA's Assessment:
FDA agrees with the Applicant's presentation of patient demographics and baseline characteristic as presented in Table 7. See Section 8.1.2 for more detail. The median age of patients enrolled in COHORT A1 of LITESPARK-015 was 52 years old. While LITESPARK 015 allowed enrollment of patients 12 years of age and older, no patients less than 18 years old enrolled into Cohort A1.

Adequacy of the safety database:

The Applicant's Position:
The safety database is of an adequate size, considering prevalence of the disease, 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:
FDA agrees with the Applicant's assessment of the adequacy of the safety database to support review of the NDA.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
Data quality assurance included QA and QC oversight activities implemented at the investigation sites and centrally by the Applicant in accordance with ICH GCP 5.1. The Applicant conducted periodic, independent audits to ensure the accuracy and integrity of the clinical study data. There

were no issues with data integrity or analysis that precluded the inclusion of data in the safety analysis. The sNDA submission contains all required components. The overall quality and integrity of the application is sufficient for substantive review to be completed.

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

Categorization of Adverse Event

The Applicant's Position:
Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence, severity, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs were monitored throughout LITESPARK-015 Cohort A1, and graded in severity according to the guidelines outlined in the NCI CTCAE version 5.0. AEs were coded using MedDRA version 27.0.

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

Routine Clinical Tests

The Applicant's Position:
Participants underwent routine evaluation for safety events, including laboratory testing, vital signs, physical examination, and AE monitoring.

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

8.2.4. Safety Results

Table 18: Applicant – Adverse Event Summary (Cohort A1; APaT Population)

	Belzutifan 120 mg QD	
	n	(%)
Participants in population	72	
with one or more adverse events	72	(100.0)
with no adverse event	0	(0.0)
with drug-related[a] adverse events	71	(98.6)
with toxicity grade 3-5 adverse events	51	(70.8)
with toxicity grade 3-5 drug-related adverse events	35	(48.6)
with serious adverse events	26	(36.1)
with serious drug-related adverse events	8	(11.1)
with dose modification[b] due to an adverse event	34	(47.2)
with dose interruption due to an adverse event	29	(40.3)
with dose reduction due to an adverse event	10	(13.9)
who died	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)
discontinued drug due to an adverse event	2	(2.8)
discontinued drug due to a drug-related adverse event	2	(2.8)
discontinued drug due to a serious adverse event	1	(1.4)
discontinued drug due to a serious drug-related adverse event	1	(1.4)

[a] Determined by the investigator to be related to the drug.
[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
MedDRA Version: 27.0 preferred "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE 5.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 23MAY2024.

Source: [P015V02MK6482: adam-adsl; adae]

Deaths

The Applicant's Position:
No fatal AEs were reported in Cohort A1 for this study [Table 12].

The FDA's Assessment:
Of the 18 deaths that occurred in Cohort A1 of LITESPARK-015, FDA agrees that all were due to progression and that there were no on-treatment deaths.

One of the 18 deaths occurred within 30 days of discontinuation of treatment with belzutifan

(Patient ID [redacted](b) (6)). This occurred in a 67-year-old female patient who died of a heart attack at home on Day 144 (last dose of belzutifan was on Day 141). According to the narrative, the patient discontinued belzutifan due to progressive disease documented by imaging on Day 122 which demonstrated new lesions and non-target lesion progression per investigator based on RECIST 1.1. On Day 142, the patient experienced Grade 3 fatigue, ongoing Grade 2 vomiting, Grade 3 decreased appetite, decreased hemoglobin, increased WBC and neutrophils, decreased sodium and increased potassium. The narrative states that the patient died due to a heart attack at home due to malignant neoplasm progression and uncontrolled secretory syndrome on Day 144. No other underlying cause was identified and the participant´s hypertension had been well controlled while on study treatment. However, given the recent imaging documenting widely progressive disease, FDA does not consider this death to be related to study therapy.

Serious Adverse Events

Data:

Table 19: Applicant – Participants With Serious Adverse Events by Decreasing Incidence (Incidence >0%; Cohort A1; APaT Population)

	Belzutifan 120 mg QD	
	n	(%)
Participants in population	72	
with one or more adverse events	26	(36.1)
with no adverse events	46	(63.9)
Anaemia	3	(4.2)
Dyspnoea	2	(2.8)
Hypertension	2	(2.8)
Hypoxia	2	(2.8)
Pneumonia	2	(2.8)
Pyelonephritis	2	(2.8)
Acute respiratory failure	1	(1.4)
Atrial fibrillation	1	(1.4)
Basal cell carcinoma	1	(1.4)
Biliary obstruction	1	(1.4)
COVID-19	1	(1.4)
COVID-19 pneumonia	1	(1.4)
Cardiac failure	1	(1.4)
Chest pain	1	(1.4)
Constipation	1	(1.4)
Dehydration	1	(1.4)
Epistaxis	1	(1.4)
Faecaloma	1	(1.4)
Headache	1	(1.4)
Hypertensive crisis	1	(1.4)

	Belzutifan 120 mg QD	
	n	(%)
Infection	1	(1.4)
Medullary compression syndrome	1	(1.4)
Nausea	1	(1.4)
Orthostatic hypotension	1	(1.4)
Paraparesis	1	(1.4)
Pharyngeal haemorrhage	1	(1.4)
Pleural effusion	1	(1.4)
Presyncope	1	(1.4)
Pulmonary embolism	1	(1.4)
Scrotal abscess	1	(1.4)
Tumour lysis syndrome	1	(1.4)
Tumour pain	1	(1.4)
Upper respiratory tract infection	1	(1.4)
Urinary tract infection	1	(1.4)
Vomiting	1	(1.4)

Every participant is counted a single time for each applicable row and column.
Serious AEs up to 90 days of last dose of treatment phase.
MedDRA Version: 27.0 preferred "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 23MAY2024.

Source: [P015V02MK6482: adam-adsl; adae]

The Applicant's Position:

The most frequently reported SAEs were anemia, dyspnea, hypertension, hypoxia, pneumonia, and pyelonephritis [Table 13]. The majority of SAEs were Grade 3. Three participants experienced Grade 4 SAEs (acute respiratory failure, hypertensive crisis, and paraparesis). All of these Grade 4 SAEs were confounded by the participants' comorbid conditions. Paraparesis was confounded by multiple bone metastases to the spine with an intramedullary lesion from D8 (T8) to the medullary cone (L1) and was not resolved at DCO. Acute respiratory failure was confounded by COVID-19 infection with subsequent cardiac failure and resolved at DCO. The participant with the AE of hypertensive crisis initiated belzutifan and experienced Grade 2 nonserious hypotension on Day 2 and thereafter had reduction and discontinuation of all baseline antihypertensive medication. Approximately 1 week later, the participant experienced a hypertensive crisis; resumption of antihypertensives resulted in resolution of the AE. At DCO, 73.1% of SAEs had resolved, 15.4% were unresolved, 7.7% were resolving, and 3.8% had resolved with sequelae.

The FDA's Assessment:

Overall, FDA agrees with the Applicant's position with the exception of characterization of hypertension. The FDA group term used for hypertension (blood pressure increased, hypertension, and hypertensive crisis) captured one additional patient with an event.

FDA agrees that serious adverse events occurred in 36% of patients who received belzutifan. The most frequent serious adverse reactions occurring in ≥2% of patients were anemia and hypertension (4.2% each) and pyelonephritis, pneumonia, hypoxia, dyspnea and hemorrhage (2.8% each).

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:
AEs leading to discontinuation of belzutifan were reported in 2 (2.8%) participants [Table 12]. The reported AEs leading to discontinuation, in 1 participant each, were ALT increased and paraparesis.

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

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

The Applicant's Position:
AEs leading to dose reduction of belzutifan were reported for 10 (13.9%) participants [Table 12]. Of the AEs leading to dose reduction of belzutifan, hypoxia was reported in 3 (4.2%) participants, and anemia and fatigue were each reported in 2 (2.8%) participants; all others were reported in 1 participant.

AEs leading to interruption of belzutifan were reported in 29 (40.3%) participants [Table 12]. The most frequently reported AEs leading to treatment interruption were hypoxia and nausea, reported in 3 (4.2%) participants each.

The FDA's Assessment:
FDA agrees with the Applicant's position. Dose reductions of belzutifan due to an adverse reaction occurred in 14% of patients. The most frequently reported adverse reaction which required dose reduction was hypoxia (4.2%).

Dosage interruptions of belzutifan due to an adverse reaction occurred in 40% of patients. Adverse reactions which required dosage interruption in >3% of patients were hypoxia, nausea and fatigue (4.2% each).

Significant Adverse Events

Data:
Table 20: Applicant - Participants With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence >0%; Cohort A1; APaT Population)

	Belzutifan 120 mg QD	
	n	(%)
Participants in population	72	
with one or more adverse events	51	(70.8)
with no adverse events	21	(29.2)
Anaemia	16	(22.2)
Hypertension	9	(12.5)
Hypoxia	7	(9.7)
Fatigue	6	(8.3)
Weight increased	5	(6.9)
Alanine aminotransferase increased	3	(4.2)
Lymphopenia	3	(4.2)
Arthralgia	2	(2.8)
Aspartate aminotransferase increased	2	(2.8)
COVID-19	2	(2.8)
Decreased appetite	2	(2.8)
Dizziness	2	(2.8)
Lymphocyte count decreased	2	(2.8)
Muscular weakness	2	(2.8)
Orthostatic hypotension	2	(2.8)
Pneumonia	2	(2.8)
Pyelonephritis	2	(2.8)
Abdominal pain	1	(1.4)
Acute respiratory failure	1	(1.4)
Asthenia	1	(1.4)
Atrial fibrillation	1	(1.4)
Biliary obstruction	1	(1.4)
COVID-19 pneumonia	1	(1.4)
Cardiac failure	1	(1.4)
Cellulitis	1	(1.4)
Chronic kidney disease	1	(1.4)
Constipation	1	(1.4)
Contrast media allergy	1	(1.4)
Dyspnoea	1	(1.4)
Ejection fraction decreased	1	(1.4)
Electrocardiogram QT prolonged	1	(1.4)
Epistaxis	1	(1.4)
Faecaloma	1	(1.4)
Gamma-glutamyltransferase increased	1	(1.4)
Headache	1	(1.4)
Hyperkalaemia	1	(1.4)
Hypertensive crisis	1	(1.4)
Intracranial pressure increased	1	(1.4)
Medullary compression syndrome	1	(1.4)

	Belzutifan 120 mg QD	
	n	(%)
Musculoskeletal chest pain	1	(1.4)
Myalgia	1	(1.4)
Nausea	1	(1.4)
Paraparesis	1	(1.4)
Pharyngeal haemorrhage	1	(1.4)
Pleural effusion	1	(1.4)
Presyncope	1	(1.4)
Scrotal abscess	1	(1.4)
Syncope	1	(1.4)
Thrombocytopenia	1	(1.4)
Tumour lysis syndrome	1	(1.4)
Tumour pain	1	(1.4)
Urinary tract infection	1	(1.4)
Vertigo	1	(1.4)
Vomiting	1	(1.4)

Every participant is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA Version: 27.0 preferred "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE 5.0.
Database Cutoff Date: 23MAY2024.

Source: [P015V02MK6482: adam-adsl; adae]

The Applicant's Position:

The most frequently reported Grade 3 to 5 AEs (≥5% of participants) were anemia, hypertension, hypoxia, fatigue, and weight increased [Table 14]. All of these events are known ADRs for belzutifan, except hypertension. Hypertension is consistent with the underlying disease state and was the most frequently reported medical history condition in participants (81.9%). Overall, 9/13 of these hypertension events were Grade 3 and resolved without dose modification. Five Grade 4 events were reported: acute respiratory failure, hypertensive crisis, lymphocyte count decreased, paraparesis, and thrombocytopenia. Thrombocytopenia and lymphocyte count decreased were nonserious events; the remainder were SAEs and were confounded by the participants' comorbid conditions (refer to Serious Adverse Events).

No Grade 5 events were reported.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of Grade 3-5 treatment emergent adverse events (TEAEs).

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 21: Applicant - Participants With Adverse Events by Decreasing Incidence (Incidence ≥5%; Cohort A1; APaT Population)

	Belzutifan 120 mg QD	
	n	(%)
Participants in population	72	
with one or more adverse events	72	(100.0)
with no adverse events	0	(0.0)
Anaemia	69	(95.8)
Fatigue	28	(38.9)
Dyspnoea	22	(30.6)
Headache	21	(29.2)
Back pain	19	(26.4)
Dizziness	18	(25.0)
Nausea	18	(25.0)
Arthralgia	17	(23.6)
Constipation	17	(23.6)
Oedema peripheral	16	(22.2)
Alanine aminotransferase increased	13	(18.1)
Hypertension	13	(18.1)
Asthenia	12	(16.7)
COVID-19	12	(16.7)
Aspartate aminotransferase increased	11	(15.3)
Cough	11	(15.3)
Diarrhoea	11	(15.3)
Decreased appetite	10	(13.9)
Hypoxia	9	(12.5)
Muscle spasms	9	(12.5)
Muscular weakness	9	(12.5)
Weight increased	9	(12.5)
Abdominal pain	7	(9.7)
Myalgia	7	(9.7)
Nasal congestion	7	(9.7)
Palpitations	7	(9.7)
Vomiting	7	(9.7)
Blood thyroid stimulating hormone increased	6	(8.3)
Influenza like illness	6	(8.3)
Lymphocyte count decreased	6	(8.3)
Proteinuria	6	(8.3)
Blood alkaline phosphatase increased	5	(6.9)
Gastrooesophageal reflux disease	5	(6.9)

	Belzutifan 120 mg QD	
	n	(%)
Nasopharyngitis	5	(6.9)
Paraesthesia	5	(6.9)
Pyrexia	5	(6.9)
Rash	5	(6.9)
Tumour pain	5	(6.9)
Vision blurred	5	(6.9)
Chest pain	4	(5.6)
Haematuria	4	(5.6)
Hyperglycaemia	4	(5.6)
Hyperhidrosis	4	(5.6)
Hypokalaemia	4	(5.6)
Hypotension	4	(5.6)
Insomnia	4	(5.6)
Neutrophil count decreased	4	(5.6)
Pain in extremity	4	(5.6)
Sinusitis	4	(5.6)
Toothache	4	(5.6)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA Version: 27.0 preferred "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 23MAY2024.

Source: [P015V02MK6482: adam-adsl; adae]

The Applicant's Position:

Treatment Emergent Adverse Events

The most frequently reported AEs (≥25% of participants) were anemia, fatigue, dyspnea, headache, back pain, dizziness, and nausea [Table 15]. Anemia, fatigue, dyspnea, dizziness, and nausea are known ADRs for belzutifan. Overall, frequently reported AEs were predominantly Grade 1 or 2 in severity, with the exception of anemia, which was predominantly Grade 2 or 3.

Adverse Drug Reactions

In addition to the above noted ADRs, hypoxia is also a known ADR for belzutifan. Anemia and hypoxia are the most clinically important ADRs for belzutifan. The percentage of participants reporting AEs of anemia and hypoxia are presented in [Table 15]. No treatment discontinuations due to anemia or hypoxia were reported.

