PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

POST-AUTHORIZATION STUDY (PAS) INFORMATION

Title	Non-interventional post-authorization study of belzutifan in adult patients with von Hippel-Lindau disease-associated renal cell carcinoma, pancreatic neuroendocrine tumor and/or central nervous system hemangioblastoma
Protocol No./version No.	6482-026/3.0
Protocol Date	28-Nov-2023
Date and Version of Previous Protocol	23-May-2023, Version 2.0
EU PAS register No.	To be registered
Active substance	belzutifan (ACT code: L01XX74)
Medicinal product	belzutifan
Product reference	WELIREG®
Procedure number	Not applicable
Marketing authorization holder(s) (MAH)	Merck Sharp & Dohme (UK) Ltd. 120 Moorgate, London, EC2M 6UR United Kingdom (hereafter referred to as Sponsor or MSD)
Joint PAS	No
Research question and objectives	The primary aim of this registry is to further characterize the effectiveness of belzutifan for patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC) and/or central nervous system (CNS) hemangioblastoma treated in real-world clinical practice. The primary effectiveness parameter includes tumor reductive procedures given the clinical importance of this parameter and association with subsequent morbidity and mortality of disease. Secondary aims are to describe potential serious adverse events (SAEs), occurence of new VHL disease-associated tumors or tumor type, and metastasis during belzutifan use, and to evaluate treatment patterns.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

Countries of study	United States. As needed, additional countries and sites will be evaluated for inclusion once local marketing authorization is obtained and reimbursement for cost of the drug is available.
Author	PPD PhD, MS Sr. Principal Scientist, Epidemiology PPD PhD Sr. Principal Scientist, Clinical Research Merck & Co., Inc., Rahway, NJ 07065 USA
Marketing authorization holder(s) including MAH contact person	Merck Sharp & Dohme (UK) Ltd. 120 Moorgate, London, EC2M 6UR United Kingdom Contact: msdukregulatory@msd.com
MSD final repository (REDS) date	12-DEC-2023
Date of health authority approval of protocol	November 9, 2023 (Medicines and Healthcare products Regulatory Agency conditional approval) December 15, 2023 (Submission of finalized version with mandatory changes completed)

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

TABLE OF CONTENTS

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

LIST OF TABLES

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AJCC	American Joint Committee on Cancer
AR	adverse reaction
CI	confidence interval
CNS	central nervous system
CRF	case report form
CT	computer tomography
DSUR	Development Safety Update Report
EDC	electronic data capture
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
GPP	Good Pharmacoepidemiology Practice
IEC	independent ethics committee
IRB	institutional review board
MAH	market authorization holder
MRI	magnetic resonance imaging
NSAR	non-serious adverse reaction
PAS	post-authorization study
PBRER	Periodic Benefit Risk Evaluation Report
pNET	pancreatic neuroendocrine tumor

PQC	product quality complaint
PSUR	Periodic Safety Update Report
PT	preferred term
RCC	renal cell carcinoma
SAE	serious adverse vent
SAP	statistical analysis plan
SAR	serious adverse reaction
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SQI	significant quality issue
TFLs	tables, figures and listings
US	United States
VHL	Von Hippel-Lindau

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

1 RESPONSIBLE PARTIES

Responsible parties are listed below:

Principal Investigator	Not applicable
Coordinating Investigator for each Country in which the Study is to be Performed	Not applicable
Sponsor Contacts	PPD PhD, MS Biostatistics and Research Decision Sciences, Epidemiology Merck & Co., Inc., Rahway, NJ 07065 USA
Other Contacts	PPD Epidemiology Operations Global Clinical Trial Operations Merck & Co., Inc., Rahway, NJ 07065 USA
Supplier/ Collaborator	Parexel International Corporation 195 West Street Waltham, MA 02451, USA
Investigators	See Annex 1
Shared Responsibilities	Not applicable

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

2 ABSTRACT

Title	Non-interventional post-authorization study of belzutifan in adult patients with von Hippel-Lindau disease-associated renal cell carcinoma, pancreatic neuroendocrine tumor and/or central nervous system hemangioblastoma
Protocol No./Version No.	6482-026/3.0
Date	28-Nov-2023
Author	PPD PhD, MS Sr. Principal Scientist, Epidemiology PPD MD Sr. Principal Scientist, Clinical Research Merck & Co., Inc., Rahway, NJ 07065 USA
Rationale & Background	Von Hippel-Lindau (VHL) disease is a rare autosomal dominant disease occurring in approximately one in 36,000 people worldwide. The disease is characterized by an increased prevalence of recurring benign and malignant tumors including renal cell carcinomas (RCCs), central nervous system (CNS) hemangioblastomas, pancreatic neuroendocrine tumors (pNETs), retinal angiomas, pheochromocytomas and paragangliomas, inner ear endolymphatic sac solid tumors, and other cysts. The only systemic therapy approved for the treatment of certain patients with VHL disease-associated neoplasms is belzutifan (WELIREG®), which was initially approved by the United States (US) Food and Drug Administration (FDA) in August 2021 for the treatment of adult patients with VHL disease who require therapy for associated RCC, CNS hemangioblastoma, or pNET, not requiring immediate surgery. Approval was based on a single-arm study (MK-6482-004) which enrolled 61 patients with VHL disease-associated RCC including patients with other VHL disease-associated neoplasms, the most common of which was CNS hemangioblastoma occurring in 51/61 patients (84%) per local assessment. The global registration status of WELIREG® is rapidly evolving. Marketing applications are under review worldwide, and indications for use may vary by region. The study aims to evaluate the treatment effectiveness and long-term safety of patients treated with belzutifan in routine clinical practice.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

Research Question(s) & Objective(s)	Primary objectives are: 1. Among new users of belzutifan with VHL disease-associated RCC, to describe the proportion of patients who undergo at least one renal tumor reductive surgery (e.g., nephrectomy) or locally directed therapy (e.g., radiofrequency ablation). 2. Among new users of belzutifan with VHL disease-associated CNS hemangioblastoma, to describe the proportion of patients who undergo at least one CNS tumor reductive surgery (e.g., craniectomy) or locally directed therapy (e.g., radiation therapy). Secondary objectives are: 1. Among all new users of belzutifan, to describe: a. Proportion of patients with treatment emergent SAEs, including the nature of these events. b. Treatment patterns including the: i. Duration of therapy ii. Proportion of patients who discontinued treatment, time to treatment discontinuation, and summary of reasons for discontinuation iii. Proportion of patients who interrupted treatment, time to treatment interruption, duration of treatment interruption, and summary of reasons for treatment interruption iv. Proportion of patients with dose reductions, and reason for dose reduction. 2. Among new users of belzutifan with VHL disease-associated RCC and, separately, VHL disease-associated CNS hemangioblastoma, to describe the proportion of patients who develop metastatic disease (for RCC only), and proportion with occurrence of new VHL tumors or tumor type.
Study Design	This is a prospective observational cohort study evaluating the effectiveness and safety of belzutifan treatment in routine clinical practice. The planned minimum follow-up for each patient will be 3 years. The planned maximum follow-up for patients in the registry will be up to 5-6 years.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

