PASS INFORMATION

Belzutifan special drug use results survey in radically unresectable or metastatic renal cell carcinoma: a post-authorization safety study (PASS)

Product Name:	WELIREG® 40mg
Compound number:	MK-6482
Name of Marketing Authorization Holder or Applicant:	MSD K.K. （hereafter referred to as the Sponsor or MSD）
Protocol Number	6482-045
Version:	v1.0
Effective date:	15-JAN-2026

VERSION HISTORY

Version	Effective date	Changes	
0.1	17-NOV-2025	Initial	Not applicable
0.2	09-DEC-2025	Revision	Section 6.6: Clinical laboratory parameters updated to align with case report form (inclusion of prothrombin time as a test for hemorrhage). Correction of minor typographical, editorial, or formatting errors.
1.0	15-JAN-2026	Revision	Refinement of anticipated milestone achievement timing.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Not Applicable

LIST OF ABBREVIATIONS

ADI	Acceptable Daily Intake
ADR	Adverse Drug Reaction
AE	Adverse Event
APTT	Activated Partial Thromboplastin Time
BOR	Best Overall Response
CNS	Central Nervous System
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DSUR	Development Safety Update Report
EC	Ethics Committee
ECOG PS	Eastern Cooperative Oncology Group Performance Status
(e)CRF	Electric Case Report Form
EDC	Electronic Data Capture
ERC	Ethical Review Committee
GPP	Good Pharmacoepidemiology Practices
GPSP	Good Post-marketing Study Practices
GVP	Good Pharmacovigilance Practices
HA	Health Authority
Hb	Hemoglobin
HCP	Healthcare providers
IMDC	International Metastatic RCC Database Consortium
IRB	Institutional Review Board
JCOG	Japan Clinical Oncology Group
J-PSUR	Japanese Periodic Safety Update Report
J-RMP	Japan Risk Management Plan
KPS	Karnofsky Performance Score
MAH	Marketing authorization holder
MR	Medical Representative

MSD	Merck Sharp & Dohme
NCI	National Cancer Institute
NSADR	Non-Serious Adverse Drug Reaction
NSAE	Non-Serious Adverse Event
ORR	Objective Response Rate
PASS	Post-Authorization Safety Studies
PD	Progressive Disease
PMDA	Pharmaceuticals and Medical Devices Agency
PQC	Product quality complaint
PR	Partial Response
PRS	Programming requirements and specification document
PT	Preferred Term
PT	Prothrombin Time
PT/INR	Prothrombin Time/International Normalized Ratio
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SADR	Serious Adverse Drug Reaction
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
SpO2	Saturation of Percutaneous Oxygen
VHL	Von Hippel-Lindau disease

LIST OF APPENDICES

The below are maintained separate from the protocol.

Appendix 1 Implementation Outline

Appendix 2 Registration form

Appendix 3 Case report form

1 RESPONSIBLE PARTIES

Responsible party	Role & Responsibility for this Post-authorization Safety Study (PASS)
MSD KK	Address: 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo Scope of work: Manage overall study operations, Coordinate with internal and external parties, Ensure regulatory compliance (e.g., GVP, GPSP), Oversight of Data collection and quality, Oversight of outsourced work, Monitoring of study progress, Report preparation, Communication with Health Authority (HA) and submission of required documents
PPD	Scope of work outsourced: Development, operation and data management of EDC system, subjects' registration, data management, tabulation analysis, writing, Contract proceedings, Progress management of survey at the sites, Monitoring, etc.
PPD .	PPD Scope of work outsourced：Support for site contracting.
PPD	Scope of work outsourced: The following Good Post-marketing Study Practice (GPSP) duties associated with this study. selection of the prospective institutions participating in the study and contract procedure in writing, progress management of the study at the institutions participating in the study.

2 STUDY SYNOPSIS

Title	Belzutifan special drug use results survey in radically unresectable or metastatic renal cell carcinoma: a post-authorization safety study (PASS)
Product information	Therapeutic Category Anticancer drug - Hypoxia-inducible factor 2α inhibitor Active substance belzutifan Brand name WELIREG® Tablets 40 mg
Milestones	Anticipated timeframes for the following major milestones are as follows: Study period MAR 2026 – FEB 2031 (60 months) Registration period APR 2026 – MAR 2029 (36 months) Registration may be discontinued when the target number of cases is reached. Data analysis start MAR 2031 Final report MAY 2032 (There are no planned interim reports.)
Rationale and background	The purpose of this PASS is to comprehensively collect and verify safety information under actual use conditions in domestic subjects based on Japan's GPSP regulations, and to conduct a descriptive investigation. This PASS is being conducted as an additional safety monitoring activity described in the Japanese risk management plan for belzutifan.

Safety Concerns as delineated in the J-RMP for this study	Important Identified Risks Anemia and hypoxia Important Potential Risks Hemorrhage and fractures Important Missing Information NA
Objective	Among Japanese subjects with radically unresectable or metastatic RCC treated with belzutifan in routine practice, Primary Objective 1) To monitor the risk of occurrence of hemorrhages and fractures during the administration of belzutifan in subjects with RCC. In doing so, we will observe the percentage of subjects occurring hemorrhage and fractures during the administration of belzutifan and contrasted the results obtained in this study with the percentage of subjects occurring the relevant AEs observed in the Everolimus group of the Study 005. Secondary Objective 1) The overall safety of belzutifan, including safety concerns in subjects with RCC 2) The effectiveness of belzutifan in subjects with RCC
Study design	Special Survey This study is a non-interventional, descriptive, longitudinal, multi-center collaborative survey.
Study subjects	Subjects in Japan with RCC (not Von Hippel-Lindau disease (VHL)-associated) who have received belzutifan in routine clinical practice for the first time as indicated by the current local label.
Planned subject number	403 subjects (safety analysis set)

Study method	The study will be conducted with the use of EDC system by means of a central registration method. At each site, subjects that meet the inclusion/exclusion criteria will be approached for informed consent. Subjects may be prospectively identified and registered/enrolled at the time of treatment initiation or retrospectively identified and registered/enrolled after treatment initiation but before the end of the registration period.
Endpoint and its measurement	Safety endpoints will include investigator reported adverse events, summarized by frequency and severity, and for secondary effectiveness endpoints, response to treatment by local investigator assessment.
Data Analysis	Study endpoints will be analyzed using descriptive statistical methods such as mean, standard deviation, median, interquartile range, and/or minimum/maximum/range for continuous variables. For any categorical variables, e.g., AE analysis, frequency and percentage will be reported. There is no hypothesis testing. To assess whether demographic and/or clinical characteristics impact safety endpoints, these characteristics will be analyzed using descriptive statistical methods and reported for all registered subjects, the safety evaluation group, and presence/absence of AEs/select protocol-specified AEs. Details of the statistical analysis will be specified separately in the statistical analysis plan.