Grade 3 anemia was reported in 16 (22.2%) participants; there were no Grade 4 or 5 events of anemia reported. At DCO, AEs of anemia had resolved or were resolving in 30.4% and 13.0% of participants, respectively. Dose modification and/or treatment with ESAs/blood transfusions were important modalities for the management of anemia AEs.

Of the AEs of hypoxia, Grade 3 AEs were reported for 7/9 participants; there were no Grade 4 or 5 events of hypoxia reported. Hypoxia events were manageable with dose modification and/or oxygen therapy, and most resolved (8 [88.9%]).

Of the AEs of dyspnea Grade 3 dyspnea was reported in 1 (1.4%) participant; there were no Grade 4 or 5 events reported. Seven (31.8%) participants with dyspnea received oxygen therapy. Most dyspnea AEs were resolved (63.6%) or resolving (9.1%).

The FDA's Assessment:

FDA generally agrees with the Applicant's summary. The overall safety profile is generally consistent with the safety profile described for belzutifan in the current product labeling.

FDA's analysis utilized grouped preferred terms to accurately capture the incidence of adverse reactions. These terms were agreed upon by the Applicant and revised in the label.

The most common (≥25%) adverse reactions, including laboratory abnormalities were anemia, fatigue, musculoskeletal pain, decreased lymphocytes, increased alanine aminotransferase, increased aspartate aminotransferase, increased calcium, dyspnea, increased potassium, decreased leukocytes, headache, increased alkaline phosphatase, dizziness, and nausea.

Based on the mechanism of action of belzutifan hypoxia and anemia are considered on-target effects. In Cohort A1 of LITESPARK-015, hypoxia occurred in 13% of patients and 10% had Grade 3 hypoxia. Median time to onset of hypoxia was 35 days (range: 6 days to 23.9 months). Of the patients with hypoxia, 67% were treated with oxygen therapy. Anemia occurred in 96% of patients and 22% had Grade 3 events. Median time to onset of anemia was 29 days (range: 1 day to 22.1 months). Of the patients with anemia, 20% received transfusions only, 26% received erythropoiesis stimulating agents (ESAs) only, and 6% received both transfusion and ESAs.

Adverse events reported in ≥10% of patients in Cohort A1 of LITESPARK-015 along with Grade 3-4 incidences are presented in Table 22 based on FDA's analyses.

Table 22 Adverse Reactions Occurring in ≥10% of Patients with PPGL Who Received

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Adverse Reaction	Belzutifan (n=72)	
	All Grades* (%)	Grade 3-4 (%)
Blood and Lymphatic		
Anemia	96	22
General		
Fatigue†	56	10
Edema†	24	0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain†	56	6
Muscle spasms	13	0
Muscle weakness	13	2.8
Respiratory, Thoracic, and Mediastinal		
Dyspnea†	33	1.4
Cough	15	0
Hypoxia	13	10
Nasal congestion	10	0
Nervous System		
Headache	29	1.4
Dizziness†	26	2.8
Peripheral neuropathy†	13	0
Gastrointestinal		
Nausea	25	1.4
Constipation	24	1.4

Adverse Reaction	Belzutifan (n=72)	
	All Grades* (%)	Grade 3-4 (%)
Diarrhea	15	0
Abdominal Pain†	13	1.4
Vomiting	10	1.4
Vascular Disorders		
Hypertension†	21	13
Hypotension†	10	2.8
Hemorrhage†	10	2.8
Infections		
COVID-19	17	2.8
Metabolism and Nutrition Disorders		
Decreased appetite	14	2.8
Investigations		
Weight increased	13	7
Cardiac Disorders		
Arrhythmia†	11	2.8
Palpitations	10	0

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

Laboratory Findings

The Applicant's Position:
For participants with a shift in postbaseline laboratory values, at least 73% of the highest postbaseline toxicity grades in each individual category were Grade 1 and 2. The most frequently

reported laboratory shifts of all grades (≥30% participants) were hemoglobin decreased (90.3%), lymphocytes decreased (53.5%), ALT increased (50.7%), AST increased (42.3%), calcium increased (33.8%), and potassium increased (31.0%).

A worsening of laboratory values to Grades 3 or 4 was observed for hemoglobin decreased (20.8%), lymphocytes decreased (14.1%), AST increased and ALT increased (4.2% each), potassium increased (2.8%); and albumin decreased, neutrophils decreased, platelets decreased, potassium decreased, and creatinine increased (1.4% each).

The FDA's Assessment:
FDA generally agrees with the Applicant's summary of laboratory findings. FDA independently verified laboratory data submitted by the Applicant. Results of laboratory abnormalities (≥20%) are displayed below in Table 23. The laboratory abnormalities remain consistent with the current product labeling for belzutifan with no knew laboratory abnormalities identified.

Table 23 Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients with PPGL Who Received Belzutifan in LITESPARK-015

Laboratory Abnormality	Belzutifan (n=72)	
	All Grades %	Grades 3 or 4 %
Hematology		
Decreased hemoglobin	90	21
Decreased lymphocytes	54	14
Decreased leukocytes	30	0
Decreased neutrophils	24	1.4
Decreased platelets	21	1.4
Chemistry		
Increased ALT	51	4.2
Increased AST	42	4.2
Increased calcium	34	0

Increased potassium	31	2.8
Increased alkaline phosphatase	25	0
Increased creatinine	24	1.4
Decreased sodium	21	0

Vital Signs and Physical Examinations

The Applicant's Position:
Clinically meaningful abnormalities in vital signs, physical examinations, and ECGs were reported as AEs. Overall, body weight increased from baseline over time; weight increased is a known ADR for belzutifan. Mean percent change from baseline in body weight was 1.66% (std dev: 2.30%) at Week 3; 5.98% (std dev: 8.29%) at Week 45; 11.01% (std dev: 11.61%) at Week 113; and 17.00% (std dev: 22.36%) at Week 137.

The FDA's Assessment:
FDA agrees with the Applicant's description. Refer to Efficacy Results – Secondary or exploratory endpoints in Section 8.1.2 for FDA's comprehensive review of blood pressure changes.

Electrocardiograms (ECGs)

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

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

QT

The Applicant's Position:
A maximum postbaseline QTcF of >500 msec was reported for 1 (1.4%) participant who had a baseline value <450 msec. No AEs of arrhythmia were reported for this participant and the prolonged QTcF subsequently resolved on treatment.

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

Immunogenicity

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

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

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:
No submission-specific safety issues were identified.

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

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
Results from patient-reported outcome analyses are in Section 8.1.2.

The FDA's Assessment:
See description of patient-reported tolerability in section 8.1.1.3.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:
Analyses of AEs by the prespecified subgroups of age, baseline ECOG PS (0, 1), race, region, and sex were generally consistent with the APaT population. Sample sizes within some subgroups are limited, precluding meaningful interpretation of results.

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

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees with the Applicant's position

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:
No new information concerning human carcinogenicity or tumor development is provided in this supplement.

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

Human Reproduction and Pregnancy

The Applicant's Position:
There were no pregnancies in Cohort A1 of LITESPARK-015; therefore, no new information concerning human reproduction and pregnancy is provided in this supplement.

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

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:
Efficacy and safety in pediatric participants are discussed in Section 10.

The FDA's Assessment:
The safety and effectiveness of belzutifan in pediatric patients less than 12 years of age has not been established.

Refer to Additional Efficacy Considerations in Section 8.1.3 for review regarding extrapolation of data to support the proposed indication of belzutifan in pediatric patients 12 years and older. Assessment of the safety of belzutifan in adolescent patients will be required as part of a PMR. See Section 13 for details regarding the PMR.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:
No overdoses were reported in Cohort A1 of LITESPARK-015. Potential for drug abuse or dependence on belzutifan has not been characterized. Based on the mechanism of action, belzutifan is unlikely to show abuse potential. Withdrawal or rebound effects were not evaluated after discontinuing belzutifan.

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

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:
The safety profile of belzutifan was summarized in the PSUR covering the period 13-FEB-2024 through 12-AUG-2024. There are no records of any belzutifan registration being revoked or withdrawn for safety reasons in any country.

The FDA's Assessment:

FDA agrees with the Applicant's position. See Section 8.1.3 (Additional Efficacy Considerations, *Inclusion of adolescent patients*) for a summary of post-marketing safety in adolescent patients treated for off-label indications.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:
Postmarket data from the safety reporting database is routinely reviewed for belzutifan. The Applicant's postmarketing safety database contains all data from postmarket sources, including health care providers, consumers, and scientific literature as well as competent authorities worldwide. There are no specific safety concerns associated with subpopulations not adequately represented in the safety database.

The FDA's Assessment:
See Section 13 for additional clinical postmarketing requirements (PMRs) for the pediatric population. FDA otherwise agrees with the Applicant's position.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:
The results from Cohort A1 in LITESPARK-015 show that the safety profile of belzutifan is generally manageable and tolerable in participants with locally advanced, unresectable, or metastatic PPGL, and is consistent with the known safety profile of belzutifan monotherapy for the approved indications. No treatment discontinuations were reported because of anemia, hypoxia, or dyspnea. No new safety signals were identified.

The FDA's Assessment:

The review of safety focused on the population of 72 patients with advanced, unresectable, or metastatic PPGL in Cohort A1 of LITESPARK-015. In this population, serious adverse events occurred in 36% of patients who received belzutifan. The most frequent serious adverse events were anemia and hypertension (4.2% each) and pyelonephritis, pneumonia, hypoxia, dyspnea and hemorrhage (2.8% each).

Permanent discontinuation due to an adverse event occurred in 2 patients (2.8%) who received belzutifan. Adverse events which resulted in permanent discontinuation were increased alanine aminotransferase and paraparesis (1.4% each).

The most common (≥25%) adverse events, including laboratory abnormalities, that occurred in patients who received belzutifan were anemia, fatigue, musculoskeletal pain, decreased lymphocytes, increased alanine aminotransferase, increased aspartate aminotransferase, increased calcium, dyspnea, increased potassium, decreased leukocytes, headache, increased alkaline phosphatase, dizziness, and nausea.

Overall, the adverse events observed are generally consistent with the current product labeling.

In the LITESPARK-015 trial adolescent safety data is limited. A PMR will be issued with the approval of belzutifan to characterize adolescent safety in a larger number of patients. See Section 13 for a discussion of the PMR.

The review team considers the safety profile of belzutifan to be acceptable when assessed in the context of a life-threatening disease. In addition, although belzutifan can cause serious and severe toxicities, the safety concerns are well-described in product labeling and belzutifan will be prescribed by oncologists who are trained to monitor and treat such treatment-related toxicities.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:

There were no major statistical issues noted in the review of this application. The primary efficacy evaluation of LITESPARK-015 Study Cohort A1 was based on the APaT population of 72 patients. Data from the third interim analysis (DCO date: May 23, 2024) was provided with the original sNDA submission, however the primary efficacy evaluation is based on results from the 90-day efficacy update with 5 additional months of follow-up submitted during the review window (DCO: October 23, 2024).

The confirmed ORR per RECIST v1.1 by BICR assessment was 26% (95% CI: 17, 38). Exploratory subgroup analyses of ORR were generally consistent across key prespecified subgroups and ORR assessment by investigator was similar to ORR by BICR. With an estimated median duration of study follow-up of 30.8 months, the median DOR was 20.4 months (95% CI: 8.3, NR). Among the 19 responders, 2 (11%) patients were censored with a follow-up less than 6 months from the time of onset of response; 8 (42%) patients were censored before reaching the median and all due to ongoing response. Additional follow-up data for DOR will be collected as part of a postmarketing commitment (PMC) for 12 months of follow-up post onset of response.

An important exploratory endpoint with clinical implications assessed on the trial was sustained reduction in total daily dose of blood pressure medication from baseline. The proportions of patients who had a reduction of at least 25% and 50% in at least one BP medication and maintained for at least 6 months from baseline, were 33% and 32%, respectively.

While enrollment of pediatric patients 12 years and older was permitted, Cohort A1 did not include any patients under 18 years of age. The inclusion of patients 12 years of age and older in the indication is based on similarities of the disease between adolescent and adult patients, the targeted mechanism of action of belzutifan, available PK data (Refer to Section 6), reported clinical safety experience through the expanded access program, literature reports, and extrapolation from adolescent patients enrolled in Cohorts C and D of LITESPARK-015.

Due to the single-arm setting, FDA considers time-to-event and PRO endpoints to be uninterpretable to assess treatment effect without a comparator and are considered descriptive only. Additionally, results from subgroup analyses are considered exploratory and should be interpreted with caution, particularly those with small sample sizes.

In summary, the primary efficacy results for ORR and DOR supported by sustained reductions in use of BP medications in LITESPARK-015 Cohort A1 demonstrate clinically meaningful and durable anti-tumor activity of belzutifan in the treatment of patients with locally advanced, unresectable, or metastatic PPGL.

8.4 **Conclusions and Recommendations**

The FDA's Assessment:

LITESPARK-015 is a multi-center, multi-cohort, single-arm study evaluating the safety and efficacy of belzutifan as a single agent in patients with advanced PPGL (Cohort A1), pancreatic neuroendocrine tumors (PNET) (Cohort A2), VHL disease-associated tumors (Cohort B1), advanced gastrointestinal stromal tumors (Cohort C), or advanced solid tumors with HIF-2α-related genetic alterations (Cohort D). The primary endpoint for Cohort A1 is objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by blinded independent central review (BICR). Secondary endpoints included duration of response (DOR) and overall survival (OS). Exploratory endpoints included reduction in all BP medication (total daily dose) from baseline and duration among patients who were on antihypertensive medications at baseline. This endpoint is considered clinically meaningful because a reduction in hypertension, a key contributor to morbidity associated with PPGL that is caused by the underlying tumor, appears to correlate with decreased tumor activity and is a direct benefit to patients.

The proposed supple mental application is based on the results of Cohort A1 which enrolled 72

patients with locally advanced, unresectable, or metastatic PPGL who received belzutifan 120 mg once daily. At the DCO date of October 23, 2024, the confirmed ORR by BICR was 26% (95% CI: 17, 38). The median DOR was 20.4 (95% CI: 8.3, NR) months. A large proportion of patients, 89% and 53% respectively, maintained their response for at least 6 and 12 months. Among patients who were on antihypertensive medication at baseline and have received at least one dose of study drug, 32% achieved a sustained ≥50% reduction in their total daily dose of at least one blood pressure medication dose for at least 6 months.

Analyses of safety from LITESPARK-015 (COHORT A1) and the overall clinical safety database demonstrate an acceptable safety profile for belzutifan in the intended population. Overall, the adverse events observed are generally consistent with the current product labeling and there were no significant differences identified. The most common (≥25%) adverse reactions, including laboratory abnormalities, that occurred in patients who received belzutifan were anemia, fatigue, musculoskeletal pain, decreased lymphocytes, increased alanine aminotransferase, increased aspartate aminotransferase, increased calcium, dyspnea, increased potassium, decreased leukocytes, headache, increased alkaline phosphatase, dizziness, and nausea. The observed safety profile is acceptable in the context of the treatment of a rare, life-threatening disease. Belzutifan will be prescribed by oncologists who know how to monitor, identify, and manage the toxicities described in the USPI.