Population	Adult (≥18 years of age) patients with VHL disease for which a decision has been made by the treating physician to intiate belzutifan treatment within the prescribing conditions of the product label. Recruitment will initially start in the US. As needed, additional countries and sites will be evaluated for inclusion once local marketing authorization is obtained and reimbursement for cost of the drug is available.
Variables	Primary exposure is belzutifan treatment. Primary effectiveness outcome is surgery or locally directed therapy, and key secondary effectiveness outcomes include metastasis (RCC only), occurrence of other VHL disease-associated tumors during belzutifan use, treatment patterns, and primary safety outcome are SAEs. Additional data will be collected on study eligibility, dates of clinic visits, patient demographics, medical history (including, but not limited to, prior anticancer treatments, oncologic therapies, and VHL diagnosis), tumor characteristics, concomitant medications, other baseline and follow-up measures such as hemoglobin values, blood pressure, behavioral risk factors (alcohol and smoking, [baseline only]), and estimated glomerular filtration rate (baseline only, RCC patients).
Data Sources	The main source of clinical and patient data will be the patients' medical record. Baseline characteristics will be extracted by the investigator from the medical records to the extent possible and recorded in the study case report forms (CRFs). Data reported on the index date or subsequent follow-up visits will be captured by the site in CRFs using an electronic data capture (EDC) system.
Study Size	Up to 100 patients with VHL disease-associated RCC, CNS hemangioblastoma or pNET will be enrolled in the study. This includes approximately 40 patients with VHL disease-associated RCC and approximately 40 patients with VHL disease-associated CNS hemangioblastoma that require treatment per investigator's judgment for the primary effectiveness analysis. All patients enrolled in the registry will be included in the safety analysis.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

<table>
<tr><td>Data Analysis</td><td>All statistical analyses will be performed using Statistical Analysis System® (Cary, North Carolina version 9.4 or higher) unless otherwise stated.

No formal statistical hypothesis testing will be performed, and all the analyses will be primarily descriptive in nature. When appropriate, and unless otherwise specified, 95% confidence intervals (CIs) will be displayed.</td></tr>
<tr><td>Milestone</td><td><table>
<tr><td>Registration in the EU PAS register</td><td>To be determined</td></tr>
<tr><td>First patient first visit</td><td>Expected Q1-Q2 2024</td></tr>
<tr><td>Study progress report</td><td>Expected Q1-Q2 2027 (or earlier with completion of enrollment).</td></tr>
<tr><td>Last patient last visit</td><td>Expected Q1-Q2 2029-2030</td></tr>
<tr><td>Final report of study results</td><td>Q3-Q4 2029-2030</td></tr>
</table>EU=European Union; PAS=post authorization study</td></tr>
</table>

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

3 AMENDMENTS AND UPDATES

Protocol Version	Approval Date	Section of Study Protocol	Summary of Changes
1.0 (Original)	CORE DRC: 11-OCT-2022 CRC PRC: 20-OCT-2022	N/A	N/A
2.0 (Amendment 1)	CORE DRC: 06-Jun-2023 CRC PRC: Not applicable (N/A)	2. Abstract	• Reflected relevant updates made in the protocol amendment 1.
		3. Amendments and Updates	• Amendment history table added.
		4. Milestones	• Milestone table updated based on the latest information.
		5. Rationale and Background	• Clarified that indications for use for belzutifan may be different in different regions. Investigator should refer to the current WELIREG® approved local product label in the region for detailed prescribing information.
		7.1. Study Design	• Clarified that patients will have the planned minimum follow-up of 3 years. • Clarified that the planned maximum follow-up for patients in the registry will be up to 5-6 years. • Updated the planned enrollment period based on current site feasibility assessment.
		7.3.2 Outcomes	• Clarified that during follow-up, data on all new tumor types and number of lesions should be collected. • Added that if available, best response to treatment per local radiology assessment for primary tumors will be also captured at the time of belzutifan discontinuation.
		7.3.3 Other Study Variables	• Modified family history of cancer to family history of VHL disease. • Modified VHL mutation “type” to VHL “variant”. • Combined tumor characteristics tumor laterality and directionality to one characteristic: Location (i.e., RCC: left, right; CNS hemangioblastoma: cerebellum, spine, other; pNET: head, body/tail).

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

Protocol Version	Approval Date	Section of Study Protocol	Summary of Changes
			• Added number of lesions to be collected with new VHL tumors. • Added collection of hemoglobin, blood pressure and oxygen saturation during follow-up, and estimated glomerular filtration rate (baseline only, RCC patients). • Clarified that the only behavioral risk factors are baseline alcohol and smoking data.
		7.4 Table 1	Revised table summarizing data collection to be consistent with other relevant changes to protocol.
		7.7.3.2 Patient Disposition and Withdrawals 8.1 Informed Consent	Added data collection for age (in years) and sex for patients approached but who do not consent to participate in the study and reason(s) for not participating.
		Overall sections	Administrative updates, including formatting, cross references, abbreviations, and editorial changes for overall consistency.
V3.0 (Amendment 2)	CORE DRC: 28-NOV-2023 CRC PRC: N/A	Revised based on final feedback from regulatory authority (MHRA)	
		1. Responsible Parties	Added name of supplier
		2. Abstract 4. Milestones	Updated the study milestones
		5. Rationale and Background	Added information on germline mutation and common clinical management guidelines, and belzutifan indication statement in Great Britain.
		7.1 Study Design	Added reference to study design in accordance with quality assurance principles defined for registries, plan to leverage existing registries within countries with marketing approval and national reimbursement (as applicable), and lack of attrition expected among study sites.
		7.3.3 Other Study Variables	Added reference to data entry guidelines for VHL tumor(s) requiring treatment
		7.4 Data Source	Added further details on data collection, as available, from the patient's medical records.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

Protocol Version	Approval Date	Section of Study Protocol	Summary of Changes
		7.6 Data Management	Added further details on data management consistent with quality principles defined for registries.
		7.7.4 Primary Efficacy Analysis	Added details on subgroup analysis if the study includes patients enrolled in different countries, and plans for benchmarking single-arm treatment registry results using data from natural history studies.
		7.9 Limitations of the Research Methods	Added further details on potential limitations related to lack of external control arm and generalizability of results and mitigation plans.
		11. References	Added reference to Agency for Healthcare Research and Quality (US) quality assurance principles for registries.

