PROSPECTIVE REGISTRY-BASED STUDY EVALUATING THE EFFECTIVENESS AND SAFETY OF ODEVIXIBAT IN PARTICIPANTS WITH ALAGILLE SYNDROME (ALGS)

STUDY PROTOCOL

STUDY NUMBER: CLIN-60240-033
[IPN60240]

Final version 4.0 (with Amendment 3): 10 December 2024
Final Version 3.0 (with Amendment 2): 03 September 2024
Final Version 2.0 (with Amendment 1): 23 July 2024
Final Version 1.0: 08 February 2024

Sponsor
Ipsen Pharma SAS
65, quai Georges Gorse
92100 Boulogne-Billancourt
Paris, France
Tel: PPD

PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the protocol CLIN-60240-033 entitled "Prospective Registry-Based Study Evaluating the Effectiveness and Safety of Odevixibat in Participants with Alagille Syndrome (ALGS)". 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: 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: Fatine Elaraki
TITLE: Global Medical Affairs Director SIGNATURE: _____

DATE: _____
OFFICE: Ipsen Pharma SAS
65, quai Georges Gorse
92100 Boulogne-Billancourt
Paris, France

Signature: PPD

Email:

LIST OF ABBREVIATIONS

AE	Adverse Event
ALGS	Alagille Syndrome
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CA	Competent Authority
CCDS	Company Core Data Sheet
CI	Confidence Interval
eCRF	Electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FSV	Fat-Soluble Vitamin
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 Normalized Ratio
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Studies
PT	Preferred Term
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Service Provider
UDCA	Ursodeoxycholic Acid

TABLE OF CONTENTS

LIST OF TABLES

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:	Prospective Registry-Based Study Evaluating the Effectiveness and Safety of Odevixibat in Participants with Alagille Syndrome (ALGS)
Rationale and Background:	Odevixibat is a medical treatment for ALGS, a rare, multisystem disorder. Approximately 95% of patients with ALGS present with chronic cholestasis, usually within the first 3 months of life. A substantial proportion (45% to 88%) of patients with ALGS present with severe, intractable pruritus, which can be disabling. 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. Odevixibat was authorized for the treatment of cholestatic pruritus in patients with ALGS ≥ 12 months of age by the United States Food and Drug Administration on 13 June 2023. This will be a long-term, observational, and voluntary participation registry-based study designed to examine the real-world usage of odevixibat in the chronic treatment of ALGS using prospectively collected data.
Research Questions and Objectives:	The aim of this registry-based study is to assess real-world safety data and to describe the effectiveness of odevixibat treatment in participants with ALGS. **Primary objective:** To evaluate the incidence of biliary diversion surgery, liver transplantation, and all-cause mortality in participants with ALGS chronically treated with odevixibat. **Secondary objectives:** • To evaluate the growth and development of participants with ALGS treated with odevixibat. • To evaluate the incidence of fat-soluble vitamin (FSV) deficiencies and their possible sequelae in participants with ALGS treated with odevixibat. • To evaluate the incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment. • To evaluate the incidence of bleeding events in participants with ALGS treated with odevixibat. • To assess real-world safety data of odevixibat in participants with ALGS.
Study Design:	This will be a long-term, observational, prospective, and voluntary participation registry-based study designed to examine the real-world usage of odevixibat for the chronic treatment of ALGS. The registry-based study will recruit participants with ALGS treated with odevixibat as prescribed by their treating physician. Data typically collected during the routinely indicated medical visits will be captured and analyzed. No additional evaluations are planned.
Study Duration:	This registry-based study will follow participants for ≥ 2 years. Following enrolment, participants will continue to participate in the study until the time point of withdrawal of consent, for up to 180 days

	after last dose of odevixibat (in case of treatment discontinuation), death, the end of data collection, or sponsor decision to stop the study. The duration of the study is approximately 5 years. Enrolment will close 3 years after the start of the study to ensure participants are followed for ≥ 2 years.
Study Population:	The population will comprise participants with ALGS enrolled into the Ipsen odevixibat ALGS registry-based study. Participants with ALGS who have been prescribed odevixibat by their treating physician will be eligible. Inclusion criteria: To be included in the registry-based study the participants should fulfil the following inclusion criteria: (1) Diagnosed with ALGS. (2) On (or starting) active odevixibat treatment. (3) Signed informed consent and assent, as appropriate. Consent/assent from the participant or legal representative should be obtained, as appropriate, before any study data collection is conducted. Participants who turn 18 years of age (or legal age per country/state) while participating in the study will be required to provide consent for themselves. Exclusion criteria: Participants will not be included in the registry-based study if: (1) Currently participating in a clinical trial with odevixibat. (2) Currently participating in any interventional clinical trial for ALGS. (3) Have any contraindication to odevixibat as per the locally approved label. (4) Had liver transplant before enrolment.
Study Treatment:	This is an observational registry-based study. 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 willingness of the participant to be included in the study.
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-based study, but the goal will be to enroll approximately 30 to 45 participants with ALGS based on current estimates.
Variables:	This registry-based study 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 registry-based study. 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. 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 pseudonymized 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). This registry-based study will only collect variables related to the objectives and be dependent on the availability and routine assessment of data, including: *Baseline*: • Age, sex, weight, height, ALGS genetic variant, date of birth (MM/YYYY), and date of ALGS diagnosis • General medical and surgical history • Prior surgical procedures related to ALGS, including but not limited to prior biliary diversion surgery (date and type of surgery) and liver transplantation (date and donor information) • Prior medications refer only to medications related to the treatment of ALGS, including but not limited to rifampicin, ursodeoxycholic acid [UDCA], and/or other IBAT inhibitors, taken up to 9 months prior to the first odevixibat dose • Concomitant medications (include ALGS and non-ALGS oriented treatments, 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 the first odevixibat dose are to be collected. • Planned biliary diversion surgery (planned date and indication) • Listing for liver transplantation (planned date and indication) • Laboratory parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR), albumin, creatinine, sodium, platelet count, serum bile acid levels, and FSV levels. Historical values (the most recent values in the last 9 months prior to the first odevixibat dose) are also to be provided if available. • FSV deficiency questionnaire *Periodic Data Collection (odevixibat and concomitant medications and surgery):* • Odevixibat dose (if changed/discontinued, provide date and reason) • Concomitant medication