Although safety data for adolescents is limited in LITESPARK-015, FDA considers the magnitude and duration of ORR and reduction in blood pressure medication in adults, the similarity of the disease between adolescents and adults, and FDA's internal PK review allowing for appropriate adolescent dose selection, to be factors supporting a labeled indication for adolescent patients. A PMR will be issued with the approval of belzutifan to characterize adolescent safety in a larger number of patients.

FDA determined that the data submitted in this sNDA provide substantial evidence of effectiveness of belzutifan for the treatment of patients with locally advanced, unresectable, or metastatic PPGL. Based on a favorable benefit- risk assessment for this population with a rare, life threating disease with no FDA-approved therapeutic options, the evidence submitted in this application meets the statutory evidentiary standard for traditional approval of belzutifan for the following indication:

Belzutifan (WELIREG) is indicated for the treatment of adult and pediatric patients 12 years and older with locally advanced, unresectable, or metastatic pheochromocytoma and paraganglioma.

X	X
Primary Statistical Reviewer Yi Ren	Statistical Team Leader Flora Mulkey
X	X
Primary Clinical Reviewer Marjilla Seddiq	Clinical Team Leader Amy Barone

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
FDA did not refer this application to an advisory committee or seek input from other external consultants because this application did not raise significant public health questions regarding the role of belzutifan for the proposed indication.

10 Pediatrics

The Applicant's Position:

The pediatric indication for patients ≥12 years of age in advanced, unresectable, or metastatic PPGL was sought. While enrollment in LITESPARK-015 (Cohort A1) was open to participants ≥12 years of age, no participant under 18 was enrolled. However, supportive data are available for the use of belzutifan in patients <18 years of age in Cohorts C and D of LITESPARK-015 [Figure 1] and from the Applicant's postmarketing safety database. Therefore, an extrapolation approach, based on the disease biology of PPGL, response to therapy, belzutifan pharmacology and PK modeling, and supportive data of belzutifan monotherapy in adolescents, collectively supports belzutifan monotherapy as a new treatment option for pediatric patients with advanced, unresectable, or metastatic PPGL.

The biology and presentation for PPGL are generally similar between adult and pediatric patients. The underlying genetic syndromes for pediatric PPGL are also generally similar to those in adult patients, tending towards higher frequency of genetic predisposition in pediatric metastatic PPGL. There is no evidence that treatment response is different in pediatric patients compared with adults, and current treatment of pediatric PPGL is predominately the same as for adults. Additionally, as pediatric PPGL has similar biochemical targets as adults, treatment with belzutifan has the same mechanistic rationale for adults. Compared with adults, pediatric cases are more commonly due to variants in Cluster 1 genes (eg, VHL, SHDx, and EPAS1) [13], which are associated with pseudohypoxia by stabilization of HIF-2α, belzutifan as a HIF-2α inhibitor has strong mechanistic rationale for use in a pediatric population as well as an expected similar therapeutic effect and could be very impactful.

There were 3 pediatric participants enrolled in Cohort C and D of LITESPARK-015. The observed exposure data from the 3 adolescents in Cohorts C and D appear to be consistent with and fall within the range of exposures historically observed in adults after first dose and at steady state. Consequently, the simulated PK parameters at steady state in the adolescents are also in the range of model-simulated adult data.

A search of the Applicant's pharmacovigilance safety database as of 09-AUG-2024 identified 13 spontaneous cases (9 cases from US), 3 literature cases (all cases from US), and 2 solicited cases (both cases from US) on the use of belzutifan in patients under 18 years of age. Upon review of the postmarketing data, there were no new safety concerns identified.

Although the available clinical data are very limited, based on data available from pediatric participants in Cohort C and D and from the Applicant's postmarketing database, there were no new safety signals in pediatric participants treated with belzutifan, and there was evidence of antitumor activity in participants with available data.

Therefore, the Applicant considers that the extrapolation approach is appropriate to support the pediatric (≥12 years) indication and the overall response to therapy and risk-benefit profile is expected to be consistent between pediatric and adult PPGL, based on:

- Similarities in disease biology of pediatric and adult PPGL. The underlying disease characteristics represent a continuum in disease biology and the overall response to therapy and risk-benefit profile is expected to be consistent between pediatric and adult PPGL. Indeed, based on the mechanism of action of belzutifan and enrichment for Cluster 1 mutations in pediatric PPGL, there is strong mechanistic rationale for belzutifan in pediatric PPGL.
- Similarities in belzutifan PK. PK analyses and additional exposure simulations indicate that belzutifan exposure and drug pharmacology effect are expected to be similar between pediatrics and adults.
- Published results reported in pediatric Pacak-Zhuang syndrome and VHL patients, which show clinically meaningful efficacy after treatment with belzutifan [37] [38] [39].
- Belzutifan in adults and pediatric patients was well tolerated, as shown by safety data from LITESPARK-015 and supported by available data in the Applicant's postmarketing safety database.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. See Section 8.1.3 for FDA's detailed assessment for safety and efficacy in pediatric patients.

The Applicant also requested a partial waiver from the requirements for PREA for patients less than 12 years of age because malignant PPGL rarely occurs in children, making the necessary studies impossible or highly impracticable to conduct. The partial waiver was reviewed at the Oncology Subcommittee of PeRC (OCE PeRC) on April 9, 2025. OCE PeRC agreed with granting a partial wavier for this population of patients.

11 Labeling Recommendations

Data:

APPEARS THIS WAY ON ORIGINAL

Table 24: Applicant – Summary of Significant Proposed Labeling Changes

APPEARS THIS WAY ON ORIGINAL

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
PRESCRIBING INFORMATION: HIGHLIGHTS OF PRESCRIBING INFORMATION	Updated to include information based on LITESPARK-015	Text was revised for consistency with the Full Prescribing Information and now includes the dosage for pediatric patients by bodyweight for the new indication for the treatment of patients 12 years of age and older with pheochromocytoma or paraganglioma (PPGL).
INDICATIONS AND USAGE	Added indication for patients with PPGL	FDA agrees with the Applicant's proposed text to include a new indication: *WELIREG is indicated for the treatment of adult and pediatric patients 12 years and older with locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma (PPGL).*
WARNINGS AND PRECAUTIONS	Updated to include information based on LITESPARK-015	WARNINGS AND PRECAUTIONS was revised to include safety data from LITESPARK-015 for patients with pheochromocytoma or paraganglioma (PPGL).
ADVERSE REACTIONS	Updated to include study details and safety information from LITESPARK-015	In Tables 2 and 4, the adverse reactions tables, we removed (b) (4) and better represents the incidence of this adverse reaction. The safety data for the LITESPARK-015 study was reviewed and revised for consistency across oncology labelings.
DRUG INTERACTIONS		Editorial re-ordering of the text.

USE IN SPECIFIC POPULATIONS	Updated to include information based on LITESPARK-015	8.4 Pediatric Use: New text added to support the age range for the PPGL indication. *The safety and effectiveness of WELIREG have been established in pediatric patients aged 12 years and older for the treatment of locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma. Use of WELIREG in pediatric patients aged 12 years and older is supported by evidence from an adequate and well-controlled study of WELIREG in adults with additional pharmacokinetic data demonstrating that belzutifan exposure is predicted to be within range of that observed in adults, and that the course of advanced, unresectable, or metastatic pheochromocytoma or paraganglioma is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients [see Clinical Pharmacology (12.3), and Clinical Studies (14.3)].* 8.5 Geriatric Use: Age demographic information added for the LITESPARK-015 study. 8.6 Renal Impairment Text added for safety: *For patients with severe renal impairment (eGFR 15-29 mL/min estimated by MDRD), monitor for increased adverse reactions and modify the dosage as recommended.* 8.7 Hepatic Impairment Text added for safety: Hepatic Impairment "moderate and" was added to the existing text: For patients with *moderate and* severe hepatic impairment, monitor for increased adverse reactions and modify the dosage as recommended.
CLINICAL PHARMACOLOGY	Updated to include information based on LITESPARK-015	FDA agrees, all numbers were adjudicated and revised accordingly.
CLINICAL STUDIES	Added study description and efficacy results for LITESPARK-015	Text added to provide the efficacy data from the LITESPARK-015 study to support the new PPGL indication.

MEDICATION GUIDE: What is WELIREG®?	Updated to include information based on LITESPARK-015	FDA agrees. Medication Guide was reviewed by Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP).

The Applicant's Position:
[Table 16] summarizes the significant proposed labeling changes.

The FDA's Assessment: The Applicant's proposed text was reviewed and revised by FDA for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

There were no significant safety concerns identified during the NDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
The review team recommends the following PMR and PMC:

PMR

4842-1 Conduct a comprehensive, integrated safety analysis after 5 years of follow-up from clinical trials in a sufficient number of pediatric patients to adequately characterize and evaluate, in pediatric patients, the known serious risks of anemia and hypoxia following exposure to belzutifan. Include an assessment of clinical responses.

Draft Protocol Submission (Analysis Plan): 01/2026
Final Protocol Submission (Analysis Plan): 05/2026
Study Completion: 01/2034
Final Report Submission: 01/2034

PMC

4842-2 Complete Cohort A1 of the LITESPARK-015 trial and provide updated duration of response data once all patients have been followed for at least 12 months from the onset of response to further characterize the efficacy and clinical benefit of belzutifan in patients 12 years of age and older with advanced, unresectable, or metastatic pheochromocytoma or paraganglioma (PPGL). Include biomarker analyses to evaluate genetic correlates of response to belzutifan.

Trial Completion: 06/2026
Final Report Submission: 12/2026

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	__ Yes _x_ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _x_ No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _x_ No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X _____

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

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Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=Hereditary-pheochromocytomaparaganglioma&

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19.2 Financial Disclosure

The Applicant's Position:
Disclosure of financial interests and/or arrangements, including statements of due diligence for the investigators who conducted the LITESPARK-015 study, are described in FDA forms 3454, 3455, and Module 1.3.4.

Covered Clinical Study (Name and/or Number):* LITESPARK-015 (MK-6482-015)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 640		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
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:2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study:0 Sponsor of covered study: MSD		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 11		
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.

The FDA's Assessment:
FDA has reviewed the financial disclosure information and agrees with the table above. See Section 8.1.2 for more detail. FDA notes that the two investigators noted to have received significant payments were related to investigators in LITESPARK-013, an activity-estimating study of belzutifan in renal cell carcinoma, which was not related to the review for efficacy for this Application. Safety data from this study were submitted to support the Summary of Clinical safety. There were no investigators with disclosable financial interests in LITESPARK-015.

There were 11 investigators who did not return a financial disclosure form, out of a total of 640 investigators (including both principal investigators and sub-investigators for LITESPARK-013 and -015). For those investigators who did not submit a financial disclosure form, the Applicant states all required due diligence efforts were completed in accordance with the financial disclosure regulation. This included multiple attempts to reach out to the investigators to provide a completed financial disclosure form. In addition, the Applicant conducted internal searches completed by their Legal, Corporate Finance, and Licensing Departments. The Applicant states these internal searches confirmed that no proprietary and/or financial interests were reported, and no significant payments of other sorts were identified.

The 11 investigators were from 2 sites (site 9051 and site 9053) in LITESPARK-013 and 2 sites (site 0110 and site 0202) in LITESPARK-015. In LITESPARK-015, there were three patients enrolled at site 0110 and two patients at site 0202, among a total of 72 patients enrolled. FDA agrees that the low number of patients enrolled at each of these sites, respectively, together with the study design elements including blinded independent central review minimizes the risk of compromising the integrity of the study data.

19.3 Nonclinical Pharmacology/Toxicology

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:
N/A

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

Pharmacometrics analyses were conducted to evaluate doses selected for pediatric patients 12 years and older with locally advanced, unresectable, or metastatic PPGL. To achieve this goal, exposure-safety analysis for patients across various diseases or tumor types was conducted to understand the safety risk in patients with elevated exposure. In addition, population PK analysis was updated by including data from 72 patients with PPGL and applied to derive appropriate dosing in pediatric patients with different body weight through exposure-matching.

Table 25. Anticipated Model Risk for Population PK Analysis.

Elements	Details
Question of Interest	• What is the recommended dosage for pediatric patients 12 years and older (adolescents) with PPGL, especially for those weighing < 40 kg?
Context of Use	• Exposure-response analysis to understand safety risk in pediatric patients with elevated exposure following proposed dose. • Population PK modeling and simulation to derive dose in patients with lower body weight (< 40 kg).
Model Influence	• Moderate/high: No observed PK and safety data are available in patients with lower body weight (< 40 kg) in clinical trials. However, PK and safety information is available in patients with other body weight groups (≥ 40 kg). Modeling and simulation will be applied to derive dosing in patients < 40 kg.
Decision Consequence	• Moderate/high: Incorrect predictions could lead to higher belzutifan exposures and potential safety concern in adolescents with bodyweight < 40 kg compared to adults.
Model Risk	• Moderate/high: By combining Model Influence and Decision Consequence.

Source: Reviewer's analysis

In line with the expected model risk in deriving dose in pediatric patients < 40 kg, the following evaluation and criteria are considered in the review.

Table 26. Evaluation and Criteria Considered in Pharmacometrics Review.

Methodology	Objective	Model Evaluation	Section
Exposure-Safety Analysis	• To demonstrate increased safety risk in patients with elevated exposure.	Standard evaluation	18.4.2
Population Pharmacokinetics Analysis	• To simulate exposure for exposure-safety analysis. • To derive dose in patients < 40 kg through exposure-matching.	1. Standard evaluation 2. Additional analysis by removing age effects. 3. Performance evaluation on body weight effect	18.4.1

		4. Predictive performance in patients with BW near 40 kg	

Source: Reviewer's analysis

The pharmacometrics analyses support the following:

- Increased exposure is likely to increase the risk for anemia and hypoxia. Therefore, a lower dose is recommended for pediatric patients 12 years and older who weigh < 40 kg.
- Based on population PK modeling and simulation, a lower dose of 80 mg is recommended for patients with body weight < 40 kg; this dose will provide exposure within range of that in adults who receive a dose of 120 mg.

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:

The population PK model was updated with the data from Study MK-6482-015 and MK-6482-018, which included 72 patients with PPGL. Population PK simulation was subsequently conducted with the updated model to compare belzutifan exposures in adolescents to that of adults to determine the recommended dosage for adolescents. The updated population PK model only included 3 adolescents in the population PK analysis; therefore, age effects on estimated clearances and volume of distributions based on available data may not be applicable to predict belzutifan exposures in adolescents. The age effect was therefore removed from the population PK model. PK simulation predicted higher exposures in adolescents who weigh < 40 kg at the proposed recommended dose of 120 mg compared to that of adults at the same dose. A lower dose of 80 is predicted to provide belzutifan exposures in adolescents who weigh < 40 kg within range of that of adults who receive 120 mg. Due to the higher predicted exposures and lack of safety experience in patients with body weight < 40 kg, FDA recommends a lower dose of 80 mg QD for adolescents who weigh < 40 kg.