3 MILESTONE

Milestone	Planned Date or Description
Study period	MAR 2026 to FEB 2031 (60 months)
Enrollment and follow-up period	APR 2026 to MAR 2029 (36 months) Registration may be discontinued when the target number of cases is reached. Subjects will be followed up to 12 months after treatment initiation.
J-PSUR	Safety information will be reviewed comprehensively at the time of J-PSUR reporting.
Data analysis start	MAR 2031
Final report submission to Japan PMDA	MAY 2032
Milestones for evaluation and reporting, and possible further measures based on the results of the study	Based on the results of this study, the Japanese risk management plan will be reviewed and a recommendation will be made as to whether or not changes are required.

4 RATIONALE AND BACKGROUND

The purpose of this Study is to collect/ascertain more completely the number of AEs in the local population, and describe the AEs in the local population according to the local regulation.

This study is conducted as part of the pharmacovigilance plan proposed by the Japanese Risk Management Plan (J-RMP) for belzutifan. The safety concerns as delineated in the J-RMP for this study are:

1) Important Identified Risks
   Anemia and hypoxia

2) Important Potential Risks
   Hemorrhage and fractures

3) Important Missing Information
   NA

5 OBJECTIVES

5.1 Primary Objective

1) To monitor the risk of occurrence of hemorrhages and fractures during the administration of belzutifan in subjects with RCC. In doing so, we will observe the percentage of subjects occurring hemorrhage and fractures during the administration of belzutifan, and contrasted the results obtained in this study with the percentage of subjects occurring the AEs observed in the everolimus group of the Study 005.

   To address the Primary Objective, the incidence of hemorrhage AEs and the incidence of fracture AEs, including all adverse events (AEs), adverse drug reactions (ADRs), grade 3-5 AEs, grade 3-5 ADRs, serious AEs (SAEs), and serious ADRs (SADRs) will be described.

5.2 Secondary Objectives

1) The overall safety of belzutifan, including safety concerns, in subjects with RCC

2) The effectiveness of belzutifan in subjects with RCC

To address the Secondary Objectives, the following points will be addressed:

a) To describe the patient demographic and baseline clinical characteristics in;

- In the registered subjects
- in the safety evaluation group
- by presence/absence of any AEs
- by presence/absence of hemorrhage
- by presence/absence of fracture
- by presence/absence of anemia
- by presence/absence of hypoxia.
- by presence/absence of intracranial lesions

b) To describe separately the incidence of a) anemia and b) hypoxia, the incidence of AEs including all AEs, ADRs, grade 3-5 AEs, grade 3-5 ADRs, SAEs and SADRs

c) To describe the proportion of subjects of intracranial hemorrhage AEs including all AEs, ADRs, grade 3-5 AEs, grade 3-5 ADRs, SAEs and SADRs with or without pre-existing intracranial lesions

d) To describe the overall incidence and outcomes of AEs, ADRs, grade 3-5 AEs, grade 3-5 ADRs, SAEs, SADRs, unexpected SAEs, and unexpected SADRs;

e) For hemorrhage AEs, fracture AEs, anemia AEs, hypoxia AEs, all AEs, All SAEs, All ADRs, all SADRs:

- To describe the proportion of subjects who interrupt drug due and the reasons for drug interruption;
- To describe the proportion of subjects who discontinue drug and the reasons for drug discontinuation;
- To describe the proportion of subjects with dose reduction and the reasons for dose reduction;

f) To describe a) objective response rate (ORR) and b) disease control rate (DCR) in subjects that receive the recommended dose.

6 STUDY METHOD

6.1 Study Design

This is a non-interventional, descriptive, longitudinal, multi-center collaborative study.

The study includes subjects in Japan with radically unresectable or metastatic renal cell carcinoma who have received belzutifan in routine clinical practice as indicated by the current local label. There is no comparator arm.

At each site, subjects that meet the inclusion/exclusion criteria will be approached for informed consent. Subjects may be prospectively identified and registered/enrolled at the time of treatment initiation or retrospectively identified and registered/enrolled after treatment initiation but before the end of the registration period.

Study-specific CRFs will be completed by investigator or healthcare practitioners and the investigator will submit using an electronic data capture (EDC) system. Patient and treatment data will be sourced from the patient's medical records.

In the registration form/CRF, the site will enter a unique number (patient identifier), which only the treating investigator and/or authorized personnel will be able to use to identify the patient. Common to all CRFs for the patient will be a case registration number, which will be used by the Sponsor to manage the cases.

6.2 Study Subjects

1) Inclusion criteria
   - Subject who is indicated according to the local label of belzutifan and decision to receive the product is made independent of this protocol
   - Subjects who are Japanese subjects with RCC, excluding those with Von Hippel-Lindau disease-associated RCC
   - Subject who is administered with belzutifan for the first time following its approval on 24-JUN-2025 for RCC as part of routine clinical practice

2) Exclusion criteria
   - Subject who has a known contraindication according to the local label of belzutifan
   - Subjects previously treated with belzutifan before 24-JUN-2025 are excluded from this survey, as are any subjects that receive belzutifan as part of a clinical trial
   - Subjects with Von Hippel-Lindau disease (VHL)-associated RCC

6.3 Planned Subject Number

A sample size of 403 subjects (safety analysis set) is planned to address the objectives of this Study.

This number of subjects was agreed upon with PMDA. This sample size was determined a priori and was not calculated as part of the development of this protocol.

Rationale

In the global Phase 3 clinical study in subjects with advanced RCC MK-6482-005/LITESPARK-005 (Study 005), The incidence of hemorrhage-related adverse events was 12.6% (47/372 subjects), with Grade 3 or higher being 3.8% (14/372 subjects). The incidence of fracture-related adverse events was 4.8% (18/372 subjects), with Grade 3 or higher being 2.2% (8/372 subjects).

To detect 11 or more subjects of Grade 3 or higher hemorrhage-related adverse events, which occurred at an incidence rate of 3.8% in Study 005, with a probability of over 90%, a sample size of 403 subjects is required. Assuming that the incidence of adverse events for the safety evaluation items after marketing is equivalent to that in the 005 trial and setting the number of subjects for safety analysis at 403 it is possible to collect 42 subjects with hemorrhage of which 11 subjects would be anticipated to be Grade 3 or higher; 14 subjects with fractures of which 5 subjects would be anticipated to be Grade 3 or higher; 325 subjects with anemia of which 119 subjects would be anticipated to be Grade 3 or higher; 49 subjects with hypoxia of which 35 subjects would be anticipated to be Grade 3 or higher, with 90% probability under actual usage conditions. Considering dropouts and loss to follow-up, it is thought that registering 410 subjects will ensure 403 subjects for safety analysis. By setting the number of subjects for safety analysis at 403 subjects, it is anticipated to detect the occurrence of hemorrhage, fractures, anemia, and hypoxia under routine clinical practice.

6.4 Planned Site

Site(s) will be evaluated and selected based on availability of sufficient target subject pool, appropriate resources such as facilities and staffs and/or experienced investigator to address the objectives of this Study. Details on the total number of planned sites and general types of institutions is as follows:

Number of planned site(s)	Approximately 150 sites
Target institute / department at site(s)	Urology and oncology departments at general hospitals/clinics in Japan that treat subjects with RCC

6.5 Study Method

Procedures and activities during this study are outlined in Table 1.