	• Concomitant vitamin supplementation • Concomitant surgery *Periodic Effectiveness Data Collection:* • Laboratory parameters, including AST, ALT, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, and serum bile acid levels reported since the prior data collection • Biliary diversion surgery • Liver transplantation • 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 *Periodic Safety Data Collection:* • Adverse events (AEs, including suspected hepatotoxicity requiring interruption of odevixibat treatment and bleeding events) and Special Situations • Weight and height • Fat-soluble vitamin levels and FSV deficiency questionnaire • 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.
Endpoints:	**Primary Endpoints**: • Incidence of biliary diversion surgery, liver transplantation, or death in participants with ALGS chronically treated with odevixibat. • 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. **Secondary Endpoints:** • Growth and development in the form of height and weight (standard-deviation scores).

	• Incidence of AEs associated with FSV deficiencies and their possible sequelae. • Incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment. • Incidence of bleeding AEs, including events requiring emergency department care, hospitalization, or blood transfusion. • All AEs, based on the incidence, severity grade, causality, outcome, action taken, and seriousness.
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) 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 summarized. The number and relative frequency of participants who prematurely discontinue participation in the study and reasons for discontinuation will be tabulated. Demographic and baseline characteristics of participants will be summarized using descriptive statistics. **Evaluation of Primary Endpoints** The incidence of biliary diversion surgery, liver transplantation, or death will be assessed using descriptive statistics. Depending on the data available, event free survival endpoints will 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 and 12 months and then every 6 months and the associated 2-sided 95% CIs will be reported. **Evaluation of Secondary Endpoints** Adverse events (AEs) and overall safety, including but not limited to the incidence of FSV deficiencies and their possible sequelae, the incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment and bleeding events (including events requiring emergency department care, hospitalization, or blood transfusion), and growth and development (in the form of change in height and weight from baseline) will be assessed using descriptive statistics. The sponsor will review safety data on an ongoing basis. There will be regular updates in the Periodic Benefit-Risk Evaluation Reports and Periodic Safety Update Reports. Interim analyses will be performed annually and/or for sponsor decision making purposes.
Milestones:	**Start of Data Collection** • Once odevixibat is commercially available and first site approved to enroll (Planned November 2024)

	End of Data Collection • Approximately 5 years following start of data collection (Planned November 2029) **Final Report** • Planned May 2030

3 AMENDMENTS AND UPDATES

The current version of the protocol was released on 10 December 2024 and includes Amendment #3.

	DOCUMENT HISTORY		
Document	**Version**	**Date**	**Status**
Amendment 3	*4.0*	*10 December 2024*	*Effective*
Amendment 2	*3.0*	*03 September 2024*	*Replaced by V4.0 Amendment 3*
Amendment 1	*2.0*	*23 July 2024*	*Replaced by V3.0 Amendment 2*
Original Protocol	*1.0*	*08 February 2024*	*Replaced by V2.0 Amendment 1*

Amendment 3 (10 December 2024)

Overall Rationale for the Amendment:

The main changes of the protocol Amendment are linked to requests from the US Food and Drug Administration (FDA):

- Revision of prior medication related to other IBAT inhibitors ensuring that AEs leading to discontinuation are documented.

Summary change table from previous version of the protocol

Any new or amended text in the protocol is indicated in bold (IS column). Deletions are marked in strikeout text (WAS column). Minor formatting and editing are not included.

Section	WAS (Version 3.0, 03 SEPTEMBER 2024)	IS (Version 4.0, 10 DECEMBER 2024)	Rationale
Synopsis (Variables) and Section 7.2.7.1	[…] *Baseline*: […] • Prior medications refer only to medications related to the treatment of ALGS, including but not limited to rifampicin ~~and/or~~ ursodeoxycholic acid [UDCA] taken up to 9 months prior to the first odevixibat dose	[…] *Baseline*: […] • Prior medications refer only to medications related to the treatment of ALGS, including but not limited to rifampicin, ursodeoxycholic acid [UDCA], **and/or other IBAT inhibitors**, taken up to 9 months prior to the first odevixibat dose	Alignment with the modifications made to the prior medication.
Section 7.2.6 (Table 1)	[e] Prior medications refer only to medications related to the treatment of ALGS, 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.	[e] Prior medications refer only to medications related to the treatment of ALGS, including but not limited to rifampicin, UDCA **and/or other IBAT inhibitors**. Treatments used up to 9 months prior to the first odevixibat dose are to be collected **(including the dose)**. If prior medications are discontinued, the date of discontinuation is to be provided. **If the prior medication involves other IBAT inhibitors, any adverse events leading to their discontinuation will be documented, including their resolution.**	Alignment with the modification made to the prior medication.
Section 7.3.2.2	The registry-based study will assess the use of prior medication including dose, frequency, start and end dates, and reason for prescription at the Baseline Visit. This includes but is not limited to prior~~/current~~ use of ~~odevixibat~~, rifampicin, ~~and~~ UDCA. ~~The reasons for interruption of prior therapies for ALGS will be assessed~~.	The registry-based study will assess the use of prior medication**s,** including dose, frequency, start and end dates, and reason**s** for prescription, at the Baseline Visit. This includes, but is not limited to**,** the prior use of rifampicin, UDCA, **and/or any other IBAT inhibitors. If the prior medication involves other IBAT inhibitors, any adverse events leading to their discontinuation will be documented, including their resolution.**	Revision of variables related to prior medication, specifically concerning other IBAT inhibitors, as requested by the FDA.

