REGISTRY TO DOCUMENT TREATMENT EFFECTIVENESS, SAFETY, INCLUDING PROSPECTIVE LONG-TERM OUTCOMES IN PARTICIPANTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS (PFIC) WHO TAKE ODEVIXIBAT (BYLVAY)

STUDY PROTOCOL

STUDY NUMBER: CLIN-60240-030
[IPN60240]

Final Version 1.0: 02 February 2024

Sponsor

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PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the protocol CLIN-60240-030 entitled "Registry to Document Treatment Effectiveness, Safety, Including Prospective Long-term Outcomes in Participants with Progressive Familial Intrahepatic Cholestasis (PFIC) who take Odevixibat (Bylvay)". I am aware of my responsibilities as an investigator under the guidelines of Good Pharmacoepidemiology Practices, Good Pharmacovigilance Practices, any regulations (as applicable), and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: _____

TITLE: (Principal) Investigator: SIGNATURE: _____

DATE: _____

OFFICE: _____

Full study site contact details, including telephone numbers, will be documented in the Study Master File.

On behalf of the Sponsor:

NAME: PPD

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CA	Competent Authority
CI	Confidence Interval
eCRF	Electronic Case Report Form
EFS	Event-free Survival
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GMPC	Global Medical Publications and Communications
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
IBAT	Ileal Bile Acid Transporter
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalised Ratio
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Studies
PFIC	Progressive Familial Intrahepatic Cholestasis
PT	Preferred Term
QoL	Quality of Life
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Service Provider
UDCA	Ursodeoxycholic Acid

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1 RESPONSIBLE PARTIES

A list of all investigators, including contact details, will be in a stand-alone document, available upon request.

2 ABSTRACT/PROTOCOL SYNOPSIS

Registry Title:	Registry to Document Treatment Effectiveness, Safety, Including Prospective Long-term Outcomes in Participants with Progressive Familial Intrahepatic Cholestasis (PFIC) who take Odevixibat (Bylvay).
Rationale and Background:	Odevixibat is a medical treatment for PFIC, a group of rare genetic disorders that results from defects in bile secretion and presents with intrahepatic cholestasis. Odevixibat acts as a potent, selective inhibitor of the human ileal bile acid transporter, an integral brush border membrane glycoprotein that co-transports sodium and bile acids and appears to be a major regulator of the bile acids pool in animals and humans. Odevixibat was first authorised for the treatment of PFIC in patients ≥ 6 months of age by the European Medicines Agency on 16 July 2021 and by the United States Food and Drug Administration on 20 July 2021 for the treatment of pruritus in patients with PFIC ≥ 3 months of age. This will be a long-term, observational, and voluntary participation registry designed to assess the real-world usage of odevixibat in the treatment of PFIC using prospectively collected data.
Research Questions and Objectives:	The aim of this registry is to assess real-world safety data and to describe the effectiveness of odevixibat treatment in participants with PFIC. **Primary objective:** To evaluate the long-term safety of odevixibat based on adverse events (AEs). **Secondary objectives:** • To evaluate the effectiveness of odevixibat on the first clinical event (surgical biliary diversion, liver transplant, death) for the overall population of participants with PFIC as well as the sub-populations of participants with different PFIC types. • To evaluate the effectiveness of odevixibat on surgical biliary diversion-free survival for the overall population of participants with PFIC as well as the sub-populations of participants with different PFIC types. • To evaluate the effectiveness of odevixibat on liver transplant-free survival for the overall population of participants with PFIC as well as the sub-populations of participants with different PFIC types. • To evaluate the effectiveness of odevixibat on overall survival of the overall population of participants with PFIC as well as the sub-populations of participants with different PFIC types.
Registry Design:	This will be a long-term, observational, prospective, and voluntary participation registry designed to examine the real-world usage of odevixibat for the treatment of PFIC. The registry will recruit participants with PFIC (all types) treated with odevixibat as prescribed by their treating physician. Data typically collected during the routinely indicated medical visits will be analysed. No additional evaluations are planned.

Registry Duration:	This registry will follow participants in South Korea for ≥ 2 years. Following enrolment, participants will continue to participate in the registry until the time point of withdrawal of consent, treatment discontinuation, death, or the sponsor decides to discontinue the registry. The duration of the registry is approximately 7 years from first participant, first visit.
Registry Population:	The registry population will comprise participants with PFIC (all types) enrolled into the Ipsen odevixibat PFIC registry. Participants with PFIC who have been prescribed odevixibat by their treating physician will be eligible. Inclusion criteria: To be included in the registry the participants should fulfil the following inclusion criteria: (1) Diagnosed with PFIC (all types) who have been prescribed odevixibat (independently of the decision to enrol the participant in this registry) by their treating physician (2) On (or starting) active odevixibat treatment Note: Participants can remain in the registry during odevixibat treatment interruptions (3) Signed informed consent and assent, as appropriate. Consent/assent from the participant or legal representative should be obtained, as appropriate, before any registry data collection is conducted. Participants who turn 18 years of age (or legal age per country) while participating in the registry will be required to provide consent for themselves. Exclusion criteria: Participants will not be included in the registry if: (1) Currently participating in a clinical trial with odevixibat (2) Currently participating in any interventional clinical trial for PFIC (3) Have any contraindication to odevixibat as per the approved label in South Korea.
Registry Treatment:	This is an observational registry. Odevixibat will be prescribed according to clinical routine. The assignment of the participant to a particular therapeutic strategy is not decided in advance by this protocol, but falls within current practice, and the prescription of the medicine is independent from the decision to include the participant in the registry.
Sample Size:	No formal sample size calculation was performed. Enrolment will be based on the number of participants prescribed odevixibat and their willingness to participate in the registry, but the goal will be to enrol a minimum of 10 participants with PFIC (all types) in South Korea.
Variables:	This registry is strictly observational. Only data that are routinely documented in participants' medical records as part of usual care will be collected. No additional laboratory tests or assessments will be required as part of this protocol. If some assessments included in the protocol are not routinely performed by the investigator, the corresponding sections in the

	electronic Case Report Form (eCRF) do not need to be completed. All relevant data collected as part of routine medical care will be captured in the eCRF by the investigator. These data will be transmitted to the sponsor for analysis. Data transmitted will be pseudonymised and will be identified by a participant number. Data will be collected at the Baseline Visit and at each Follow-up Visit (scheduled as per routine clinical practice or as per the approved label in South Korea). This registry will only assess variables related to the registry's objectives and dependent on the availability and routine assessment of data, including: *Baseline*: • Age, sex, weight, height, PFIC type/genetic variant, date of birth (MM/YYYY) and date of PFIC diagnosis • General medical or surgical history • Prior surgical procedures related to PFIC, including but not limited to prior biliary diversion surgery (date and type of surgery) • Prior and concomitant medications (prior medications refer only to medications related to the treatment of PFIC, including but not limited to rifampicin and/or ursodeoxycholic acid taken up to 9 months prior to the first odevixibat dose) • Concomitant vitamin supplementation • Odevixibat treatment dose and start date • Clinical symptoms: pruritus and sleep disturbance, if (semi-) objective scoring data are available • Planned biliary diversion surgery (planned date and indication) • Listing for liver transplantation (planned date of transplantation and indication) • Laboratory parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), international normalised ratio (INR), albumin, creatinine, sodium, platelet count, serum bile acid levels, and fat-soluble vitamin levels. Historical values (most recent values up to 9 months prior to the first odevixibat dose) are also to be provided if available. • Pregnancy or breastfeeding status *Periodic Data Collection (Odevixibat and Concomitant Medications):* • Odevixibat dose (if changed/discontinued, provide date and reason) • Concomitant medication • Concomitant vitamin supplementation