Table 1 Schedule of Activities

Timing of implementation / Item	Before the start of administration	Observation Period (Up to a Maximum of 12 Months)				Note
		During administration	At the end of administration	From the end of administration until 30 days after the end of administration	End of observation phase (12 months)	
Informed consent / Privacy statement	X					
Inclusion/Exclusion criteria review	X					
Subject characteristics and indication(s) for use	X					
Medical history and Concurrent condition	X					For liver dysfunction, The Child-Pugh classification (Table 2) is used. Points are assigned to each item, and the total score is classified based on Table 3.
Condition of RCC before belzutifan Administration	X					
Prior Treatment for RCC before belzutifan Administration	X					

Timing of implementation / Item	Before the start of administration	Observation Period (Up to a Maximum of 12 Months)				Note
		During administration	At the end of administration	From the end of administration until 30 days after the end of administration	End of observation phase (12 months)	
Treatment with belzutifan		X	X			
Concomitant medications/Concomitant therapies		X	X	X		Concomitant medications/ therapies for RCC used during belzutifan administration period, and AE/ prophylactic use during the administration period or within 30 days after discontinuation of belzutifan.

Timing of implementation / Item	Before the start of administration	Observation Period (Up to a Maximum of 12 Months)				Note
		During administration	At the end of administration	From the end of administration until 30 days after the end of administration	End of observation phase (12 months)	
Effectiveness		X	X	X	X	Effectiveness assessments will be conducted until disease progression, initiation of other anti-cancer therapies, death, or loss to follow-up, whichever occurs first. However , the maximum assessment period will not exceeding the observation period [12 months (52 weeks) from the first belzutifan treatment date].
Status on the date of last observation					X	At 12 months (52 weeks) from the start of belzutifan administration; however, in cases where death or lost to follow-up occurs within 12 months from the start of belzutifan administration, the date of confirmation of these events shall be considered.
Adverse Event		X	X	X		Refer to Table 4,Table 5 and Table 6 for supplementary notes related to AEs.

Timing of implementation / Item	Before the start of administration	Observation Period (Up to a Maximum of 12 Months)				Note
		During administration	At the end of administration	From the end of administration until 30 days after the end of administration	End of observation phase (12 months)	
Laboratory data/test	X	X	X	X		Laboratory test values and examinations related to AEs will be collected in this survey.

6.5.1 Contract with sites

Request for the study

The request will be made to the medical institutions with a history of prescribing belzutifan and otherwise meet the criteria for participation. The objective and design of the study will be explained to the investigator in charge of the study and/or other staff of the institutions by Medical Representative (hereinafter, MR).

Contract with the sites

If the medical institution or investigator agrees to participate in the study in response to the request, a contract will be made in writing with the head of the institution (hospital director, etc.) after following the necessary process of the medical institution (e.g., IRB approval).

Study period

The study period at each site will be the period set out in the contract, which includes the period of enrollment, treatment, follow-up and (e)CRF collection.

6.5.2 Informed Consent

According to Japanese law, obtaining consent for participation and obtaining approval from the IRB/EC is not mandatory. It is legally required to collect information and submit them to the PMDA (Pharmaceuticals and Medical Devices Agency) even for cases where consent has not been obtained. Therefore, we obtain consent for the publication of survey results at the time of informed consent. If consent for publication cannot be obtained, the case is excluded from publication.

1) The investigator / program coordinator in charge of the study will confirm eligibility and explain to the subject or his/her legally acceptable representative the objective of the study, the information to be collected through the study (including the information of the subject's drug treatment and test results, etc.) and the uses of the study results (including presentation at an academic conference, etc. and publication, etc. by the sponsor of the survey) and obtain the written consent for the publication of study results from the subject or his/her legally acceptable representative.
2) In obtaining the consent for the publication of study results, the signature and date must be obtained from the subject or his/her legally acceptable representative in the consent form along with the signature and date by the person who has explained the study.

3) The investigator in charge of the study will give the subject or his/her legally acceptable representative a copy of the signed and dated consent form under the above (2) before the subject registers in the study.
4) The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to publication. The communication of this information will be adequately documented.

6.5.3 Subject registration at the site

The investigator shall enter the required information (anonymized ID number[1], sex, target tumor type, the start date of belzutifan administration, etc.) into the registration form of the EDC system and submit the form for patients meeting the inclusion/exclusion criteria.

Subjects may be prospectively identified and registered/enrolled at the time of treatment initiation or retrospectively identified and registered/enrolled after treatment initiation but before the end of the registration period.

All subjects who meet the eligibility criteria for this study at contracted sites will be registered until notified by the sponsor that registration has been terminated. The registration will continue until the target number of subjects (n=410) has been reached.

6.5.4 Subject observation

The treatment period is defined as the period from the start date of belzutifan administration until the date of the last administration. The observation period is defined as 12 months (52 weeks) from the start date of the administration. Adverse events will be collected throughout the treatment period and for 30 days following discontinuation of belzutifan treatment. However, the total follow-up period will not exceed the observation period [1 year (52weeks) from the first belzutifan treatment date].

Rationale for the observation period

In the 005 study, the median time to the first occurrence of hemorrhage was 84 days (range: 2 to 728 days), and the median time to the first occurrence of fractures was 277.5 days (range: 5 to 639 days). Additionally, most of the adverse events considered for safety concerns in this survey occurred within three months of the start of administration. To confirm the occurrence status (incidence rate, severity, treatment details, etc.) of these events, a 12-month (52-week) observation period was set.

[1] Any number or symbol that allows the investigator to identify the patient (no patient information such as medical record number required)

6.5.5 Safety endpoints and effectiveness endpoints collection

The investigator / program coordinator at each site will monitor for the occurrence of any endpoints specified within this protocol through the on-site visit, scheduled contacts, e-mails, telephone calls, and/or review of the medical records during the treatment and observation periods.

6.5.6 Entry into the case report form and transmission

The investigator will document the information collected during the treatment and observation period in the (e)CRF.

For the subjects for whom follow-up becomes difficult (e.g., transfer to other hospital, etc.), the information which can be collected until the last observation will be documented in the electronic (e)CRF.

6.5.7 Confirmed all subject at contracted site

To ensure the completeness of subject extraction at the site, after the end of the case registration period, each investigator will confirm that the studied cases are all cases in which belzutifan was administered at their own site / department using the “All Case Confirmation Form”.

6.5.8 Confirmation of inconsistency to the investigator in charge (correction request) of the registration form and the case report form and follow-up survey

1) At the time of receipt of the registration form and the surveillance form, post marketing surveillance MSD management department will verify the entered contents; if a correction request is necessary or resurvey is necessary, they will ask the investigator in charge of the surveillance to add, correct, and confirm the information.

2) Pregnant and lactating subjects must be followed up to the extent possible with the cooperation of the investigator in charge of the study and the subjects.

3) In addition to item 2) above, if an event that MSD is monitoring for information (i.e., hypoxemia etc) is reported, we will conduct follow-up investigations in collaboration with the investigator and the subjects whenever possible.

6.5.9 Management of progress of the study

1) Post marketing surveillance MSD management department must make efforts to promote the study in a systematic manner, utilizing the management schedule that describes the progress of the study.

