EU RISK MANAGEMENT PLAN (RMP) FOR belzutifan film-coated tablet

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 13 JUN 2023

Date of final sign off: 11-DEC-2024

Rationale for submitting an updated RMP:

Not applicable

Summary of significant changes in this RMP:

Not applicable.

Other RMP versions under evaluation:

Not applicable

QPPV signature: see signature page

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Experience
ATC	Anatomical Therapeutic Chemical classification system
ATMP	Advanced Therapy Medicinal Product
BID	Twice A Day
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human
CT	Computed Tomography
DUS	Drug Utilization Study
ECG / EKG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPITT	European Pharmacovigilance Issues Tracking Tool
EU	European Union
HGB	Hemoglobin
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Conference on Harmonization
IM	Intramuscular(ly)
INN	International Nonproprietary Name
IV	Intravenous(ly)
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
PAES	Post-authorization Efficacy Study
PASS	Post-authorization Safety Study
PO	Oral(ly)
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
QD	Once Daily

QOD	Every Other Day
QPPV	Qualified Person for Pharmacovigilance
QWK	Weekly
RMP	Risk Management Plan
SC	Subcutaneous
SOC	System Organ Class
SmPC	Summary of Product Characteristics
TIW	Three Times Per Week
WBC	White Blood Cell Count

PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) **(INN or Generic name)**	Belzutifan (MK-6482)
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agent (L01XX74)
Marketing Authorization Applicant	Merck Sharp & Dohme B.V. Waarderweg 39 2031 BN Haarlem The Netherlands
Number of medicinal products to which this RMP refers	1
Invented name(s) in the CCDS	WELIREG®
Marketing authorization procedure	Centralised procedure
Brief description of the product	Chemical class Small molecule hypoxia-inducible factor 2 alpha (HIF-2α) inhibitor
	Summary of mode of action: Belzutifan is a potent selective inhibitor of HIF-2α, which impairs hypoxic and pseudo-hypoxia signaling in cancer cells. Thus, in tumor cells where HIF-2α is activated, belzutifan blocks the transcription of several genes involved in oncogenesis, including CCND1, VEGFA, and others which lead to cellular proliferation, angiogenesis, and tumor growth. Belzutifan has demonstrated anti-tumor activity in mouse xenograft models of clear cell renal cell carcinoma (ccRCC), resulting in tumor stasis or regression after oral administration.
	Important information about its composition: Belzutifan is supplied as 40 mg blue, film-coated tablets with croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, mannitol, microcrystalline cellulose, and silicon dioxide.
Hyperlink to the Prescribing Information	Refer to the EU Product Information
Indication(s) in the EEA	Current: WELIREG is indicated as monotherapy for the treatment of adult patients with advanced clear cell renal cell carcinoma that progressed following two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF targeted therapies. WELIREG is indicated as monotherapy for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated, localised renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable.
	Proposed: Not applicable

Table I.1: Product Overview

Dosage in the EEA	Current: The recommended dose is 120 mg (three 40 mg tablets) administered orally once daily, with or without food.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 40 mg film-coated tablet
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication: Treatment of adult patients with VHL disease associated tumors.

Incidence and Prevalence:

The incidence of VHL disease has been reported to be between 1 in 45,000 to 1 in 27,300 live births, and VHL disease prevalence between 1 in 91,111 and 1 in 38,951 individuals based on data from different geographic populations [Ref. 5.4: 05FHNL, 05FHNH, 05FHNF, 05FHNM, 05FT7K]. Differences in estimates may reflect variation in ascertainment methods, case definition, and completeness. Although the available data originates from Western European (Germany, UK) and Northern European (Denmark) countries, there is no reason to expect that the data would be different for other regions. Considering current population estimates for the United States and Europe, the estimated number of prevalent cases would correspond to approximately 3,659-8,549 persons and 5,711-13,343 persons with VHL disease, respectively (Table SI.1) [Ref. 5.4: 05G9XT, 05GRBV]. If estimates from other data sources such as ORPHANET are considered, the prevalence estimate may be as high as 29,938 in the US and 46,728 cases in the European countries. Patients with VHL-disease are at risk of developing lesions in multiple organs, with CNS hemangioblastomas and renal cell carcinoma being the most common clinical manifestations [Ref. 5.4: 05G7WT].

Table SI.1: Estimated Prevalence of VHL Disease Based on Peer-reviewed Publications and Other Data Sources

Prevalence Reported from Peer-reviewed Publication or Other Data Source				Estimated Prevalence	
Reference		Region of data source	Reported prevalence (per 10,000)	US [a]	EU [b]
Peer-reviewed Publication	• Maher et. al. 1991 [Ref. 5.4: 05FHNM]	East Anglia, UK	0.189	6,287	9,813
	• Neumann et. al. 1991 [Ref. 5.4: 05FT7K]	Germany	0.257	8,549	13,343
	• Maddock et. al. 1996 [Ref. 5.4: 05FHNL]	North West England, UK	0.118	3,925	6,127
	• Evans et. al. 2010 [Ref. 5.4: 05FHNH] (update to Maddock et. al.)	N/A	0.110	3,659	5,711
	• Binderup et. al. 2017 [Ref. 5.4: 05FHNF]	Denmark	0.213	7,085	11,059
	Prevalence range based on peer-reviewed publications		0.110 to 0.257	3,659-8,549	5,711-13,343
Other Data Source	• Cancer.net, access 20-FEB-2020 [Ref. 5.4: 05FHYJ]	N/A	0.333	11,077	17,289
	• Mikhail and Singh. StatPearls [Internet], 2020 [Ref. 5.4: 05FHTH]	N/A	0.200	6,653	10,384
	• Orphanet (ORPHA892), access 5-MAR-2020 [Ref. 5.4: 05FTZ9]	N/A	0.1-0.9	3,326-29,938	5,192-46,728
	Prevalence range based on other data sources		0.1 to 0.9	3,326-29,938	5,192-46,728

a. Projection based on US Census Bureau 2020 midyear population estimate: 332,639,000 [Ref. 5.4: 05G9XT]
b. Projection based on EU28 plus Iceland, Liechtenstein, and Norway population on 1-JAN-2019 [Ref. 5.4: 05GRBV]
EU=European Union, N/A= not applicable; UK=United Kingdom; US=United States; VHL=von Hippel-Lindau.

Demographics of the population in the indication and risk factors for the disease:

VHL disease is a rare hereditary tumor syndrome which is transmitted in an autosomal dominant fashion with approximately 80% of cases inheriting a mutant copy of the VHL gene from an affected parent [Ref. 5.4: 05FHNP, 05FHTH]. The more common clinical manifestations include renal cell carcinoma or cysts, central nervous system (CNS) hemangioblastomas, pancreatic neuroendocrine tumors (pNETs) or cysts, and retinal hemangioblastomas with an average age of presentation of 39, 30, 36, and 25 years, respectively [Ref. 5.4: 05FHNP]. Males and females are equally affected [Ref. 5.4: 05FHTH]. The average age of presentation for VHL disease associated RCC is 39 years [Ref. 5.4: 05FHNP]. RCC is rarely the first clinical manifestation of VHL [Ref. 5.4: 05DN6H].

The main existing treatment options:

VHL disease-associated renal tumors, which are uniformly the clear cell renal cell carcinoma histological subtype [Ref. 5.4: 05MN84], are malignant tumors which can metastasize and can be fatal [Ref. 5.4: 05DL0Z]. The clinical management of VHL disease-associated renal tumors involves active surveillance until the largest renal tumor reaches the 3-cm diameter threshold, at which time nephron-sparing surgical intervention is recommended. This threshold was determined by analyses of patient data collected over a 30-year time period

that showed no metastases for patients with maximal renal tumor diameter less than 3 cm [Ref. 5.4: 05DTX6, 05DTVC, 05DTVP, 05DL0Z, 05G5M5, 05MNJY].