	Periodic Safety Data Collection: • Adverse events • Weight and height • Special situation (including pregnancy or breastfeeding status) • Death (date and cause) If AEs or their sequelae, whether or not causally related, persist after the date of odevixibat discontinuation, the investigator must ensure that the participant receives appropriate medical follow-up and this should be properly documented in the participant's medical records. *Periodic Effectiveness Data Collection:* • Laboratory parameters, including AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, serum bile acid levels, and fat-soluble vitamin levels reported since the prior data collection • Biliary diversion surgery (date and indication) • Liver transplantation (date and indication) • Cancellation of planned biliary diversion surgery and reason for cancellation • Removal from listing for liver transplantation and reason for removal from the list • Clinical symptoms: pruritus and sleep disturbance, if (semi-) objective scoring data are available
Effectiveness and Safety Endpoints:	**Safety Endpoints:** • All AEs, based on the incidence, severity, causality, outcome, action taken, and seriousness **Effectiveness Endpoints**: • Event-free survival (EFS), defined as time from the start of odevixibat treatment to the first occurrence of surgical biliary diversion, liver transplant, or death • Surgical biliary diversion-free survival, defined as time from the start of odevixibat treatment to the first occurrence of surgical biliary diversion or death • Liver transplant-free survival, defined as time from the start of odevixibat treatment to the first occurrence of liver transplant or death • Overall survival, defined as time from the start of odevixibat treatment to death
Statistical Methods:	A statistical analysis plan will provide full details of analyses and will be finalized prior to the first data analysis. Descriptive summaries of continuous variables will include the number of observations, mean, standard deviation, median, range, and 95% confidence interval (CI) of the mean, median and/or inter-quartile range

	when appropriate. Descriptive summaries of categorical variables will include frequencies and percentages. Percentages will be based on the number of non-missing observations. Missing data will also be summarised. The number and relative frequency of participants who prematurely discontinue participation in the registry and reasons for discontinuation will be tabulated. Demographic and baseline characteristics of participants will be summarized using descriptive statistics. **Evaluation of Safety Endpoints** Descriptive statistics on AEs characteristics will be presented. **Evaluation of Effectiveness Endpoints** The incidence of biliary diversion surgery, liver transplantation, or death will be assessed using descriptive statistics once the participants with PFIC (all types) treated with odevixibat have been followed for ≥ 2years. It is anticipated that the analyses for each PFIC type will be conducted if feasible. Depending upon rate of enrolment, it may be necessary to pool participants with PFIC3, PFIC4, PFIC5, and PFIC6 to achieve a sufficient number of participants for the analysis. Depending on the data available, EFS endpoints may be summarized using the Kaplan-Meier method. Median time to event with 2-sided 95% CIs and the first and third quartiles will be reported. Survival curves will be presented as well. In addition, survival probability estimates at 6, 12 months and then every 6 months and the associated 2-sided 95% CI will be reported. Interim analyses will be performed annually and/or for sponsor decision making purposes.
Milestones:	**Start of data collection** • Once odevixibat is commercially available and the first site approved to begin enrolment (Planned Q4 2024 – Q1 2025) **End of data collection** • Approximately 7 years following the start of data collection (Planned Q4 2031 – Q1 2032) **Final report of registry results** • Planned Q2 2032 – Q3 2032

3 AMENDMENTS AND UPDATES

None.

4 MILESTONES

Milestone	Planned Date
Start of data collection	Once odevixibat is commercially available and the first site approved to begin enrolment. Planned Q4 2024 – Q1 2025
End of data collection	Approximately 7 years following the start of data collection. Planned Q4 2031 – Q1 2032
Final report of registry results	Planned Q2 2032 – Q3 2032

5 RATIONALE AND BACKGROUND

5.1 Disease Background

Progressive familial intrahepatic cholestasis (PFIC) is the clinical diagnosis applied to a heterogeneous group of autosomal recessive genetic diseases, all of which result in cholestasis with impaired bile acid secretion and transport (Alissa 2008; Bull 2018). The accumulation of the components of bile within the liver, including bilirubin and bile acids, can lead to portal hypertension, liver failure, cirrhosis, and hepatocellular carcinoma (Hori 2011). As hepatic levels of components of bile increase, they are excreted into the systemic circulation leading to the development of jaundice and severe pruritus (Gunaydin 2018).

Progressive Familial Intrahepatic Cholestasis is generally categorised into three main types, PFIC1, PFIC2, and PFIC3, although at least three other types (PFIC4, PFIC5, and PFIC6) have been described in the literature (Jacquemin 2000; Srivistava 2014; Mehl 2016; Gunaydin 2018). PFIC1 and PFIC2 together represent approximately two thirds of cases of PFIC, and PFIC3 represents approximately one third of cases (Davit-Spraul 2009). Severe pruritus is common with PFIC. For most PFIC types, patients present in early childhood; however, the age of presentation can vary depending upon disease severity.

For the majority of patients, there is a high level of debilitating symptoms and morbidity associated with PFIC that have a major impact on the quality of life (QoL) of the affected children and their families (Bergasa 2000; Cies 2007). Severe pruritus is common in children diagnosed with PFIC and the need for relief is critical. The precise mechanism of cholestatic pruritus remains unclear, but elevated bile acids are commonly considered as direct or indirect pruritic mediators (Mehl 2016). Elevated levels of autotaxin, the serum enzyme that converts lysophosphatidylcholine to lysophosphatidic acid, have also been correlated with cholestatic pruritus (Kremer 2010). Significant pruritus can lead to severe cutaneous mutilation (often drawing blood), loss of sleep, irritability, poor attention, and impaired school performance (Mehl 2016). Furthermore, caring for an individual with PFIC has been shown to often cause comprehensive and meaningful burden on caregivers with reported outcome on health related QoL and work productive outcomes (e.g. mental and physical health, productivity, career prospects, sleep, relationship, finances) (Mighiu 2022).

Progressive Familial Intrahepatic Cholestasis is a rare disease estimated to affect one in every 50,000 to 100,000 children born worldwide (Davit-Spraul 2009). There are no published reports of global studies on the epidemiology of PFIC; therefore, the true incidence and prevalence of the disease remain unknown. PFIC is thought to occur worldwide. Both sexes seem to be equally affected (Davit-Spraul 2009; Davit-Spraul 2010). Progressive familial intrahepatic cholestasis represents 10% to 15% of cases of cholestasis in children and 10% to 15% of liver transplant indications in children (Davit-Spraul 2009).

Symptoms of PFIC develop early with a median age at onset of approximately 3 months; 78% of patients develop jaundice before 12 months of age (Pawlikowska 2010). Liver biopsy reveals canalicular cholestasis and, later, the appearance of portal fibrosis. Liver biochemistry shows cholestasis with hyperbilirubinemia and elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The concentrations of bile acids in serum are typically very high, while serum gamma-glutamyl transferase (GGT) is normal or low (except for PFIC3); cholesterol concentrations are typically normal (Hori 2011). Portal hypertension and decompensation may be evident in the first year of life in PFIC2 and in early childhood in PFIC1 (Davit-Spraul 2009; Srivistava 2014). Other features of PFIC include fat malabsorption resulting in weight and height below normal centiles, and fat-soluble vitamin (A, D, E, and K) deficiency.

5.2 Treatment Background

Ileal bile acid transporter (IBAT), also known as apical sodium-dependent bile acid transporter, is a luminal epithelium glycoprotein expressed mainly in the distal ileum that co-transports sodium and bile acids, efficiently moving bile acids from the lumen of the small intestine across the apical brush border membrane. As part of enterohepatic circulation, bile acids are then shuttled to the basolateral membrane, ultimately returning to the liver by the portal venous blood. Although minimal passive reabsorption of bile acids occurs throughout the intestine, active transport by IBATs is the major mechanism for bile acid reabsorption. Over 95% of the circulating bile acid pool is returned to the liver daily (Hofmann 2009; Miethke 2016). Therefore, IBAT is a key regulator of the bile acid pool and a key element in enterohepatic circulation (Dawson 2003).

Odevixibat is orally administered and acts locally in the gut where it binds reversibly to the IBAT to decrease the reuptake of bile acids into the liver, increasing the clearance of bile acids through the colon and lowering hepatic bile acid load and serum bile acid levels. Odevixibat is currently the only approved pharmaceutical treatment for PFIC, except for ursodeoxycholic acid (UDCA), which has national approval for the treatment of PFIC3 in France. The therapeutic choices are restricted to nonspecific symptomatic treatment, nutritional support, vitamin supplementation, and treatment of complications. Other medical treatment options include off-label use of UDCA, rifampicin, antihistamines, and naltrexone to treat pruritus. A minority of patients (approximately 30%) respond to these medications, some only transiently.