2) The Chief administrator of Post Marketing studies of MSD will confirm whether the study is progressing smoothly and give appropriate instructions to each of the relevant departments in the company as necessary.

6.5.10 Study system and methodology

The study will be conducted with the use of Electronic Data Capture (EDC) system by means of a central registration method.

6.6 Study Item

As possible, all the data for the following items will be collected in this study.

Category	Collection item
Subject characteristics and indication(s) for use	• Anonymized ID Number • Sex • Month/year of birth (or Age at the start of belzutifan administration) • Indication for use • Start date of treatment with belzutifan • Inpatient/outpatient (at the start of belzutifan administration) • Height • Weight • Smoking status • Pregnancy status at the start of administration of belzutifan (female only) • Lactation status at the start of administration of belzutifan (female only) • Karnofsky Performance Score (KPS) at the start of administration of belzutifan • Eastern Cooperative Oncology Group (ECOG) Performance status at the start of administration of belzutifan

Category	Collection item
Medical history and co-morbid condition	• For select conditions (e.g., liver dysfunction, renal dysfunction, respiratory diseases, cardiac diseases, osteoporosis, and others), whether they were previously present and cured versus an ongoing co-morbidity will be recorded, as well as some details on the disease/severity. For hepatic impairment, Grade information will also be collected using the Child-Pugh[2] classification. Please refer to Table 2 and Table 3 for details on the grading.
Condition of RCC before belzutifan Administration	• Date of diagnosis (at initial diagnosis, at most recent recurrence diagnosis) • TNM Staging System (at initial diagnosis, at most recent recurrence diagnosis) • International Metastatic Database Consortium (IMDC) Risk Classification • Histological subtype (i.e., ccRCC vs nccRCC) • Site of recurrence or metastasis at most recent diagnosis • Treatment line at the time of starting administration of belzutifan (including belzutifan)
Prior Treatment for RCC before belzutifan Administration	• Prior medications • Prior radiotherapy • Prior surgeries • Other prior treatments
Treatment of belzutifan	• Initiation date of belzutifan • The date of any dose for belzutifan and stop date of belzutifan after Day 1 • Daily dose • Action taken with belzutifan (e.g., dose interruption/daily dose change) • Reason for dose interruption/reason for daily dose change (if applicable)

[2] [1]

Category	Collection item
Concomitant medications	• Presence or Absence of concomitant medications For any concomitant medications: • Name of concomitant medication • Daily dose • Route of administration • Duration of medications (Start date and stop date of administration) • Reason for use
Non-pharmacological Concomitant therapies	• Presence or Absence of concomitant therapies For any concomitant therapies: • Detail of concomitant therapies (Radiotherapy, Surgical procedure, Other therapy) • Duration of treatment (Start date and stop date of therapy) or date of procedure • Reason for therapies
Effectiveness	Investigators will assess and report effectiveness as detailed below. Timing of these assessments will based upon routine follow-up evaluations. • Presence or absence of effectiveness evaluation For any effectiveness evaluations: • Assessment method Assessment methods will follow the standard procedures of each site, including but not limited to Response Evaluation Criteria in Solid Tumors guideline version 1.1 (RECIST v.1.1). Whenever possible, the same assessment method should be used consistently for each individual patient. • Tumor response assessment (Date of assessment, Tumor response)

Category	Collection item
Status on the date of last observation	• Last observation date • Condition on the last observation date • Administration status of belzutifan after 12 months of observation following the start of administration • Other treatments for RCC within 30 days after the last administration of belzutifan[3] • Date of discontinuation of belzutifan (if applicable) • Reason for discontinuation (if applicable) • Presence or absence of intracranial lesions during the observation period • Occurrence of intracranial hemorrhage up to 30 days after the last dose of belzutifan
AEs	• Presence or Absence of adverse event For any adverse event: • Adverse event term • Onset date • Seriousness • Reason for seriousness • Causal relationship by investigator with belzutifan • Factors other than belzutifan • Maximum Common Terminology Criteria for Adverse Events (CTCAE) grade • Outcome / Date of Outcome • Action taken with belzutifan after the onset of the adverse event • With or without re-administration of belzutifan • Improvement of adverse events after de-challenge of belzutifan • Recurrence of AEs after re-administration of belzutifan • Cause of Death and Autopsy Details (if applicable) • Procedures and laboratory test[4] data / test details. • Safety Considerations [Hemorrhage] • Site of hemorrhage

3 The total follow-up period will not exceed the observation period [12 months (52 weeks) from the first belzutifan treatment date]

4 Clinic al laboratory values/tests for anemia (Hb) , hypoxia (SpO2) and hemorrhage (PT, PT/INR, APTT, platelet count)

Category	Collection item
	• Volume of hemorrhage (only for intracranial hemorrhage, if applicable) • Comorbidities potentially contributing to hemorrhage • Use of drugs that affect the coagulation system (anticoagulants, antiplatelet agents, and NSAIDs) • Laboratory test [prothrombin time (PT), PT/INR, APTT, Platelet count], if applicable [Fracture] • Site of fracture • Fracture at the metastatic site [Anemia] • Use of erythropoiesis-stimulating agents following the onset of the event. • Use of blood transfusion following the onset of the event. • Laboratory test (Hb) [Hypoxia] • Symptoms/signs observed at the time of onset • Oxygen administration following the onset of the event • SpO2
Laboratory data (only if related to adverse events)	• Name of laboratory test[5] • Date of laboratory test performed (before the first administration of belzutifan, after the initiation of administration) • Laboratory results

5 Clinical laboratory values/tests other than those for anemia (Hb), hypoxia (SpO_2), and hemorrhage (PT, PT/INR, APTT, platelet count)

Category	Collection item
Test	• Name of test (including imaging) • Date of test performed • Test result/findings

Table 2 Child-Pugh classification

Score	1 point	2 points	3 points
Hepatic Encephalopathy	None	Mild (Grade Ⅰ・Ⅱ)	Coma (Grade Ⅲ≤)
Ascites	Absent	Slight	Moderate
Serum Bilirubin（mg/dL）[6]	<2.0	2.0-3.0	3.0<
Serum Albumin（g/dL）	3.5<	2.8-3.5	<2.8
Prothrombin Time Activity（%） INR	70 <1.7	40-70 1.7-2.3	<40 2.3<

Table 3 Child-Pugh Total Score

Class	Total Score
Class A	5-6 points
Class B	7-9 points
Class C	10-15 points

[1]

6.7 Endpoint Measurement

All AEs in the (e)CRFs will be classified into the System Organ Class (SOC) and the Preferred Term (PT) of AE according to the classification of MedDRA (Medical Dictionary for Regulatory Activities).

6 The serum bilirubin level is scored as 1 point if it is less than 4.0 mg/dL and 3 points if it is 10.0 mg/dL or higher in cases of cholestasis (PBC).