Natural history of the indicated condition in the VHL population, including mortality and morbidity:

Surgery is not curative, and in the great majority of patients, the tumors continue to recur (14.5% at 2 years, 45.6% at 5 years, and 83.7% at 10 years) [Ref. 5.4: 05DLN3] and repeated surgeries are required to prevent death from metastatic kidney cancer. These surgeries carry significant morbidity and, sometimes, mortality. Complications from such extensive surgery are not uncommon and can include significant blood loss, infection, loss of the kidney, pulmonary emboli, and death. A decrease in renal function after such extensive surgery is common [Ref. 5.4: 05G5MD, 05G5M4]. Extensive renal surgeries may lead to progressive decrease in renal function in these patients. Many patients will develop renal insufficiency, which may lead to shortened life span, and may require dialysis and/or renal transplantation.

Patients with VHL disease have a life expectancy of approximately 40-60 years, and with prognosis largely dependent on the development of RCC and occurrence of postoperative complications after surgery [Ref. 5.4: 05KLB2, 05G73N, 05DLN3, 05DN6H, 05G5M5]. Wilding et. al, 2012 showed that patients with VHL disease had the shortest life expectancy (52.5 years [95% CI: 41.7-63.3 years]) compared to patients with other genetic disorders such as Neurofibromatosis type 1 (71.5 years [95% CI: 68.5 to 74.6 years]), NF type 2 (69 years [95% CI: 58.9 to 79.0 years]), familial adenomatous polyposis (63.6 years [95% CI: 58.6 to 68.7 years], and Gorlin syndrome 73.4 years [95% CI: 64.0 to 80.2 years]) [Ref. 5.4: 05KLB2]. Survival for patients with VHL disease is reduced compared with non-VHL siblings, with most deaths in VHL patients being VHL-related, and with worse overall survival for woman than men [Ref. 5.4: 05KLB2, 05G73N].

Important co-morbidities:

As patients with VHL disease-associated RCC may develop other organ-specific tumors such as retinal and CNS hemangioblastomas, pheochromocytomas, pNETs, and endolymphatic sac tumors (ELSTs), patients with other organ-specific tumor types may experience clinical signs and symptoms associated with these other tumors depending on the size and location of these tumors [Ref. 5.4: 05DWWM, 05DW6L]. CNS hemangioblastomas can cause headaches, vomiting, sensory or motor deficits, and ataxia. Hemangioblastomas in the retina may cause vision loss. Pheochromocytomas, which affect the adrenal glands, may be asymptomatic, but they also may cause an array of symptoms including headaches, panic attacks, excessive sweating, episodic or sustained malignant hypertension, myocardial infarction, and cerebral vascular accident. VHL patients with ELSTs, which occur in the inner ear, may present with tinnitus, vertigo, or hearing loss. Functional pNETs include gastrinomas, insulinomas, and glucagonomas which make different kinds of hormones including gastrin, insulin, and glucagon, respectively, and other rare tumors (e.g. VIPomas, which make vasoactive intestinal peptide). VHL disease-associated pancreatic lesions rarely cause endocrine or exocrine insufficiency. However, they are malignant and may metastasize and lead to death.

Indication: Treatment of adult patients with advanced renal cell carcinoma (RCC) following immune checkpoint and anti-angiogenic therapies.

Incidence and prevalence:

The age-standardized incidence of kidney cancer (per 100,000) is highest in North America (12.2) and Northern Europe/Australia and New Zealand (10.3); rates are lowest in Middle Africa (1.0) [Ref. 5.4: 06C8B2]. More than one-third of incident cases occur in Europe, with nearly 139,000 incident cases expected in 2020 [Ref. 5.4: 06C86L]. In the US, kidney cancer incidence is anticipated to be 16.4 per 100,000, yielding roughly 76,000 new cases in 2021 [Ref. 5.4: 06CL4Y]. Approximately 85% of all primary kidney cancers are comprised by RCC, and approximately 70% have clear cell histology [Ref. 5.4: 05DMDM]. Incidence has increased over the last few decades in the US [Ref. 5.4: 06CL4Y] and most of Europe [Ref. 5.4: 04BN0K]. The 5-year prevalence of kidney cancer reported in 2020 in North America is 236,659 and Europe is 405,983 cases [Ref. 5.4: 06C8B2]. In the US, the majority (65%) of kidney cancers at diagnosis are localized and 16% of tumors are metastatic [Ref. 5.4: 06CL4Y].

Demographics of the indication population and risk factors for the disease:

Kidney cancer incidence increases by age with a median age at diagnosis of 64 years in the US [Ref. 5.4: 06CL4Y]. In most countries, it is roughly twice as common among males compared to females [Ref. 5.4: 06C8B2]. Established risk factors include excess body weight, history of hypertension, and smoking, which are thought to contribute to up to 50% of kidney cancer pathogenesis [Ref. 5.4: 08B2LP]. Accumulating evidence suggests an etiologic role for physical activity, alcohol consumption, occupational exposure to trichloroethylene, and high parity among women, though the research is inconclusive and further research is needed to determine the potential cause effect of these factors. Large consortium efforts employing genome-wide scanning techniques have also identified mutated genes of statistical significance including VHL, PBRM1, SEDT2, KDM5C, PTEN, BAP1, MTOR and TP53 [Ref. 5.4: 05CGV4].

The main existing treatment options:

Treatment options for advanced RCC includes nephrectomy and nephrectomy with adjuvant pembrolizumab or sunitinib for patients at high risk of recurrence, tumor embolization, and external-beam radiation therapy[Ref. 5.4: 088SHH] [Ref. 5.4: 07W8SG] [Ref. 5.4: 04JRFN]. Approved systemic therapies for metastatic RCC include systemic oncologic therapy including either VEGF-targeting therapies and/or immunotherapies, and mammalian target of rapamycin (mTOR) protein inhibitors [Ref. 5.4: 088SHH]. Prognosis has improved significantly in the US and Europe, due in part to the advent of TKI therapy and immunotherapies [Ref. 5.4: 053TKZ] [Ref. 5.4: 05BFQQ] [Ref. 5.4: 04WHNV] [Ref. 5.4: 04CMDR] [Ref. 5.4: 059HGM]. Although immunotherapy-based combination therapies are quickly becoming the standard of care, most patients ultimately require additional lines of therapy [Ref. 5.4: 08F2WY].

Natural history of the indicated condition (aRCC), including mortality and morbidity:

Worldwide, kidney cancer age-standardized mortality rates are highest in Central/Eastern Europe (3.4 per 100,000) and Western Europe (2.8 per 100,000) compared with 2.1 per 100,000 cases in North America [Ref. 5.4: 06C8B2]. Most cases are discovered incidentally upon imaging, with <10-15% presenting with symptoms including flank pain, hematuria or palpable masses [Ref. 5.4: 0892ZR] [Ref. 5.4: 08B2LP]. Survival is highly dependent on the stage at diagnosis. In the US, the 5-year relative survival rate for patients with localized disease is 93%, which drops to 14% for patients with distant metastasis [Ref. 5.4: 06CL4Y]. Over the last decade, age-adjusted death rates have been slightly decreasing in the US and across Europe, more sharply in Western and Northern Europe [Ref. 5.4: 06CL4Y] [Ref. 5.4: 08B2LP] [Ref. 5.4: 08F2WV]. The overall 5-year survival in Europe and the US is approximately 60% and 76%, respectively [Ref. 5.4: 06CL4Y] [Ref. 5.4: 04D76G]. Clear cell histology, accounting for the majority of RCC, is associated with a better prognosis than non-clear cell RCC [Ref. 5.4: 053GY0].