CNS=central nervous system; N/A=not applicable; pNET=pancreatic neuroendocrine tumor; RCC=renal cell carcinoma; VHL=Von Hippel-Lindau

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

4 MILESTONES

Milestone	**Planned Date**
Registration in the EU PAS register	To be determined
First patient first visit	Expected Q1-Q2 2024
Study progress report	Expected Q1-Q2 2027 (or earlier with completion of enrollment)
Last patient last visit	Expected Q1-Q2 2029-2030
Final report of study results	Q3-Q4 2029-2030

EU=European Union; PAS=post-authorization study

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

5 RATIONALE AND BACKGROUND

Von Hippel-Lindau (VHL) disease is a rare autosomal dominant disease occurring in approximately one in 36,000 people worldwide.[1] The disease is characterized by an increased prevalence of recurring benign and malignant tumors including renal cell carcinomas (RCCs), central nervous system (CNS) hemangioblastomas, pancreatic neuroendocrine tumors (pNETs), retinal angiomas, pheochromocytomas and paragangliomas, inner ear endolymphatic sac solid tumors, and other cysts.[1]

Approximately two thirds of patients with VHL disease develop renal cysts and the lifetime risk of RCC is approximately 70%.[2] Among patients 15 years and older, periodic abdominal imaging, including magnetic resonance imaging (MRI) and computer tomography (CT) scans with or without contrast of the kidneys, are recommended to monitor tumor size, location, and progression.[3,4] The clinical management of VHL disease-associated localized renal tumors involves active surveillance until the largest renal tumor reaches a 3-centimeters maximal diameter threshold, at which time nephron-sparing surgical intervention is recommended.[5] In addition to RCC, another common VHL disease-associated clinical manifestation is CNS hemangioblastoma. Between 60 to 84% of patients with VHL disease develop hemangioblastomas of the CNS, most commonly in the spinal cord and cerebellum.[6] Like the clinical guidelines for monitoring and treating RCC, small asymptomatic CNS lesions are closely monitored, and surgery is generally only considered when CNS lesions become symptomatic or they grow in an accelerated manner. The penetrance of pNETs among patients with VHL disease ranges between 8% and 17%.[7] CNS hemangioblastomas and RCCs are the leading causes of morbidity and mortality in patients with VHL disease.

In patients with VHL disease, the common underlying pathogenesis is germline VHL alterations (mutations and/or deletions) resulting in aberrant HF-2α stabilization, which leads to constitutive activation of downstream genes that are involved in oncological outcomes in multiple organs with recurrent malignant and/or non-malignant tumors. The clinical management guidelines are generally consistent across countries and regions, with active surveillance followed by surgery/ local procedures being the mainstay of treatment prior to the availability of belzutifan for certain patients.

The only systemic therapy approved for the treatment of certain patients with VHL disease associated neoplasms is belzutifan (WELIREG®), which was initially approved by the United States (US) Food and Drug Administration (FDA) in August 2021 for the treatment of adult patients with VHL disease who require therapy for associated RCC, CNS hemangioblastoma, or pNET, not requiring immediate surgery. Marketing approval was subsequently obtained in Great Britain in May 2022 for the treatment of adult patients with VHL disease who require therapy for VHL associated RCC, CNS hemangioblastoma or pNET, and for whom localised procedures are unsuitable or undesirable. The population eligible for treatment with belzutifan refers to patients from whom a tumor reducing intervention may be inevitable but is currently not a preferred option, which includes patients who prefer to delay and/or are not a suitable candidate for these procedures. Marketing approvals were based on a single-arm

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

study (MK-6482-004) which enrolled 61 patients with VHL disease-associated RCC including patients with other VHL disease-associated neoplasms, the most common of which was CNS hemangioblastoma occurring in 51/61 patients (84%) per local assessment.

The global registration status of WELIREG® is rapidly evolving. Marketing applications are under review worldwide, and indications for use may vary by region.

Refer to the current WELIREG® approved local product label in your region for detailed prescribing information.

6 RESEARCH QUESTIONS AND OBJECTIVES

The primary aim of this registry is to characterize the effectiveness of belzutifan for patients with VHL disease-associated RCC and/or CNS hemangioblastoma treated in real-world clinical practice. The primary effectiveness parameter includes tumor reductive procedures given the clinical importance of this parameter and association with subsequent morbidity and mortality of disease.

Secondary aims are to describe potential serious adverse events (SAEs), occurrence of new VHL disease-associated tumors or tumor type, and metastasis during belzutifan use and to evaluate treatment patterns among all new users of belzutifan.

6.1 Primary Objective

1. Among new users of belzutifan with VHL disease-associated RCC, to describe the proportion of patients who undergo at least one renal tumor reductive surgery (e.g., nephrectomy) or locally directed therapy (e.g., radiofrequency ablation).
2. Among new users of belzutifan with VHL disease-associated CNS hemangioblastoma, to describe the proportion of patients who undergo at least one CNS tumor reductive surgery (e.g., craniectomy) or locally directed therapy (e.g., radiation therapy).

6.2 Secondary Objectives

1. Among all new users of belzutifan[1], to describe:
    a. Proportion of patients with treatment emergent SAEs, including the nature of these events.
    b. Treatment patterns including the:
        i. Duration of therapy
        ii. Proportion of patients who discontinued treatment, time to treatment discontinuation, and summary of reasons for discontinuation
        iii. Proportion of patients who interrupted treatment, time to treatment interruption, duration of treatment interruption, and summary of reasons for treatment interruption
        iv. Proportion of patients with dose reductions, and reason for dose reduction.
2. Among new users of belzutifan with VHL disease-associated RCC and, separately, VHL disease-associated CNS hemangioblastoma, to describe:
    a. Proportion of patients who develop metastatic disease (for RCC only)
    b. Proportion of patients with occurrence of new VHL disease-associated tumor or tumor type

[1] see Section 7.2.1. (Inclusion Criteria). Depending on the approved local label, this may include patients with VHL disease-associated RCC, CNS hemangioblastoma, or pNET.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

7 RESEARCH METHODS

7.1 Study Design

This is a prospective observational cohort study evaluating the effectiveness and safety of belzutifan for patients newly assigned to belzutifan treatment ('new users') in routine clinical practice. The study has been designed with procedures to obtain data consistently and accurately in alignment with associated quality assurance principles defined for registries[8]. Timepoints for visits/assessments are not pre-specified by the protocol. All patient encounters will be performed according to the routine clinical practice at participating sites. Given the rare nature of VHL disease, the study will be conducted across several regions, commencing initially at clinical sites in the United States. As needed, additional countries and sites will be evaluated for inclusion once local marketing authorization is obtained and reimbursement for cost of the drug is available. The ability to leverage existing national registries for VHL data collection will be evaluated on a case by case basis.

During the recruitment period, once the treatment decision for use of belzutifan has been made by the patients' physician (at his/her own discretion), patients will be approached regarding study participation. Patients who meet the eligibility criteria and consent to participate prior to or within 30 days after the first initiation of belzutifan will be enrolled. Date of first administration of belzutifan will be defined as the index date for the patient. Patients will be treated per the approved product label. Baseline characteristics that are collected will include, but not be limited to, demographics, pre-existing conditions, baseline tumor characteristics, prior oncologic/VHL therapies and medications. Data reported on the index date or subsequent follow-up visits per the local standard of care will be captured by the site in case report forms (CRFs) using an electronic data capture (EDC) system (see Section 7.6).