Surgical options for the treatment of PFIC include biliary diversion and liver transplant. Treatment-resistant pruritus is the leading indication for surgical biliary diversion, particularly in patients with PFIC2 (Melter 2000; Yang 2009; Arnell 2010; Schukfeh 2012). Liver transplantation is currently the only definitive treatment for PFIC. Survival in patients with PFIC not undergoing surgical diversion or liver transplant is 50% at 10 years of age and almost none at 20 years of age, highlighting the rapid rate of progression of this life-threatening disease (Pawlikowska 2010).

Odevixibat has minimal systemic exposure at therapeutic dose ranges, and the efficacy of odevixibat is driven by the intralumenal concentrations and not by systemic exposures. By inhibiting the IBAT with high selectivity and potency, odevixibat reduces the systemic accumulation of bile acids that result from cholestasis, relieves pruritus, improves liver function, and may modify the progression of liver damage in patients with any PFIC types without surgical intervention. Because odevixibat targets the final common pathways of elevated serum bile acids and pruritus rather than the underlying specific genetic mutations, odevixibat is expected to provide clinical benefit in all PFIC types. The clinical data collected to date support this expectation.

The efficacy of odevixibat in patients with PFIC was demonstrated in two Phase 3 studies. In the pivotal Phase 3 study A4250-005, a randomised, double-blind, placebo-controlled study, odevixibat was shown to significantly reduce serum bile acid levels and pruritus. Odevixibat also reduced the percentage of days the participant required soothing, and participants less often required help falling asleep and had fewer days needing to sleep with a caregiver. Treatment with odevixibat also led to improvements from baseline in liver function test results. In the long-term, open-label Phase 3 extension study A4250-008, sustained reductions in serum bile acid as well as improvements in pruritus assessments, growth, and other markers of liver function in participants treated up to 48 weeks were observed in an interim analysis.

5.3 Rationale

Odevixibat is a medical treatment for PFIC, a group of rare genetic disorders that result from defects in bile secretion and present with intrahepatic cholestasis. Odevixibat was first authorised for the treatment of PFIC in patients ≥ 6 months of age by the European Medicines Agency (EMA) on 16 July 2021 and by the United States Food and Drug Administration (FDA) on 20 July 2021 for the treatment of pruritus in patients with PFIC ≥ 3 months of age. Long-term follow-up information is needed to provide comprehensive effectiveness and safety data.

This registry aims to assess the real-world usage of odevixibat in the treatment of PFIC using prospectively collected data.

6 RESEARCH QUESTION AND OBJECTIVES

6.1 Research Question

The aim of this registry is to assess real-world safety data and to describe the effectiveness of odevixibat treatment in participants with PFIC.

6.2 Objectives

The objectives of this registry are to document the effectiveness and safety of odevixibat treatment in participants with PFIC.

6.2.1 Primary Objective

The primary objective of this registry is to evaluate the long-term safety of odevixibat based on adverse events (AEs).

6.2.2 Secondary Objectives

The secondary objectives of this registry are to evaluate the effectiveness of odevixibat on the following:

- First clinical event (surgical biliary diversion, liver transplant, death) for the overall population of participants with PFIC as well as the sub-populations of participants with different PFIC types.
- Surgical biliary diversion-free survival for the overall population of participants with PFIC as well as the sub-populations of participants with different PFIC types.
- Liver transplant-free survival for the overall population of participants with PFIC as well as the populations of participants with different PFIC types.
- Overall survival of the overall population of participants with PFIC as well as the sub-populations of participants with different PFIC types.

7 RESEARCH METHODS

7.1 Registry Design

This will be a long-term, observational, prospective, and voluntary participation registry designed to assess the real-world usage of odevixibat for the treatment of PFIC.

This registry will be conducted in South Korea.

The registry population will comprise participants with PFIC (all types) treated with odevixibat enrolled into the Ipsen registry. Participants who are homozygous for a known, disease-causing mutation of the PFIC family, compound homozygous for two disease-causing mutations, or heterozygous for one disease-causing mutation in combination with the clinical phenotype of intrahepatic cholestasis will be eligible. Participants who started odevixibat treatment before the implementation of the registry may also be enrolled.

As this is an observational registry designed to assess real-world data, the decision to prescribe the product must be taken prior to, and independently from, the decision to enrol the participant. This decision should be made in accordance with routine/standard clinical practice. The assignment of the participant to a particular therapeutic strategy is not decided in advance by the registry protocol but falls within current practice and the prescription of the medicine is independent from the decision to include the participant in the registry.

Participants will be treated in accordance with usual medical practice during their participation in this registry. No additional assessments or tests will be required by this protocol. All relevant data collected as part of routine medical care will be captured using the electronic Case Report Form (eCRF) by the investigator and transmitted to the sponsor. If some assessments included in this protocol are not routinely performed by the investigator, the corresponding sections in the eCRF do not need to be completed.

This registry will collect data at Baseline and at each Follow-up Visit. Follow-up Visits are scheduled as per routine clinical practice (recommended to occur at least every 3 months).

The duration of the registry is approximately 7 years from first participant, first visit. Following enrolment, participants will continue to participate in the registry for ≥ 2 years or until the time point of withdrawal of consent, treatment discontinuation, death, or the sponsor decides to discontinue the registry.

The primary objective of this registry is to evaluate the long-term safety of odevixibat treatment in participants with PFIC. The secondary objectives are to evaluate the effectiveness of odevixibat treatment in participants with PFIC including the first clinical event, surgical biliary diversion-free survival, liver transplant-free survival and overall survival.

7.2 Setting

7.2.1 Inclusion Criteria

To be included in the registry, the participant should fulfil the following inclusion criteria:

(1) Diagnosed with PFIC (all types) who have been prescribed odevixibat (independently of the decision to enrol the participant in this registry) by their treating physician

(2) On (or starting) active odevixibat treatment

Note: Participants can remain in the registry during odevixibat treatment interruptions

(3) Signed informed consent and assent, as appropriate. Consent/assent from the participant or legal representative should be obtained, as appropriate, before any registry data collection is conducted. Participants who turn 18 years of age (or legal age per country) while participating in the registry will be required to provide consent for themselves.

7.2.2 Exclusion Criteria

Participants will not be included in the registry if:

(1) Currently participating in a clinical trial with odevixibat

(2) Currently participating in any interventional clinical trial for PFIC

(3) Have any contraindication to odevixibat as per the approved label in South Korea.

Individuals who do not meet the criteria for participation in this study (screen failure) or who withdraw their consent may be rescreened. Rescreened participants should be assigned a new participant number. The informed consent process is described in Section 7.13.

7.2.3 Registry Population

Eligible participants will be participants with PFIC who have been prescribed odevixibat by their treating physician. To be enrolled, participants must meet all the inclusion criteria (Section 7.2.1) and none of the exclusion criteria (Section 7.2.2).

Enrolment will be based on the number of participants prescribed odevixibat and their willingness to participate in the registry, but the goal will be to enrol a minimum of 10 participants with PFIC (all types) in South Korea.

7.2.4 Registry Duration

The duration of the registry is approximately 7 years from first participant, first visit. Participants will be followed for ≥ 2 years. Following enrolment, participants will continue to participate in the registry until the time point of withdrawal of consent, treatment discontinuation, death, or the sponsor decides to discontinue the registry.

Participant enrolment will start on the date that odevixibat is commercially available and once the investigational site has been activated.

7.2.5 Registry Place

The registry will be implemented in South Korea.

7.2.6 Registry Schedule

The schedule of assessments that will be collected during the registry is summarised in Table 1. As this is an observational registry designed to assess real-world data, these assessments are not mandated by this protocol. If some assessments included here are not routinely performed by the investigators, the corresponding sections in the eCRF do not need to be completed. No additional assessments or tests will be required for the purpose of this study.