Amendments to be implemented in the following documents:

Informed consent form	Yes ☐	No ☒
Case report form (CRF)	Yes ☒	No ☐
Statistical analysis plan (SAP)	Yes ☒	No ☐

4 MILESTONES

Milestone	Planned Date
Start of data collection	Once odevixibat is commercially available and first site approved to enroll Planned November 2024
End of data collection	Approximately 5 years following start of data collection Planned November 2029
Final report	Planned May 2030

5 RATIONALE AND BACKGROUND

5.1 Disease Background

Alagille syndrome (ALGS) is a rare, multisystem disorder with a wide variety of clinical manifestations affecting the liver, heart, skeleton, eyes, central nervous system, kidneys, and facial features. It is an autosomal dominantly inherited disorder caused by defects in components of the NOTCH signaling pathway, most commonly due to mutations in JAG1, in about 90% of the patients (Oda 1997; Turnpenny 2012; Kamath 2018). A small number of patients with ALGS have mutations in the gene for the NOTCH2 receptor (Singh 2018). Approximately 60% of the cases represent de novo mutations. The majority of patients present early, often within the first 3 months of life, with jaundice or cardiac symptoms (Turnpenny 2012; Diaz-Frias 2023).

Due to the variable clinical presentations, the diagnosis of ALGS has traditionally been difficult; even the findings on histological review of liver biopsy materials may not be definitive (Turnpenny 2012). With the advent of genetic testing, the clinical diagnosis of ALGS is confirmed or the diagnosis itself is made by finding a mutation within the sequence analysis of JAG1 or NOTCH2.

ALGS is characterized by one or more of the following organ manifestations (Krantz 1997; Turnpenny 2012):

- Hepatic manifestations: cholestasis, bile duct paucity, pruritus, xanthomas, and cirrhosis that can lead to end-stage liver disease (approximately 95%)
- Cardiac defects: peripheral pulmonic stenosis, tetralogy of Fallot, ventricular septal defect, atrial septal defect, aortic stenosis, and coarctation of the aorta (approximately 90%)
- Dysmorphic face: prominent and broad forehead, deep-set eyes, prominent ears, triangular face with pointed chin, and broad nasal bridge (approximately 90%)
- Renal abnormalities: dysplastic kidneys, glomerular mesangiolipidosis, and renal tubular acidosis (74%)
- Skeletal malformations: butterfly vertebrae, hemivertebrae, and pathologic fractures of the long bones (70%)
- Vascular abnormalities: cerebral artery stenosis and aneurysms, Moya-moya syndrome, reno-vascular abnormalities, and middle aortic syndrome (up to 15%)
- Ophthalmologic manifestations: ocular xanthelasma and posterior embryotoxon (78% to 90%)

Other features associated with ALGS include failure to thrive, short stature, immunodeficiency with recurrent infections, pancreatic insufficiency, delayed puberty, and developmental delays (Diaz-Frias 2023). The clinical presentation of ALGS is extremely variable and even patients from the same family with the same genetic mutation may have different presentations (Kamath 2003).

Approximately 95% of patients with ALGS present with chronic cholestasis, usually within the first 3 months of life (Emerick 2002). Laboratory evaluation of these patients revealed elevated serum bile acids, elevated liver function tests, and conjugated hyperbilirubinemia. Associated symptoms include xanthomas, growth failure, and pruritus. Patients with cholestatic liver disease (including ALGS) are at risk to develop fat soluble vitamin (FSV) deficiencies. Signs and symptoms of FSV deficiency include:

- Vitamin A deficiency: night blindness, blindness, dry eyes, hair loss

- Vitamin D deficiency: osteopenia, fractures, muscle weakness, impaired wound healing
- Vitamin E deficiency: muscle weakness, difficulty walking, tremors, vision problems, poor immune function
- Vitamin K deficiency: bleeding difficulties

A substantial portion (45% to 88%) of patients with ALGS present with severe, intractable pruritus, which can be disabling. Patients with ALGS and their caregivers confirm that pruritus is the most bothersome symptom (Kamath 2018).

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 via portal venous blood. Although minimal passive reabsorption of bile acids occurs throughout the intestine, active transport via IBAT 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 (Bylvay) 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 ALGS, except for Livmarli (maralixibat), another IBAT inhibitor, is approved in the United States for the treatment of cholestatic pruritus in ALGS.

The majority of patients present with severe, intractable pruritus, which can be disabling. Attempts at managing pruritus are made by including ursodeoxycholic acid (UDCA), cholestyramine, rifampin, ondansetron, and/or naltrexone in the patient's treatment regimen; these agents are at best partially effective (Singh 2018). Biliary diversion surgery is occasionally used to treat intractable pruritus with some success (Emerick 2002; Mattei 2006). Treatment of persistent cholestasis and progressive liver cirrhosis is supportive and usually includes a choleretic agent. Kasai hepatoportoenterostomy has been attempted to increase biliary flow from the liver to the intestine, but unlike patients with biliary atresia, those with ALGS who undergo the procedure have a worse outcome (Sheflin-Findling 2012). Approximately 15% to 25% of patients with ALGS will require a liver transplant during childhood. For patients with ALGS there is a positive response to transplant with about 90% of patients showing improvement in liver parameters and some degree of catch-up growth. The 5-year survival post-transplant in this population is about 80% (Pawlowska 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, and improves liver function. 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. The clinical data collected to date support this expectation.