19.4.1.2. PPK Assessment Summary

The Applicant's Position:

General Information	
Objectives of PPK Analysis	• Update population PK model for belzutifan with data from Study MK-6482-015 and MK-6482-018 • Predict belzutifan exposure metrics for E-R analysis in patients with PPGL and all subjects.

		• Simulate and compare belzutifan exposures in adolescent subjects with adults to support dose selection for adolescent patients.
Study Included		Studies in the previous population PK model: MK-6482-001, MK-6482-002, MK-6482-004, MK-6482-006, MK-6482-007, MK-6482-010, MK-6482-014, MK-6482-005, MK-6482-013, and MK-6482-025. Additional Studies in the current population PK model: Study MK-6482-015 and MK-6482-018. The studies in the population PK model were summarized in Table 21.
Dose(s) Included		20 – 240 mg QD 120 – 160 mg BID 160 – 200 mg TID
Population Included		Healthy: 121 (12.9%) Patients with PPGL (ITT): 72 (7.7%) Patients with other diseases: 747 (79.5%)
Population Characteristics (Table 22 and Table 23)	General	Age median: 59 (15, 90; 31% >=65; 7.8% >=75) years old Weight median: 78.1 (40, 166) kg 616 (66%) Male Race: 713 (76%) White 43 (4.6%) Black 143 (15%) Asian 41 (4.4%) Other or missing
	Organ Impairment	Hepatic (NCI-ODWG): 872 (93%) Normal function 64 (6.8%) Mild impairment 1 (0.1%) Moderate impairment 3 (0.3%) Missing

		Renal: 215 (23%) Normal function 432 (46%) Mild impairment 280 (30%) Moderate impairment 3 (0.3%) Severe impairment 10 (1.1%) Missing	
	Pediatrics	3 Adolescents. Age median:16 (15,16) years old Weight median: 61 (49, 92) years old No adolescents with body weight < 40 kg were included in the analysis.	
No. of Patients, PK Samples, and BLQ		11,775 PK samples from 946 subjects. 704 (6.4%) post-dose BLQ and 906 (7.7%) pre-dose BLQ samples were excluded from the analysis.	
Sampling Schedule		Study MK-6482-015 Week 1 Day 1 and Week 3 Day 1: pre-dose; 1, 2, and 4 hours post-dose Week 5 Day 1: pre-dose (or at discontinuation if before week 5) Study MK-6482-018 Week 1 Day 1, Week 3 Day 1: pre-dose; 0.5, 1, 1.5, 2, 4 and 6 hours post-dose Week 1 Day 2: pre-dose; 2 hours post-dose Week 2 Day 1, Week 4 Day 1, Week 9 Day 1, Week 13 Day 1: pre-dose	
Covariates Evaluated		No additional covariates were evaluated in the updated population PK model. The covariates in the previous population PK model for belzutifan are listed in Table 24.	
Final Model		**Summary**	**Acceptability**

		[FDA's comments]
Software and Version	The population PK analysis was performed using the nonlinear mixed effects modeling approach with NONMEM®, version 7.5.1 (ICON, Hanover, MD, USA). PsN (psn.sourceforge.net) and R version 4.3.1 were used for the data analysis.	Acceptable
Model Structure	2-compartment model with first-order absorption and linear elimination	Acceptable
Model Parameter Estimates	Table 25	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	PK parameters were estimated with good precision. The η-shrinkage was low for CL/F and acceptable for Ka. The η-shrinkage was higher for Vc/F and Vp/F (43% and 62%, respectively), as noted previously.	Empirical Bayes estimates for V_p/F are less informative due to the η-shrinkage.
BLQ for Parameter Accuracy	Post-dose BLQ samples were excluded from the analysis	Acceptable
GOF, VPC	Figure 7 and Figure 8; The model was able to describe the data in Study 018 adequately based on the pcVPC. However, in Study 015, the model appeared to overpredict variability, and therefore, it predicted lower exposure especially at the 5th percentile.	Under-estimations were observed for pred-corrected concentration in Study MK-6482-014, MK-6482-015 and MK-6482-025.
Significant Covariates and Clinical Relevance	NA	
Analysis Based on Simulation (optional)	Model-based comparisons and simulations of belzutifan PK in	There were only 3 adolescents

	adolescents aged 12 to 17 years relative to exposures achieved in adults. 2000 virtual adolescents at each age from 12 to 17 years old and 2000 virtual adults sampled from National Health and Nutrition Examination Survey (NHANES) database were involved in the population PK simulation and results were shown in Figure 9.	included in the updated population PK analysis. The age effects on clearances and volume of distributions estimated based on available data may not be applicable to the simulation in adolescents.
Labeling Language	**Description**	**Acceptability** **[FDA's comments]**
12.3 Pharmacokinetics	Specific Populations Patients who are poor metabolizers of UGT2B17 and CYP2C19 had higher belzutifan AUC. There were no clinically significant differences in the pharmacokinetics of belzutifan based on age (19 to 90 years), sex, ethnicity (non-Hispanic, Hispanic), race (White, Black, Asian, Native American, Pacific Islander), or body weight (42 to 166 kg) (b) (4) *Patients with Renal Impairment* (b) (4) no clinically	FDA's comments on labeling language are provided in labeling discussion.

	significant differences in the mean belzutifan exposure were observed between subjects with normal renal function and those with mild (b) (4) moderate renal impairment (b) (4) [redacted] *Patients with Hepatic Impairment* (b) (4) [redacted] no clinically significant differences in the mean belzutifan exposure were observed between subjects with normal liver function (total bilirubin and AST ≤ ULN), and those with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1 to 1.5 x ULN and any AST). (b) (4) [redacted] Patients with severe hepatic impairment have not been studied.	

Table 27. Summary of Studies Included in the Population PK Analysis

Study No.	Description	N	Formulation	Doses	Population
PT2977-101/ MK-6482-001	Ph 1 dose-escalation/ expansion	95 Escalation: N=43 (22 RCC and 21 ST); Expansion: N=52 (all RCC)	FFP	Escalation: 20, 40, 80, 120, 160, and 240 mg QD (N=6-7 each), 120 mg BID (N=6) Expansion: 120 mg QD	ST/RCC
PT2977-103/ MK-6482-002	Ph 1 food-effect	16	FFP	120 mg SD fed and fasted	HV
PT2977-202/ MK-6482-004	Ph 2 single arm	61	Participants switched from FFP to FMF	120 mg QD	VHL-RCC
PT2977-104/ MK-6482-006	Ph 1 cross-over relative bioavailability	18	FFP vs. FMF	120 mg SD Formulation A (FFP) 120 and 200 mg SD Formulation B (FMF)	HV
MK-6482-007	Ph 1 Japan PK	49	FMF	40 mg SD	HV
MK-6482-014	Ph 1 food effect study	14	FMF	120 mg SD in fasting and non-fasting state	HV
MK-6482-005	Ph 3 parallel design vs. active comparator (everolimus)	Planned: 736 (1:1 ratio MK-6482 or everolimus), actual 381 in MK-6482 arm	FMF	120 mg QD MK-6482 or 10 mg QD everolimus	Advanced RCC
MK-6482-013	Ph 2 120 mg QD vs 200 mg QD	Planned: 150 (1:1 ratio 120 mg QC or 200 mg QD); actual 154	FMF	120 mg QD or 200 mg QD of MK-6482	Advanced RCC
MK-6482-025	Ph 1 80 mg vs 120 mg once as a single dose	24	FMF	80 mg or 120 mg SD of MK-6482	HV
MK-6482-010	Ph 1 monotherapy and in combination with lenvatinib (only monotherapy included)	24	FMF	120 mg QD	Advanced RCC
MK-6482-015	Ph 2 study to evaluate efficacy and safety in participants with advanced PPGL, pNET, VHL-disease-associated tumors, GIST, or ST with HIF-2α related genetic alterations	81 (Cohorts A1, C, and D)	FMF	120 mg QD	PPGL / GIST / advanced ST with HIF-2α-related genetic alterations
MK-6482-018	Ph 1 dose-escalation study in participants with advanced ccRCC	29	FMF	120 mg QD, 160 mg BID, 160 mg TID, 200 mg TID	ccRCC

Abbreviations: BID = twice daily; ccRCC = clear cell renal cell carcinoma; FFP=fit-for-purpose formulation; FMF= final market formulation; GIST = gastrointestinal stromal tumors; HIF = hypoxia-inducible factor; HV=healthy volunteer; N = number of subjects; Ph = Phase; PK=pharmacokinetics; pNET = pancreatic neuroendocrine tumor; PPGL = pheochromocytoma / paraganglioma; QD = once daily; RCC= renal cell carcinoma; SD=single dose; ST = solid tumors; TID = 3 times daily; VHL = von Hippel-Lindau

Source: Population PK Analysis of MK-6482 in RCC, PPGL & ST (08PTYF), Page 12-13, Table 1.

Table 28. Summary of Continuous Covariates in Population PK Analysis

	Previous studies (N=831)	Study 015 (N=80)	Study 018 (N=29)	Overall (N=940)
Age (years)				
Mean (Stdev)	58.9 (12.3)	49.3 (13.7)	61.3 (11.8)	58.2 (12.7)
Median [Min, Max]	60.0 [19.0, 90.0]	50.0 [15.0, 77.0]	63.0 [34.0, 77.0]	59.0 [15.0, 90.0]
Body weight (kg)				
Mean (Stdev)	79.6 (20.5)	76.8 (16.5)	90.1 (20.0)	79.7 (20.2)
Median [Min, Max]	77.9 [40.0, 166]	78.2 [45.3, 110]	88.6 [49.9, 133]	78.1 [40.0, 166]
Body mass index (kg/m²)				
Mean (Stdev)	27.0 (5.53)	26.3 (5.30)	29.9 (6.00)	27.0 (5.55)
Median [Min, Max]	26.4 [15.4, 52.0]	25.8 [17.2, 39.1]	28.7 [22.0, 43.3]	26.4 [15.4, 52.0]
Missing	4 (0.5%)	3 (3.8%)	2 (6.9%)	9 (1.0%)
Height (cm)				
Mean (Stdev)	171 (10.7)	171 (8.71)	175 (9.01)	171 (10.5)
Median [Min, Max]	171 [144, 199]	173 [154, 189]	177 [150, 193]	172 [144, 199]
Missing	4 (0.5%)	3 (3.8%)	2 (6.9%)	9 (1.0%)
eGFR (mL/min/1.73m²)				
Mean (Stdev)	67.5 (22.6)	86.6 (32.5)	64.9 (19.0)	69.1 (24.1)
Median [Min, Max]	63.9 [19.6, 171]	82.0 [37.4, 220]	60.0 [38.6, 114]	64.7 [19.6, 220]
Missing	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)
Aspartate aminotransferase (U/L)				
Mean (Stdev)	22.1 (14.3)	26.1 (12.3)	21.2 (10.2)	22.4 (14.1)
Median [Min, Max]	19.0 [5.00, 240]	23.0 [6.00, 77.0]	20.0 [9.00, 67.0]	19.0 [5.00, 240]
Missing	3 (0.4%)	0 (0%)	0 (0%)	3 (0.3%)
Alanine aminotransferase (U/L)				
Mean (Stdev)	22.6 (21.6)	27.4 (17.3)	22.8 (14.5)	23.0 (21.1)
Median [Min, Max]	17.0 [5.00, 320]	22.4 [4.70, 107]	21.0 [5.00, 81.0]	18.0 [4.70, 320]
Missing	3 (0.4%)	0 (0%)	0 (0%)	3 (0.3%)

Source: Population PK Analysis of MK-6482 in RCC, PPGL & ST (08PTYF), Page 22-23, Table 4.

Table 29. Summary of Categorical Covariates in Population PK Analysis.

	Previous studies (N=831)	Study 015 (N=80)	Study 018 (N=29)	Overall (N=940)
Sex				
Male	546 (65.7%)	46 (57.5%)	24 (82.8%)	616 (65.5%)
Female	285 (34.3%)	34 (42.5%)	5 (17.2%)	324 (34.5%)
Disease Status				
Healthy volunteer	121 (14.6%)	0 (0%)	0 (0%)	121 (12.9%)
RCC	628 (75.6%)	0 (0%)	0 (0%)	628 (66.8%)
ST	21 (2.5%)	7 (8.8%)	0 (0%)	28 (3.0%)
VHL-RCC	61 (7.3%)	0 (0%)	0 (0%)	61 (6.5%)
ccRCC	0 (0%)	0 (0%)	29 (100%)	29 (3.1%)
PPGL	0 (0%)	72 (90.0%)	0 (0%)	72 (7.7%)
pNET	0 (0%)	0 (0%)	0 (0%)	0 (0%)
GIST WT	0 (0%)	1 (1.3%)	0 (0%)	1 (0.1%)
Food status				
Fasted	798 (96.0%)	80 (100%)	29 (100%)	907 (96.5%)
Fed	15 (1.8%)	0 (0%)	0 (0%)	15 (1.6%)
Missing	18 (2.2%)	0 (0%)	0 (0%)	18 (1.9%)
Formulation				
Formulation A (FFP)	177 (21.3%)	0 (0%)	0 (0%)	177 (18.8%)
Formulation B (FMF)	654 (78.7%)	80 (100%)	29 (100%)	763 (81.2%)
Hepatic dysfunction (NCI-ODWG)				
Normal	774 (93.1%)	70 (87.5%)	28 (96.6%)	872 (92.8%)
Mild	53 (6.4%)	10 (12.5%)	1 (3.4%)	64 (6.8%)
Moderate	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)
Missing	3 (0.4%)	0 (0%)	0 (0%)	3 (0.3%)
Renal impairment				
Normal	172 (20.7%)	38 (47.5%)	5 (17.2%)	215 (22.9%)
Mild	389 (46.8%)	29 (36.3%)	14 (48.3%)	432 (46.0%)
Moderate	262 (31.5%)	10 (12.5%)	8 (27.6%)	280 (29.8%)
Severe	3 (0.4%)	0 (0%)	0 (0%)	3 (0.3%)
Missing	5 (0.6%)	3 (3.8%)	2 (6.9%)	10 (1.1%)
CYP2C19 phenotype				
Poor	64 (7.7%)	1 (1.3%)	0 (0%)	65 (6.9%)
Intermediate	214 (25.8%)	19 (23.8%)	9 (31.0%)	242 (25.7%)
Extensive	321 (38.6%)	30 (37.5%)	12 (41.4%)	363 (38.6%)
Rapid	195 (23.5%)	26 (32.5%)	8 (27.6%)	229 (24.4%)
Ultrarapid	6 (0.7%)	3 (3.8%)	0 (0%)	9 (1.0%)
Missing	31 (3.7%)	1 (1.3%)	0 (0%)	32 (3.4%)
UGT2B17 phenotype				
Poor	152 (18.3%)	8 (10.0%)	2 (6.9%)	162 (17.2%)
Intermediate	358 (43.1%)	36 (45.0%)	13 (44.8%)	407 (43.3%)
Extensive	293 (35.3%)	35 (43.8%)	14 (48.3%)	342 (36.4%)
Missing	28 (3.4%)	1 (1.3%)	0 (0%)	29 (3.1%)
UGT2B17 & CYP2C19 status				
PM-PM	38 (4.6%)	0 (0%)	0 (0%)	38 (4.0%)
PM-IM/EM	103 (12.4%)	4 (5.0%)	2 (6.9%)	109 (11.6%)
PM-RM/UM	11 (1.3%)	4 (5.0%)	0 (0%)	15 (1.6%)
PM-MM	0 (0%)	0 (0%)	0 (0%)	0 (0%)
IM-PM	18 (2.2%)	1 (1.3%)	0 (0%)	19 (2.0%)
IM-IM/EM	233 (28.0%)	27 (33.8%)	11 (37.9%)	271 (28.8%)
IM-RM/UM	105 (12.6%)	8 (10.0%)	2 (6.9%)	115 (12.2%)
IM-MM	2 (0.2%)	0 (0%)	0 (0%)	2 (0.2%)
EM-PM	8 (1.0%)	0 (0%)	0 (0%)	8 (0.9%)
EM-IM/EM	198 (23.8%)	18 (22.5%)	8 (27.6%)	224 (23.8%)
EM-RM/UM	85 (10.2%)	17 (21.3%)	6 (20.7%)	108 (11.5%)