Table 1 Schedule of Assessments

Assessment/Procedure	Baseline Visit Day 1	Follow-up Visit(s) (as per routine clinical practice) / End of Study Visit[a]
Clinic visit	X	X
Informed consent[b]	X	-
Inclusion/exclusion criteria	X	-
Demographics and baseline characteristics[c]	X	-
Weight and height	X	X
Prior surgical procedures related to PFIC	X	-
General medical or surgical history	X	-
Prior and concomitant medications[d]	X	X
Concomitant vitamin supplementation[e]	X	X
Treatment with odevixibat (dates of treatment, dose, and interruption/discontinuation)	X	X
Biliary diversion surgery (date, type of surgery, and indication)	X	X
Liver transplantation (date and indication)[f]	X	X
Clinical symptoms[g]	X	X
Laboratory parameters[h]	X	X
Concomitant surgical procedures	X	X
AEs and Special Situations[i]	X	X
Death report form	-	X
Study discontinuation	-	X

AE=adverse event; ALT=alanine aminotransferase; AST= aspartate aminotransferase; GGT=gamma-glutamyl transferase; INR= international normalised ratio; PFIC=Progressive Familial Intrahepatic Cholestasis; UDCA=ursodeoxycholic acid.

[a] Follow-up Visits are recommended to occur at least every 3 months or as per the approved label in South Korea.

[b] If participant < 18 years of age (or the legal age of consent in the jurisdiction in which the registry is taking place), assent and parent or legally authorised representative consent will also be required. Participants who turn 18 years of age (or legal age per country) while participating in the registry will be required to provide consent for themselves.

[c] Including age, sex, PFIC type/genetic variant, date of birth (MM/YYYY), and date of PFIC diagnosis.

[d] Prior medications refer only to medications related to the treatment of PFIC, including but not limited to rifampicin and/or UDCA (dose). Treatments used up to 9 months prior to the first odevixibat dose are to be collected. If rifampicin and/or UDCA are discontinued, the date of discontinuation is to be provided. Concomitant medications include PFIC and non-PFIC oriented, including but not limited to rifampicin and/or UDCA.

[e] Type and dose of to be collected.

[f] At Baseline, listing for liver transplantation, including planned date of transplantation to be collected.

[g] Includes pruritus and sleep disturbance, if (semi-) objective scoring data are available. For non-naïve participants at Baseline: most recent values prior to first odevixibat dose to be collected.

[h] Laboratory parameters include, but are not limited to, AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, serum bile acid levels, and fat-soluble vitamin levels reported since the prior data collection. At the Baseline visit, historical (most recent values up to 9 months prior to the first odevixibat dose) values are also to be provided if available.

[i] Adverse event collection begins once the informed consent has been signed and will end 30 days after the last odevixibat dose (unless consent was withdrawn). Special situations include pregnancy or breastfeeding status and overdose, off-label use, misuse, abuse, occupational exposure, medication error, and lack of effectiveness (Section 9.1.3).

7.2.7 Registry Visit(s)

Visits will be done in accordance with routine clinical practice (Follow-up Visits are recommended to occur at least every 3 months). The registry will assess data collected at the Baseline Visit and Follow-up Visits.

7.2.7.1 Baseline

Investigators at participating sites will identify participants who fulfil the inclusion and none of the exclusion criteria. Signed informed consent should be obtained prior to enrolment according to local regulations, and once inclusion and exclusion criteria have been satisfied. If the participant is < 18 years old (or the legal age of consent in the jurisdiction in which the registry is taking place), assent and parent or legally authorised representative consent will also be required.

For this registry, the following variables will be captured from Baseline Visit records as available:

- Age, sex, weight, height, PFIC type/genetic variant, date of birth (MM/YYYY), and date of PFIC diagnosis
- General medical or surgical history
- Prior surgical procedures related to PFIC, including but not limited to prior biliary diversion surgery (date and type of surgery)
- Prior and concomitant medications
    - Prior medications refer only to medications related to the treatment of PFIC, including but not limited to rifampicin and/or UDCA taken up to 9 months prior to the first odevixibat dose
    - Concomitant medications include PFIC and non-PFIC oriented, including but not limited to rifampicin and UDCA
- Concomitant vitamin supplementation
- Odevixibat treatment dose and start date
- Clinical symptoms: pruritus and sleep disturbance, if (semi-) objective scoring data are available. For non-naïve participants: most recent values prior to first odevixibat dose to be collected.
- Planned biliary diversion surgery (planned date and indication)
- Listing for liver transplantation (planned date of transplantation and indication)
- Laboratory parameters, including ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, GGT, international normalised ratio (INR), albumin, creatinine, sodium, platelet count, serum bile acid levels, and fat-soluble vitamin levels. Historical values (most recent values up to 9 months prior to the first odevixibat dose) are also to be provided at baseline if available.
- Pregnancy or breastfeeding status

7.2.7.2 Follow-up Visit(s)/End of Study Visit

The participants will attend a clinic visit and assessments will be performed according to routine clinical care. For this registry, the following variables will be captured from medical records as available:

Odevixibat and Concomitant Medications Data Collection:

- Odevixibat dose (if changed/discontinued, provide date and reason)
- Concomitant medication (PFIC and non-PFIC oriented, including but not limited to rifampicin, UDCA)
- Concomitant vitamin supplementation

Periodic Safety Data Collection:

- Adverse events
- Weight and height
- Special situation (including pregnancy or breastfeeding status)
- Follow-up of children delivered to women who were exposed to odevixibat during pregnancy or while breastfeeding for up to 12 months (in case of live birth). Note: follow-up data to be collected via routine pharmacovigilance activities.
- Death (date and cause)

Periodic Effectiveness Data Collection:

- Laboratory parameters, including AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, serum bile acid levels, and fat-soluble vitamin levels reported since the prior data collection
- Biliary diversion surgery (date and indication)
- Liver transplantation (date and indication)
- Cancellation of planned biliary diversion surgery and reason for cancellation
- Removal from listing for liver transplantation and reason for removal from the list
- Clinical symptoms: pruritus and sleep disturbance, if (semi-) objective scoring data are available

7.2.8 Registry Discontinuation/Withdrawal

The participant can withdraw (or be withdrawn if the participant is a child upon legal representative's decision) from the registry at any time. The date and primary reason for withdrawal should be recorded in the eCRF as well as if the participant stopped odevixibat or not.

For registry results to remain unbiased, it is important that no data are modified; as a result, the data collected in clinical studies need to remain untouched for results to be trusted. Should the participant withdraw from the registry, no further data will be collected; nevertheless, data collected up to the time of the withdrawal will be kept for analysis, safety, and integrity of registry results.

The participant will be withdrawn from the registry if:

- They enrol in any interventional clinical trial
- The participant is no longer receiving odevixibat (except if odevixibat is discontinued due to a safety concern, in such cases the participant will be monitored for safety, see Section 9.4 for follow-up of AEs and Section 9.1.3.1 for follow-up of pregnancies)

Investigators may decide to stop their participant's participation in the registry at any time without consequences on the normal participant follow-up.

7.2.9 Treatment Discontinuation

Odevixibat treatment may be discontinued based on the judgement of the treating physician, including in the event of any serious adverse events (SAEs), AEs, or Special Situations (see Section 9.1.3 for definition of Special Situations) deemed by the investigator to warrant treatment discontinuation. In the event of pregnancy, odevixibat treatment may be discontinued based on the judgement of the treating physician (Section 9.1.3.1).

Discontinuation of treatment due to AEs should be distinguished from discontinuation/withdrawal from the registry due to participant/parent decision or end of follow-up.

If AEs or their sequelae (any AE, based on the investigator's opinion, not only those assessed as related) persist after the date of odevixibat discontinuation the investigator must ensure that the participant receives appropriate medical follow-up and this should be properly documented in the participant's medical records.

All participants discontinuing odevixibat treatment will be followed up to 30 days after last odevixibat dose (unless consent is withdrawn).

7.2.10 Early Registry Termination

The sponsor can decide at any time to discontinue the registry for any reason. Investigators will be informed of the decision. Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) and Competent Authorities (CAs) will also be informed if required by local regulations.