Patients will be followed from enrollment and treatment until the end of observation, defined as the earliest of withdrawal of consent, loss to follow-up, death, or until the end of the study. The planned minimum follow-up for each patient will be 3 years, noting that with a median duration of treatment follow-up of 2.4 years in the pivotal trial (MK-6482-004)[2], the majority of surgeries and reports of disease progression occurred within ~3 years of treatment, and the highest exposure-adjusted event rate occurred within 3 months of treatment. The non-interventional study duration considers the feasibility of running a long-term prospective observational cohort study while maintaining scientifically robust assessments. With a planned enrollment of patients within 2-3 years, the planned maximum follow-up for patients in the registry will be up to 5-6 years.

Up to 100 patients with VHL disease-associated RCC, CNS hemangioblastoma or pNET will be enrolled in the registry. This includes approximately 40 patients with VHL disease-associated RCC and approximately 40 patients with VHL disease-associated CNS

[2] 15-Jul-2021 database lock

hemangioblastoma that require treatment per investigator's judgment for the primary effectiveness analysis. Minimal attrition is expected during the duration of the study as most patients will likely remain under the care of the treating physician, as observed for patients in the MK-6482-004 clinical trial (~90% of participants still on study with a median duration of ~ 3 years) given that these sites provide specialized care for patients with VHL disease. Enrollment will be closely monitored during the enrollment period and enrollment of patients with each VHL disease-associated tumor type (RCC, CNS hemangioblastoma) will be stopped once the target sample size for that tumor type is reached with overall recruitment into the registry stopped once the sample size requirement for both tumor types is met. As one patient can have both RCC and CNS hemangioblastoma requiring treatment, each would contribute to the required sample size for that tumor type. If this were to occur, it would result in less than 80 patients included in the effectiveness analysis. All eligible patients receiving belzutifan treatment (including those patients with VHL disease-associated pNET) will be included in the safety analysis.

Effectiveness analyses will be restricted to patients with VHL disease-associated RCC and/or VHL disease-associated CNS hemangioblastoma given these are the most common clinical manifestations and are associated with the greatest morbidity and mortality. All patients enrolled in the registry will be included in the safety analysis.

7.2 Setting

This prospective observational cohort study will be conducted at participating clinical sites within the US. Potential patients at participating clinical sites will be approached about study participation once the treatment decision with belzutifan is made by the treating physician. Patients who fail Screening may be rescreened for eligibility after consultation between the investigator and the Sponsor.

7.2.1 Inclusion Criteria

Patients will be included if they meet the following criteria at the index date[3]:

1. ≥18 years of age.
2. Diagnosed with VHL disease based on a germline test or clinical diagnosis.
3. A decision has been made by the treating physician (at his/her discretion) to initiate the first belzutifan treatment (i.e., belzutifan 'new users'), within the prescribing conditions of the approved product label.
4. Signed informed consent prior to or within 30 days after the first initiation of belzutifan.

[3] index date for the patient is defined as the date of first administration of belzutifan

7.2.2 Exclusion Criteria

1. Anti-cancer systemic therapy within 2 weeks prior to the index date.
2. Unable to consent to participate in the study.
3. History of VHL disease-related metastasis or advanced cancer.

7.3 Variables

Variables (exposures, outcomes, and other study variables) are defined in this section. See Section 7.4.1 for data collection timing.

7.3.1 Exposure

Treatment initiation and subsequent dose modification will be at the discretion of the treating physician. Exposure will be documented from the date the patient received a first dose of belzutifan (index date).

Primary exposure definition: Patients included in this registry will be considered exposed to belzutifan if they receive at least one dose. Participants will be followed until the end of observation, defined as the earliest of withdrawal of consent, loss to follow-up, death, or until the end of the study.

For the analysis of safety, patients will be considered as treated for up to 90 days after discontinuation of therapy or 30 days after a treatment switch.

Data captured on belzutifan treatment exposure, e.g.,:

- Start date, starting dose, duration of therapy
- As applicable, treatment interruption, reason for interruption, and date that drug was resumed
- As applicable, treatment discontinuation and reason for discontinuation
- As applicable, dose reduction and reason for dose reduction

7.3.2 Outcomes

The primary effectiveness outcome is the proportion of patients who undergo surgery or other tumor reductive procedure. Reason for surgery and tumor characteristics preceding surgery will also be collected.

The secondary effectiveness outcomes include:

1. Metastatic disease (RCC only)

2. Treatment patterns (e.g., duration of use, proportion of patients who interrupt, reasons for interruption) will be evaluated using data captured on belzutifan treatment exposure.
3. Occurrence of new VHL disease-associated RCC, CNS hemangioblastoma, pNET or other VHL disease-associated tumor type (pheochromocytoma, paraganglioma, retinal hemangioblastoma, endolymphatic sac tumor)

During follow-up, data on all new tumor types and number of lesions will be collected and all VHL disease-associated procedures, anti-cancer medications, and concomitant medications will be collected. If available, best response to treatment per local radiology assessment for primary tumors will be also captured at the time of belzutifan discontinuation.

Safety outcomes will include SAEs (including fatal outcome) as well as the nature of these events.

Any herein described health outcomes, collected per the protocol, will be summarized as part of any interim analysis (if required) and in the final study report in addition to being reported in real-time as individual adverse events (AEs)/product quality complaints (PQCs) if the criteria in Section 9 are met. Refer to Section 9 for AE reporting requirements and procedures.

7.3.3 Other Study Variables

Patients' demographics, including:

1. Age (at index date)
2. Sex
3. Race and ethnicity
4. Height and weight
5. Country of residence

Clinical characteristics will include general medical history, history of VHL diagnosis, primary VHL disease-associated tumor(s), prior oncologic treatment, and other baseline measures. Specifically, the following measures will be collected:

General medical history, including:

1. Family history of VHL disease
2. History of cancer, cancer type, metastasis

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

3. Comorbidities (e.g., diabetes, hypertension, anemia, pulmonary disease, history of heart failure, history of coronary artery disease)
4. Concomitant medications

History of VHL diagnosis, including:

1. Age at VHL diagnosis
2. Genetic confirmation of VHL diagnosis
3. Clinical confirmation of VHL diagnosis
4. VHL mutation variant (amplification/gain, deletion, duplication, fusion, indel, partial deletion, rearrangement/translocation, single nucleotide variant, small insertion)

Information on VHL disease-associated tumor(s) at index date, including:

1. Primary tumor type(s) requiring belzutifan treatment (RCC, CNS hemangioblastoma, pNET). In the data entry guidelines, the physician will be instructed to document if the patient is being treated for a single VHL tumor type (e.g. RCC) or multiple VHL tumor types (e.g. RCC and CNS hemangioblastoma).