6.7.1 Primary endpoints

Safety items

The following will be set as endpoints for the risk of hemorrhage and fractures using investigator reported adverse events, including frequency and severity of these events:

- Adverse Events (AEs), Serious Adverse Event (SAEs), Grade 3-5 AEs
- Adverse Drug Reactions (ADRs), Serious ADRs (SADRs), Grade 3-5 ADRs

6.7.2 Secondary endpoints

Safety items

The following will be set as endpoints for the risk of anemia and separately hypoxia using investigator reported adverse events, including frequency and severity of these events:

- AEs, SAEs, Grade 3-5 AEs
- ADRs, SADRs, Grade 3-5 ADRs

The following will be set as endpoints for the risk of intracranial hemorrhage with or without pre-existing intracranial lesions using investigator reported AEs, including frequency and severity of these events:

- AEs, SAEs, grade 3-5 AEs,
- ADRs, SADRs grade 3-5 ADRs

The following will be set as endpoints for overall safety using investigator reported adverse events, including frequency and severity of these events:

- AEs, SAEs, Grade 3-5 AEs, Unexpected SAEs
- ADRs, SADRs, Grade 3-5 ADRs, Unexpected SADRs,

Effectiveness items

The following will be calculated.

- Overall Response Rate (ORR): Complete Response (CR) or Partial Response (PR)
- Disease Control Rate (DCR): CR, PR, or Stable Disease (SD)

6.7.3 Definition of safety related information

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event 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 adverse event.

Disease progression of "RCC" to be investigated in this study will not be regarded as an AE as long as the investigator judges it to be an expected progression.

Adverse Drug Reaction (ADR)

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

Serious Adverse Event (SAE) / Serious Adverse Drug Reaction (SADR)

An adverse event or adverse reaction 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 subject 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.

Non-serious Adverse Event (NSAE)

An adverse event that does not meet any of the serious criteria in above 3).

Collection period of adverse event

Adverse events will be collected throughout the treatment period and for 30 days following discontinuation of belzutifan treatment. The follow up period for each subject will vary according to the treatment of belzutifan, but the maximum follow-up period will not exceed the observation period [12 months (52weeks) from the first date of belzutifan treatment.]

6.7.4 Evaluation of adverse event

An investigator who is qualified will evaluate all adverse events with respect to the elements outlined in this section. The investigator assessment of causality is required for each adverse event.

Causality assessment

An investigator who is qualified will assess the causality according to his/her best clinical judgment.

The investigator will use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product) :

- There is evidence of exposure to the Sponsor's product.
- The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable.
- The AE is more likely explained by the Sponsor's product than by another cause.

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event.

AE seriousness assessment

An investigator who is qualified will evaluate the seriousness of each AE. SAE is any AE occurring at any dose or during any use of Sponsor's product as shown in Table 4.

Table 4 Criteria for Defining Serious Adverse Events (SAEs)[7]

Results in death	–
Is life-threatening	or places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred (Note: It does not refer to an event which hypothetically might have caused death if it were more severe); or
Requires inpatient hospitalization or prolongation of existing hospitalization	Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.);
Results in a persistent or significant disability/incapacity	Substantial disruption of one's ability to conduct normal life functions
Is a congenital anomaly/birth defect	In offspring of subject taking the product regardless of time to diagnosis
Is an otherwise 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 subject 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.

AE severity evaluation

AE severity is assessed based on the worst grade according to CTCAE in collection period of AEs.

The severity of each adverse event (AE) will be evaluated by a qualified investigator.

The definition of severity will follow the CTCAE version 5.0, developed by the U.S. National Cancer Institute (NCI). For Japanese investigators, the Japanese translation provided by the Japan Clinical Oncology Group (JCOG) [8] will be used as a reference to ensure consistency in interpretation and grading.

[7] Based on ICH E2A and Japanese regulatory guidance (e.g., MHLW and PMDA)

8 The CTCAE v5.0 (JCOG version) is publicly available at: https://jcog.jp/doctor/tool/ctcaev5/

Definition of severity is listed below in Table 5:

Table 5 CTCAE v5.0 (JCOG version)

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) [9].
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[10].
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

AE expectedness assessment

The Sponsor will assess the expectedness (labeled or unlabeled / listed or unlisted) of each selected AE according to the latest HA's approved local product circular.

6.7.5 Evaluation of Effectiveness

Tumor Response Evaluation

- The assessment of effectiveness is recommended to follow the RECIST v.1.1; however, it is not limited to this method. The choice of assessment method shall be based on the standard procedures of each participating site.
- RECIST v.1.1 provides standardized criteria for assessing changes in tumor burden, including definitions for CR, PR, SD, and PD.
- The guideline is widely used in oncology clinical trials to ensure consistency and comparability of tumor response assessments across studies.
- Whenever possible, the same assessment method should be consistently applied for each individual subject throughout the study period.
- Tumor response, including CR, PR, SD, and PD, and best overall response (BOR) will be assessed by the investigator in accordance with local methods used in routine clinical practice.

9 Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

10 Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.8 Data Management

The sponsor / program coordinator is responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that this program is conducted, and data are generated, documented, and reported in compliance with the protocol, accepted standards of all applicable laws, rules and regulations relating to the conduct of the study.

Data management will be performed in accordance with applicable MSD/CRO standards and data cleaning procedures to ensure the integrity and accuracy of the data, e.g., removing errors and inconsistencies in the data. MSD may also conduct a quality assurance assessment and/or audit of the site records during the execution period to ensure the integrity and accuracy of the data and the compliance with all applicable regulatory requirements.

All AEs in the (e)CRFs will be classified into the SOC and the PT of AE according to the classification of MedDRA, which is the most current version in use when the summary tabulation is generated.

6.9 Data Analysis and Statistical Analysis

Each endpoint will be analyzed using descriptive statistical methods such as mean, standard deviation, median, interquartile range, and/or minimum/maximum/range for continuous variables. For any categorical variables, frequency and percentage will be reported.

Each evaluation item will be subjected to descriptive statistical analysis in accordance with the statistical analysis plan.

The safety and effectiveness in subjects who are in violation of this protocol including inclusion/exclusion criteria (i.e. protocol violation cases) will be separately presented.

Patient background (age, sex, pregnancy status, lactation status, medical history and comorbidities, prior treatments/concomitant medications, etc.) will be summarized descriptively.

6.9.1 Subject composition

Subject attrition will be reported, including:

- Number of the registered subjects
- Number of the subjects for whom the study form has been collected
- Number of the subjects for whom the study form has been finalized (Number of subjects whom the survey form has been quality checked per 6.5.8)

- Number of the subjects included in safety tabulation/subjects excluded from the tabulation and the reason

  The subjects that meet the criteria for safety analysis, are treated with belzutifan at least once, complete at least one follow up visit (e.g., re-visit etc.), and are identified by an investigator whether AE occurred or not will be included in the subjects for the safety evaluation. The 'safety tabulation' group will be used for all analyses below unless otherwise noted.

- Number of the subjects included in effectiveness evaluation/subjects excluded from the evaluation and the reason

  Only subjects in which a) belzutifan was administered at the recommended dose throughout the observation period or until belzutifan discontinuation and b) have an effectiveness evaluation will be included in the effectiveness analyses.

6.9.2 Primary Objective analysis

The incidence of hemorrhage AEs and the incidence fracture AEs reported by investigator, including all AEs, ADRs, grade 3-5 AEs, grade 3-5 ADRs, SAEs, and SADRs will be analyzed and reported as categorical variables.