7.3 Endpoints and Variables

7.3.1 Endpoints

7.3.1.1 Safety Endpoints

- All AEs, based on the incidence, severity, causality, outcome, action taken, and seriousness

7.3.1.2 Effectiveness Endpoints

- Event-free survival (EFS), defined as time from the start of odevixibat treatment to the first occurrence of surgical biliary diversion, liver transplant, or death
- Surgical biliary diversion-free survival, defined as time from the start of odevixibat treatment to the first occurrence of surgical biliary diversion or death
- Liver transplant-free survival defined as time from the start of odevixibat treatment to the first occurrence of liver transplant or death
- Overall survival, defined as the time from the start of odevixibat treatment to death

7.3.2 Variables

Only the data collected as part of routine medical care will be captured using the eCRF by the investigator. If some assessments included here are not routinely performed by the investigator, the corresponding sections in the eCRF do not need to be completed.

7.3.2.1 Demographic and Baseline Characteristics

- Age, sex, weight, height, PFIC type/genetic variant, date of birth (MM/YYYY), and date of PFIC diagnosis

- Prior surgical procedures related to PFIC, including but not limited to prior biliary diversion surgery (date and type of surgery)
- Laboratory parameters, including ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, serum bile acid levels, and fat-soluble vitamin levels. Historical values (most recent values up to 9 months prior to the first odevixibat dose) are also to be provided at baseline if available.
- Clinical symptoms: pruritus and sleep disturbance, if (semi-) objective scoring data are available. For non-naïve participants: most recent values prior to first odevixibat dose to be collected.
- Pregnancy or breastfeeding status
- Planned biliary diversion surgery (planned date)
- Listing for liver transplantation (planned date of transplantation)

7.3.2.2 Prior and Concomitant Medication and Vitamin Supplementation

The registry will assess the use of prior and concomitant medication and vitamin supplementation (e.g., dose, frequency, start and end dates, and reason for prescription at the Baseline Visit and at the Follow-up/End of Study Visits if available). This includes but is not limited to prior/current use of odevixibat, rifampicin, and UDCA. The reasons for prescription should be reported in medical history or as an AE if the event occurs after enrolment.

7.3.2.3 Concomitant Surgery

The registry will assess the following data on concomitant surgery (including biliary diversion surgery and liver transplantation as outlined in Section 7.3.1.1) at the Baseline Visit and at the Follow-up/End of Study Visits if available:

- Surgical procedure name
- Indication
- Reason for concomitant surgery
- Date of surgery

7.3.2.4 Weight and Height

The registry will assess weight and height for all participants at the Baseline Visit and at the Follow-up/End of Study Visits (only if clinic visit) if available.

7.3.2.5 Safety Variables

The registry will assess the following AE data from the signing of the informed consent form (ICF) until 30 days after the last dose of odevixibat:

- Adverse Events. Note: any change in laboratory values in registry participant deemed as clinically significant by the investigator will be reported as an AE
- Death (date and cause), irrespective of causality, including date and cause of death
- Special situations (including pregnancy or breastfeeding status; Section 9.1.3)

If AEs or their sequelae (any AE, based on the investigator's opinion, not only those assessed as related) persist after the date of odevixibat discontinuation the investigator must ensure that the participant receives appropriate medical follow-up and this should be properly documented in the participant's medical records.

Any parameters collected during the registry (e.g., laboratory parameters) may be assessed from a safety perspective.

7.3.2.6 Effectiveness Variables

- Longitudinal serum biochemical parameters, including pre- and post-odevixibat treatment changes (as far as available) of AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, serum bile acid levels, and fat-soluble vitamin levels
- Clinical outcomes: surgical biliary diversion, liver transplantation, and overall survival
- Clinical symptoms: pruritus and sleep disturbance, if (semi-) objective scoring data are available

7.3.2.7 Treatment Variables

The registry will collect the following data on odevixibat treatment at the Baseline Visit and at the Follow-up/End of Study Visits if available:

- Odevixibat start date, dosage, and treatment end date
- Reasons for dose modification/treatment discontinuation

7.4 Data Sources

Source data include any data collected as part of routine medical care which will be captured in an eCRF by the investigator and transmitted to the sponsor for analysis.

7.5 Registry Size

No formal sample size calculations have been performed for this registry.

Enrolment for this registry will be based on the number of participants prescribed odevixibat and their willingness to participate in the registry, but the goal will be to enrol a minimum of 10 participants with PFIC (all types) in South Korea.

7.6 Data Management

Data management will be conducted by a Service Provider (SP) directed by the sponsor's Global Medical Affairs Biometry Department. All data management procedures will be completed in accordance with the Standard Operating Procedures (SOPs) of Ipsen and the contracted SP.

7.6.1 Data Collection

The specific data to be collected at each visit, if available, are summarised in the schedule of assessments (Table 1).

All relevant data collected as part of routine medical care will be captured using the eCRF by the investigator and transmitted to the sponsor. If some assessments included in the protocol are not routinely performed by the investigator, the corresponding sections in the eCRF do not need to be completed.

Data will be collected in an eCRF available on the internet utilising a secured website. The sponsor and the SP will ensure that the eCRF developed is appropriate to capture the data required by the protocol. The sponsor will ensure that the entrusted SP uses adequate technology to ensure data security transfer and backup.

Each site is required to have a computer and internet connection available for site entry of clinical data. Data entry in the eCRF will be performed by the investigator or by the designated person from their team and to ensure confidentiality and security of the data, all entries into the

eCRF will be made under the electronic signature (e-signature) of the person performing the action (username and password). Only sponsor-authorised users will be given access to the eCRF as appropriate for their responsibilities. All users must have successfully undergone software application training prior to entering data into the eCRF.

Once the signed informed consent (and assent, if applicable) has been obtained, the eCRF will provide a numeric participant identifier to pseudonymise the data from each participant. Data for each participant must be entered into the eCRF within 5 days of the participant's enrolment, each Follow-Up Visit, and the End of Study Visit. Data transmitted will be pseudonymised and will be identified only by the participant number. Only investigating sites will be able to link the numeric identifier to each participant's identity.

In compliance with Good Pharmacoepidemiology Practices (GPP), the participant's medical records should be clearly marked and permit easy identification of their participation in this registry.

Medical and surgical history, vitamin supplementation, concomitant surgeries, Special Situations, and AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and prior/concomitant medication will be coded using the World Health Organization Drug Dictionary by the contracted SP and reviewed by the sponsor.

Queries will be edited in English and addressed to the investigational site using the eCRF.

Investigators or authorised registry staff members will answer the queries directly into the eCRF.

The eCRF will be signed electronically by the investigator to certify that all the data recorded in it are consistent with the source documents and reflect the status of the participant during the corresponding part of the registry.

7.6.1 Data Archiving and Retention

During the site initiation visits, the monitor must ensure that the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

Registry documents should be retained for at least 10 years after registry completion. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

If the investigator relocates or retires, or otherwise withdraws their responsibility for maintenance and retention of registry documents, the sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

7.7 Data Analysis

7.7.1 Analyses Population Definitions

Safety Population: all participants who have taken at least one dose of odevixibat following enrolment.

7.7.2 Statistical and Analytical Methods

A statistical analysis plan describing the planned statistical analysis in detail with table, figure, and listing templates will be developed as a separate document and will be finalized prior to the first data analysis.

Analyses will be primarily descriptive.

Descriptive summaries of continuous variables will include the number of observations, mean, standard deviation, median, range, and 95% confidence interval (CI) of the mean, median and/or inter-quartile range when appropriate. Descriptive summaries of categorical variables will include frequencies and percentages. Percentages will be based on the number of non-missing observations. Missing data will also be summarised.

The number and relative frequency of participants who prematurely discontinue participation in the registry and reasons for discontinuation will be tabulated. Demographic and baseline characteristics of participants will be summarized using descriptive statistics.

7.7.2.1 Safety Evaluations

Descriptive statistics on AEs incidence and characteristics will be presented.

Adverse events will be coded according to MedDRA and will be classified by preferred term (PT) and system organ class (SOC). Adverse event listings will be presented by participant, SOC, and PT. All AEs and Special Situations will be included in the participant data listings.

The incidence of all reported AEs, serious and nonserious treatment-related AEs, all SAEs, all nonserious AEs, AEs leading to death, AEs leading to treatment discontinuation, and Special Situations will be tabulated separately. In addition, summary tables for AEs will be presented by severity and drug relationship (investigator-reported causality assessment).