For RCC, CNS hemangioblastoma, and/or pNET

2. Date of tumor diagnosis
3. Stage of primary tumor(s) (T, N, M staging, defined by Staging Classification System (American Joint Committee on Cancer [AJCC])
4. Grade of primary tumor(s), if available (e.g., RCC, pNET)
5. Location (i.e., RCC: left, right; CNS hemangioblastoma: cerebellum, spine, other; pNET: head, body/tail)
6. Number of tumors
7. Longest diameter
8. Presence of other VHL disease-associated tumors (pheochromocytoma, paraganglioma, retinal hemangioblastoma, endolymphatic sac tumor) and number of lesions

Prior oncologic treatment, including:

1. Systemic therapy

2. Surgery for primary VHL disease-associated tumor(s) (partial nephrectomy, nephrectomy, craniotomy, partial pancreatectomy, pancreatectomy, other [specify])
3. Procedures for reduction of primary VHL disease-associated tumors (radiofrequency ablations, laser ablations, cryotherapy, cryoablations, radiation therapy, other [specify])
4. Other VHL related surgeries

Other baseline and follow-up measures:

1. Hemoglobin
2. Oxygen saturation percentage by pulse oximetry
3. Blood pressure
4. Behavioral risk factors (alcohol use [current, recent, abstain], smoking habits [current, recent, former]) (baseline only)
5. Estimated glomerular filtration rate (baseline only, RCC patients)

The data collected on these pre-defined events will include as much detail as is available within each patient's record, including but not limited to histopathologic results, and relevant laboratory and imaging results.

7.4 Data Sources

The main source of clinical and patient data will be the patients' medical record. Baseline characteristics (outlined in Section 7.3) will be extracted by the investigator from the medical records to the extent possible and recorded in the study CRFs. Data reported on the index date or subsequent follow-up visits will be captured by the site in CRFs.

Patients will be enrolled in the study at the location where they receive medical care for VHL. Baseline medical information and history will be abstracted at study entry and follow-up data collection will be conducted every 6 months throughout the study period. Data will be recorded in the EDC system by personnel at each study site using standardized approaches. All variables will be collected, as available, from the patient's medical records. As this is a non-interventional study, there are no mandatory requirements or collection timepoints for variables. The collected data will be available in the medical records as part of normal clinical practices, and all patient visits will be conducted according to the treatment physician's normal clinical practice. Thus, this study does not include mandatory visits, tests, or assessments, if data are not available in the patient's medical records, it will not be solicited. At the time of study start at each site, study personnel will provide general training on the expectations for data entry and sites are provided in the data entry guidance which will be used to guide medical chart abstractions and CRF completion.

7.4.1 Study Procedures

Study procedures to be performed at each visit are provided in Table 1.

Table 1 Data Collection Timing

Data collection	Index date[a] /enrollment visit	Routine follow-up visits[b] during the treatment
Informed consent	X[c]	
Inclusion/exclusion criteria	X	
Demographics	X	
Behavioral risk factors (alcohol, smoking)	X	
Medical history and comorbidities	X	
Concomitant medications	X	X
Disease/tumor characteristics	X	X
Prior anticancer treatment(s) (medications and procedures)	X	
Belzutifan treatment administration	X[a]	X
Hemoglobin	X	X
Oxygen saturation by pulse oximetry	X	X
Blood pressure	X	X
Estimated glomerula filtration rate (RCC patients only)	X	
Serious adverse events	X	X
Subsequent anticancer treatment(s) (medications or procedures)		X
End of observation/patient status (e.g., death, loss to follow-up, withdrawal of consent)		X

IEC=independent ethics committee; IRB=institutional review board; RCC=renal cell carcinoma

[a] Date of first administration of belzutifan will be defined as the index date for the patient. The index date is the baseline date for data collection during belzutifan treatment exposure for patients who consent to participate in the study. Signed informed consent must be obtained prior to or within 30 days after the first initiation of belzutifan.

[b] Clinic visits and data collected will be per the local standard of care, and is not dictated per protocol (only secondary data that was collected as part of usual care, for a purpose other than the study, will be used). The investigator will not be requested to undertake any assessment that they would not carry out in their normal practice.

[c] Age (in years) and sex for patients who were approached but who do not consent to participate in the study and reason(s) for not participating may be collected if agreed by IRBs/IECs.

7.5 Study Size

The study is descriptive, and there is no hypothesis testing. Up to 100 patients with VHL disease-associated RCC, CNS hemangioblastoma or pNET will be enrolled in the registry.

The target sample size for the primary effectiveness analysis includes approximately 40 eligible patients with VHL disease-associated RCC and approximately 40 patients with VHL disease-associated CNS hemangioblastoma requiring treatment. Enrollment will be closely monitored during the enrollment period and enrollment of patients with each VHL disease-associated tumor type (RCC and CNS hemangioblastoma) will be stopped once the target sample size for that tumor type is reached with overall recruitment into the registry stopped once the sample size requirement for both tumor types is met. Given the frequency of tumor reductive procedures in MK-6482-004 (8% of RCC patients and 6% of CNS hemangioblastoma patients, with surgery or locally directed therapy during a median follow-up of ~3 years)[4], this target sample size provides greater than 90% probability of observing at least one RCC procedure or one CNS procedure during follow-up.

A target sample of 40 RCC patients in the registry, offers reasonable statistical precision for estimating the true population estimate with an upper limit of the 95% confidence bound below the point estimate of 29% of patients in a separate VHL disease-associated RCC natural history study[5] having at least one tumor reductive procedure within 2 years of follow-up (Table 2). There is limited published data on the natural history of patients with VHL disease-associated CNS hemangioblastoma.

[4] based on 01-Apr-2022 cutoff (preliminary analysis)

[5] unpublished data from MSD study (EP05047.00)

Table 2 95% CI for the Cumulative Incidence of Health Outcome of Interest (Exact Confidence Interval; Clopper-Pearson Method; PASS 2021)

Assumed incidence for RCC surgery and/or locally directed therapy	**40 patients**	
	LL	UL
4%	0.3%	15.5%
6%	1.0%	18.3%
8%	1.8%	21.1%
10%	2.8%	23.7%

CI=confidence interval, LL=lower limit, UL=upper limit, PASS=Power Analysis & Sample Size, RCC=renal cell carcinoma

As one patient can have both VHL disease-associated RCC and CNS hemangioblastoma requiring treatment, each would contribute to the required sample size for that tumor type. If this were to occur, it would result in less than 80 patients included in the effectiveness analysis.

All patients treated with belzutifan will be included in the safety analysis.

7.6 Data Management

A data management plan specifying all functions, procedures, and specifications for data collection, retrieval, cleaning, and validation will be created before data collection begins. The study and data management team for the registry will follow standard operating procedures that define the processes and staff responsibilities for the collection, cleaning, control, and archiving of data entered in the data management system.