Important co-morbidities:

Cardiovascular or cerebrovascular diseases, hypertension, chronic obstructive pulmonary disease, diabetes, and other prevalent comorbidities among elderly populations are frequently observed in cancer patients [Ref. 5.4: 04VW4L] [Ref. 5.4: 08F28R].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Belzutifan (MK-6482) has been evaluated in nonclinical safety pharmacology studies, genetic toxicity assays (in vitro and in vivo), and in a phototoxicity study in rats, in which no belzutifan-related effects were observed. Belzutifan evaluated in oral repeat-dose toxicity studies of up to 3 months duration in rats and dogs, and an embryo-fetal development study in rats resulted in important findings, summarized in Table SII.1.

Carcinogenicity studies are ongoing.

Table SII.1: Summary of Important Safety Findings From Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Repeat-dose toxicity studies Effects on red blood cells: In the 28-day or 13-week repeat-dose studies in mice, rats and dogs, dose-dependent reduction in the RBC compartment (RBC count, HGB and HCT levels) was observed in all 3 species at exposure below or similar to the human exposure at 120 mg QD. In the 28-day rasH2 transgenic mice study, HGB was approximately -20%, -24%, -27%, and -34% at 30, 60, 150, and 600 mg/kg/day respectively. In the 13-week Sprague Dawley rat study, HGB was approximately -8.3%, -11%, -17%, and -23% at 2, 6, 20 and 200 mg/kg/day, respectively. In the 13-week Wistar Han rat study, HGB was approximately -15%, -30%, -39%, at 30, 100, and 300 mg/kg/day. In the 13-week dog study, HGB was approximately -37%, -42.4%, and -47% at 1, 5, and 30 mg/kg/day, respectively. The effects were reversible and considered pharmacologically mediated by HIF-2α inhibition [Ref. 5.4: 05BTDF].	Risk for anemia, monitored by periodic hemoglobin levels and managed by dose modification and/or using Erythropoietin Stimulating Agent (ESA) and/or blood transfusions as needed.

Table SII.1: Summary of Important Safety Findings From Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Testicular toxicity: In the 28-day or 13-week toxicity studies in rasH2 transgenic mice, Sprague Dawley rats, and Wistar Han rats, effects on testes included smaller/soft testes or decreased testes weight, associated with hypospermatogenesis, germ cell degeneration or multinucleated giant cells (testes), or oligospermia (epididymis). The testicular toxicity was not reversible up to 26-week recovery period and the testes findings were associated with decreased sperm motility and sperm counts, and increased number of abnormal sperm in Sprague Dawley rats. The NOAEL in male rasH2 transgenic mice was <60 mg/kg/day, in male Sprague Dawley rats was 2 mg/kg/day, and in male Wistar Han rats was <30 mg/kg/day (below the human exposure at 120 mg QD). No belzutifan-related testicular toxicity was observed in dogs from 28-day or 13-week toxicity studies.	The relevance to humans (males) is unknown. Limited clinical data from a Male Fertility Study (N=12) demonstrated no impact on male fertility hormones but was inconclusive regarding any abnormalities in semen analysis data. No further studies are planned.
Female Fertility: Nonclinical fertility studies have not been conducted with belzutifan. However, published data indicate a functional role of HIF-2α in the uterus during embryo implantation and establishment of pregnancy in mice [Ref. 5.4: 06CKL9] [Ref. 5.4: 06CKLC] [Ref. 5.4: 06CKKM]. Additional published work suggests that similar HIF2α-mediated mechanisms are involved in human pregnancy [Ref. 5.4: 06CKLF] [Ref. 5.4: 06CKKS]. Therefore, HIF-2α inhibition by the exposure to belzutifan has the potential to interfere with embryo implantation, leading to impairment of female fertility.	The relevance to humans (females) is unknown.
Reproductive and Early Fetal Development Belzutifan administered to pregnant rats at doses of 6, 60, and 200 mg/kg/day from gestation Day 6 through 17, was associated with developmental toxicity. The effects consisted of increased embryo-fetal lethality at ≥60 mg/kg/day (below the human exposure at 120 mg QD), as well as reduced fetal body weight, reduced ossification, and malformations at 6 and 60 mg/kg/day. Since cardiovascular defects and lethality have been reported in HIF-2α gene knockout mouse embryos [Ref. 5.4: 05FRRV] [Ref. 5.4: 05FRS2], the observed embryo-fetal toxicity in rats may be related to the anti-angiogenic properties of belzutifan.	Risk of embryo-fetal loss or harm in humans is unknown. Pregnant women are not allowed to enroll in clinical studies. Women of child-bearing potential are required to use effective contraception as specified in clinical protocols.

ESA=Erythropoiesis-stimulating agents; HIF-2α=Hypoxia inducible factor; NOAEL= no-observed-adverse-effect level; QD=once daily; RBC=red blood cell; HGB=hemoglobin; HCT=hematocrit.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Indications:

- **Treatment of adult patients with VHL disease associated tumors.**
- **Treatment of adult patients with advanced renal cell carcinoma (RCC) in later lines of therapy.**

The results of the safety evaluation of belzutifan in the indication population of adult patients with VHL disease who require therapy for associated RCC, CNS hemangioblastomas, or pNETs, not requiring immediate surgery is from the pivotal Study MK-6482-004 (Study 004) at a dose of 120mg QD, as of the data cut-off (DCO) of 01-APR-2022. Study MK-6482-004 is an ongoing, open-label, Phase 2 study to evaluate the efficacy and safety of belzutifan for the treatment of VHL-associated RCC.

The results of the safety evaluation of belzutifan in the indication population of adult patients with advanced RCC that have progressed after prior PD-1/L1 and VEGF-targeted therapies is from the pivotal Study MK-6482-005 (Study 005) belzutifan group compared to the everolimus group, as of the DCO of 13-JUN-2023. Study 005 is a Phase 3, open-label, multicenter, randomized, active-controlled study to compare the efficacy and safety of belzutifan with that of everolimus in participants with advanced RCC that has progressed on or after prior PD-1/L1 and VEGF-targeted therapies. Eligible participants were randomized in a 1:1 ratio to receive 120 mg belzutifan QD or 10 mg QD everolimus until disease progression or until study discontinuation criteria were met. As treated population includes 372 participants who received belzutifan and 360 participants who received everolimus.

Supportive pooled safety data for belzutifan 120mg QD are provided in the form of CRSD, which predominantly includes participants with advanced RCC from Study 005 as well as participants with advanced solid tumors in the Phase 1 study MK-6482-001 (Study 001), participants with VHL-associated RCC in Study 004, and participants with advanced RCC with clear cell component after prior therapy in study MK-6482-013 (Study 013).

Study MK-6482-001 (Study 001) is an ongoing, Phase 1 study in patients with advanced solid tumors and ccRCC to evaluate safety, PK, and PD of belzutifan. The CRSD includes data only for participants treated with 120 mg QD belzutifan (N=58). The data cutoff date for Study 001 is 01-APR-2022.

MK-6482-013 (Study 013) is a Phase 2 ongoing open-label randomized study in participants with advanced RCC who have experienced disease progression on or after treatment with anti-PD-1/L1 therapy (either monotherapy or combination therapy [eg, with anti-CTLA 4 or VEGFR-targeted TKI]). The CRSD includes data only for participants treated with belzutifan 120 mg QD (N=76). The data cutoff date for Study 013 is 10-FEB-2023.