	Previous studies (N=831)	Study 015 (N=80)	Study 018 (N=29)	Overall (N=940)
EM-MM	2 (0.2%)	0 (0%)	0 (0%)	2 (0.2%)
MM-PM	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MM-IM/EM	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)
MM-RM/UM	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MM-MM	27 (3.2%)	1 (1.3%)	0 (0%)	28 (3.0%)
Race				
White	611 (73.5%)	74 (92.5%)	28 (96.6%)	713 (75.9%)
Black	38 (4.6%)	4 (5.0%)	1 (3.4%)	43 (4.6%)
Asian	142 (17.1%)	1 (1.3%)	0 (0%)	143 (15.2%)
Native American	3 (0.4%)	0 (0%)	0 (0%)	3 (0.3%)
Pacific	2 (0.2%)	0 (0%)	0 (0%)	2 (0.2%)
Other	10 (1.2%)	1 (1.3%)	0 (0%)	11 (1.2%)
Missing	25 (3.0%)	0 (0%)	0 (0%)	25 (2.7%)
Ethnicity				
Hispanic/Latino	88 (10.6%)	4 (5.0%)	2 (6.9%)	94 (10.0%)
Not Hispanic/Latino	701 (84.4%)	74 (92.5%)	27 (93.1%)	802 (85.3%)
Unknown/Missing	42 (5.1%)	2 (2.5%)	0 (0%)	44 (4.7%)
Dosing regimen				
20 mg QD	6 (0.7%)	0 (0%)	0 (0%)	6 (0.6%)
40 mg QD	55 (6.6%)	0 (0%)	0 (0%)	55 (5.9%)
80 mg QD	18 (2.2%)	0 (0%)	0 (0%)	18 (1.9%)
120 mg QD	650 (78.2%)	80 (100%)	3 (10.3%)	733 (78.0%)
160 mg QD	6 (0.7%)	0 (0%)	0 (0%)	6 (0.6%)
200 mg QD	83 (10.0%)	0 (0%)	0 (0%)	83 (8.8%)
240mg QD	7 (0.8%)	0 (0%)	0 (0%)	7 (0.7%)
120 mg BID	6 (0.7%)	0 (0%)	0 (0%)	6 (0.6%)
160 mg BID	0 (0%)	0 (0%)	6 (20.7%)	6 (0.6%)
160 mg TID	0 (0%)	0 (0%)	10 (34.5%)	10 (1.1%)
200 mg TID	0 (0%)	0 (0%)	10 (34.5%)	10 (1.1%)
Race-country				
Asian from Japan	89 (10.7%)	0 (0%)	0 (0%)	89 (9.5%)
Asian from China	24 (2.9%)	0 (0%)	0 (0%)	24 (2.6%)
Other Asian	29 (3.5%)	1 (1.3%)	0 (0%)	30 (3.2%)
Non-Asian	689 (82.9%)	79 (98.8%)	29 (100%)	797 (84.8%)

Source: Population PK Analysis of MK-6482 in RCC, PPGL & ST (08PTYF), Page 23-25, Table 5.

Table 30. Summary of Covariates in the Previous Population PK Model.

Covariates	Reason for Investigation	Parameter
Age	Standard covariate	CL/F, Vc/F
Body weight	Standard covariate	CL/F, Vc/F, Q/F, Vp/F
Formulation	Evaluate impact of formulation change	ka, Tlag
Fed vs. fasted dosing	Incorporate impact of food	ka, Tlag
Genotype (UGT2B17 and CYP2C19 polymorphisms)	Glucuronidation (catalyzed by UGT2B17) and oxidative metabolism (catalyzed by CYP2C19) are primary pathways of elimination	CL/F, relative F, IIV on CL/F

Abbreviations: CL/F = apparent clearance; F = bioavailability; IIV=interindividual variability; ka = absorption rate constant; Q/F = apparent intercompartmental clearance; Tlag = absorption lag time; Vc/F = apparent central volume of distribution; Vp/F = apparent peripheral volume of distribution.

Source: Population PK Analysis of MK-6482 in RCC, PPGL & ST (08PTYF), Page 18, Table 2.

Table 31. Parameter Estimates of Final Population PK Model.

Parameter	Estimate	RSE (%)	Asymptotic 95% CI	Shrinkage (%)
Fixed Effects				
CL/F (L/h)	(b) (4)			
V_c/F (L)				
Q/F (L/h)				
V_p/F (L)				
Ka (/h)				
Lag time (h)				
Fed status effect on Ka				
Body weight exponent on CL/F and Q/F				
Body weight exponent on V_c/F and V_p/F				
UGT2B17 extensive metabolizer effect on CL/F				
UGT2B17 poor metabolizer effect on CL/F				
CYP2C19 poor metabolizer effect on CL/F				
CYP2C19 rapid or ultrarapid metabolizer effect on CL/F				
UGT2B17 poor metabolizer effect on F				
FMF effect on Ka				
Age exponent on V_c/F				
Age exponent on CL/F				
Random Effects				
IIV on CL/F				
Scaling factor on IIV for CL/F in UGT2B17 poor metabolizers				
IIV on V_c/F				
IIV on V_p/F				
IIV on Ka				
Residual Error				
RES HV				
RES PAT				
EPS				

Abbreviations: CI=confidence interval; CL/F=apparent clearance; CYP=Cytochrome P450; EPS=ε (residual error); F=bioavailability; FMF=final market formulation; HV=healthy volunteer; IIV=inter-individual variability; Ka=absorption rate constant; PAT=patient; Q/F=apparent intercompartmental clearance; RES=proportional residual error; RSE=relative standard error; UGT=Uridine 5'-diphospho-glucuronosyltransferase; V_c/F=apparent central volume of distribution; V_p/F=apparent peripheral volume of distribution.

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Source: Population PK Analysis of MK-6482 in RCC, PPGL & ST (08PTYF), Page 27-28, Table 6.

Figure 9. Goodness-of-Fit Plots for Final Population PK Model.

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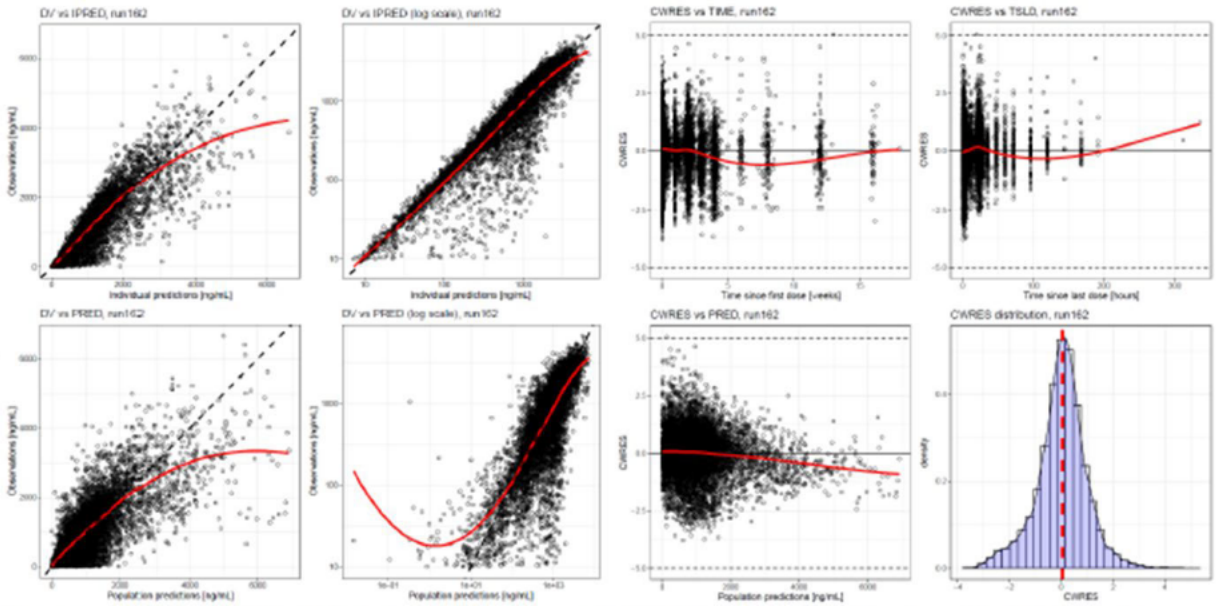
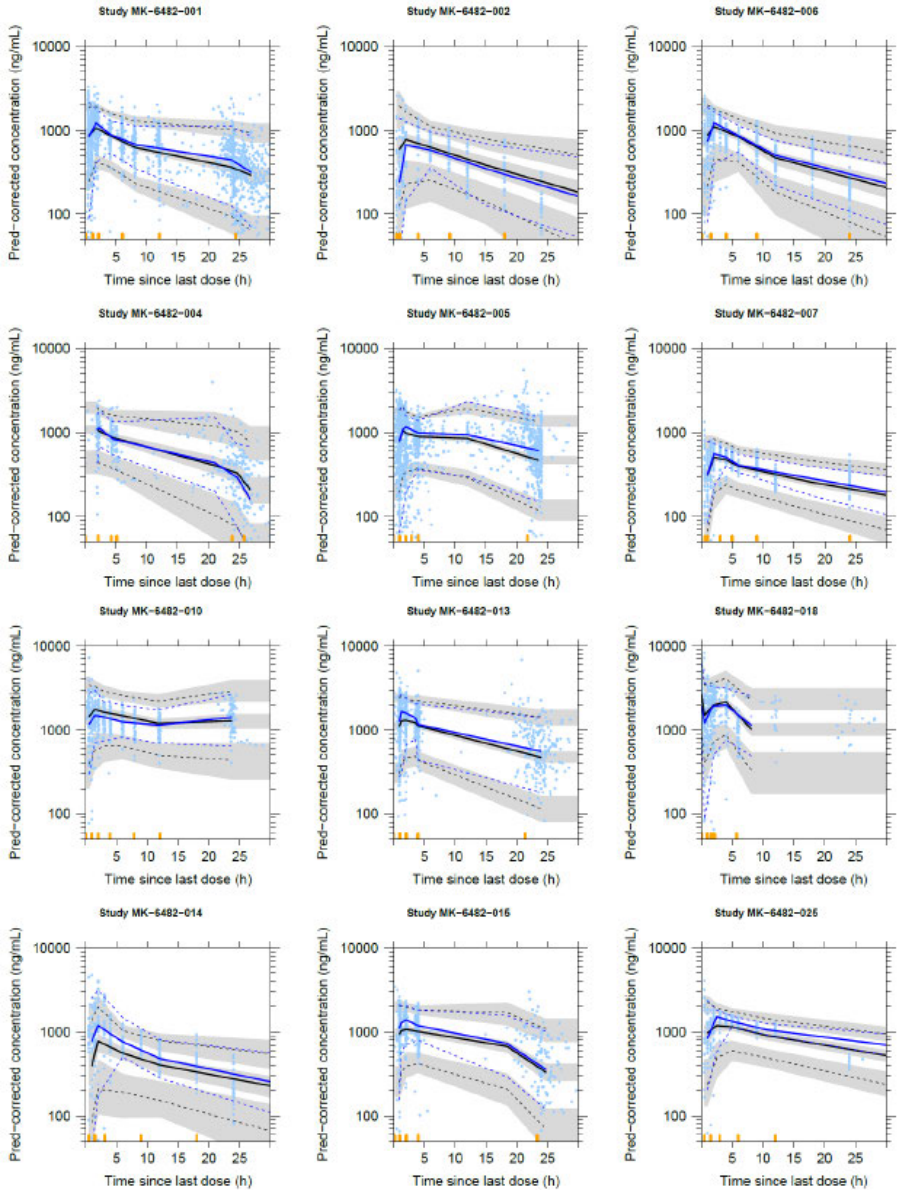


Abbreviations: CWRES=conditional weighted residuals; DV=dependent variable (MK-6482 concentration); GOF=goodness-of-fit; IPRED=individual predictions; PRED=population predictions; TSLD=time since last dose.

Source: Population PK Analysis of MK-6482 in RCC, PPGL & ST (08PTYF), Page 29, Figure 2.

Figure 10. Prediction-Corrected VPC by Study for Final Population PK Model.

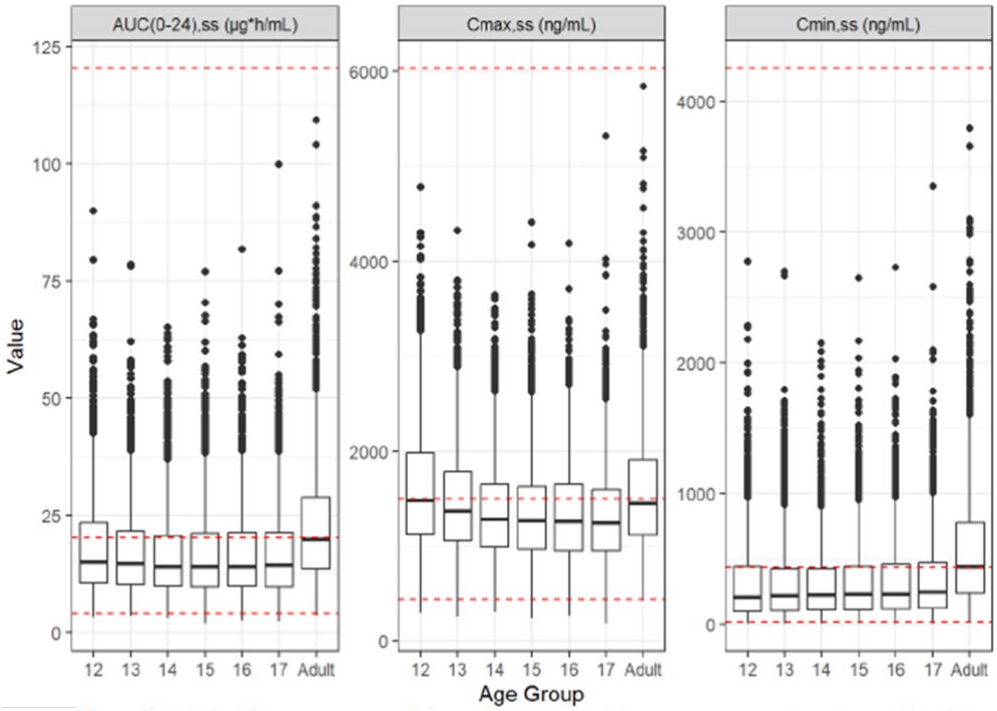


Abbreviations: Pred-corr=prediction-corrected; VPC=visual predictive check.