7.7.2.2 Effectiveness Evaluations

Effectiveness data will be included in the participant data listings using the Safety Population. Analyses and summary tables will be presented. Data will be tabulated descriptively.

The incidence of biliary diversion surgery, liver transplantation, or death will be assessed using descriptive statistics once the participants with PFIC (all types) treated with odevixibat have been followed for ≥ 2years. It is anticipated that the analyses for each PFIC type will be conducted if feasible. Depending upon rate of enrolment, it may be necessary to pool participants with PFIC3, PFIC4, PFIC5, and PFIC6 to achieve a sufficient number of participants for the analysis. Depending on the data available, EFS endpoints may be summarized using the Kaplan-Meier method. Median time to event with 2-sided 95% CIs and the first and third quartiles will be reported. Survival curves will be presented as well. In addition, survival probability estimates at 6, 12 months and then every 6 months and the associated 2-sided 95% CI will be reported.

7.7.2.3 Treatment Evaluation

The treatment duration as well as the dose of odevixibat at each visit will be described. The mean dose/year will be calculated. Dose modifications, interruptions, and duration of treatment will be summarised.

7.7.3 Subgroup Analyses

Depending on the rate of enrolment, effectiveness and safety endpoints will be analysed for the overall population of participants with PFIC as well as the sub-populations of participants with different PFIC types.

7.7.4 Interim Analyses

Interim analyses will be performed-annually and/or for sponsor decision making purposes.

7.8 Quality Control

7.8.1 Routine Monitoring and Monitoring Procedures

The monitoring procedures of the registry may be conducted by an external SP directed by the sponsor's Global Medical Affairs, Clinical Operations Department. All monitoring activities will be completed in accordance with Ipsen and the SP's SOPs and as per the monitoring plan. The monitoring of the registry should ensure that the rights and wellbeing of the participants are protected, that the registry data are accurate (complete and verifiable to source data) and that the registry is conducted in compliance with the protocol, GPP (ISPE 2015), and regulatory requirements.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry.

Ipsen monitoring standards require full verification for the presence of informed consent/assent, adherence to the inclusion/exclusion criteria, and documentation of SAEs and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the registry-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

The frequency of the monitoring may be adapted according to participant recruitment rate or any other suitable reason. The investigator will allow direct access to all relevant files (for all participants) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site investigator or authorised registry staff members must complete the eCRF in a timely manner and on an ongoing basis to allow regular review by the registry monitor.

Whenever a participant's name is revealed on a document required by the sponsor (e.g. laboratory printouts), the name must be blacked out permanently by the site personnel and annotated with the participant number as identification.

Before initiation, at a site initiation visit or remote site initiation visit, an Ipsen/delegated SP representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the registry, Ipsen (or designee) employs several methods of ensuring protocol, GPP, and Good Pharmacovigilance Practices (GVP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture/data entry, the adherence to the protocol and to GPP and GVP, and the progress of enrolment. Key registry personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralised Ipsen/delegated SP. In addition to on-site monitoring visits, the sites will receive regular monitoring phone calls from monitors, to:

- Allow for early identification and direct solving of any issue with the site
- Follow the enrolment of the participants listed in the participant screening log, to remind the sites to propose the registry to all eligible participants presenting for a consultation, and to identify any issue related to recruitment (e.g. to identify a site with specific difficulties in collecting informed consents, etc.)
- Follow the included participants and avoid/limit the drop out of participants
- Answer any questions related to the completion of the eCRF

7.8.2 Inspections and Auditing Procedures

Authorised personnel from external CA and sponsor-authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory, and quality requirements are fulfilled in all studies performed by the sponsor.

Auditors and inspectors must have direct access to registry documents and site facilities, and to any other locations used for the purpose of the registry in question (e.g. laboratories).

In the event of the site being notified directly of a regulatory inspection, the investigator must notify the sponsor representative as soon as possible, to assist with preparations for the inspection.

7.8.3 Source Data Verification

According to the registry monitoring plan, during monitoring visits, the monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported in the eCRF. However, this verification will only address key data of the eCRF and only be based on available investigator's participant notes.

The source documents must, as a minimum, contain the following:

- A statement that the participant is included in a registry
- The date on which informed consent (and assent, if applicable) was obtained prior to participation in the registry
- The identity of the registry, diagnosis, eligibility criteria, visit dates, any AEs, and associated concomitant medication

Definitions for source data and source documents are given below:

- Source data: all original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the registry. Source data are contained in source documents (original records or certified copies)
- Source documents: original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the registry)

The participant (if an adult) or their parent/legally authorised representative (if the participant is not an adult) must have consented to their medical records being viewed by sponsor authorised personnel, and by local, and possibly foreign, CA. This information is included in the ICF.

7.8.4 Data Quality

The investigator is responsible for the validity of all data collected and must provide an e-signature, consisting of an individual and confidential username and password combination, to each eCRF to attest to the accuracy and completeness of all the data. This e-signature is declared to be the legally binding equivalent of the handwritten signature.

The eCRF is a validated system with restricted access to staff only with a personal username and password. The eCRF data transferred from the investigational site to the assigned Data

Management group will be reviewed for completeness, consistency, and protocol compliance. Inadequate data can be queried for clarification and any queries generated during the data management process will be tracked by the contracted data management SP according to the Data Handling Manual.

Data consistency and accuracy will be ensured by running real-time checks at the time of data entry in the eCRF. All corrections to the eCRF data are recorded in the system audit trail which automatically tracks the data changes, the user, the time, and the reason. The audit trail function will also allow the changes and clarifications made to be viewed.

7.9 Limitations of the Research Methods

This is an observational, prospective registry designed to collect and assess real-world data on participants with PFIC treated with odevixibat. Participants will be treated and monitored in accordance with usual medical practice during their participation in this registry. Only relevant data collected as part of routine medical care will be captured using an eCRF by the investigator. If some assessments in the protocol are not routinely performed by the investigator, the corresponding sections in the eCRF do not need to be completed. Therefore, some key data may be missing, and the assessments performed and the data provided from different sites may vary depending on local medical practice. This, however, is an inherent limitation to the observational design of this registry, crucial in gathering real-world data on participants with PFIC treated with odevixibat.

No formal statistical testing will be performed and all the analyses will be primarily descriptive in nature.

7.10 Other Aspects

None.

7.11 Regulatory and Ethics Approval

The SP and/or sponsor will ensure that all legal and regulatory aspects are covered, including submitting the protocol to the national CA in accordance with local regulatory requirements and obtaining any necessary approvals from the appropriate regulatory authorities prior to registry initiation.

Before initiating the registry, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the registry protocol/amendment(s), ICF, any ICF updates, participant recruitment procedures (e.g. advertisements), any written information to be provided to participants such as the Participant Information Sheet, and a statement from the IEC/IRB that they comply with local requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

Any changes to the protocol after IEC/IRB approval will require a formal protocol amendment. Changes that do not affect participant safety or data integrity are classified as administrative changes and generally do not require ethics approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethics approval of administrative changes will be obtained if required by local/site IEC/IRB. Any protocol amendments will be submitted to CA and IECs/IRBs according to local regulatory requirements.

7.12 Compliance with Good Pharmacoepidemiology Practice and Ethical Considerations

This registry will be conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (Helsinki 1964, and all subsequent amendments), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the International Ethical Guidelines for Epidemiological Studies, Council for International Organizations of Medical Sciences (2009).

This registry is observational and falls outside the scope of European Commission European Union (EU) Directive 2005/28/EC and Regulation (EU) 536/2014.

This registry complies with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.

This registry will also follow the recommendations of the International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research (GEP 2007), the International Society for Pharmacoepidemiology Guidelines for GPP (ISPE 2015), the EMA Guideline on GVP (Module VI; Module VIII) (unless safety data collection and reporting is dictated by relevant local legislation in which case that must be followed instead), and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP 2010).

This registry will also be conducted in compliance with the ENCePP Code of Conduct for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies (ENCePP 2011), Ipsen's Code of Ethical Conduct, and any other applicable local regulations.