The efficacy of odevixibat in patients with ALGS was demonstrated in the Phase 3 study A4250-012 (ASSERT), a randomized, double-blind, placebo-controlled study. In this study,

odevixibat treatment resulted in statistically significant improvements in pruritus when compared with placebo.

5.3 Study Rationale

Odevixibat is a medical treatment for ALGS, a rare, multisystem disorder with a wide variety of clinical manifestations affecting the liver, heart, skeleton, eyes, central nervous system, kidneys, and facial features. Odevixibat was authorized for the treatment of cholestatic pruritus in patients with ALGS ≥ 12 months of age by the United States Food and Drug Administration on 13 June 2023. Long-term follow-up information is needed to provide comprehensive effectiveness and safety data.

This registry-based study aims to collect real-world data on the usage of odevixibat in the chronic treatment of ALGS using prospectively collected data.

6 RESEARCH QUESTION AND OBJECTIVES

6.1 Research Question

The aim of this registry-based study is to collect real-world safety data and to describe the effectiveness of chronic odevixibat treatment in participants with ALGS.

6.2 Objectives

6.2.1 Primary Objective

To evaluate the incidence of biliary diversion surgery, liver transplantation, all-cause mortality in participants with ALGS chronically treated with odevixibat.

6.2.2 Secondary Objectives

- To evaluate the growth and development of participants with ALGS treated with odevixibat.
- To evaluate the incidence of FSV deficiencies and their possible sequelae in participants with ALGS treated with odevixibat.
- To evaluate the incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment.
- To evaluate the incidence of bleeding events in participants with ALGS treated with odevixibat.
- To assess real-world safety data of odevixibat in participants with ALGS.

7 RESEARCH METHODS

7.1 Study Design

This will be a long-term, observational, prospective, and voluntary participation registry-based study designed to collect and assess real-world data on participants with ALGS chronically treated with odevixibat.

The study population will comprise participants with ALGS treated with odevixibat enrolled into the registry-based study. Participants who started odevixibat treatment before the implementation of the registry-based study may also be enrolled.

As this is an observational study designed to assess real-world data, the decision to prescribe the product must be taken prior to, and independently from, the willingness of the participant to be included in the registry-based study. 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 study protocol but falls within current practice.

Participants will be treated and monitored in accordance with usual medical practice during their participation in this registry-based study. 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-based study will collect data at Baseline and at each Follow-up Visit. Follow-up Visits are scheduled as per routine clinical practice (expected to occur at least every 6 months or more frequently, based on the investigator's judgement).

The duration of this registry-based study is approximately 5 years. Following enrolment, participants will continue to participate in the study for ≥ 2 years or until the time point of withdrawal of consent, for up to 180 days after last dose of odevixibat (in case of treatment discontinuation), death, the end of data collection, or the sponsor decides to discontinue the study.

The primary objective of this registry-based study is to evaluate the incidence of biliary diversion surgery, liver transplantation, and all-cause mortality in participants with ALGS chronically treated with odevixibat. The secondary objectives are to evaluate the growth and development, incidence of FSV deficiencies and their possible sequelae, evaluate the incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment and bleeding events (including events requiring emergency department care, hospitalization, or blood transfusion) and assess real-world safety data of odevixibat in participants with ALGS.

7.2 Setting

7.2.1 Inclusion Criteria

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

(1) Diagnosed with ALGS.

(2) On (or starting) active odevixibat treatment.

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

7.2.2 Exclusion Criteria

Participants will not be included in the registry-based study if:

(1) Currently participating in a clinical trial with odevixibat.

(2) Currently participating in any interventional clinical trial for ALGS.

(3) Have any contraindication to odevixibat as per the locally approved label.

(4) Had liver transplant before enrolment.

Individuals who do not meet the criteria for participation in this registry-based 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 Study Population

Eligible participants will be participants with ALGS 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-based study, but the goal will be to enroll approximately 30 to 45 participants with ALGS.

7.2.4 Study Duration

The duration of the registry-based study is approximately 5 years. Participants will be followed for ≥ 2 years. Enrolment will close 3 years after the start of the study to ensure participants are followed for ≥ 2 years. Following enrolment, participants will continue to participate in the study until the time point of withdrawal of consent, for up to 180 days after last dose of odevixibat (in case of treatment discontinuation), death, the end of data collection, or the sponsor decides to discontinue the study.

Participant enrolment will start on the date that the investigational site has been activated.

7.2.5 Study Place

The registry-based study will be implemented in the United States.

7.2.6 Study Schedule

The schedule of assessments that will be collected during the registry-based study is summarized in Table 1. As this is an observational study 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 investigator, 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)[a,b]
Clinic visit	X	X
Informed consent[c]	X	-
Inclusion/exclusion criteria	X	-
Demographics and baseline characteristics[d]	X	-
Weight and height	X	X
Prior surgical procedures related to ALGS	X	-
General medical or surgical history	X	-
Prior medications[e]	X	-
Concomitant medications[f]	X	X
Concomitant vitamin supplementation[g]	X	X
Treatment with odevixibat (dates of treatment, dose, and changes/discontinuation)	X	X
Planned Biliary diversion surgery / Liver transplantation[h]	X	X
Biliary diversion surgery cancellation / Liver transplantation removal from listing	-	X
Clinical symptoms[i]	X	X
Laboratory parameters[j]	X	X
Concomitant surgical procedures	X	X
AEs and Special Situations[k]	X	X
Fat-soluble vitamin deficiency questionnaire[l]	X	X
Death report	-	X
Study discontinuation	-	X[b]

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ALGS=Alagille syndrome; AST=aspartate aminotransferase; GGT=gamma-glutamyl transferase; INR=international normalized ratio; UDCA=ursodeoxycholic acid.