Notes: Blue dots are the prediction-corrected observed data points; the blue lines are the 50th (solid), 5th (dashed) and 95th (dashed) percentiles of observed concentrations; and the black lines are the 50th (solid), 5th (dashed) and 95th (dashed) percentiles of simulations. The grey bands represent the 95% prediction intervals for the corresponding black lines based on 500 simulations. Short yellow lines indicate bin intervals. TSLD3 was used for plotting actual time since last dose.

Source: Population PK Analysis of MK-6482 in RCC, PPGL & ST (08PTYF), Page 31, Figure 3.

Figure 11. Steady State Exposures by Age in Population PK Simulation



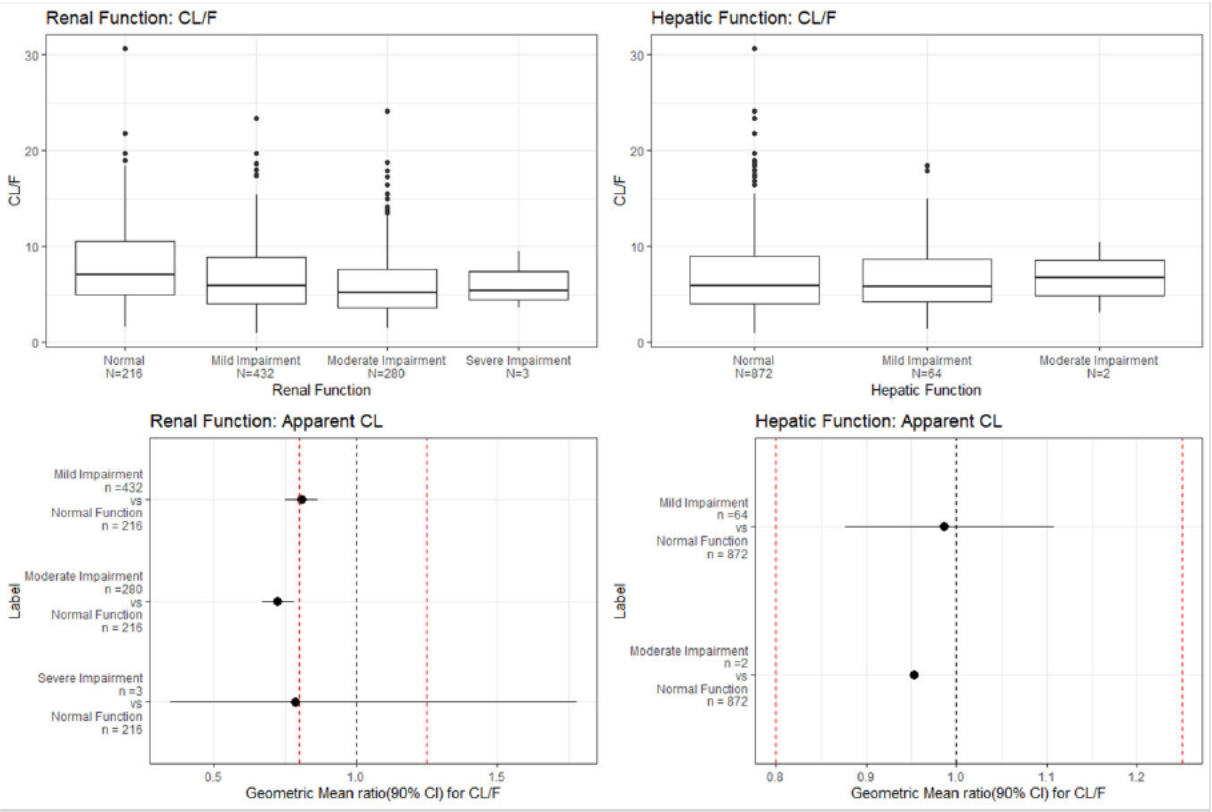
Notes: Red dashed lines represent median, maximum, and minimum parameter values observed in adults following a 120 mg QD dose.
Abbreviations: AUC(0-24)=area under the concentration – time curve between 0 and 24 hours after dose; Cmax=maximum concentration ; Cmin=minimum concentration; FS=focal subject.

Source: Simulations of MK-6482 Pharmacokinetics and Exposure in Adolescents (08PV05), Page 23, Figure 6.

The FDA's Assessment:

The comparison of empirical Bayes estimates of CL/F in participants with different renal or hepatic function groups based on the final population PK model are shown in Figure 10. No clinically significant differences in CL/F were observed between participants with normal renal function and those with mild or moderate renal impairment. Similar results are observed for participants with normal hepatic function and those with mild hepatic impairment.

Figure 12. Comparison of Empirical Bayes Estimates of CL/F in Subjects with Different Renal or Hepatic Function Groups.



Source: Reviewer's analysis.

19.4.1.3. PPK Review Issues

Population PK analysis was conducted 1. to understand change in exposure for patients with lower bodyweight and 2. to derive a dose for patients who weigh less than 40 kg. Given the moderate/high model risk, additional evaluation and independent analyses were performed.

19.4.1.4. Reviewer's Independent Analysis

Only 3 adolescents (age: 15 – 16 years old, bodyweight: 49 - 92 kg) were included in the population PK analysis, leaving uncertainty on whether the effect of age could be reliably estimated. Therefore, additional population PK analysis was performed to evaluate the effect of body weight on the exposure without an age effect.

Age effects was removed from the final population PK model. The parameter estimates are summarized in Table 26 and goodness-of-fit plots and pcVPC are shown in Figure 11 - Figure 15. The model performance based on standard model evaluation is similar as the model with age

effects. (Ref to section 18.4.1.2). The model appears to adequately describe the observed data. Between subject variability on key PK parameters such as clearance over the bodyweight range down to 40 kg could be well described by the PK model (Figure 13). Additionally, the model could well describe the observations from patients with body weight close to 40 kg (40 -50 kg), providing additional assurance to predict the exposures for subjects with body weight less than 40 kg (Figure 14 and Figure 15).

Through PK simulation, belzutifan exposure in adolescents with body weight < 40 kg (range: 29 - 40 kg, sampled in adolescents from NHANES dataset) at the proposed dose of 120 mg is predicted to be higher than that of adults at the same dose. Additional simulations predict that belzutifan exposures at a dose of 80 mg in adolescents who weigh < 40 kg will be within range of that of adults at a dose of 120 mg (Figure 16 and Table 27). Due to the higher predicted PK exposures and lack of safety experience in patients with body weight < 40 kg, FDA recommends a lower dose of 80 mg for adolescents with body weight < 40 kg.

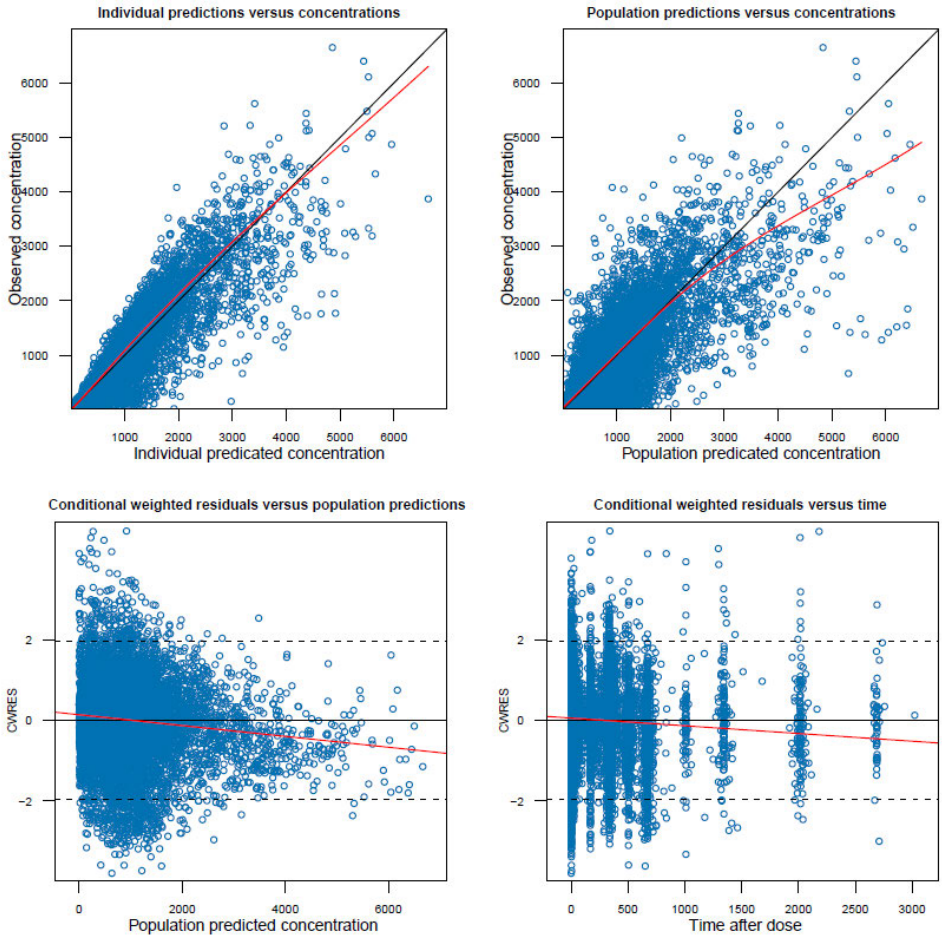
Table 32. Parameter Estimates of Final Population PK Model without Age Effects.

Parameter	Estimate	RSE	Shrinkage
Fixed Effects			
CL (L/h)	5.73	2.30%	
V_c (L)	87.6	1.40%	
Q (L/h)	5.64	8.50%	
V_p (L)	32.3	5.80%	
Ka (/h)	2.43	6.40%	
Lag time (h)	0.165	0.60%	
Fed status effect on Ka	-0.864	0.60%	
Body weight exponent on CL/F and Q/F	0.6	9.70%	
Body weight exponent on Vc/F and Vp/F	1.02	3.20%	
UGT2B17 extensive metabolizer effect on CL/F	0.41	10.90%	
UGT2B17 poor metabolizer effect on CL/F	-0.411	5.40%	
CYP2C19 poor metabolizer effect on CL/F	-0.223	20.10%	
CYP2C19 rapid or ultrarapid metabolizer effect on CL/F	0.0986	35.70%	
UGT2B17 poor metabolizer effect on F	0.138	18.90%	
FMF effect on Ka	-0.416	5.10%	
Random Effects			
IIV on CL/F	0.169	5.6%	7%

Scaling factor on IIV for CL/F in UGT2B17 poor metabolizers	0.787	8.2%	
IIV on V_c/F	0.0154	15.4%	41.8%
IIV on V_p/F	0.159	22.8%	60.2%
IIV on Ka	1.18	5.7%	19%
Residual Error			
RES HV	0.256	0.50%	
RES PAT	0.32	0.60%	

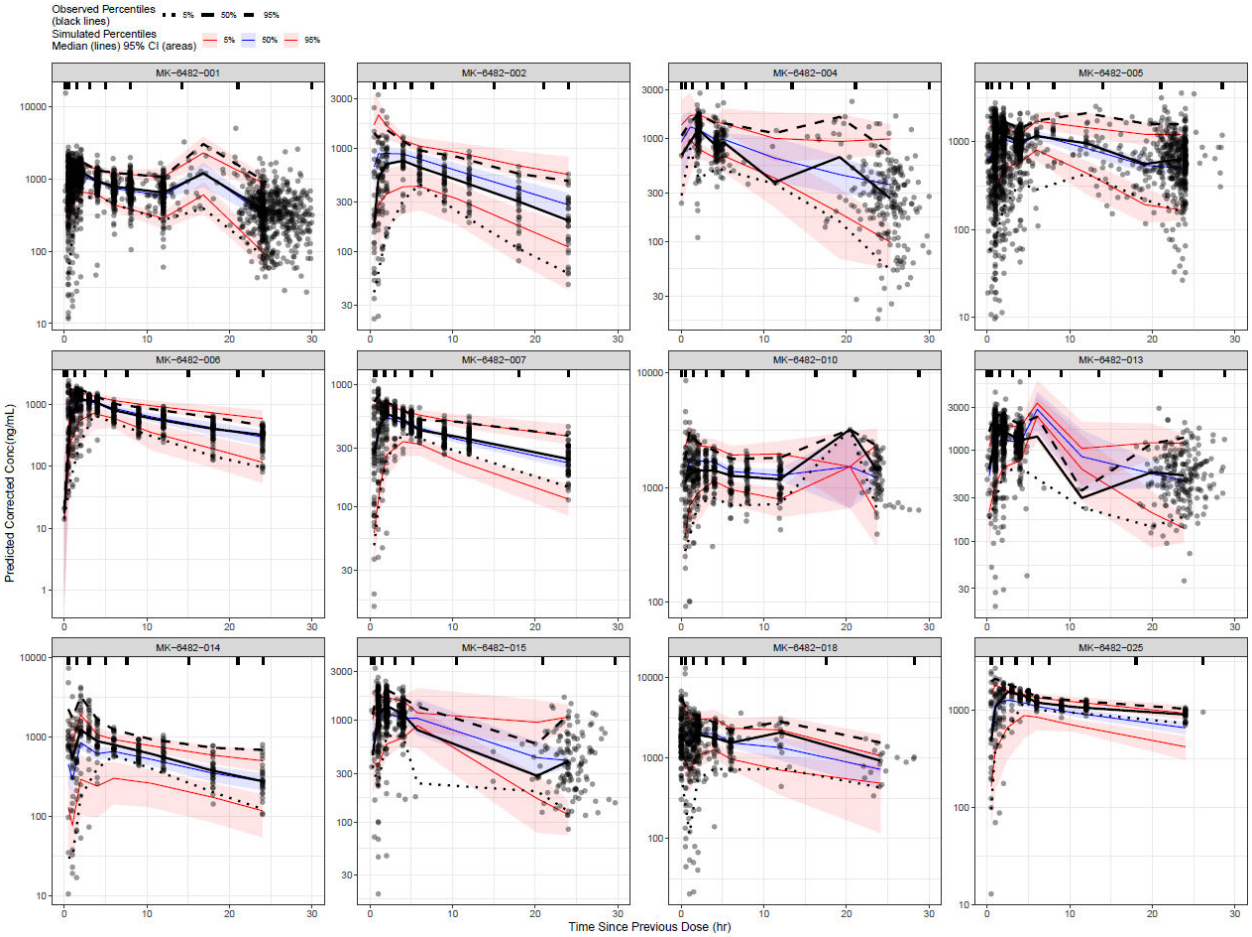
Source: Reviewer's analysis.

Figure 13. Goodness-of-Fit Plots for Final Population PK Model without Age Effects.