7.13 Informed Consent

Prior to the registry entry, the investigator (or a person designated by the investigator) will explain the nature, purpose, benefits, and risks of participation in the registry to each participant, the participant's parents, or the participant's legally authorised representative. Participants (if adult) or parents/legally authorised representatives (if not an adult) will be provided with a Participant Information Sheet containing information in readily understood language on the benefits and risks associated with participating in the registry and will be given sufficient time to discuss any concerns and to consider their decision to participate. The signed informed consent (and assent, if applicable) must be obtained prior to the participant entering the registry and maintained during the registry. The sponsor will provide a template of the ICF.

The ICF and any participant recruitment materials will follow ICH Good Clinical Practice (GCP), local regulatory requirements, and legal requirements, including applicable privacy laws.

The final versions of the forms must be approved by the sponsor and the IEC/IRB and must contain all the elements included in the template form, in language readily understood by the participant. Each participant's original ICF, personally signed and dated by the participant, the participant's parents, or the participant's legally authorised representative, and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply all enrolled participants with a copy of their signed ICF.

The ICF may need to be revised during the registry if new information becomes available that may be relevant to the safety of the participant or as a result of protocol amendments. In this instance, approval should always be given by the IEC/IRB. It is the investigator's responsibility

to ensure that all participants subsequently entered into the registry, as well as those currently in the registry, sign the amended form. This is documented as previously described. Parents of participants (or participants' legally authorised representatives) and participants having completed the registry should be informed of any new information that may impact on their welfare/wellbeing.

The investigator should, with the consent/assent of the participant, the consent of the participant's parents, or the participant's legally authorised representative, inform the participant's primary General Practitioner about their participation in the registry.

For participants already enrolled in the registry, eligibility must be reconfirmed, and a new written informed consent must be obtained as per local regulations for any substantial protocol amendments before implementing them.

Participants already enrolled in the registry that reach the legal age of consent as per the jurisdiction in which the study is taking place must provide a new written informed consent to remain in the study.

8 PROTECTION OF HUMAN PARTICIPANTS

8.1 Data Collection, Privacy, and Confidentiality

After recruitment, each site will be assigned a unique identification number. At enrolment, each participant will be assigned a unique identification number by the sponsor.

Data will be collected in an eCRF available on the internet utilising a secured website. Data entry in the eCRF will be performed by the investigator or by the designated person from their team to ensure confidentiality and security of the data.

Any data transmitted will be pseudonymised and will be identified only by the participant number. Only investigating sites will be able to link the numeric identifier to each participant's identity.

The participant must be informed that their personal registry-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent/assent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by the sponsor's auditors or other authorised personnel appointed by the sponsor, by appropriate IEC/IRB members, and by inspectors from regulatory authorities.

In case of public data presentation or publication, personal identifiers of participants will not be used.

8.2 Data Protection

As the data controller (registry sponsor) is in France, this registry will be conducted in compliance with EU data protection requirements and in particular the EU General Data Protection Regulation 2016/679 and French Act n°78-17 of 6 January 1978 on Data Processing, Data Files, and Individual Liberties.

In addition, the sponsor will ensure that all applicable local regulatory requirements for data protection are met.

8.3 Insurance

Insurance may be contracted according to local regulatory requirements.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Events

AE Definition
An AE is any untoward medical occurrence in a patient/participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Note: An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not related to the medicinal product.

Events <u>Meeting</u> the AE Definition
Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition. New condition detected or diagnosed after treatment administration even though it may have been present before the start of the registry. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either registry treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. For studies involving marketed products in established indications: The signs, symptoms, and/or clinical sequelae resulting from lack of effectiveness will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless judged by the investigator to be more severe than expected for the participant's condition. Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the registry that do not worsen.

9.1.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other important medical event Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse. Any radiological or clinical fracture must be reported as serious (seriousness criteria should be "important medical event" if no other seriousness criteria are present (e.g. hospitalisation)).
Is a suspected transmission of any infectious agent by an authorised medicinal product

9.1.3 Special Situations

A Special Situation is any incidence of drug exposure during pregnancy (i.e. drug exposure to a foetus in utero (whether the foetus is exposed by the mother taking the product)) or breastfeeding, overdose, off-label use, misuse, abuse, occupational exposure, medication errors, or lack of therapeutic effectiveness whilst using the medicinal product. A "Special Situation" should be collected by the investigator and reported to Ipsen whether or not these "Special Situations" are associated with an AE.

9.1.3.1 Pregnancy or Breastfeeding Status

Pregnancy

There are no or limited data from the use of odevixibat in pregnant participants. Animal studies have shown reproductive toxicity. Odevixibat is not recommended during pregnancy and in participants of childbearing potential not using contraception.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the product has interfered with a contraceptive method. If pregnancy occurs whilst using the medicinal product, the outcome of the pregnancy will then need to be collected. This applies irrespective of whether the pregnancy is considered related to interference by the product with a contraceptive method.

Details of all pregnancies in participants will be collected from the signing of the ICF and the participant will be followed throughout her pregnancy and the health status of the baby will be verified up until one year of age.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital abnormalities, ectopic pregnancy) are considered SAEs. If there is an abnormal pregnancy outcome or an AE is reported in the foetus/neonate/child following exposure to a marketed Ipsen product, attempt to follow-up until one year after delivery.

The investigator must instruct all participants to inform them immediately should they become pregnant whilst using odevixibat.

Reports of pregnancy must be reported to Ipsen within 24 hours of the investigator's knowledge.

Breastfeeding

It is unknown whether odevixibat or its metabolites are excreted in human milk. Odevixibat has low absorption following oral administration, and breastfeeding is not expected to result in exposure of the infant at the recommended doses. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from odevixibat therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the mother.

Reports of breastfeeding must be reported to Ipsen within 24 hours of the investigator's knowledge.

9.1.3.2 Overdose, Off-label Use, Misuse, Abuse, Occupational Exposure, Medication Error, and Lack of Effectiveness

Overdose

Overdose refers to any dose higher than the maximum recommended dose in the approved label in South Korea. For products which require gradual titration, any dose (initial or maintenance) which is higher than the recommended regime or labelling text will be assessed as 'overdose'. Overdose should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be

reported in the AE eCRF page and AE number should be mentioned in Special Situations eCRF page. All overdoses should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

Off-label Use

Off-label use relates to situations where the medicinal product is intentionally prescribed and used for a medical purpose not in accordance with the terms of the marketing authorisation.

Off-label use should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in Special Situation eCRF page. All off-label use should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the Marketing Authorisation.

Misuse should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in Special Situations eCRF page. All misuse should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

Abuse

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Abuse should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in Special Situations eCRF page. All abuse should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

Occupational Exposure

Occupational exposure refers to the exposure to a medicinal product as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Occupational exposure should be reported in the Special Situations eCRF. All occupational exposure should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

Medication Error

Medication error is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the participant.

Medication error should be reported in the Special Situations eCRF whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be

reported in the AE eCRF page and AE number should be mentioned in Special Situation eCRF page. All medication error should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

Lack of Effectiveness

Lack of effectiveness can be defined as the extent to which a drug does not achieve its intended effect in the usual clinical setting.

Lack of therapeutic effectiveness should be reported in the Special Situations eCRF page whether or not it was associated with an AE. If the Special Situation is associated with an AE, the AE should be reported in the AE eCRF page and AE number should be mentioned in Special Situation eCRF page. All lack of therapeutic effectiveness should be reported to Ipsen within 7 calendar days using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable.

9.1.4 Adverse Events of Special Interest

Not applicable.

9.2 Time Period and Frequency for Collecting and Reporting of AE, Special Situation, and SAE Information

9.2.1 Collection of AEs/SAEs/Special Situations in the eCRF

The collection and reporting of AEs will follow regulations related to non-interventional studies (NIS).

All AEs, whether they are serious/nonserious or related/unrelated, and all Special Situations should be collected in the eCRF during the registry. Adverse events will be assessed according to severity, causality, outcome, action taken, and seriousness.

All AEs will be collected in the eCRF from the signing of the ICF until 30 days after the last dose of odevixibat or until consent is withdrawn.