Data collection:

Data reported on the index date or subsequent follow-up visits will be captured by the site in CRFs with an EDC system. The EDC and electronic CRFs will be designed with structured and scientific and medical input from a multifunctional team including a medical monitor, epidemiologist, observational research and data management experts, as well as, statisticians. Baseline medical information and history will be abstracted by sites at study entry, and follow-up data collection will be conducted every 6 months throughout the study period. Data will be recorded in the electronic CRFs by personnel at each study site using standardized approaches.

Prior to deployment of the study-specific EDC database, user acceptance testing will be performed. All reported data from sites participating in the study will be entered via a secure web-based EDC study database. Site personnel will be provided with secure usernames and passwords to enter study data into the EDC system. All electronic CRFs should be

completed by designated, trained personnel or the study coordinator, as appropriate. The electronic CRF should be reviewed, electronically signed, and dated by the investigator. All changes or corrections to the electronic CRFs will be documented in an audit trail and an adequate explanation will be required. All participating sites will only have access to the data entered by the individual site on their own enrolled patients through the EDC system.

Data cleaning and quality assurance:

High data quality standards will be maintained, with processes and procedures utilized to ensure that the data are as clean and accurate as possible when presented for analysis. To ensure quality of the data entered, two documents will be developed and included a part of the study documentation: a data dictionary and rules for data validation. Data quality will be enhanced through a series of programmed data quality checks in the electronic CRFs that automatically detect anomalous data and provide immediate feedback if critical data are missing, out-of-range, illogical or potentially erroneous. Queries are built to automatically run on the data that is stored in the EDC and will run on a regular cadence established between the MAH and the contract research organization. Other procedures are included in the EDC to ensure quality of the data that is entered and stored including automated queries for data cleaning. Regular query reports will be run allowing for the reconciliation of any inconsistencies or errors that are found during these processes. Standardized coding will be used for medical terms using the latest versions of MedDRA and WhoDrug dictionaries. All data will be stored on the secure RAVE cloud system or servers. Concurrent manual data review will be performed by study monitors based on parameters dictated by the plan. All modifications to the data will be recorded.

To ensure quality of the data entered in the system, structured general training on the protocol, electronic CRF and EDC will be provided to the study sites. In addition, sites will be given electronic data entry guidance on how to enter data and the expectations for which elements should be entered from the medical record. The electronic CRF data entry guidance will be available in both PDF and embedded within the EDC for sites to use as a guide when entering data to ensure all protocol required elements are captured if they are available. Study personnel will be provided reminders to the sites of data entry deadlines for each study participant so that data is entered into the electronic CRF in a timely manner.

For observational studies, it is accepted that data could be missing or incomplete per the physician records. Incomplete and missing electronic CRF data will be flagged and collected as part of ongoing data quality monitoring in the study. Where information is not available, trained personnel or the study coordinator who are completing the electronic CRFs will be able to click a checkbox which records these data as ‘Not Available’. Clicking this checkbox will lock all related fields in the form, thus reducing the probability of missing queries. Incomplete and missing electronic CRF data not related to critical data items will be flagged as non-critical or queried as ‘Not Available’ or ‘Unknown’ in the electronic CRF.

Patient-level data for all patients enrolled in the study will be provided proactively by participating sites and will be anonymized. During the study, the MAH or designee may make site visits to review protocol compliance, compare electronic CRFs and individual patient's medical records to ensure that the study is being conducted according to pertinent regulatory requirements. Checking of the electronic CRFs for completeness and clarity, and cross-checking with source documents, may be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs/ IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out given due consideration to data protection and medical confidentiality.

The principal investigator (PI) at each study site will be responsible for maintaining a delegation log. Only those who have been trained on the protocol, assigned as eligible to enter data by the PI, and those that have completed the electronic CRF/EDC training will have access and ability to enter data. No study members will be able to access the EDC without proper system training. Training will be performed at the site initiation visit, when a new member joins the study team, and when retraining is necessary due to a quality concern. A data entry coordinator will review the medical record and enter data according to the electronic CRF completion guidelines that are provided to the site.

Archiving:

Data archiving and retention will be in accordance with Article 12.2 of the implementation regulations (EU/520/2012) from the EU. Pharmacovigilance data and documents relating to individual authorized medicinal products will be retained if the product is authorized and for at least 10 years after the marketing authorization has ceased. However, the documents will be retained for a longer period where MAH, EU, or national law require.

7.7 Data Analysis

The information provided in this section may be subject to changes that will be indicated in the final statistical analysis plan (SAP) of this study. The SAP will be developed as a separate document and approved prior to database lock, containing a description of the planned statistical analysis in detail with tables, figures and listings (TFLs) templates.

7.7.1 General Consideration

All statistical analyses will be performed using Statistical Analysis System® (Cary, North Carolina version 9.4 or higher) unless otherwise stated. No formal statistical hypothesis testing will be performed, and all the analyses will be primarily descriptive in nature. When appropriate, and unless otherwise specified, 95% confidence intervals (CIs) will be displayed.

A 95% exact binomial CI (based on Clopper and Pearson method) will be calculated for proportion outcomes (e.g., primary outcome proportion of patients who undergo surgery or locally directed therapy).

Descriptive statistics will include the number of available data, number of missing data and the following:

- Mean, standard deviation (SD), minimum, median, maximum, first and third quartiles and 95% CIs for means/medians.
- Counts and percentages of each category for categorical variables with 95% CIs.

Percentages will be based on the number of non-missing observations.

Missing data will not be replaced. Imputation rules will be detailed in the SAP, as appropriate (e.g., for incomplete dates).

7.7.2 Analysis Populations

Effectiveness population: All patients with RCC and/or CNS hemangioblastoma meeting inclusion/exclusion criteria and receiving at least one dose of belzutifan.

Safety population: All patients treated with at least one dose of belzutifan.

As the approved indication statement for belzutifan may differ between countries included in the study, subgroup analyses may be performed for countries with similiar indication statements if sufficient sample size warrants.

7.7.2.1 Populations Analyzed

All effectiveness analyses will be performed on the effectiveness population. Safety analyses will be performed on the safety population.

7.7.2.2 Patient Allocation and Reasons for Exclusion from the Analyses

The rules for the allocation of patients to each of the analysis populations will be defined and documented during a data review meeting held prior to database lock.

7.7.3 Statistical and Analytical Methods

See Section 7.7.1 for general consideration.

7.7.3.1 Demographic and Other Baseline Characteristics

Demographic and clinicopathological characteristics will be tabulated and reported using mean, SD, median, minimum, and maximum for continuous variables; numbers and percentages for each category will be provided for categorical variables.

7.7.3.2 Patient Disposition and Withdrawals

The number and percentages of patients in each population will be tabulated. The reasons for patient exclusions from each of the populations will also be tabulated. In addition, the number of patients who were treated and who died will be tabulated. Primary reasons for withdrawal from the study treatment will be tabulated.