Study 004 included participants with VHL disease-associated RCC who were younger, with fewer comorbidities, and with nonmetastatic cancer with no prior systemic therapy compared to Studies 001, 005, and 013 which included participants with advanced solid tumors/advanced RCC who had experienced disease progression on or after prior treatment including anti-PD-1/L1 and/or VEGF-targeted therapies. These baseline differences, along with differences in sample size, and significantly longer exposure in Study 004 compared with the CRSD, should be considered when making AE comparisons with the pooled safety dataset or with the belzutifan group of Study 005.

However, taking differences between studies and datasets into consideration, the observed safety profile of belzutifan has been consistent between study populations and the pooling strategy detailed above helps contextualize the comprehensive safety experience with belzutifan.

Table SIII.1: Clinical Trial Exposure by Duration

Clinical Trial Exposure to Belzutifan by Duration
(APaT Population)

	MK-6482-005 Data for Belzutifan 120 mg QD (N=372)			MK-6482-004 Data for Belzutifan 120 mg QD (N=61)			Cumulative Running Safety Dataset for Belzutifan 120 mg QD[a] (N=576)		
	n	(%)	Person-time	n	(%)	Person-time	n	(%)	Person-time
Duration of Exposure									
> 0 m	372	(100.0)	337.0	61	(100.0)	171.2	576	(100.0)	647.2
≥ 1 m	343	(92.2)	335.6	61	(100.0)	171.2	535	(92.9)	645.1
≥ 3 m	249	(66.9)	320.7	59	(96.7)	170.8	413	(71.7)	626.0
≥ 6 m	201	(54.0)	303.2	58	(95.1)	170.5	336	(58.3)	597.1
≥ 9 m	170	(45.7)	283.8	57	(93.4)	169.8	291	(50.5)	569.0
≥ 12 m	144	(38.7)	261.4	57	(93.4)	169.8	254	(44.1)	537.2
≥ 18 m	97	(26.1)	200.2	55	(90.2)	167.4	177	(30.7)	437.4
≥ 24 m	46	(12.4)	110.5	53	(86.9)	163.8	115	(20.0)	329.0

Each participant is counted once on each applicable duration category row.

Duration of exposure is calculated as last dose date - first dose date + 1.

[a] Includes all participants who received at least one dose of belzutifan 120 mg QD in MK-6482-001 Part 1A, 1B, MK-6482-004, MK-6482-013, and MK-6482-005 including participants from the Japan safety run-in cohort.

Database cutoff date for MK-6482-001: 01APR2022

Database cutoff date for MK-6482-004: 01APR2022

Database cutoff date for MK-6482-013: 10FEB2023

Database cutoff date for MK-6482-005: 13JUN2023

Data on File

Table SIII.2: Clinical Trial Exposure by Age Category and Sex

Clinical Trial Exposure to Belzutifan by Age Category and Sex
(APaT Population)

Age Category (Years)	Cumulative Running Safety Dataset[a]								
	Participants			Mean Duration (days)			Person-time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
18-64	286	84	370	399.3	543.4	432.0	312.7	125.0	437.6
65-74	122	35	157	363.2	397.5	370.8	121.3	38.1	159.4
75-84	30	15	45	341.1	479.7	387.3	28.0	19.7	47.7
≥85	3	1	4	121.7	530.0	223.7	1.0	1.5	2.5
Total	441	135	576	383.5	498.4	410.4	463.0	184.2	647.2

Duration of Exposure is calculated as last dose date - first dose date + 1.

[a] Includes all participants who received at least one dose of belzutifan 120 mg QD in MK-6482-001 Part 1A, 1B, MK-6482-004, MK-6482-013, and MK-6482-005 including participants from the Japan safety run-in cohort.

Database cutoff date for MK-6482-001: 01APR2022

Database cutoff date for MK-6482-004: 01APR2022

Database cutoff date for MK-6482-013: 10FEB2023

Database cutoff date for MK-6482-005: 13JUN2023

Table SIII.3: Clinical Trial Exposure by Race

Clinical Trial Exposure to Belzutifan by Race
(APaT Population)

Race	Cumulative Running Safety Dataset[a]		
	Participants	Mean Duration (days)	Person-time (years)
American Indian Or Alaska Native	3	220.0	1.8
Asian	55	419.0	63.1
Black Or African American	10	405.8	11.1
Multiracial	6	305.5	5.0
Native Hawaiian Or Other Pacific Islander	2	85.5	0.5
White	475	415.9	540.8
Unknown	2	1084.5	5.9
Other	2	295.5	1.6
Missing	21	301.0	17.3
Total	576	410.4	647.2

Duration of Exposure is calculated as last dose date - first dose date + 1.

[a] Includes all participants who received at least one dose of belzutifan 120 mg QD in MK-6482-001 Part 1A, 1B, MK-6482-004, MK-6482-013, and MK-6482-005 including participants from the Japan safety run-in cohort.

Database cutoff date for MK-6482-001: 01APR2022

Database cutoff date for MK-6482-004: 01APR2022

Database cutoff date for MK-6482-013: 10FEB2023

Database cutoff date for MK-6482-005: 13JUN2023

Source: [ISS: adam-adexsum]

Table SIII.4: Clinical Trial Exposure by Ethnicity

Clinical Trial Exposure to Belzutifan by Ethnicity
(APaT Population)

Ethnicity	Cumulative Running Safety Dataset[a]		
	Participants	Mean Duration (days)	Person-time (years)
Hispanic Or Latino	61	382.8	63.9
Not Hispanic Or Latino	478	423.9	554.8
Not Reported	28	277.0	21.2
Unknown	7	361.0	6.9
Missing	2	52.5	0.3
Total	576	410.4	647.2

Duration of Exposure is calculated as last dose date - first dose date + 1.

[a] Includes all participants who received at least one dose of belzutifan 120 mg QD in MK-6482-001 Part 1A, 1B, MK-6482-004, MK-6482-013, and MK-6482-005 including participants from the Japan safety run-in cohort.

Database cutoff date for MK-6482-001: 01APR2022

Database cutoff date for MK-6482-004: 01APR2022

Database cutoff date for MK-6482-013: 10FEB2023

Database cutoff date for MK-6482-005: 13JUN2023

Source: [ISS: adam-adexsum]