[a] Follow-up Visits are expected to occur at least every 6 months according to routine clinical care or more frequently, based on the investigator's judgement. Investigators are encouraged to contact the participants (e.g., text-based reminders or phone calls to caregivers) to ensure follow-up visits are attended and to facilitate rescheduling, if necessary.

[b] End of study for participants: the last Follow-up Visit as per routine clinical practice before the planned end of data collection (Section 4), withdrawal of consent, lost-to follow up, or 180 days after treatment discontinuation, whichever comes first. In case of treatment discontinuation, the last Follow-up Visit is recommended to happen onsite approximately 180 days after last dose of odevixibat.

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

[d] Including age, sex, date of birth (MM/YYYY), and date of ALGS diagnosis

[e] Prior medications refer only to medications related to the treatment of ALGS, including but not limited to rifampicin, UDCA and/or other IBAT inhibitors. Treatments used up to 9 months prior to the first odevixibat dose are to be collected (including the dose). If prior medications are discontinued, the date of discontinuation is to be provided. If the prior medication involves other IBAT inhibitors, any adverse events leading to their discontinuation will be documented, including their resolution.

[f] Concomitant medications include ALGS and non-ALGS oriented treatments, including but not limited to rifampicin and/or UDCA.

[g] Type and dose of to be collected.

[h] Planned date and indication are to be collected.

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

[j] Laboratory parameters include AST, ALT, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, and serum bile acid levels reported since the prior data collection. At the Baseline visit, historical (the most recent values in the last 9 months prior to the first odevixibat dose) values are also to be provided if available.

[k] AEs collection begins once the informed consent has been signed and will end 180 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).

[l] The fat-soluble vitamin deficiency questionnaire will be included in the eCRF and completed by the investigator (Section 7.6.1).

7.2.7 Study Visit(s)

Visits will be done in accordance with routine clinical practice (Follow-up Visits are expected to occur at least every 6 months or more frequently, based on the investigator's judgement). Investigators are encouraged to contact the participants (e.g., text-based reminders or phone calls to caregivers) to ensure follow-up visits are attended and to facilitate rescheduling, if necessary.

The registry-based study will assess data collected at the Baseline Visit and Follow-up Visits.

The End of Study for participants will be the last Follow-up Visit as per routine clinical practice performed before the planned end of data collection (approximately 5 years after the start of data collection, see Section 4), withdrawal of consent, lost-to follow up, or 180 days after treatment discontinuation, whichever comes first.

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 based on 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 study is taking place), assent and parent or legally authorized representative consent will also be required.

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

- Age, sex, weight, height, ALGS genetic variant, date of birth (MM/YYYY), and date of ALGS diagnosis
- General medical or surgical history
- Prior surgical procedures related to ALGS, including but not limited to prior biliary diversion surgery (date and type of surgery) and liver transplantation (date and donor information)
- Prior medications
    - Prior medications refer only to medications related to the treatment of ALGS, including but not limited to rifampicin, UDCA, and/or other IBAT inhibitors, taken up to 9 months prior to the first odevixibat dose
- Concomitant medications
    - Concomitant medications include ALGS and non-ALGS oriented treatments, 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 the first odevixibat dose are to be collected.
- Planned biliary diversion surgery (planned date and indication)
- Listing for liver transplantation (planned date and indication)
- Laboratory parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR), albumin, creatinine, sodium, platelet count, serum bile acid levels, and FSV levels. Historical

values (the most recent values in the last 9 months prior to the first odevixibat dose) are also to be provided at baseline if available.

- FSV deficiency questionnaire
- Pregnancy or breastfeeding status

7.2.7.2 Follow-up Visit(s)

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

Odevixibat and Concomitant Medications and Surgery Data Collection:

- Odevixibat dose (if changed/discontinued, provide date and reason)
- Concomitant medication (ALGS and non-ALGS oriented treatments, including but not limited to rifampicin, UDCA)
- Concomitant vitamin supplementation
- Concomitant surgical procedures (including but not limited to biliary diversion surgery (date, indication, and type of surgery) and liver transplantation (date and donor information))

Periodic Safety Data Collection:

- Adverse events (including suspected hepatotoxicity requiring interruption of odevixibat treatment and bleeding events) and Special Situation
- Weight and height
- Fat-soluble vitamins levels and FSV deficiency questionnaire
- Death (date and cause)

Periodic Effectiveness Data Collection:

- Laboratory parameters, including AST, ALT, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, and serum bile acid levels reported since the prior data collection
- Planned Biliary diversion surgery (planned date and indication)
- Listing for liver transplantation (planned 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 Study Discontinuation/Withdrawal

The participant can withdraw (or be withdrawn if the participant is a child upon legal representative's decision) from this registry-based study 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 study 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 study, 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 study results.

The participant will be withdrawn from the registry-based study if:

- They enroll in any interventional clinical trial
- The participant is no longer receiving odevixibat and has completed the last follow-up visit up to 180 days after last dose of odevixibat (see Section 9.4 for follow-up of AEs and Section 9.1.3.1 for follow-up of pregnancies)

  Note: Participants can remain in the registry-based study during odevixibat treatment interruptions.