6.9.3 Secondary Objective analysis

1) Patient demographic and clinical characteristics will be analyzed and reported as noted above according to whether they are a categorical or continuous variables for:

   a) the registered subjects

   b) the safety evaluation group

   c) by presence/absence of any adverse event

   d) by presence/absence of hemorrhage

   e) by presence/absence of fracture

   f) by presence/absence of anemia

   g) by presence/absence of hypoxia

   h) by presence/absence of intracranial lesions

2) The incidence of anemia AEs and the incidence hypoxia AEs, including all AEs, ADRs, grade 3-5 AEs, grade 3-5 ADRs, SAEs, and SADRs reported by the investigator will be separately analyzed and reported as categorical variables

3) The incidence of intracranial hemorrhage AEs with or without pre-existing intracranial lesions, including all AEs, ADRs, grade 3-5 AEs, grade 3-5 ADRs, SAEs, and SADRs reported by the investigator will be separately analyzed and reported as categorical variables

4) The incidence of overall safety events reported by investigator, including all AEs, ADRs, grade 3-5 AEs, grade 3-5 ADRs, SAEs, SADRs, unexpected SAEs, and unexpected SADRs, will be analyzed and reported as categorical variables

5) The following will be analyzed and reported as categorical variables for a) hemorrhage AEs, b) fracture AEs, c) anemia AEs, d) hypoxia AEs, e) all AEs, f) all SAEs, g) all ADRs and h) all SADRs reported by the investigator:

   - the proportion of subjects who interrupt drug due and the reasons for drug interruption
   - the proportion of subjects who discontinue drug and the reasons for drug discontinuation
   - the proportion of subjects with dose reduction and the reasons for dose reduction

6) The following will be analyzed and reported as categorical variables for the effectiveness analysis population based on the investigator's overall assessment after completion of administration, as detailed in the stand-alone statistical analysis plan:
   - ORR: best overall response rate (CR or PR)
   - DCR: best response rate of (CR, PR, SD)

6.9.4 Exploratory analysis

For all Primary objectives noted within, the results of this survey, as well as results from other relevant, published studies (LS005 etc.) will be qualitatively compared and reported. In addition to noting any similarities/differences in observed trends, any differences between this study and other relevant, published studies (LS005 etc.), including methodologies or study population, will be reported, as will any other limitations that may impede assessment of comparability. Given the inherent limitations associated with cross-study comparisons—such as differences in study design, patient demographics, and assessment methodologies—no formal statistical testing will be conducted. These analyses are intended to provide contextual understanding of the safety profile of belzutifan and are not designed to support formal statistical inference.

6.10 Limitations of the methodology

Due to its observational nature, there are several potential sources of bias including selection bias and information bias. In terms of potential selection bias, the study sites willing to participate in the study may not be fully representative of all sites treating patients of interest in Japan and may be different from patients treated in other healthcare systems in Japan or

other countries. As for information bias, there can be information loss during medical chart abstraction, based on recall, or transcription of information for database capture. As well, the adverse events are based on investigator reports and not defined by specific diagnostic tests. Additionally, causality assessment is decentralized and assessed by each investigator, therefore there may be differences in conclusions by investigator. Furthermore, as it relates to effectiveness data, response assessments may not be based on validated nor standardized measures (e.g., RECIST v.1.1). Lastly, the association of outcomes with treatment cannot be directly evaluated in this study given the lack of an internal comparator and inability to control for confounders or effect modifiers. There is also limited power and precision given the small sample size. As a result of the potential biases and limited power/precision, all analyses are descriptive in nature. Overall, these results offer a limited view of the safety/effectiveness of belzutifan and cannot be statistically compared to previous trials or other observational reports and should be interpreted with caution.

7 PROTECTION OF HUMAN SUBJECTS

Informed consent requirements will adhere to IRB/ERC requirements, applicable laws and regulations within Japan. Additional information on the informed consent process for this protocol are described in 6.5.2.

This study will require IRB/EC review at each site as noted in 6.5.1.

The Company recognizes that personal data may be received and understands that certain information may be considered sensitive in accordance with legal regulations. All information and personal data collected by the Company during the program will be preserved and protected according to local data privacy protection laws; if applicable, this data can be shared globally within the company with those handling adverse events, quality complaints or responding to medical queries, as well as with regulatory authorities.

8 MANAGEMENT OF ADVERSE EVENT AND REPORTABLE INFORMATION

Introduction

This is a hybrid data collection non-interventional study being conducted within routine medical practice. All direction for medication usage is at the discretion of a investigator in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol.

8.1 Adverse Event Reporting

Any Adverse Event (AE) including death due to any cause which occurs to the subject during the timeframe noted in the study protocol (during the administration period or within 30 days after discontinuation of belzutifan) after belzutifan is administered, must be reported to the Sponsor according to Table 6 AE Reporting Timeframes and Process for Investigators / the Program Coordinator.

Please refer to Section 6.7.3 “Definition of safety related information” for the definition of each reportable information type and 6.7.4 “Evaluation of adverse event” for the detail.

Table 6 AE Reporting Timeframes and Process for Investigators / the Program Coordinator

Reportable information	Reporting timeframe Investigator to Sponsor/ Program coordinator to PV area	Reporting method
SAE/SADR	24 hours from receipt	If AE(s) occurs during the observation period, the investigator should promptly notify the MR, without waiting for the end of the observation period per the noted reporting timeframe by: • Filling in the(e)CRF and submitting it • Contacting the MR in charge
NSAE/NSADR	10 calendar days from receipt	