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Patients less than 18 years of age	VHL disease associated RCC and advanced RCC are rare in patients less than 18 years of age.	No	MK-6482 is not indicated for use in patients less than 18 years old.
Pregnant or breast-feeding patients	Pregnant or breast-feeding patients were excluded due to potential risk of embryo-fetal toxicity. No information is available on the secretion of belzutifan in breast milk.	No	Embryo-fetal toxicity is an important potential risk for MK-6482. Risk associated with pregnancy and breast-feeding is adequately labeled in the SmPC (sections 4.3, 4.4, and 4.6) and guidance on contraception is included in the SmPC (section 4.6) and in the Package Leaflet (section 2).
Baseline hemoglobin level < 10 g/dL	Given the mechanism of action, this patient population was excluded to minimize the potential risk of severe anemia.	No	Anemia due to decreased erythropoietin is an expected on-target toxicity and an identified risk of MK-6482. It is adequately labeled in the SmPC (sections 4.2 and 4.4) and in the Package Leaflet (section 2).
Prior treatment with MK-6482, another HIF-2α inhibitor, or any systemic anti-cancer therapy (Study 004 only); use of an investigational agent or device; surgical procedure for VHL disease (Study 004 only) or major surgical procedure, or radiation therapy performed within protocol specified time prior to study enrollment.	To avoid factors that may confound understanding of the safety and efficacy of MK-6482, and to ensure appropriate interpretation of the efficacy and safety data.	No	These exclusion criteria are not related to any specific safety concerns and therefore would not be considered missing information.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Has a known additional malignancy that is progressing or has required active treatment within the past 2-3 years with the exception of adequately treated basal or squamous cell carcinoma of the skin, or carcinoma in situ.	To ensure patients are receiving optimal treatment, per their physician's discretion for their co- morbid conditions which may not always be possible within the confines of a clinical trial.	No	These exclusion criteria are not related to any specific safety concerns and therefore would not be considered missing information.
Has malabsorption due to prior gastrointestinal (GI) surgery or GI disease	To exclude patients who may have inadequate absorption, so that patients receive optimal dose of MK-6482 treatment for assessment of the safety and efficacy of MK-6482.	No	These exclusion criteria are not related to any specific safety concerns and therefore would not be considered missing information.
Has hypersensitivity to the active pharmaceutical ingredient or any component in the formulation	To avoid potential hypersensitivity reactions (such as severe and life-threatening reactions).	No	Physicians are used to ascertain for hypersensitivity prior to recommending the administration of drugs.
Has had significant cardiovascular disease as specified in study protocol.	This population with prior significant cardiovascular events is at a higher risk of developing additional cardiovascular events, thus was excluded to avoid factors that may confound understanding of the safety profile of MK-6482, and to ensure appropriate interpretation of the safety data.	No	These exclusion criteria are not related to any specific safety concerns and therefore would not be considered missing information.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.	To avoid potential confounding of interpretation of safety data, minimize discontinuation of participants for non-protocol specified reasons, and ensure appropriate participant selection.	No	These exclusion criteria are not related to any specific safety concerns and therefore would not be considered missing information.
Has any of the following, hypoxia defined by pulse oximeter reading <92% at rest, or requires intermittent supplemental oxygen, or requires chronic supplemental oxygen. (Study 005 only)	To avoid confounding of interpretation of safety data and exclude patients with existing hypoxia in order to minimize risk of hypoxia exacerbation.	No	Hypoxia is an identified risk of MK-6482. It is adequately labeled in the SmPC (sections 4.2 and 4.4) and in the Package Leaflet (section 2).

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development program is unlikely to detect certain types of adverse reactions such as uncommon adverse reactions (due to limited safety database size), adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program Clinical pharmacology studies in participants with moderate hepatic impairment (MK-6482-020) and end stage renal disease (MK-6482-021) have been conducted.
Population with relevant different ethnic origin	Refer to Table SIII.5 and Table SIII.6 for racial and ethnic characteristics
Subpopulations carrying relevant genetic polymorphisms	CYP2C19 and UGT2B17 phenotypes have been evaluated in the clinical development program in both patients and healthy adult participants who have received belzutifan and these data are included in the PopPK model.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

Belzutifan was first approved in the US on 13-AUG-2021 under the brand name WELIREG based on results of study MK-6482-004 (Study 004) for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system hemangioblastomas (CNS-HB), or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. Belzutifan received additional approval in the US on 14-DEC-2023 based on the results of study MK-6482-005 (Study 005) for the treatment of adult patients with advanced renal cell carcinoma following a programed cell death receptor-1 (PD-1) or programed cell death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

As of September 2024, WELIREG has also been approved in Great Britain, Canada, Australia, United Arab Emirates, Brazil, South Korea, Hong Kong, Israel, Switzerland, Saudi Arabia, Kuwait, Argentina, Bahrain, Lebanon, Qatar, Oman. The registration status is evolving with other applications under review worldwide.

SV.1.1 Method Used to Calculate Exposure

Patient exposure estimates were calculated from our Company's internal distribution data from the Financial Sharing Area (FSA) database(s). Patient exposure estimates were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide. The effects of this update may be apparent when comparing current estimates of patient exposure to those of prior reporting periods.

It is important to note that the estimated Patient Years of Treatment (PYT) are not equivalent to the absolute number of patients treated. It should also be noted that the overall PYT estimates are likely to underestimate the true number of patients exposed to belzutifan, due to the fact that PYT estimates are a calculated number of patients who could have been treated for one year based on the tablets distributed.

Number of belzutifan 40 mg tablets distributed, divided by three tablets per (120 mg) dose, divided by an average 365.25 days per year.

SV.1.2 Exposures

The estimated number of doses of belzutifan distributed worldwide from product launch through 12-AUG-2024 is 2,596,832. This corresponds to 2,370 estimated PYT.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Belzutifan will be available by medical prescription only. Neither belzutifan nor its components are known to possess addictive properties.

The MAH has not been made aware of any reports for misuse for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Table SVII.1.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	CNS Hemorrhage in VHL patients with CNS hemangioblastoma Embryo-fetal toxicity
Missing information	Long term safety

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Fatigue, nausea, dyspnea, dizziness and weight increased.

Other reasons for considering the risks not important:

- Anemia due to decreased erythropoietin: this identified risk is an expected on-target toxicity of belzutifan and has been adequately labeled in Sections 4.2 and 4.4. of the SmPC and in Section 2 of the Package Leaflet. This identified risk does not require additional pharmacovigilance activities or additional risk minimization measures.
- Hypoxia: this identified risk has been adequately labeled in Sections 4.2 and 4.4. of the SmPC and in Section 2 of the Package Leaflet. This identified risk does not require additional pharmacovigilance activities or additional risk minimization measures.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table SVII.1.2.1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety concern	Benefit risk impact
Important identified risks	
None	N/A
Important potential risks	
CNS Hemorrhage in VHL patients with CNS hemangioblastoma	Patients with VHL-related tumors are at increased risk of bleeding, including hemorrhage from CNS hemangioblastomas, in which the reported incidence in the literature is between 2.5%- 4.0% [Ref. 5.4: 085YP5], [Ref. 5.4: 0862HF]. There is no established mechanism of increased risk, and no evidence of CNS hemorrhage related to belzutifan or HIF-2α inhibition has been observed in nonclinical rodent models. In addition, the belzutifan monotherapy trials do not appear to have rates beyond what is described in the literature. However, serious events of CNS hemorrhage have been reported in patients with VHL-associated CNS-HB after starting belzutifan treatment.
Embryo-Fetal Toxicity	Belzutifan is a first-in-class HIF-2α inhibitor intended for use in a population that includes females of childbearing potential and male partners of females of childbearing potential. The risk of embryofetal loss or harm in humans is unknown. However, cardiovascular defects and lethality have been reported in HIF-2α gene knock-out mouse embryos. In addition, embryo-fetal toxicity was observed in the rat study with belzutifan at exposure levels similar or below the human exposure at 120 mg QD.
Missing information	
Long term safety	Long term safety has not been studied with belzutifan; however, protocol MK-6482-004 includes long term follow-up for all until withdrawal of consent or death. The anticipated long-term use of belzutifan and the current limited data due to limited follow-up time makes it relevant for inclusion in the RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

There are no important identified risks for belzutifan.

Important Potential Risk: CNS Hemorrhage in VHL patients with CNS hemangioblastoma

Potential Mechanisms:

The mechanism by which treatment with belzutifan may potentially influence the occurrence of CNS hemorrhage is unknown. Based on review of published literature, no evidence of hemorrhagic events of CNS related to belzutifan or HIF-2α inhibition has been observed in nonclinical rodent models.

Evidence Source(s) and strength of evidence:

Reports of serious adverse events of CNS bleeding have been reported in patients with VHL-associated CNS-HB after starting belzutifan treatment.

Characterization of the risk:

In MK-6482-004, 2 out of 61 participants (3.3%) experienced CNS hemorrhage, which were comprised of one Grade 2 Hemorrhage intracranial event and one Grade 3 Hemorrhage intracranial event.