Investigators may decide to stop their participant's participation in the study 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 study 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 180 days after last odevixibat dose (unless consent is withdrawn) or until the end of data collection, whichever comes first.

7.2.10 Early Study Termination

The sponsor can decide at any time to discontinue this registry-based study 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 Primary Endpoints

- Incidence of biliary diversion surgery, liver transplantation, or death in participants with ALGS chronically treated with odevixibat.
- 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.

7.3.1.2 Secondary Endpoints

- Growth and development in the form of height and weight (standard-deviation scores).

- Incidence of AEs associated with FSV deficiencies and their possible sequelae.
- Incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment.
- Incidence of bleeding AEs, including events requiring emergency department care, hospitalization, or blood transfusion.
- All AEs, based on incidence, severity grade, causality, outcome, action taken, and seriousness.

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, ALGS genetic variant, date of birth (MM/YYYY), and date of ALGS diagnosis
- General medical or surgical history
- Prior surgical procedures related to ALGS, including but not limited to prior biliary diversion surgery (date and type of surgery) and liver transplantation (date and donor information)
- Laboratory parameters, including ALT, AST, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, serum bile acid levels, and FSV levels. Historical values (the most recent values in the last 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, the most recent values prior to the first odevixibat dose are to be collected.
- Pregnancy or breastfeeding status
- Planned biliary diversion surgery (planned date and indication)
- Listing for liver transplantation (planned date and indication)

7.3.2.2 Prior Medication

The registry-based study will assess the use of prior medications, including dose, frequency, start and end dates, and reasons for prescription, at the Baseline Visit. This includes, but is not limited to, the prior use of rifampicin, UDCA, and/or any other IBAT inhibitors. If the prior medication involves other IBAT inhibitors, any AEs leading to their discontinuation will be documented, including their resolution.

7.3.2.3 Concomitant Medication and Vitamin Supplementation

The registry-based study will assess the use of concomitant medication including dose, frequency, start and end dates, and reason for prescription at the Follow-up Visits if available. This includes but is not limited to current use of odevixibat, rifampicin, and UDCA.

Concomitant vitamin supplementation will also be assessed.

7.3.2.4 Concomitant Surgery

The registry-based study 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 Visits if available:

- Surgical procedure name
- Indication
- Reason for concomitant surgery
- Date of surgery
- Type of surgery (for Biliary diversion surgery)
- Donor (for Liver transplantation)

7.3.2.5 Weight and Height

The registry-based study will assess growth and development (in the form of weight and height) for all participants at the Baseline Visit and at the Follow-up Visits (only if clinic visit) if available.

7.3.2.6 Safety Variables

The registry-based study will assess the following safety data from the signing of the informed consent form (ICF):

- Adverse Events (including suspected hepatotoxicity requiring interruption of odevixibat treatment and bleeding events) and Special Situations (including pregnancy or breastfeeding status; Section 9.1.3) until 180 days after the last dose of odevixibat
  - Note: any change in laboratory values deemed as clinically significant by the investigator will be reported as an AE
- Fat-soluble vitamin levels and FSV deficiency questionnaire
  - Note: the questionnaire will assess FSV deficiencies and possible sequelae of FSV deficiency, including whether participants are refractory to clinically recommended vitamin supplementation. The FSV questionnaire will be included in the eCRF and completed by the investigator (See Section 7.6.1 for details on Data Collection)
- Death (date and cause), irrespective of causality, including date and cause of death

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 study (e.g. laboratory parameters) may be assessed from a safety perspective.

7.3.2.7 Effectiveness Variables

- Longitudinal serum biochemical parameters, including pre- and post-odevixibat treatment changes (as far as available) of AST, ALT, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, and serum bile acid levels
- Clinical outcomes: surgical biliary diversion, liver transplantation, and overall survival

- Clinical symptoms: pruritus and sleep disturbance, if (semi-) objective scoring data are available

7.3.2.8 Treatment Variables

The registry-based study will collect the following data on odevixibat treatment at the Baseline Visit and at the Follow-up 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 Study Size

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

Enrolment will be based on the number of participants prescribed odevixibat and their willingness to participate in the study, but the goal will be to enroll approximately 30 to 45 participants with ALGS.

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 summarized 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 via the internet utilizing 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-authorized users will be given access to the eCRF as appropriate for their study 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 pseudonymize the data from each participant. Data for each participant must be entered into the eCRF within 5 days of the participant's enrolment and each Follow-Up Visit. Data transmitted will be pseudonymized 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-based study.

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

Queries will be addressed to the investigational site using the eCRF.

Investigators or authorized study 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 study.

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.

Study documents should be retained for at least 10 years after study 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 study 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 (SAP) describing the planned statistical analysis in detail with table, figure, and listing templates will be developed as a separate document.

Analyses will be primarily descriptive.

Descriptive summaries of continuous variables will include the number of observations, mean, standard deviation, median, range, and 95% confidence intervals (CIs) 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 summarized.

Demographic and baseline characteristics of participants will be summarized using descriptive statistics.

The number and relative frequency of participants who prematurely discontinue participation in the study and reasons for discontinuation will be tabulated.

7.7.2.1 Evaluation of Primary Endpoint

The incidence of biliary diversion surgery, liver transplantation, or death will be assessed using descriptive statistics. Depending on the data available, event free survival endpoints will 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 months, 12 months, and then every 6 months and the associated 2-sided 95% CIs will be reported.