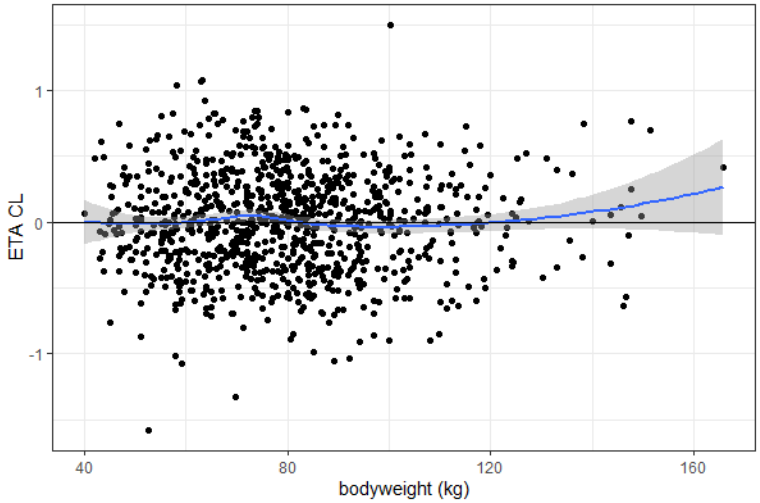
Source: Reviewer's analysis.

Figure 14. Prediction-Corrected VPC by Study for Final Population PK Model without Age Effects.



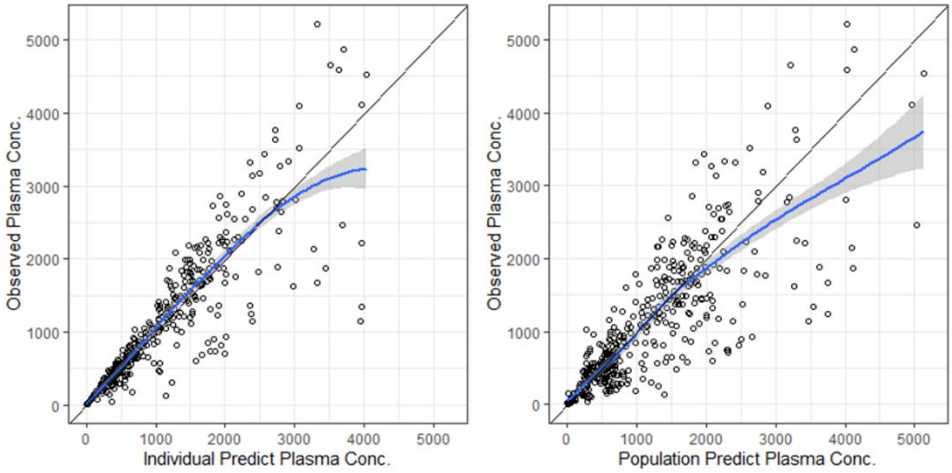
Source: Reviewer's analysis.

Figure 15. ETA CL vs Bodyweight in Reviewer's Population PK Model.



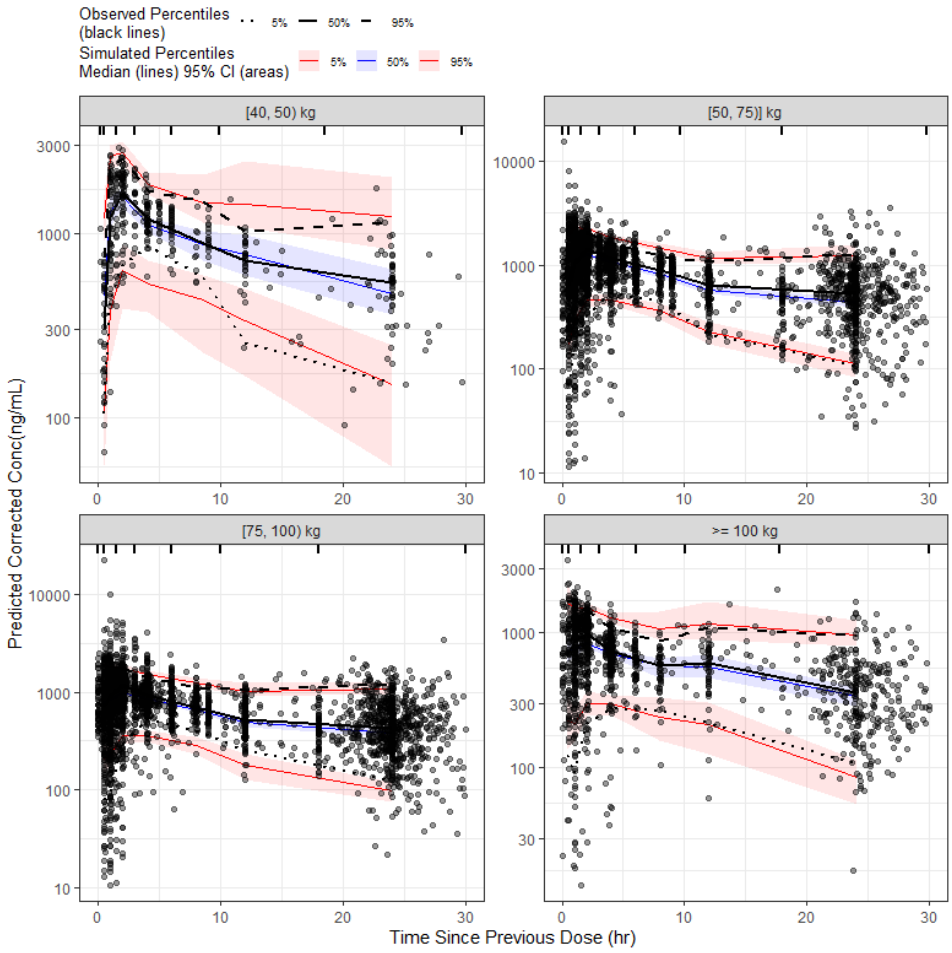
Source: Reviewer's analysis.

Figure 16. Individual and Population Prediction vs Observation for Subjects with Bodyweight < 50 kg in Reviewer's Population PK Analysis.



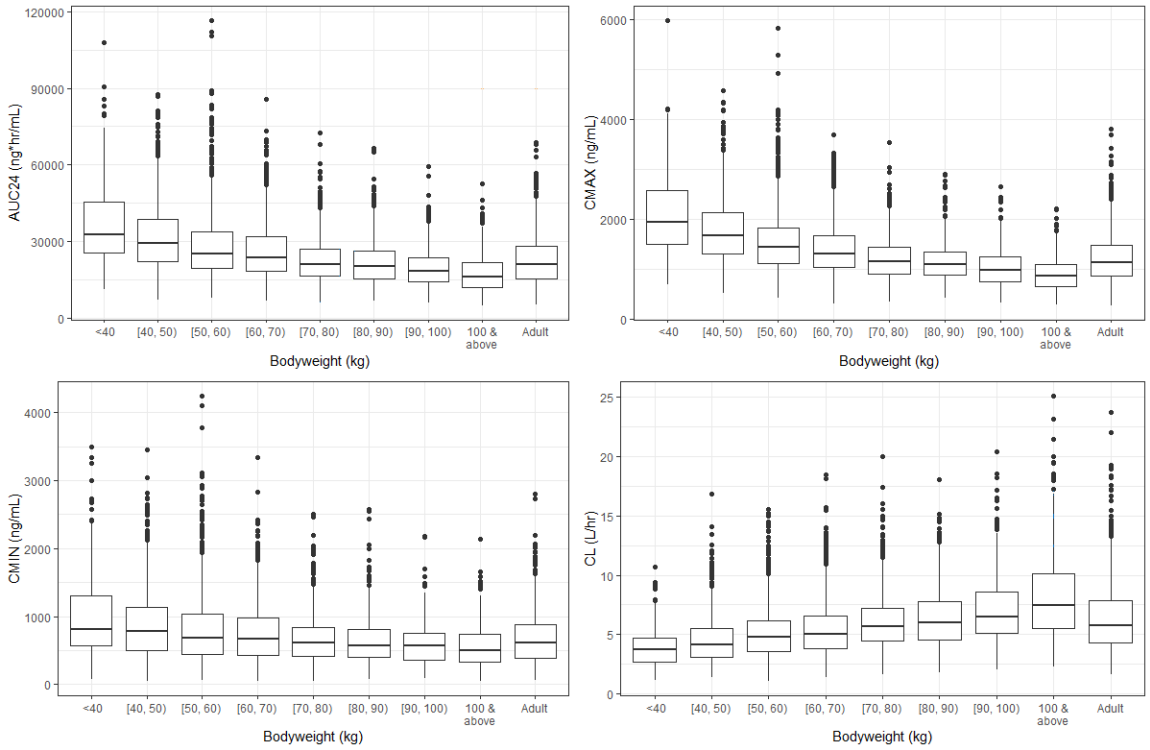
Source: Reviewer's analysis.

Figure 17. Prediction-Corrected VPC by Bodyweight Group for Final Population PK Model without Age Effects.



Source: Reviewer's analysis.

Figure 18. Comparison of Belzutifan Exposures at Steady State in Reviewer's Simulation.



Source: Reviewer's analysis.

Table 33. Summary of Belzutifan Exposures at Steady State in Reviewer's Simulation.

Age Group	Bodyweight Group (kg)	Predicted PK Exposures, Geometric Mean (CV%)			
		AUC24 (ng*hr/mL)	Cmax (ng/m)	Cmin (ng/mL)	CL (L/hr)
Adolescent	<40 (120 mg)	33668 (44)	1956 (39)	794 (79)	3.6 (44)
	<40 (80 mg)	22883 (44)	1340 (39)	534 (76)	3.5 (44)
	[40, 50)	28966 (43)	1635 (39)	727 (73)	4.1 (43)
	[50, 60)	25587 (44)	1421 (40)	658 (73)	4.7 (44)
	[60, 70)	23795 (43)	1301 (38)	633 (68)	5 (43)
	[70, 80)	21113 (40)	1141 (36)	574 (63)	5.7 (40)
	[80, 90)	20066 (42)	1082 (36)	549 (66)	6 (42)

	[90, 100)	18288 (45)	963 (41)	519 (66)	6.6 (45)
	[100, 166]	16152 (46)	843 (41)	467 (68)	7.4 (46)
Adult	[35.6, 254]	20660 (46)	1113 (43)	566 (70)	5.8 (46)

Source: Reviewer's analysis.

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (safety) Executive Summary

The FDA's Assessment:

In the original submission, E-R safety analysis was conducted by the Applicant to characterize the E-R relationships between belzutifan exposure and selected endpoints including anemia all grades and grade ≥3, hypoxia all grades and grade ≥3, dose reduction, dose interruption, discontinuation from participants with PPGL from Study MK-6482-015 (Cohort A1). To better characterize the E-R relationship, FDA requested that the applicant evaluate the relationships using all available safety data across various disease or tumor types and multiple dose levels of belzutifan. In the E-R safety analysis in pooled population, positive E-R relationships were observed for all safety endpoints except for discontinuation.

19.4.2.2. ER (safety) Assessment Summary

The Applicant's Position:

General Information	
Goal of ER analysis	• Explore the E-R relationship between belzutifan exposure and selected safety endpoints based on data from participants with PPGL from Study MK-6482-015 (Cohort A1) or Pooled studies.
Study Included	Studies MK-6482-001, MK-6482-004, MK-6482-005, MK-6482-013, MK-6482-015, MK-6482-018
Population Included	72 subjects with PPGL 714 subjects with other disease or tumor types
Endpoint	Anemia all grades and grade ≥3 Hypoxia all grades and grade ≥3

	Dose reduction Dose interruption Discontinuation		
No. of Patients (total, and with individual PK)	786 subjects across various disease or tumor types and multiple dose levels of belzutifan		
Population Characteristics	General	Age median: 61 (15,-90) years Weight median: 80.5 (42,166) kg 200 (26%) male Race: 674 (86%) White 23 (2.9%) Black or African American 45 (6.2%) Asian 40 (5.1%) Other or missing	
	Pediatrics (if any)	3 Adolescents. Age median:16 (15,16) years old Weight median: 61 (48.8, 92) years old No adolescents with bodyweight < 40 kg were included in the analysis.	
Dose(s) Included	Study MK-6482-015 (Cohort A1): 120 mg QD Other studies: 20 – 240 mg QD 120, 160 mg BID 160, 200 mg TID		
Exposure Metrics Explored (min, max)	AUC_{avgeot} (µg*h/mL) Anemia: 0.67,128 Hypoxia: 0.67, 116		
Covariates Evaluated	NA		
Final Model Parameters	**Summary**		**Acceptability**

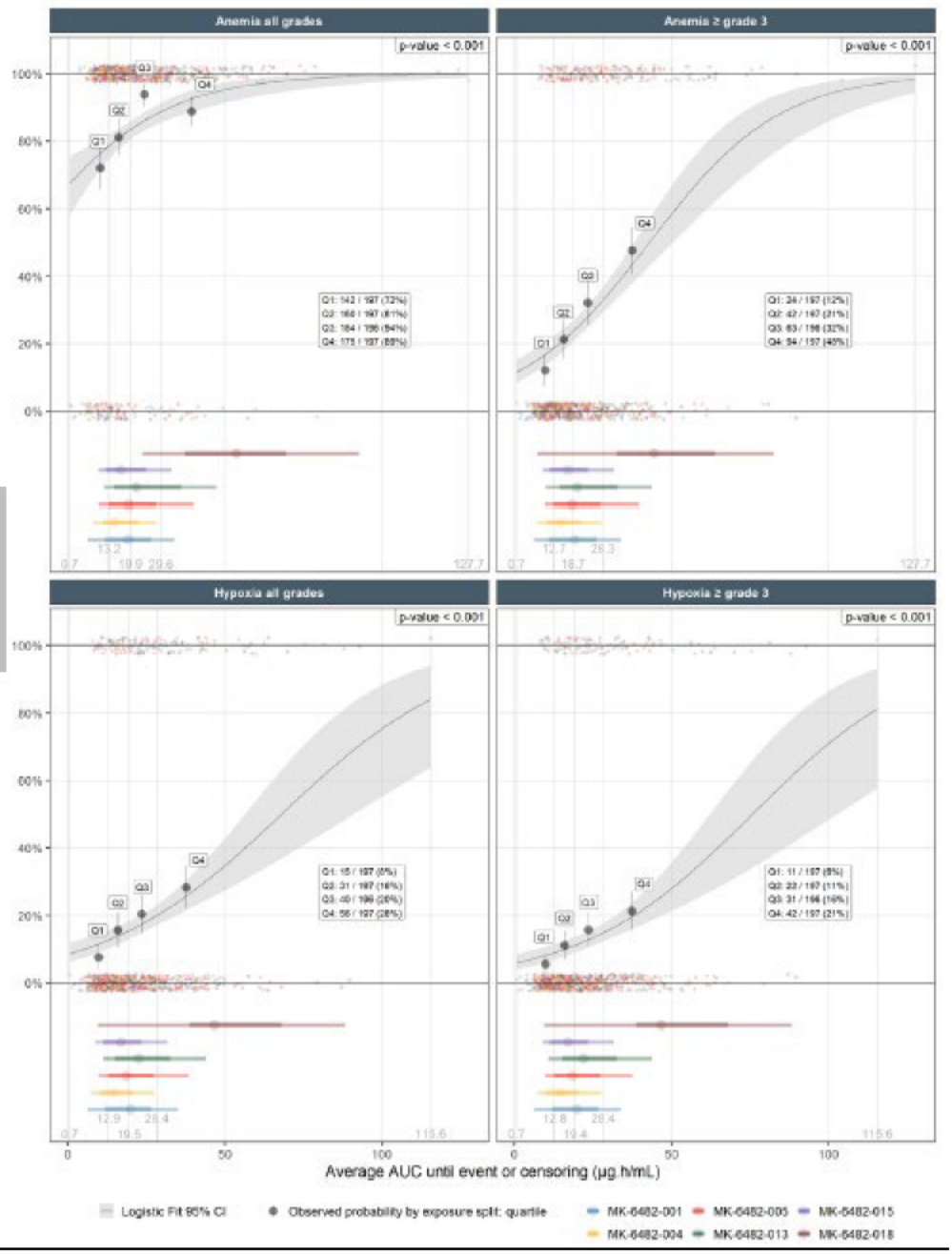
		[FDA's comments]
Model Structure	Anemia and Hypoxia all grades and grade ≥ 3, dose reduction, dose interruption and discontinuation: logistic regression and time-to-event analysis	**Acceptable**
Model Parameter Estimates	Table 28	Acceptable
Model Evaluation	NA	
Covariates and Clinical Relevance	NA	
Simulation for Specific Population	NA	
Visualization of E-R relationships	Figure 17 - Figure 19	Acceptable
Overall Clinical Relevance for ER	Positive E-R relationships were observed for all safety endpoints except for dose discontinuation.	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	NA	