Risk Factors and Risk Groups:

Published literature on bleeding in patients with VHL disease is limited to case reports and other small studies. Despite the vascular nature of CNS hemangioblastomas, reported incidence in 2 case series is between 2.5%-4.0% [Ref. 5.4: 085YP5],[Ref. 5.4: 0862HF]. One study, by Glasker S, et al [Ref. 5.4: 0862HF], drew from a database of 277 patients with CNS hemangioblastomas. Of these, data was available for 204 subjects (90 with VHL) with a mean follow-up time of 14 years/patient (range: 1-33 years). Five of the 204 patients experienced ICH. The average size of the tumor for these 5 patients was 3 cm (range 1.5-4.5 cm). An additional 2 patients bled after surgery for their hemangioblastoma. Chibawanye E, et al [Ref. 5.4: 085YP5] conducted a retrospective analysis of 55 cases of CNS hemangioblastomas from the clinical database at University of Washington using patient records from the years 2004 to 2014. Three cases (5.5%) experienced ICH. Two of these patients had hemangioblastoma sizes <1.5 cm, prompting the authors to postulate that not only are there hemodynamic factors at play with direct shunting of arterial blood into the venous vasculature, but likely genetic and cytokine-related factors as well.

Preventability:

The development of CNS hemorrhage cannot be completely prevented. If suspected, patients should be promptly evaluated for CNS hemorrhagic events for early recognition and treatment.

The use of a targeted follow-up questionnaire may help further characterize this important potential risk.

Impact on the Risk-Benefit Balance of the Product:

The rates of CNS hemorrhagic events reported in MK-6482-004 do not appear to be beyond what has been described in the literature in the VHL population. However, these events can be serious and potentially debilitating or even fatal. This is balanced against the morbidity of chronic disease associated with repeated surgeries and the fatal outcome of untreated cancer.

Public Health Impact:

This risk has minimal public health impact outside its effects on individual patients.

Important Potential Risk: Embryo-fetal Toxicity

Potential Mechanisms:

Cardiovascular defects and lethality have been reported in HIF-2α gene knock-out mouse embryos [Ref. 5.4: 05FRRV] [Ref. 5.4: 05FRS2]. The observed embryo-fetal toxicity in the rat study may be related to mechanism of action of belzutifan. There are limited data from the use of belzutifan in pregnant women.

Evidence source(s) and strength of evidence:

Rat embryo-fetal development study.

Characterization of the risk:

In a rat embryo-fetal development study, administration of belzutifan during organogenesis caused embryo-fetal lethality up to 100%, reduced fetal body weight, and fetal skeletal abnormalities at exposures similar to or below the human exposure at the recommended dose of 120 mg daily.

Risk factors and risk groups:

Female patients of childbearing potential.

Preventability:

Belzutifan is contraindicated during pregnancy in patients with VHL-associated tumors.

The pregnancy status of women of childbearing potential should be verified prior to initiating treatment with belzutifan.

Belzutifan may cause embryo-fetal harm, including fetal loss, when administered to a pregnant woman. Women of childbearing potential should be informed of the potential risk to a fetus.

Women of childbearing potential have to use highly effective contraception during treatment with belzutifan and for at least 1 week after the last dose. Use of belzutifan may reduce the efficacy of hormonal contraceptives. Patients using hormonal contraceptives should be advised to use an alternative non-hormonal contraceptive method or have their male partner use a condom during treatment with belzutifan.

Additional risk minimization measures (ARMMs) for embryo-fetal toxicity are described in Part V.2 “Additional Risk Minimization Measures”.

Impact on the risk-benefit balance of the product:

Given the morbidities of chronic disease associated with repeated surgeries and the fatal outcome of untreated cancer, the risk of embryofetal toxicity which can be prevented, is outweighed by the potential benefit.

Public health impact:

This risk has minimal public health impact outside its effects on individual patients.

SVII.3.2 Presentation of the Missing Information

Missing information: Long term safety

Evidence Source:

Protocol MK-6482-004

Population in Need of Further Characterization:

Long term safety has not been studied with belzutifan; however, Study MK-6482-004 includes long term follow-up for all patients until withdrawal of consent or death. The anticipated long-term use of belzutifan and the current limited data due to limited follow-up time makes it relevant for inclusion in the RMP.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	CNS Hemorrhage in VHL patients with CNS hemangioblastoma Embryo-Fetal Toxicity
Missing information	Long term safety

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Not applicable.

Specific Adverse Reaction Follow-Up Questionnaires for CNS Hemorrhage:

Routine pharmacovigilance post-approval includes a targeted follow-up questionnaire for post-marketing reports of CNS Hemorrhage in VHL patients with CNS hemangioblastoma (Annex 4).

III.2 Additional Pharmacovigilance Activities

None

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
An open-label Phase 2 Study to Evaluate Belzutifan for the treatment of Von-Hippel-Lindau (VHL) Disease-Associated Renal Cell Carcinoma (MK-6482-004) (ongoing)	To confirm long term efficacy and safety of belzutifan in participants with VHL disease-associated tumours	Long- term efficacy and safety	Final Analysis	1Q 2027
A Phase 2 Study to Evaluate the Efficacy and Safety of Belzutifan Monotherapy in Participants with VHL Disease-Associated Tumors (MK-6482-015 Cohort B1) (ongoing)	To confirm efficacy and safety of belzutifan in at least 64 participants with VHL disease-associated tumours, with at least 24 months follow-up	Additional efficacy and safety	Interim report	1Q 2027

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table V.1.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
CNS Hemorrhage in VHL patients with CNS hemangioblastoma	Sections 4.4 and 4.8 of the SmPC Section 4 of the Patient Leaflet
Embryo-Fetal Toxicity	Sections 4.3, 4.4, 4.5 and 4.6 of the SmPC Section 2 of the Patient Leaflet
Long term safety	No routine risk minimization measures have been proposed.

V.2 Additional Risk Minimization Measures

Table V.2.1: Description of Additional Risk Minimisation Measures by Safety Concern

Safety Concern	Additional Risk Minimisation Activities

Embryo-fetal toxicity	**Proposed Actions:**
	• Safety advice tools:
	  ○ Patient card
	  ○ Guide for healthcare professionals
	
	Objectives:
	To minimize the risk of embryo-fetal toxicity.
	
	Rationale for the Additional Risk Minimization Activity:
	To inform patients and educate healthcare professionals of the important potential risk of embryo-fetal toxicity, the need for suitable contraception measures, and the need to discontinue treatment with belzutifan if a pregnancy is planned or a pregnancy is detected.
	
	Target audience and Planned Distribution Path:
	• Female patients of childbearing potential
	• Oncologists and other physicians who may prescribe belzutifan to treat female patients of childbearing potential within the approved indication(s)
	
	A package containing a letter explaining the rationale for the educational materials and describing their intended use and a copy of the Guide for healthcare professionals will be distributed to oncologists and other physicians who may prescribe belzutifan to treat female patients of childbearing potential within the approved indication(s). The patient card is provided in the product package. The healthcare professional will be requested in the letter to provide contraceptive counselling to women of childbearing potential prior to the prescription of the product and inform them of the purpose of the patient card.

	Plans to Evaluate the Effectiveness of the Intervention and Criteria for Success: Clinical features of all reports received describing exposure to belzutifan during pregnancy will be reviewed as part of routine pharmacovigilance processes. An analysis of these cases will be presented in the PSUR, in the context of the guidance within the SmPC, Package Leaflet and additional risk minimization measures, and appropriate measures will be considered if information is obtained that indicates that updates to the risk minimization measures are warranted. Records will be retained of the distribution of the package containing the educational material to oncologists and other physicians who may prescribe belzutifan to treat female patients of childbearing potential within the approved indication(s).