Additionally, age (in years) and sex for patients approached but who do not consent to participate in the study and reason(s) for not participating may be collected and summarized separately if agreed by institutional review boards (IRBs)/independent ethics committee (IECs).

7.7.4 Primary Effectiveness Analysis

To analyze the primary effectiveness objective, number and the proportion of patients who undergo surgery or other tumor reductive procedures will be summarized descriptively along with associated 95% CI separately for VHL disease-associated RCC and VHL disease-associated CNS hemangioblastoma.

To contextualize and benchmark results from this single-arm post-authorization study of belzutifan, data on the number and proportion of patients who undergo surgery and/or locally directed therapy in the absence of systemic therapy will be used. This will include, but may not be limited to, estimates and findings from a recently completed natural history study (EP05047.001) of VHL RCC patients collected during routine clinical surveillance at the US National Cancer Institute, and results of a second natural history study planned for patients with VHL disease-associated CNS hemangioblastoma.

Further details will be included in the SAP.

7.7.5 Secondary Effectiveness Analysis

The analysis of secondary effectiveness objectives will be presented as follows:

Number and proportion of patients who develop metastatic disease (RCC only), number and proportion of patients with occurrence of new VHL disease-associated RCC, CNS hemangioblastoma, or other VHL disease-associated tumor type, and treatment patterns will be summarized descriptively using frequency of counts or descriptive statistics such as n, mean, 95% CI of the mean, SD, median, minimum, maximum separately for VHL disease-associated RCC and VHL disease-associated CNS hemangioblastoma.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

7.7.6 Secondary Safety Analysis

Safety outcomes will include the proportion of patients with SAEs (including with fatal outcome) as well as the nature of SAEs as classified by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and system organ class (SOC). For the analysis of safety, patients will be considered as treated for up to 90 days after discontinuation of therapy or 30 days after a treatment switch.

An overall summary table of all SAEs will be presented with the number and proportion of patients and the number of events, number and proportion of SAEs with fatal outcome, and number and proportion of SAEs that led to study treatment discontinuation. Additionally, the SAEs will be summarized by number and proportion of SAEs by PT and SOC.

Listings of all reportable AEs (including special situations), and product quality complaints (PQCs) reported in accordance with pharmacovigilance requirements (Section 9) will also be included in the final study report.

7.8 Quality Control

By signing this protocol, all parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP)[9], and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g., GPP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study patients and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

7.9 Limitations of the Research Methods

Limitations of this prospective observational cohort study and how they will be addressed are summarized in Table 3.

As this is a real-world study with patients treated under routine clinical practice, patients may be lost to follow-up. Those patients who are lost to follow-up may have different clinical and demographic characteristics than those who remain in the study leading to bias of the study results.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

Table 3 Limitations of the Research Methods

Potential Limitation	Description	Mitigation
Enrollment uncertainty	VHL is a rare disease with an evolving treatment landscape which may pose challenges in enrollment.	Feasibility assessments of sites will be performed to identify those sites with adequate projected patient counts. Enrollment will be closely monitored and extended to additional sites and countries, as required and feasible.
Selection bias	External validity: Patients who enroll in this study may not be generally representative of the overall VHL population (e.g., patients prescribed belzutifan may have different disease prognosis) Internal validity: As this is a real-world study with patients treated under routine clinical practice, patients may be lost to follow-up. Those patients who are lost to follow-up may have different clinical and demographic characteristics than those who remain in the study leading to bias of the study results.	Patients will be enrolled from different sites. An evaluation of patient clinical and demographic characteristics will inform the assessment of the extent of selection bias.
Unmeasured risk factors for study outcomes	There may be unmeasured clinical or demographic characteristics that are related to the study outcomes impacting the interpretation of the effectiveness or safety outcomes.	To the extent possible, known clinical and demographic factors related to the study outcome will be collected from the patients' medical record. If a clinically meaningful unmeasured factor is identified, the feasibility of sensitivity analyses to determine the impact will be explored.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

Potential Limitation	Description	Mitigation
Lack of internal comparator	The study will enroll only patients receiving belzutifan, leading to the inability to place into context the outcome assessments. Comparison of the efficacy of belzutifan with other treatment modalities will not be performed as differences in measured and unmeasured prognostic variables between the treatment groups would likely render any comparison of treatment effectiveness or safety invalid in a non-randomized setting.	External information from other studies in this population (e.g., natural history study of VHL) will be used to provide context around study estimates and findings.
Generalizable results	Given differences in the indication statement, results may not be generalizable.	As the approved indication statement for belzutifan may differ between countries included in the study, subgroup analyses will be performed, as relevant, for countries with different indication statements.
Information bias	Study assessments will be obtained through the patients' medical record and may not be verified against a gold standard leading to misclassification.	The data collected will include as much detail as is available within each patient's record, including but not limited, to histopathologic results, and relevant laboratory and imaging results.

VHL=Von Hippel-Lindau

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

8 PROTECTION OF HUMAN SUBJECTS

8.1 Informed Consent

Consent must be documented by the patient's dated signature or by the patient's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the patient before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the patient must receive the IRB/IEC's approval/favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the patient's dated signature or by the patient's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

Additionally, age (in years) and sex for patients approached but who do not consent to participate in the study and reason(s) for not participating may be collected if agreed by IRBs/IECs.

8.1.1 Consent and Collection of Specimens for Future Biomedical Research

Not applicable; the study does not involve specimen collection.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse Event (AE) and Product Quality Complaint (PQC) Reporting Language for Non-Interventional Study Protocols

Introduction

This is a non-interventional study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

9.1 Adverse Event and Product Quality Complaint Reporting

9.1.1 Investigator Responsibility

Although AEs and PQCs are not actively solicited in this study, there are certain circumstances in which individual AEs and/or PQCs will be reported. For example, during review of medical records or physicians notes (paper or electronic), to collect data as required by the protocol, if a notation of an AE* or PQC to belzutifan or any other Sponsor products as identified, the AE/PQC must be reported according to Table 4. If any health outcomes are described in Section 7.3.2, they must be assessed for AE reportability according to Table 4 (refer to Section 7.3.2 for more information).