9.2.2 Reporting of SAEs, Nonserious Adverse Drug Reactions, and Special Situations to Sponsor Pharmacovigilance

Investigators must report to Ipsen Pharmacovigilance all the following events using the electronic data collection tool or the "Adverse Event and Special Situation reporting form for non-interventional studies" (134232-FOR) if the electronic data collection tool is unavailable (Table 2):

- All SAEs: related and non-related
- All related nonserious AEs (adverse drug reactions)
- Any Special Situations (see definitions in Section 9.1.3)

Table 2 Primary Data Collection Non-Interventional Studies

Safety Event	Collected on the eCRF	Reported on the "AE and Special Situation NIS Form" (134232-FOR) to Ipsen Global Pharmacovigilance (if the electronic data collection tool is unavailable)
Nonserious AE	All AEs related or not	Only the related AEs — within 7 calendar days of awareness
SAE	All SAEs related or not	All — within 24 hours of awareness
Pregnancy	All pregnancies	All — within 24 hours of awareness[a]
Special Situations	All Special Situations related or not (regardless of whether associated with an AE)	All (regardless of whether associated with an AE) — within 7 calendar days of awareness

AE=adverse event; eCRF=electronic case report form; NIS=Non-interventional study; SAE=serious adverse event.

[a] Drug Exposure during Pregnancy Form (080479-FOR) should also be completed for all pregnant and/or breastfeeding participants who consented to follow-up and up until 12 months of the pregnancy outcome (in case of live birth).

All SAEs and pregnancies (Special Situation) will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours (once known), as indicated below. The investigator will submit any updated SAE and pregnancy data to the sponsor within 24 hours of it being available.

All nonserious related AEs and Special Situations (except pregnancy) will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 7 calendar days (once known), as indicated below.

AE (related), SAE, and Special Situation Reporting to the sponsor by an Electronic Data Collection Tool

- The primary mechanism for reporting an AE (related), SAE, or Special Situation to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper NIS AE form (134232-FOR) to report the SAE and pregnancy within 24 hours of awareness of the event and to report nonserious related AE and Special Situation (excluding pregnancy and Special Situations associated with an SAE) within 7 calendar days. The site will enter the AE (related), SAE, and Special Situation data into the electronic system as soon as it becomes available again.
- After the registry is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new AE (related), SAE, or Special Situation from a participant or receives updated data on a previously reported AE (related), SAE, or Special Situation after the electronic data collection tool has been taken off-line, then the site can report this information on a paper NIS AE form (134232-FOR) (see next section).

All AEs will be processed by Ipsen according to their relevant SOPs. This includes the follow up of AE reports with the investigator, as required.

If an AE occurs with a "non-Ipsen product", the investigator should consider informing the CA in the Member State where the event occurred or to the Marketing Authorisation Holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

9.2.3 Mandatory Information for reporting an Adverse Event

The following information is the minimum that must be provided to Ipsen's Pharmacovigilance contact within 24 hours of awareness for SAE and pregnancy or within 7 days of awareness for a nonserious related AE for each AE:

- Participant identifier
- Product name
- Adverse event description including assessment of causal relationship and seriousness
- Investigator name and contact details

The additional information included in the AE report form must be provided to Ipsen as soon as it is available.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications. The investigator should also provide the batch number and expiry date of the concerned product wherever possible.

9.3 Method of Detecting AEs, SAEs, and Special Situations

The method of recording, evaluating, and assessing causality of AEs, SAEs, and Special Situations and the procedures for completing and transmitting SAE/related AE reports are provided below.

Care will be taken not to introduce bias when detecting AEs, SAEs, and/or Special Situations. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

AE/SAE/Special Situation Recording
• When an AE/SAE/Special Situation occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/Special Situation information in the eCRF. • It is not acceptable for the investigator to send photocopies of the participant's medical records to sponsor pharmacovigilance in lieu of completion of the AE/SAE/Special Situation eCRF page. • There may be instances when copies of medical records for certain cases are requested by sponsor pharmacovigilance. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor pharmacovigilance.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/Special Situation.

Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the registry and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in their assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor pharmacovigilance. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to sponsor pharmacovigilance.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

9.4 Follow-up of AEs, SAEs, and Special Situations

After the initial AE/SAE/Special Situation report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs including SAEs (defined in

Section 9.1) and Special Situations (defined in Section 9.1.3) will be followed until resolution, the event is otherwise explained, the participant is lost to follow-up, or up to 30 days after last dose of odevixibat. Further information on follow-up procedures is provided below.

Follow-up of AEs, SAEs, and Special Situations
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the registry or during a recognised follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

9.5 Regulatory Reporting Requirements for SAEs and Related AEs

Prompt notification by the investigator to the sponsor of a SAE/related AE is essential so that legal obligations and ethical responsibilities towards the safety of participants are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of any medicinal product. The sponsor will comply with country-specific post-authorisation regulatory requirements relating to safety reporting to the regulatory authorities, IECs/IRBs, and investigators.

An investigator who receives an investigator safety report describing a SAE, a non-serious drug-related adverse event or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it and will notify the IEC/IRB, if appropriate according to local requirements.

9.6 Expectedness of Events

The expectedness of an AE shall be determined by the sponsor according to the approved label in South Korea.

The reference document for assessing expectedness of AEs/events in this registry will be the current approved label in South Korea for odevixibat.

9.7 Safety Review

The sponsor will review safety data on an ongoing basis as per routine pharmacovigilance and sponsor governance. There will be regular updates in the Periodic Benefit-Risk Evaluation Reports and Periodic Safety Update Reports.

10 PLANS FOR DISSEMINATING AND COMMUNICATING REGISTRY RESULTS

10.1 Registry Reports

A final report will be prepared once the registry is complete.

10.2 Publication Policy

10.2.1 Ethical Obligation to Publish

Ipsen is committed to disclosing information about the studies it sponsors. Results may be communicated at scientific meetings and all reasonable efforts must be made to seek publication of key data in a peer-reviewed scientific journal.

As a minimum, summary results of the final data should be posted in an associated publicly available database.

10.2.2 Company-sponsored Publications

Specific publication concepts, including data to be covered, target congress/journal, and proposed authors, should be discussed with the appropriate Global Medical Publications and Communications (GMPC) Manager, reviewed by the Publications Strategy Group, and incorporated in the relevant publication plan before initiation.

All company-sponsored publications arising from this registry will be reviewed by relevant functions at Ipsen, coordinated by GMPC as per the applicable SOP. Requests and suggestions for changes will be discussed with all authors (and medical writer, if applicable). Resolution of scientific differences in the presentation or interpretation of the registry findings will be conducted along principles of honest scientific debate and mediated by the lead author. Review comments must be answered before a final version for submission can be approved by the authors. All company-sponsored manuscripts should be published as immediate open access.

10.2.3 Non-company-sponsored Publications

For publications not sponsored by Ipsen, the sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or manuscript before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. Ipsen will undertake to comment on the draft documents within the time period agreed in the contractual arrangements (different time periods are allowed according to the types of publication), including registry agreements, governing the relationship between Ipsen and authors (or the author's institution). Requested amendments should be carefully considered by the author(s), provided they do not alter the scientific value of the material. Where possible, non-company-sponsored manuscripts should be published as immediate open access.

10.2.4 Authorship

Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors guidelines (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). Those named as authors, whether employed by Ipsen or an Ipsen affiliate, or external investigators, 'should have participated sufficiently in the work to take public responsibility for the content'. Time spent on authorship activities should not be reimbursed.

Authorship should be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved

All authors of a publication should meet all four criteria. Every author must agree to their inclusion in the list of authors. Professional medical writing support may be used.

10.2.5 Intellectual Property

If patentability would be adversely affected by data publication, publication will be delayed until (i) a patent application has been filed for the content of the publication in accordance with applicable provisions of the registry agreement concerned, (ii) Ipsen consents to the publication, or (iii) after such a time as may be agreed in the contractual arrangements, including registry agreements, governing the relationship between Ipsen and authors (or authors' institution) after receipt of the proposed publication by Ipsen, whichever of these provisos (i), (ii), or (iii) is satisfied first.

The author(s) undertake(s) to reasonably consider Ipsen's request for delay to the proposed publication should the sponsor reasonably deem it premature to publish the results obtained at the stage of the registry concerned.

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