V.3 Summary of Risk Minimization Measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk minimization Measures	Pharmacovigilance Activities
CNS Hemorrhage in VHL patients with CNS hemangioblastoma	**Routine risk minimization measures:** Sections 4.4 and 4.8 of the SmPC Section 4 of the Patient Leaflet **Additional risk minimization measures:** None	**Routine pharmacovigilance activities** beyond adverse reaction reporting and signal detection: Questionnaire **Additional pharmacovigilance activities:** None
Embryo-Fetal Toxicity	**Routine risk minimization measures:** Sections 4.3, 4.4, 4.5, and 4.6 of the SmPC Section 2 of the Patient Leaflet **Additional risk minimization measures:** Patient card and Guide for healthcare professionals	**Routine pharmacovigilance activities** beyond adverse reaction reporting and signal detection: None **Additional pharmacovigilance activities:** None
Long term safety	**Routine risk minimization measures:** None. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities** beyond adverse reaction reporting and signal detection: None **Additional pharmacovigilance activities:** None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for WELIREG (belzutifan)

This is a summary of the risk management plan (RMP) for WELIREG. The RMP details important risks of WELIREG, how these risks can be minimized, and how more information will be obtained about risks and uncertainties (missing information) of WELIREG.

WELIREG's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how WELIREG should be used.

Important new concerns or changes to the current ones will be included in updates of the WELIREG RMP.

I. The Medicine and What it is Used for

WELIREG is authorized as monotherapy for the treatment of adult patients with advanced clear cell renal cell carcinoma that progressed following two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF targeted therapies.

WELIREG is also authorized as monotherapy for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated, localised renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable.

It contains belzutifan as the active substance and it is given by oral administration as a 40mg film-coated tablet.

Further information about the evaluation of WELIREG's benefits can be found in WELIREG's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage < link to the EPAR summary landing page>.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of WELIREG, together with measures to minimize such risks and the proposed studies for learning more about risks of WELIREG are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of WELIREG is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of WELIREG are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of WELIREG. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	CNS Hemorrhage in VHL patients with CNS hemangioblastoma Embryo-Fetal Toxicity
Missing information	Long term safety

II.B Summary of Important Risks

Table II.B.1: Important Potential Risk: CNS Hemorrhage in VHL patients with CNS hemangioblastoma

Evidence for linking the risk to the medicine	Reports of serious adverse events of CNS bleeding have been reported in patients with VHL-associated CNS-HB after starting belzutifan treatment.
Risk factors and risk groups	Published literature on bleeding in patients with VHL disease is limited to case reports and other small studies. Despite the vascular nature of CNS hemangioblastomas, reported incidence in the literature is between 2.5%-4.0%.
Risk minimization measures	Routine risk minimization measures: Sections 4.4 and 4.8 of the SmPC Section 4 of the Patient Leaflet Additional risk minimization measures: None

Table II.B.2: Important Potential Risk: Embryo-fetal toxicity

Evidence for linking the risk to the medicine	Rat embryo-fetal development study.
Risk factors and risk groups	Female patients of childbearing potential.
Risk minimization measures	Routine risk minimization measures: Sections 4.3, 4.4, 4.5 and 4.6 of the SmPC Section 2 of the Patient Leaflet Additional risk minimization measures: Patient card and Guide for healthcare professionals

Table II.B.3: Missing Information: Long Term Safety

Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

The following studies are conditions of the Marketing Authorisation:

Table II.C.1.1: Studies Which are Conditions of the Marketing Authorisation

Study Title	Objectives
Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations	
An open-label Phase 2 Study to Evaluate Belzutifan for the treatment of Von-Hippel-Lindau (VHL) Disease-Associated Renal Cell Carcinoma (MK-6482-004) (ongoing)	In order to confirm the efficacy and safety of belzutifan as monotherapy for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated, localised renal cell carcinoma (RCC), central nervous system (CNS) haemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable, the MAH should submit the final results of the ongoing study MK-6482-004, an open-label Phase II single-arm study to further investigate the long-term efficacy and safety of belzutifan for the treatment of von-Hippel-Lindau disease-associated Renal Cell Carcinoma.
A Phase 2 Study to Evaluate the Efficacy and Safety of Belzutifan Monotherapy in Participants with VHL Disease-Associated Tumors (MK-6482-015 Cohort B1) (ongoing)	In order to confirm the efficacy and safety of belzutifan as monotherapy for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated, localised RCC, CNS haemangioblastomas, or pNET, and for whom localised procedures are unsuitable, the MAH should submit efficacy and safety data from at least 64 patients with at least 24 months follow-up of cohort B1 for the ongoing study MK-6482-015, an uncontrolled Phase II study to evaluate the efficacy and safety of belzutifan in patients with von Hippel Lindau disease-associated tumours who have at least 1 measurable RCC, pNET, or pheochromocytoma/paraganglioma (PPGL) tumour.

II.C.2 Other Studies in Post-Authorisation Development Plan

None

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ANNEXES

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents:

[Letter Date]

[Correspondence Contact Name]
[Institution]
[Address]
[Address 2]
[City], [STATE], [Zip Code]

Dear [Correspondence Contact Name],

We have been notified of a report concerning an event of following exposure to belzutifan.

Patient Name	[Patient Name]
Patient Initials	[PATIENT INITIALS]
Age	[Patient Age]
Gender	[Patient Gender]
Product (All Merck suspect products)	[INSERT, ALL, PRODUCTS, SEPARATED, BY, COMMA, AND, SPACE, LIKE, THIS,]
Event(s) – All events	[INSERT, ALL, EVENT PREFERRED TERMS, SEPARATED, BY, COMMA, AND, SPACE, LIKE, THIS,

The information will be used for surveillance and may be provided to regulatory authorities such as the Food and Drug Administration, European Medicines Agency, or other regulatory agencies, Merck subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

Enclosed is a form that Merck respectfully suggests you complete and return to us at your earliest convenience. The objective is to obtain additional information to better understand the experience you reported which may improve patient safety. Your assistance in this matter is greatly appreciated. You may provide this information by calling us at 800-705-1885, Monday-Friday 8AM to 5PM ET, or you can return the completed form via fax at 215-616-5677.

The information provided concerning the reported event will be handled according to current worldwide regulatory requirements. Please read more about Merck's privacy commitment at https://www.msdprivacy.com/

Sincerely

Global Clinical Safety & Pharmacovigilance
Phone: 1-800-705-1885
Fax: 215-616-5677

Journal: [Literature Information Journal]

Title: [Literature Information Title]

UNDERLYING ETIOLOGY;

Is there any known underlying etiology of the central nervous system (CNS) hemorrhage?	☐ Yes, specify: ☐ No
Does the patient have history of CNS hemangioblastoma? *If yes, specify (include date of first diagnosis, method of diagnosis (imaging findings of brain and spine, including tumor size, before start of treatment and during treatment, if applicable)).*	☐ Yes, specify: ☐ No ☐ Unknown

HISTORY / PATIENT CHARACTERISTICS:

Does the patient have a history of CNS hemorrhage (other than the reported event)? *If yes, specify date of onset, location and volume of bleed, cause, duration, outcome, and sequelae.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient smoke or have a smoking history? *If yes, specify (include duration and extent).* *If ex-smoker indicate how long since cessation.*	☐ Yes, specify: ☐ No ☐ Unknown
Is the patient a passive smoker (exposed to second-hand smoke)? *If yes, specify age, duration, and extent of exposure.*	☐ Yes, specify: ☐ No ☐ Unknown
Is there any past or present history of excessive alcohol consumption? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown
Is there any past or present history of drug/substance abuse? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown
Is there any past or present history of any hormonal treatment? *If yes, specify product, dose, and duration of exposure (start and stop dates, last date taken prior to event).*	☐ Yes, specify: ☐ No ☐ Unknown
What anatomic sites are affected by Von Hippel-Lindau (VHL) disease?	Specify: ☐ Unknown
Does this patient have any other history of cancer? *If yes, specify type of cancer and date.*	☐ Yes, specify: ☐ No ☐ Unknown