7.7.2.2 Evaluation of Secondary Endpoints

Safety data, including but not limited to the incidence of FSV deficiencies and their possible sequelae, the incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment and bleeding events (including events requiring emergency department care, hospitalization, or blood transfusion), and growth and development (in the form of change in height and weight from baseline) will be collected, and descriptive statistics 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). In addition, the incidence of all AEs associated with FSV deficiencies, and the incidence of all suspected hepatotoxicity requiring interruption of odevixibat treatment events and bleeding AEs (including events requiring emergency department care, hospitalization, or blood transfusion) will be tabulated.

Signs and symptoms of FSV deficiency will be summarized at each study visit using descriptive statistics. For each sign and symptom, the change from baseline by visit and the last assessment during treatment will be summarized by a shift table.

Change from baseline in growth (i.e. height [cm], weight [kg], body mass index [kg/m^2], and corresponding Z-score [standard deviation from P50 standard growth curve]), will be summarized by visit for participants age < 18 using descriptive statistics.

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 and interruptions will be summarized.

7.7.3 Subgroup Analyses

Subgroup analyses may be defined in the SAP.

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 study 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 study should ensure that the rights and wellbeing of the participants are protected, that the study data are accurate (complete and verifiable to source data) and that the

study 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 study-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 authorized study staff members must complete the eCRF in a timely manner and on an ongoing basis to allow regular review by the study 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 study 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 study, 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 study 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 centralized 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-based study 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

Authorized personnel from external CA and sponsor-authorized 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 study documents and site facilities, and to any other locations used for the purpose of the study 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 study 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-based study
- The date on which informed consent (and assent, if applicable) was obtained prior to participation in the registry-based study
- The identity of the registry-based study, 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 study. 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 study)

The participant (if an adult) or their parent/legally authorized representative (if the participant is not an adult) must have consented to their medical records being viewed by sponsor authorized 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 study 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-based study designed to collect and assess real-world data on participants with ALGS chronically treated with odevixibat. Participants will be

treated and monitored in accordance with usual medical practice during their participation in this study. 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 study sites may vary depending on local medical practice. This, however, is an inherent limitation to the observational design of this study, crucial in gathering real-world data on participants with ALGS chronically 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 study initiation.

Before initiating the study, the investigator/institution should have written and dated approval/favorable opinion from the IEC/IRB for the study 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-based study 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-based study is observational and falls outside the scope of European Commission European Union (EU) Directive 2005/28/EC and Regulation (EU) 536/2014.

This registry-based study 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-based study 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 European Medicines Agency Guideline on GVP (Module IV; 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-based study 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 entering this registry-based study, the investigator (or a person designated by the investigator) will explain the nature, purpose, benefits, and risks of participation in the study to each participant, the participant's parents, or the participant's legally authorized representative. Participants (if adult) or parents/legally authorized 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 study 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 study and maintained during the study. The sponsor will provide a template of the ICF.

The ICF and any participant recruitment materials will follow ICH Good Clinical Practice, 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 authorized 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 study 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 study, as well as those currently in the study, sign the amended form. This is documented as previously described. Parents of participants (or participants' legally authorized representatives) and participants having completed the study 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 authorized representative, inform the participant's primary General Practitioner about their participation in a registry-based study.

For participants already enrolled in the study, 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 study 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 via the internet utilizing 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 pseudonymized 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 study-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 authorized personnel appointed by the sponsor, by appropriate IRB/IEC 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 (study sponsor) is in France, this study 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 unfavorable 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 Meeting the AE Definition
Any abnormal laboratory test results (hematology, 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 study treatment administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study 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 NOT 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 study 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 hospitalization or prolongation of existing hospitalization In general, hospitalization 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 hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization 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, diarrhea, 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 hospitalization but may jeopardize 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 hospitalization, 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. hospitalization]).
Is a suspected transmission of any infectious agent via an authorized medicinal product

9.1.3 Special Situations

A Special Situation is any incidence of drug exposure during pregnancy (i.e. drug exposure to a fetus in utero [whether the fetus is exposed via 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, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) are considered SAEs. If there is an abnormal pregnancy outcome or an AE is reported in the fetus/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 locally approved label. 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 authorization.

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 Authorization.

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 study. Adverse events will be assessed based on incidence, severity grade, causality, outcome, action taken, and seriousness.

All AEs will be collected in the eCRF from the signing of the ICF until 180 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 for 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 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 via 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 study 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 study 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 or to the Marketing Authorization 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 CRF 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 grade for each AE and SAE reported during the study 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 180 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 study or during a recognized 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-authorization regulatory requirements relating to safety reporting to the regulatory authorities, IRBs/IECs, 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 IRB/IEC, 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 Reference Safety Information (RSI) contained within the Company Core Data Sheet (CCDS).

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 STUDY RESULTS

10.1 Study Reports

A report will be prepared for each annual interim analysis. A final report will be prepared once the study 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-based study 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 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 study 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 study agreement concerned, (ii) Ipsen consents to the publication, or (iii) after such a time as may be agreed in the contractual arrangements, including study 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 study concerned.

11 REFERENCES

Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. Official Journal of the European Union 2005, L 91/13. Available at https://ec.europa.eu.

Dawson PA, Haywood J, Craddock AL, et al. Targeted deletion of the ileal bile acid transporter eliminates enterohepatic cycling of bile acids in mice. J Bio Chem. 2003;278(36):33920-33927.

Diaz-Frias J, Kondamudi NP. Alagille Syndrome. [Updated 2019 Dec 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Aug-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507827/.