8.2 AE Reconciliation

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

9 PUBLICATION

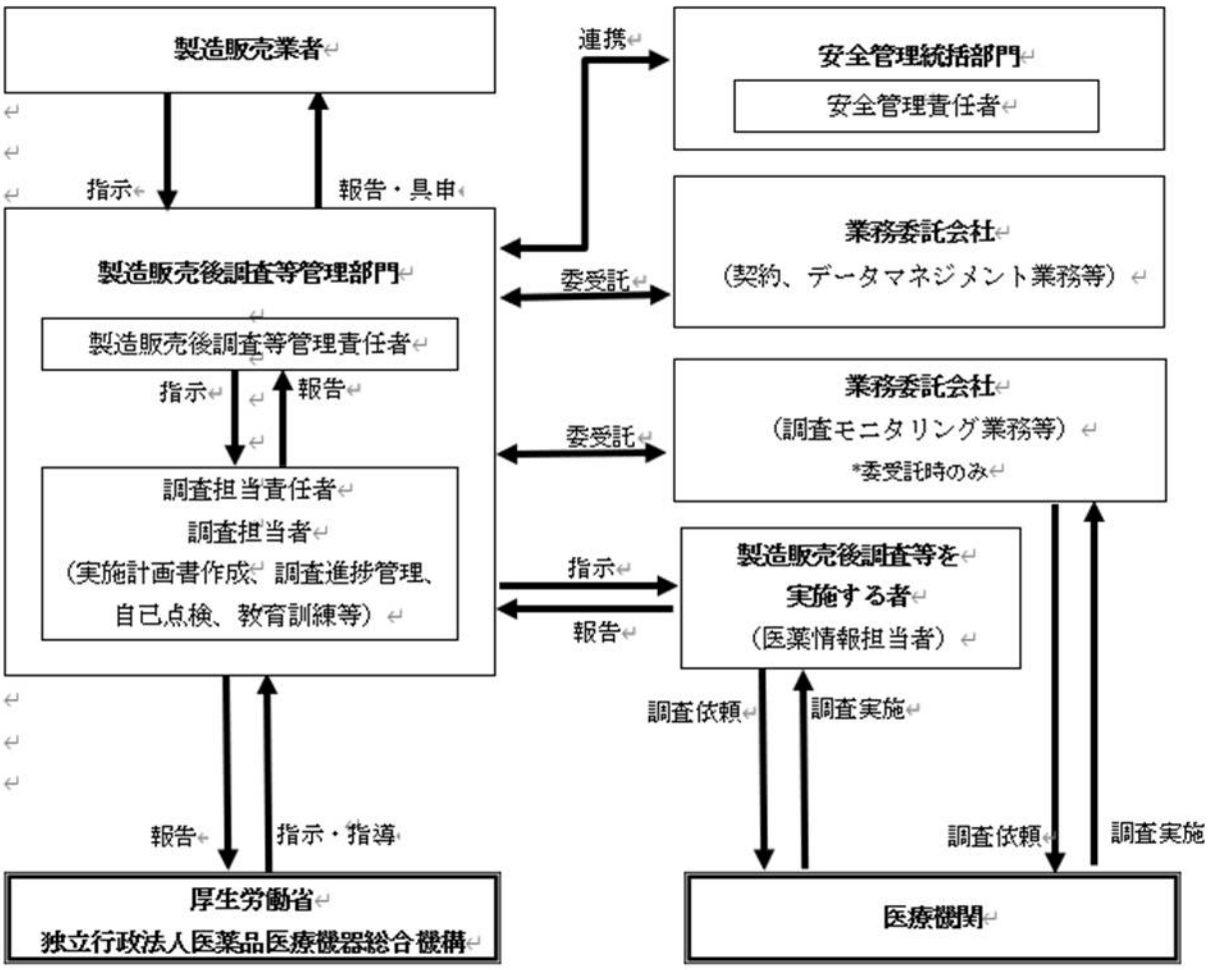
The final results of the study may be published at academic conferences or in the article to be submitted. In both cases, the information on the subjects’ privacy and the sites will not be disclosed.

10 REFERENCE

[1] Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the Oesophagus for bleeding Oesophageal varices. Brit J Surg 1973;60(8):646-9. [03RVDY]

11 ORGANIZATIONAL STRUCTURE FOR CONDUCTING THE STUDY (JAPANESE)

< Organizational Structure for Post-Marketing Surveillance and Related Activities >



PART B PASS INFORMATION

Title	Special survey for belzutifan in patients with radically unresectable or metastatic renal cell carcinoma: a post-authorization safety study (PASS)
Protocol Version identifier	6482-045
Date of last version of protocol	09-DEC-2025
HMA-EMA Catalogues No:	Study not yet registered (anticipated 1Q2026)
Active substance	belzutifan (ATC code: L01XX74)
Medicinal product:	Welireg®, belzutifan
Joint PASS	No
Research question and objectives	Among Japanese subjects with radically unresectable or metastatic RCC treated with belzutifan in routine practice, **Primary Objective** 1) To monitor the risk of occurrence of hemorrhages and fractures during the administration of belzutifan in subjects with RCC. In doing so, we will observe the percentage of subjects occurring hemorrhage and fractures during the administration of belzutifan and contrasted the results obtained in this study with the percentage of subjects occurring the relevant AEs observed in the Everolimus group of the Study 005. **Secondary Objective** 1) The overall safety of belzutifan, including safety concerns in subjects with RCC 2) The effectiveness of belzutifan in subjects with RCC
Country(-ies) of study	Japan

Author	PPD Safety Program Operation MSD K.K. (hereafter referred to as Sponsor or MSD) 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo, Japan PPD Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA
Marketing authorisation holder(s) including MAH Contact Person	MSD K.K. (hereafter referred to as Sponsor or MSD) 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo, Japan PPD
MSD Final Repository (REDS) Date	22-JAN-2026
Effective date:	15-JAN-2026
Health Authority Approval date:	23-JAN-2026

1. RESEARCH METHODS

1.1 Programming Quality

This study will incorporate the following quality checks for data analysis and reporting programming:

- Creating a program requirements and specification document (PRS)
- Developing and testing of statistical programs which includes ensuring the programs run successfully and all output are reviewed to ensure they meet the criteria included in the (PRS). This includes validating that all inputs (metadata or parameter values) are correctly specified in the programs and are consistent with the PRS.
- Independent Review and Testing, conducted by a second programmer to ensure that the input and outputs of the programs created by the first programmer meet the documented PRS. This includes the following 2 activities:
    - Review of code to ensure the program aligns with the PRS
    - Execution of code and review of results for some or all scenarios

And may include the following activity:

    - Parallel programming of a small piece of critical code
- Independent Double Programming, conducted by second programmer. After programming is completed, the programs and results of the second programmer and compared to those of first programmer to ensure consistency. If discrepancies are found, the programmers will discuss and repeat steps until consistency is achieved.
- Review of outputs/results to ensure accuracy and format of each deliverable.

1.2 Quality Control

Participating medical institutions sign contracts stating that the healthcare providers (HCPs) will conduct the survey based on the protocol and physicians guide, and in compliance with governing laws and regulations including the Good Post-marketing Study Practices (GPSP). The site contract stipulates that quality control procedures will be followed for the conduct of the study.

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, 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.

2. MANAGEMENT OF ADVERSE EVENT (AE) AND REPORTABLE INFORMATION

Introduction

This is a hybrid data collection non-interventional study being conducted within routine medical practice. All direction for medication usage is at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol.

2.1 Reporting of Other safety information / Product Quality Complaint (PQC)

Safety information/product quality complaints for Sponsor products that are not solicited/collected as part of the surveillance/results survey must be reported to MSD K.K. as per Appendix 1, if the investigator becomes aware of them. Refer to Appendix 1 for AE/PQC reporting requirements, timelines and procedures.

Additionally, if the investigator elects to submit AEs for non-Sponsor products, they can 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.

2.2 AE/PQC Reconciliation

Reconciliation will be performed between the safety database and surveillance/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.

2.3 Sponsor Responsibility for Reporting Adverse Event

All adverse events will be reported to HA and IRB/EC (Institutional Review Board/Ethics Committee) (if applicable) in accordance with all applicable global and local laws and regulations.

APPENDICES

Appendix 1. Reporting of Other safety information/ Product Quality Complaint

If PQCs, or special situations are identified following use of belzutifan, then they must be reported per the table below. Additionally, any SAEs and/or NSARs for belzutifan that occur more than 30 days after the end of administration must also be reported per the table below, if identified.

While SAEs, NSARs, special situations and PQCs for *other* Sponsor products are not solicited, they must be reported to the Sponsor according to the table below if identified.