*For the purposes of this protocol, the term “AE” for reporting outlined in Table 4 collectively refers to the following reportable events (refer to Section 9.2 for definitions):

- Serious adverse reactions (SARs), including death
- Non-serious adverse reactions (NSARs)
- Special situations

AEs, PQCs, and AEs that occur in combination with PQCs, or spontaneously reported events, should all be captured using the AE/PQC report form for each patient and reported according to Table 4.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

Table 4 AE and PQC Reporting Timeframes and Process for Investigators and Suppliers

AEs and PQCs	**Investigator Timeframes** **Investigator to Supplier [1], [2]**	**Supplier Timeframes** **Supplier to Sponsor [3]**
SAR Serious Special Situations, regardless of causality	24 hours from receipt	1 BD/3 CD from time of receipt from investigator
NSAR Non-serious Special Situation, regardless of causality	10 CD from receipt	10 CD from time of receipt from investigator
PQC with or without an AE (SAR/NSAR/Special situation)	24 hours from receipt	24 hours from time of receipt from investigator
Follow-up to any AE/PQC-submit using above timeframes		
BD-Business Day; CD-Calendar Day		
Non-Sponsor Products: If the investigator elects to submit AEs/PQCs for **non-Sponsor products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations.		
[1] Investigator to Supplier: AEs and PQCs for Sponsor study product and other Sponsor products are submitted to Supplier via fax or secure email. **[2]** Supplier enters AEs for Sponsor study product into study database (or equivalent repository) for tabulation in study report. **[3] Supplier to Sponsor:** Supplier submits AEs and PQCs for Sponsor study product and *other* Sponsor products to Sponsor for reporting to worldwide regulatory agencies as appropriate.		
Submitting AEs and PQCs to Local Designated Point of Contact (DPOC): All AEs and PQCs must be submitted to Local DPOC mailbox Fax in English using the AE/PQC reporting form: **For United States** Fax PPD preferred or secure email dpoc.usa@merck.com **For United Kingdom** Fax PPD preferred or secure email dpoc.uk@msd.com **For Canada** Fax PPD or PPD preferred or secure email dpoc_canada@merck.com		

9.1.2 Study Report

The final study report, and any planned interim analysis, will include a summary of all reported AEs and special situations collected for belzutifan and will be provided to regulatory agencies by the Sponsor as required.

9.1.3 Periodic Safety Update Reports

Any relevant safety information will be summarized and the Sponsor will include in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Report (DSUR) if required.

9.2 Definitions

9.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation patient administered Sponsor's product and which does not necessarily have to have a causal relationship with this

product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an AE.

9.2.2 Adverse Reaction (AR), also Referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the AE is at least a reasonable possibility.

9.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An AE or AR that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

9.2.4 Non-serious Adverse Reaction (NSAR)

An AR that does not meet any of the seriousness criteria in Section 9.2.3.

9.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent
- Unexpected therapeutic benefit/effect

All reports of lack of efficacy occurring in Canada will be assessed by the Sponsor to identify cases of unusual failure in efficacy for new drugs, and be reported accordingly to Health

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

Canada as per Canadian regulations. Records of the annual summary reports and AE/adverse drug events case reports are retained by Sponsor for at least a minimum of 25 years or longer after the date on which they were created, or source document received.

9.2.6 Product Quality Complaint (PQC)

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

9.2.7 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

9.2.8 Sponsor's Product

Sponsor’s product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

9.2.9 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the AE. Causality must be recorded on the AE form by the investigator for each reported event in relationship to a Sponsor's product.

Secondary Data Collection

Only AEs with an explicit and definitive notation (by a healthcare provider) of a causal relationship with a product in the medical records or other secondary data being reviewed should be reported as NSAR/SARs. During review of secondary data, causality should never be assigned retrospectively.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

9.3 AE/PQC Reconciliation

Reconciliation will be performed between the safety database and study data to ensure all reportable AEs and PQCs were reported and received. Starting from when the first patient is enrolled through the end of data collection, all AEs and PQCs will be reconciled on a periodic basis.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Progress and final reports will be submitted to regulatory authorities as required.

There are plans to disseminate the results of this study in peer-reviewed journals and at scientific conferences. Authorship will follow guidelines established by the International Committee of Medical Journal Editors (http://www.icjme.org/), and all publications will follow Good Publication Practices and other relevant MSD internal SOPs.

The Risk Management Subteam (RMST) Lead/Clinical Safety Risk Management (CSRM) Physician will be notified if any safety data are generated in the final study report or any interim report. The safety and conclusion sections of the final study report or interim report must be reviewed by the RMST Lead/CSRM Physician prior to finalization of the report. The review by the CSRM Physician must occur prior to any release of results into the public domain in the form of abstracts, posters, presentations, or manuscripts.

11 REFERENCES

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PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

12 ANNEXES

Annex 1 List of Stand-Alone Documents

No.	Document Reference No	Date	Title
1.	TBD	TBD	List of investigational sites will be available upon request

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

Annex 2 Administrative and Regulatory Details

Confidentiality:

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence if applicable such information will be divulged to IRB, IEC or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Patient Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. If study documents will be photocopied during the process of verifying worksheet/case report form information, the patient will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel (if applicable), may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- Name, address, telephone number and email address
- Hospital or clinic address and telephone number
- Curriculum vitae or other summary of qualifications and credentials
- Other professional documentation

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. By signing this protocol, the investigator expressly consents to these uses and disclosures. Additionally,

the investigator's name and business contact information may be included when reporting certain SAEs to regulatory agencies or to other investigators. The investigator is hereby notified that the collection, processing and sharing of their personal data with respect to AE reports to the Sponsor and regulatory agencies occurs on the basis of performance of a legal obligation, and the investigator expressly consents to these uses and disclosures when reporting such events to other investigators.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

Administrative:

Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US FDA Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a Financial Disclosure Form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the US for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GPP and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

The investigator also agrees to allow monitoring, audits, IRB/IEC review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from patients, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

The investigator shall prepare and maintain complete and accurate study documentation in compliance with GPP, standards and applicable federal, state and local laws, rules and regulations; and, for each patient participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/CRF.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/CRF, advertising for patient participation, AE reports, patient source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or patient files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multicenter study (including multinational). When more than one study site is open in an EU country, MSD, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of patient cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDA Modernization Act (FDAMA) and the FDA Amendments Act (FDAAA), the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, such as European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAMA/FDAAA mandated studies. Information posted will allow patients to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this study or its results to the Clinical Trials Data Bank.

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

13 SIGNATURES

13.1 Sponsor's Representative

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

13 SIGNATURES

13.1 Sponsor's Representative

PRINTED NAME	PPD PhD, MS
TITLE	Sr. Principal Scientist, Epidemiology
SIGNATURE	PPD
DATE SIGNED	December 01, 2023

28-NOV-2023 PASS SDC 12

28-NOV-2023 PASS SDC 12

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

13.2 Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other project plans and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and the Use and Disclosure of Personal Data notice provided to me, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

13.3 Supplier

1

PRODUCT: MK-6482	PROTOCOL/AMENDMENT VERSION NO.: 6482-026/3.0
REVOPS ID NO: NIS102327 EPIDEMIOLOGY NO. (PE STUDIES ONLY): EP05047.006	CORE DRC APPROVAL DATE: 28-NOV-2023 CRC PRC APPROVAL DATE: N/A

1.1 Supplier

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and in order to perform any agreement between myself and the Sponsor, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	PPD MPH PharmD PhD
TITLE	PPD Epidemiology
SIGNATURE	PPD
DATE SIGNED	01DEC23

28-NOV-2023 PASS SDC 12