RISK FACTORS:

Does the patient have hypertension? *If yes, specify age at onset, type of hypertension, most recent blood pressure readings prior to the event, medications.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have dyslipidemia? *If yes, specify age at onset, most recent cholesterol and lipid levels prior to the event or outcome of other investigations, medications.*	☐ Yes, specify: ☐ No ☐ Unknown
1 Does the patient have diabetes? *If yes, specify age at onset, type of diabetes and level of diabetic control, most recent HbA1C prior to the event, medications.*	☐ Yes, specify: ☐ No ☐ Unknown
2 Does the patient have a family history of CNS hemorrhage? **3** *If yes, specify degree of family relation, date and type of occurrence*	**4** ☐ Yes, specify: ☐ No ☐ Unknown
5 Does the patient have a history of extreme physical exertion preceding the event? **6** *If yes, specify the nature of the physical exertion*	☐ Yes, specify: ☐ No ☐ Unknown
7 Does the patient have a history of coagulopathy? **8** *If yes, specify the type of coagulopathy*	☐ Yes, specify: ☐ No ☐ Unknown
9 Does the patient have a history of hepatic failure? **10** *If yes, specify the nature of the hepatic failure*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have any inflammatory diseases, e.g. vasculitis, arteritis? **11** *If yes, specify disease and date of onset.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have history of CNS metastases? **12** *If yes, specify (anatomical location and date of onset).*	☐ Yes, specify: ☐ No ☐ Unknown
13 Does the patient have a history of cerebral arteriovenous malformation, aneurysm, or Moyamoya disease? *If yes, specify which condition*	☐ Yes, specify: ☐ No ☐ Unknown

Presence or absence of any (risk factors for) other possible causes of CNS Hemorrhage

Does the patient have any hematological abnormalities? *If yes, specify which abnormality.*	☐ Yes, specify: ☐ No ☐ Unknown
Did the patient experience any recent head injury or trauma preceding the event? *If yes, specify type and date*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have increased homocysteine levels? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown
List all medications, including anticoagulants, the patient was taking when the event occurred Specify which medication, dose and duration of exposure.	☐ Medications: ☐ Unknown
Did the patient undergo any recent procedure or thrombolysis?	☐ Yes, specify: ☐ No ☐ Unknown

EVENT DETAILS:

Date of first signs and symptoms of the event	
What were the presenting signs and symptoms of the event, and what was their chronological order?	
How was the event diagnosed? Include date of diagnosis	
Was the hemorrhage related to any other CNS condition preceding the event (beyond CNS hemangioblastoma)?	
Which treatments were given? On which dates?	
What was the course of the illness following treatment?	
What was the outcome of the event over time, in terms of residual disability	
Is there any other relevant information about the event?	

RELEVANT DIAGNOSTIC PROCEDURES:

What was the method of diagnosis of the CNS hemorrhage?	
Have the following tests been performed? *If yes, specify the dates and the results of the tests, in particular in relation to the CNS hemorrhage. Please include location and volume of CNS hemorrhage.*	**Results**
MRI ☐ Yes ☐ No ☐ Unknown	
MRA ☐ Yes ☐ No ☐ Unknown	
CT-scan ☐ Yes ☐ No ☐ Unknown	
CTA ☐ Yes ☐ No ☐ Unknown	
Cerebral Angiogram ☐ Yes ☐ No ☐ Unknown	
Please describe any other relevant tests and test results:	

RELEVANT LABORATORY VALUES:

Have the following tests been performed? *If yes, specify the dates, the results of the tests, and laboratory normal ranges...*	**Values and Normal Ranges (Units)**
PT/APTT/INR ☐ Yes ☐ No ☐ Unknown	
Liver enzymes ☐ Yes ☐ No ☐ Unknown ALP/ ALT/ AST/ GGT:	
Albumin ☐ Yes ☐ No ☐ Unknown	
AT III level/activity ☐ Yes ☐ No ☐ Unknown	
Protein S level/activity ☐ Yes ☐ No ☐ Unknown	
Protein C level/activity ☐ Yes ☐ No ☐ Unknown	
Factor VII ☐ Yes ☐ No ☐ Unknown	
Factor VIII ☐ Yes ☐ No ☐ Unknown	
Prothrombin mutation G20210 ☐ Yes ☐ No ☐ Unknown	
Platelet Count ☐ Yes ☐ No ☐ Unknown	
APC resistance (factor V Leiden) ☐ Yes ☐ No ☐ Unknown	☐ Homozygous ☐ Heterozygous ☐ Unknown whether it is homozygous - or heterozygous
Antiphospholipid antibodies (SLE/lupus) ☐ Yes ☐ No ☐ Unknown	
Homocysteine blood Levels ☐ Yes ☐ No ☐ Unknown	
Additional information *Please specify any additional information not provided above*	

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Additional Risk Minimisation Activities: Patient Card and Guide for Healthcare Professionals

Approved key messages of the additional risk minimisation measures

Prior to the launch of WELIREG in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the guide for health care professionals, including communication media, distribution modalities, and any other aspects of the safety advice tool, with the National Competent Authority. The patient card is provided in the product package.

The safety advice tools are aimed at informing about appropriate contraceptive measures to prevent pregnancies in female patients treated with belzutifan.

The MAH shall ensure that in each Member State where WELIREG is marketed, all healthcare professionals and female patients of childbearing potential who are expected to prescribe or use WELIREG, respectively, have access to/are provided with the following educational package:

- Guide for healthcare professionals
- Patient card

Educational material for healthcare professionals:

- The Summary of Product Characteristics
- Guide for healthcare professionals

Guide for healthcare professionals:

- Belzutifan may cause embryo-foetal harm, including foetal loss, when administered to a pregnant woman.
- Belzutifan is contraindicated in pregnant women treated for von Hippel-Lindau (VHL) disease-associated tumours.
- Belzutifan should not be used during pregnancy in women treated for renal cell carcinoma unless the clinical condition requires treatment with belzutifan.

- Details on how to reduce the potential risk of exposure during pregnancy for women of childbearing potential based on the following:

    - A pregnancy test should be performed before start of treatment with belzutifan.

    - Women of childbearing potential have to use highly effective contraception method during treatment with belzutifan and up to at least 1 week after the last dose.

    - Explain to patient that belzutifan may reduce the efficacy of hormonal contraceptives. Therefore, a non-hormonal contraceptive method should be used or have their male partner use a condom.

    - The female patients of childbearing potential should be informed about the potential risk of embryo-foetal harm and appropriate contraceptive measures before start of treatment with belzutifan.

- Need to discontinue treatment with belzutifan if a pregnancy is planned or a pregnancy is detected.

  A patient card is included in the product package. Healthcare professionals should inform each female patient of childbearing potential prior to the start of treatment about the purpose of the patient card.

Patient Card:

- Belzutifan should not be used by pregnant women because the use of belzutifan can cause foetal harm, including foetal loss, when used during pregnancy.

- Language describing how to reduce the potential risk of exposure during pregnancy based on the following:

    - A pregnancy test should be performed before start of treatment with belzutifan.

    - Women of childbearing potential have to use highly effective contraception method during treatment with belzutifan and up to at least 1 week after the last dose.

    - Belzutifan may reduce the efficacy of hormonal contraceptives. Therefore, a non-hormonal contraceptive method should be used or have their male partner use a condom.

    - If a pregnancy occurs during treatment with belzutifan contact your treating physician immediately.

- Contact details of the belzutifan prescriber.
- Women of childbearing potential should be instructed to talk to their healthcare professional about contraception while taking belzutifan.
- Instruct patient to refer to the package leaflet for additional information about the safety of belzutifan.