Table 1A AE/PQC Reporting Timeframes and Process for Investigators

Reportable information	Reporting timeframe Investigator to Sponsor	Reporting method
SAE (Primary Data) SADR (Secondary Chart Review) PQC Special situation	24 hours from receipt	If AE(s) occurs during the observation period, the investigator should promptly notify the MR, without waiting for the end of the observation period per the noted reporting timeframe by: • Filling in the(e)CRF and submitting it • Contacting the MR in charge
NSADR	10 CD from receipt	

Study Report:

The final study report 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.

Periodic Safety Update Reports:

Any relevant safety information will be summarized and the Sponsor will include in the appropriate Periodic Safety Reports (PSUR/DSUR) if required.

Additional Definitions:

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 adverse event is at least a reasonable possibility.

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

An adverse event or adverse reaction 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 subject 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.

Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria above.

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

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.

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.

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.

Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Refer to the section on ‘Evaluation of adverse event – causality assessment’.

Sponsor Responsibility for Reporting Adverse Events

All adverse events will be reported to regulatory agencies, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

ANNEXES

Annex 1: ENCePP Checklist for Study Protocols (Revision 4)

EUROPEAN NETWORK
OF CENTRES FOR
PHARMACOEPIDEMIO

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and

does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Special survey for belzutifan in patients with radically unresectable or metastatic renal cell carcinoma: a post-authorization safety study (PASS)

EU PAS Register® number: To be assigned

Study reference number (if applicable): 6482-045

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[11]	☒	☐	☐	3
1.1.2 End of data collection[12]	☒	☐	☐	3
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	Part B PASS Information
1.1.6 Final report of study results.	☒	☐	☐	3

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4
2.1.2 The objective(s) of the study?	☒	☐	☐	5
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	6.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	2

Comments:

[11] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[12] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	6.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	6.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	6.7, 6.9
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	6.9
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	6, 8, Part B 2 & 3

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	6.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	3, 6.5
	4.2.2 Age and sex	☒	☐	☐	6.2 See below (1)
	4.2.3 Country of origin	☒	☐	☐	6.2
	4.2.4 Disease/indication	☒	☐	☐	6.2
	4.2.5 Duration of follow-up	☒	☐	☐	6.5.4
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	6.2

Comments:

(1) Study inclusion/exclusion criteria is not directly based on age or sex, but instead may be limited on these factors as the current local label will primarily drive eligibility.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	6.6
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	See below (1)
5.3 Is exposure categorised according to time windows?	☐	☒	☐	See below (2)
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	6.6
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	See below (3)
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	See below (4)

Comments:

(1) Treatment exposure is reported directly by site using information in medical records, and there is no source verification.

(2) There are no time windows for exposure categorization- only follow-up of patients and treatment exposure during the 1-year follow-up after treatment initiation.

(3) Dose information is included in the current product label. Dose reductions/ modifications are specific study objective.

(4) Per the study design, only patients treated with belzutifan will be included.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	6.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	6.5, 6.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	See below (1)
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

(1) Outcomes are reported directly by site using information in medical records, and there is no source verification.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	6.10

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	6.6, 6.9

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	6.5, 6.6
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	6.5, 6.7
9.1.3 Covariates and other characteristics?	☒	☐	☐	6.6
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	6.5, 6.6
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	6.5, 6.7
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	6.6
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Part B PASS Information
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	6.6, 6.7, 6.8, 8
9.3.3 Covariates and other characteristics?	☐	☒	☐	See below (1)
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	6.8

Comments:

(1) As noted in 6.5.6, an eCRF will be utilized to standardize data collection of information within and across sites.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	6.9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	6.3
10.3 Are descriptive analyses included?	☒	☐	☐	6.9
10.4 Are stratified analyses included?	☒	☐	☐	6.9.2
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	6.5
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	6.8
11.2 Are methods of quality assurance described?	☒	☐	☐	Part B Section 1
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	3 See below (1)

Comments:

(1) A final report will be shared with the Japan PMDA

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	6.10
12.1.2 Information bias?	☒	☐	☐	6.10
12.1.3 Residual/unmeasured confounding?	☐	☒	☐	
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	6.3, 6.4

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	7
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	See below (1)
13.3 Have data protection requirements been described?	☒	☐	☐	7

Comments:

(1) IRB/EC review will be sought and any outcomes requiring actions will be addressed at that point in time.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Amendments

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	3, 9
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	9

Comments:

Name of the main author of the protocol: PPD

Date: 09-Dec-2025

Signature: PPD

Name of the main author of the protocol: PPD

Date: 18-Nov-2025

Signature: PPD

Annex 2: Administrative and Regulatory Details

Depending upon the nature of the study and the local legal and regulatory requirements, not all the elements in this section of the protocol will be applicable.

Confidentiality:

Confidentiality of Data

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 Institutional Review Board, Ethics Review Committee 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 Subject Records

The investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (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 subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

Confidentiality of Investigator Information

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 e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- 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 serious adverse events 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 adverse event 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 Law, Audit and Debarment

The investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice 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, Institutional Review Board/Independent Ethics Committee 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 subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject 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/case report forms.

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/case report forms, advertising for subject participation, adverse event reports, subject 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 subject 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.

Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), as well as the European Medicines Agency GVP Module VIII, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to one or more study registries such as the HMA-EMA Catalogue of RWD Studies. The Sponsor will review this protocol and submit the information necessary to fulfill these requirements for all post-marketing safety and efficacy studies. Information posted will allow subjects to identify potentially appropriate primary data collection 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.

The investigator acknowledges that the statutory obligations under FDAMA/FDAAA and EMA GVP Module VIII are that of the Sponsor and agrees not to submit any information about this study or its results to a study registry without consulting with the Sponsor.

Annex 3: Global Qualified Person for Pharmacovigilance (GQPPV), EU/UK QPPV

PPD
Global Qualified Person for Pharmacovigilance (GQPPV)
EU/UK QPPV
Tel: +32 475 771034,
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PPD
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Emergency/Out of Hours: As above or via +44 (0)208 154 8000

Dear Sir/Madam,

Re: Global, EU/UK QPPV Signature Page for PASS

Product: Welireg®, belzutifan
Protocol No: 6482-045-01-v0
Epidemiology No: EP05047.014
Protocol Date: 15-JAN-2025
MAH: MSD K.K.

In line with the Guideline on Good Pharmacovigilance Practice (GVP), Module VIII - Post-Authorization Safety Studies (PASS) and according to MSD internal SOPs, this study has been reviewed and approved by the Global Qualified Person for the Pharmacovigilance (GQPPV), EU/UK QPPV.

Yours faithfully

PPD

PPD

Global Qualified Person for Pharmacovigilance (GQPPV)
EU/UK QPPV

Annex 4: List of Stand-alone Documents

The below are maintained separate from the protocol.

1. Informed Consent Document
2. Statistical Analysis Plan

SIGNATURES

Sponsor's Representatives

PRINTED NAME	PPD
TITLE	PPD
SIGNATURE	
DATE SIGNED	

PRINTED NAME	PPD
TITLE	PPD
SIGNATURE	
DATE SIGNED	