Table 34. Parameter Estimates of the Logistic Regression Model for Incidence of Anemia ≥ Grade 3 Including AUCavg and Baseline Hgb as Predictors

Parameter	Estimate	Standard Error	*P* value
Anemia All Grades			
Intercept	4.25	0.834	3.43e-07
AUCavg	0.042	0.010	1.94e-05
Baseline Hgb	-0.267	0.060	9.69e-06
Anemia ≥ Grade 3			
Intercept	4.41	0.753	4.54e-09
AUCavg	0.045	0.007	4.22e-11
Baseline Hgb	-0.518	0.060	<2e-16

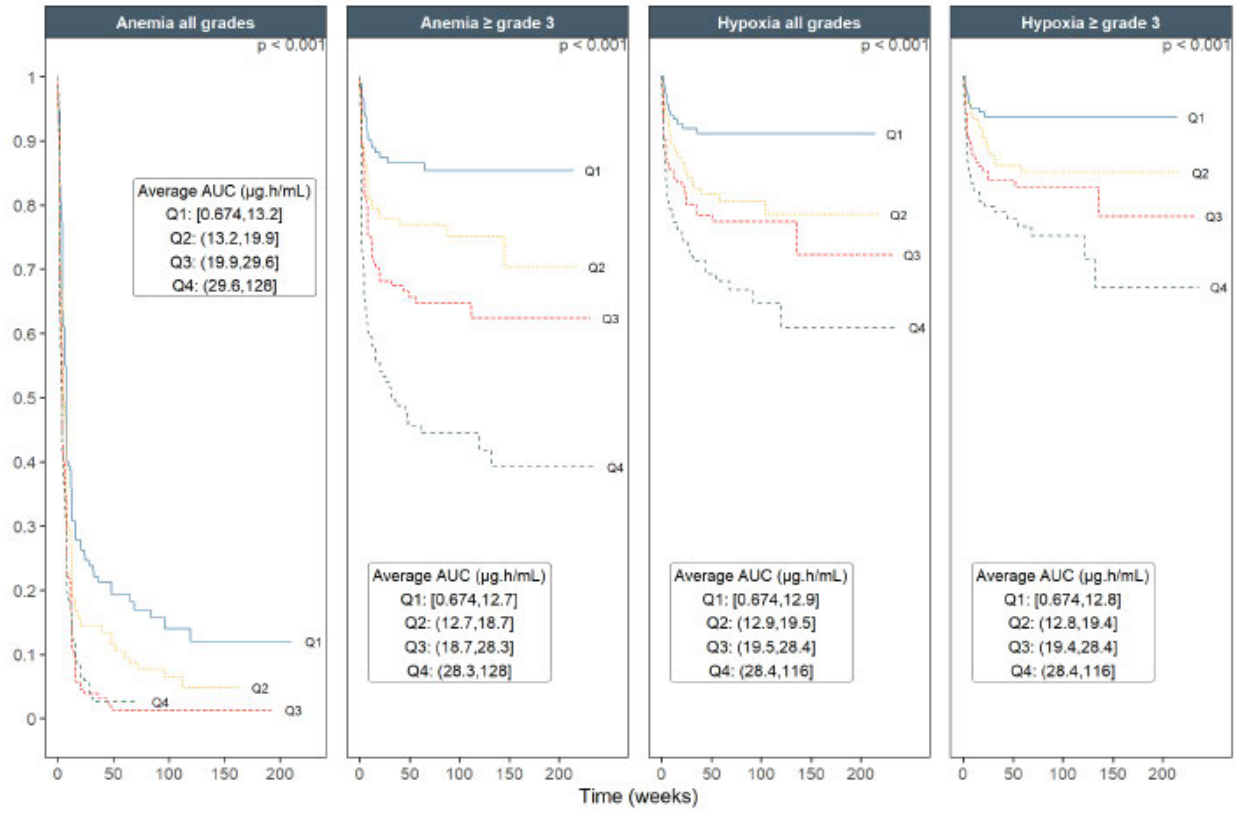
Source: E-R Pooled Safety Analysis of MK-6482, Page 39, Table 7.

Figure 19. Incidence of Anemia All Grades, Anemia ≥ Grade 3, Hypoxia All Grades and Hypoxia ≥ Grade 3 vs. AUCavg, with Incidence Grouped by AUCavg Quartile and a Linear Logistic Regression Fit



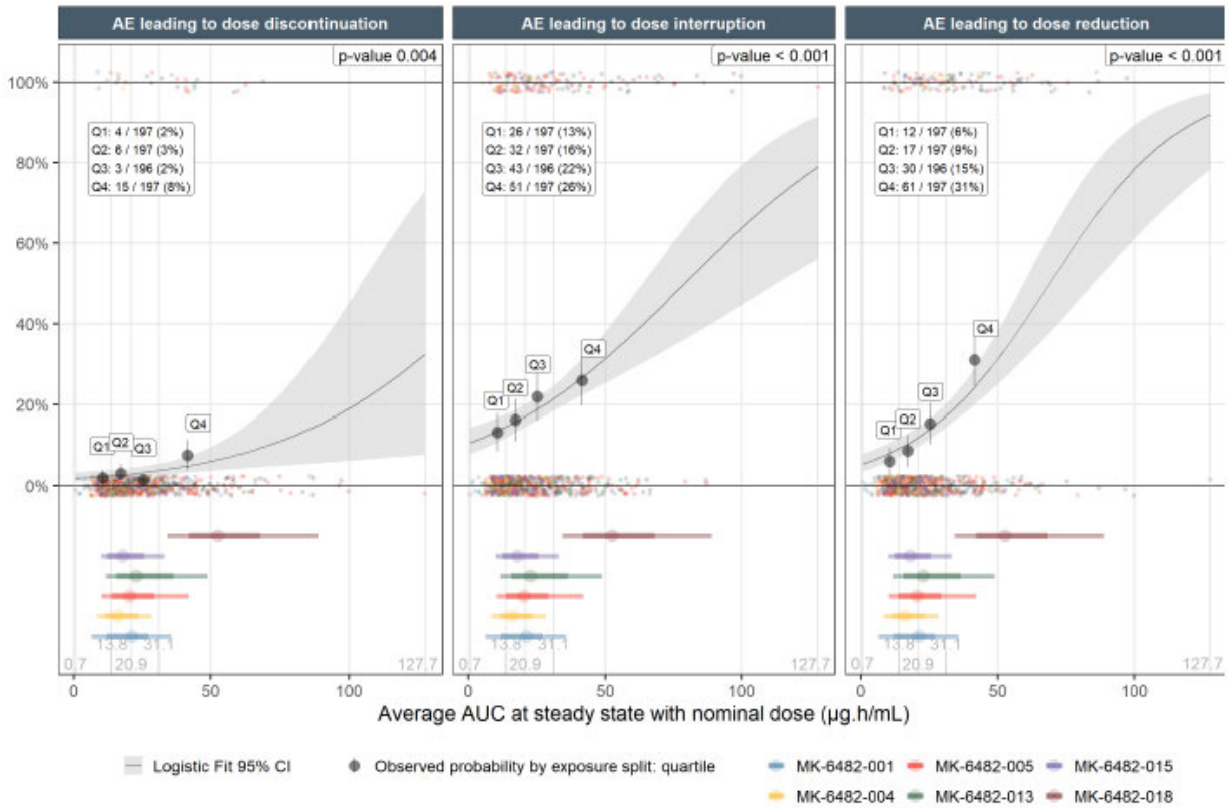
Source: E-R Pooled Safety Analysis of MK-6482, Page 38, Figure 12.

Figure 20. Kaplan-Meier Curves by AUCavg Quartile for Anemia and Hypoxia



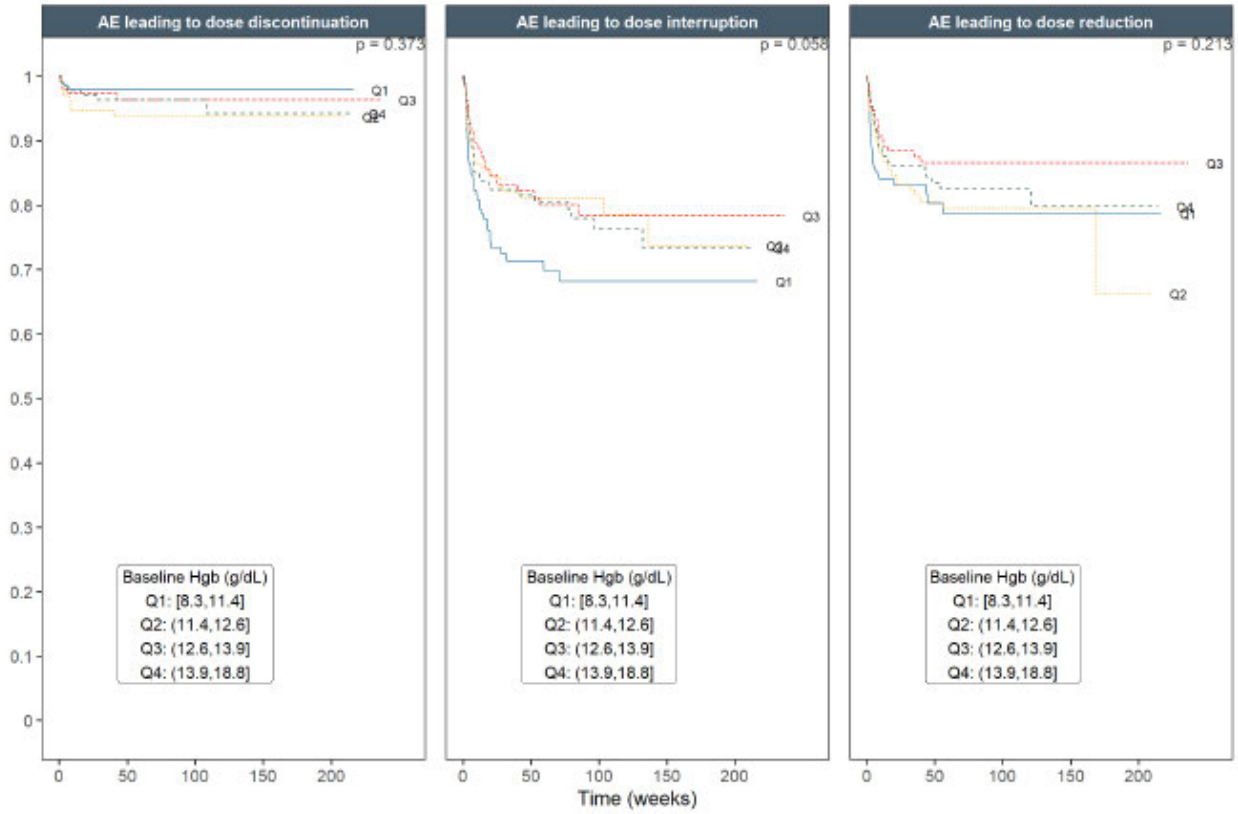
Source: E-R Pooled Safety Analysis of MK-6482, Page 42, Figure 14.

Figure 21. Incidence of Dose Discontinuation, Interruption and Reduction due to Drug-related AE vs. AUCnom, with Incidence Grouped by AUCnom Quartile and a Linear Logistic Regression Fit



Source: E-R Pooled Safety Analysis of MK-6482, Page 44, Figure 15.

Figure 22. Kaplan-Meier Curves by AUCnom Quartile for Dose Discontinuation, Interruption and Reduction



Source: E-R Pooled Safety Analysis of MK-6482, Page 45, Figure 16.

19.5 Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
N/A

NDA 215383 S-012				
Signatures				
DISCIPLINE	**REVIEWER**	**OFFICE/DIVISION**	**SECTIONS AUTHORED/ APPROVED**	**AUTHORED/ APPROVED**
Clinical Pharmacology Reviewer	Ritu Chadda, PhD	OCP/DCP II	Sections: 6	**Select one:** ☒Authored ☐Approved
	Signature: Ritu Chadda -S Digitally signed by Ritu Chadda -S Date: 2025.05.13 09:24:36 -04'00'			
Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach, PhD	OCP/DCP II	Sections: 6	**Select one:** ☐Authored ☒Approved
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Pharmacogenomics Team Leader	Sarah Dorff, PhD	OCP/DTPM	Sections: 2.1, 6	**Select one:** ☐Authored ☒Approved
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Clinical Reviewer	Marjilla Seddiq, MD	OOD/DO2	Sections:	**Select one:** ☒Authored ☐Approved
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Clinical Team Leader	Amy Barone, MD	OOD/DO2	Sections:	**Select one:** ☒Authored ☒Approved
	Signature: See electronic signature.			
Statistical Reviewer	Yi Ren, PhD	OB/DBV	Sections: 1, 8	**Select one:** ☒Authored ☐Approved
	Signature: YI REN -S Digitally signed by YI REN -S Date: 2025.05.12 16:23:18 -04'00'			
Statistical Team Leader	Flora Mulkey, MS	OB/DBV	Sections: 1, 8	Authored ☒Approved
	Signature: Flora M. Mulkey -S Digitally signed by Flora M. Mulkey -S Date: 2025.05.12 16:45:08 -04'00'			
Supervisory Mathematical Statistician	Anup Amatya, PhD	OB	Sections: 8	☒Approved
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	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2025.05.13 08:21:59 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Amy Barone, MD	OOD/DO2	Sections: All	**Select one:** ☒Authored ☒Approved
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Deputy Division Director (Clinical)	Nicole Drezner, MD	OOD/DO2	Sections: All	**Select one:** ☒Approved
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