Emerick KM, Whitington PF. Partial external biliary diversion for intractable pruritus and xanthomas in Alagille syndrome. Hepatology. 2002:35:1501-1506.

European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Revision 2). Available at https://www.ema.europa.eu.

European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices (GVP), Module VIII – Post-authorisation safety studies (Revision 3). Available at https://www.ema.europa.eu.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 11). EMA/95098/2010 Rev. 11. Available at http://www.encepp.eu/standards_and_guidances.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies (Revision 4). EMA/929209/2011 Rev. 4. Available at http://www.encepp.eu/code_of_conduct.

Hofmann AF. The enterohepatic circulation of bile acids in mammals: form and functions. Frontiers Biosci. 2009;14:2584-2598.

International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research (GEP), 2007. Available at https://ieaweb.org.

International Ethical Guidelines for Epidemiological Studies, prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), Geneva 2009. Available at https://cioms.ch.

International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP), 2015. Available at https://www.pharmacoepi.org.

Kamath BM, Bason L, Piccoli DA, Krantz ID, Spinner NB. Consequences of JAG1 mutations. J Med Genet. 2003;40:891-895.

Kamath BM, Baker A, Houwen R, et al. Systematic review: the epidemiology, natural history, and burden of Alagille syndrome. J Pediatr Gastroenterol Hepatol. 2018;67:148-156.

Krantz ID, Piccoli DA, Spinner NB. Alagille syndrome. J Med Genet. 1997;34:152-157.cons

Mattei P, von Allmen D, Picolli D, et al. Relief of intractable pruritus in Alagille syndrome by partial external biliary diversion. J Pediatr Surg. 2006:41;104-107.

Miethke AG, Zhang W, Simmons J, et al. Pharmacological inhibition of ASBT changes bile composition and blocks progression of sclerosing cholangitis in mdr2 knockout mice. Hepatology. 2016;63(2):512-523. doi: 10.1002/hep.27973.

Oda T, Elkahloun AG, Pike BL, et al. Mutations in the human Jagged1 gene are responsible for Alagille syndrome. Nat Genet. 1997;16:235-243.

Pawlowska J, Socha P, Jankowska I. Factors affecting catch-up growth after liver transplantation in children with cholestatic liver diseases. Ann Transplant. 2010:15;72-76.

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, and repealing Directive 95/46/EC (General Data Protection Regulation). Available at https://publications.europa.eu.

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Available at https://ec.europa.eu.

Sheflin-Findling S, Arnon R, Lee S, et al. Partial internal biliary diversion for Alagille syndrome: case report and review of the literature. J Pediatr Surg. 2012:47;1453-1456.

Singh SP, Pati GK. Alagille syndrome and the liver: current insights. Euroasian J Hepato-Gastroenterol. 2018:8:140-147.

Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. Eur J Hum Gen. 2012;20:251-257.

World Medical Association Declaration of Helsinki – Ethical principles for medical research involving human subjects. 2013. Available at https://www.wma.net.

12 APPENDICES

Appendix 1 Amendment Form #1

Amendment 1 (23 July 2024)

Overall Rationale for the Amendment:

The main changes of the protocol Amendment are linked to requests from the US Food and Drug Administration (FDA):

- Additional safety objectives have been defined, with corresponding endpoints, to assess the occurrences of hepatic-related and bleeding events.
- A description of the safety data assessed by the fat-soluble vitamin (FSV) deficiency questionnaire has been added to explain that clinical manifestations of FSV deficiencies and their sequelae will be assessed by the investigator and captured in the electronic Case Report Form (eCRF).
- The duration of data collection has been extended to 180 days after last dose of odevixibat in case of treatment discontinuation or until the end of data collection, whichever comes first.
- Additionally, as the aim of this observational study is to assess real-world data, the frequency of follow-up visits was revised to an expected window of 6 months in between visits, or more frequently, based on the expected routine clinical practice and the investigator's judgement. A footnote has also been added to the schedule of activities to encourage the investigator to actively contact participants to minimize the risks of missed follow-up visits.

Summary change table from previous version of the protocol

Any new or amended text in the protocol is indicated in bold (IS column). Deletions are marked in strikeout text (WAS column). Minor formatting and editing are not included.

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
Protocol Signature	On behalf of the Sponsor: ~~Christof Mauckscb~~	On behalf of the Sponsor: **Fatine Elaraki**	Change of sponsor's representative
List of Abbreviations		[…] **CCDS: Company Core Data Sheet** […] **RSI: Reference Safety Information** […] **SAP: Statistical Analysis Plan**	
Synopsis (Research Questions and Objectives) and Section 6.2.2	Secondary objectives: • […] • To evaluate the incidence of fat-soluble vitamin (FSV) deficiencies and their ~~long-term~~ sequelae in participants with ALGS treated with odevixibat. • […]	Secondary objectives: • […] • To evaluate the incidence of fat-soluble vitamin (FSV) deficiencies and their **possible** sequelae in participants with ALGS treated with odevixibat. • **To evaluate the incidence of hepatic-related events in participants with ALGS treated with odevixibat.** • **To evaluate the incidence of bleeding events in participants with ALGS treated with odevixibat.** • […]	Addition of 2 safety objectives to ensure broader safety collection as requested by the FDA.
Synopsis (Study Duration) and Section 7.2.4	This registry-based study will follow participants for ≥ 2 years. Following enrolment, participants will continue to participate in the study until the time point of withdrawal of consent, treatment discontinuation, death, or sponsor decision to stop the study. The duration of the study is approximately 5 years. Enrolment will close 3 years after the start of the study to ensure participants are followed for ≥ 2 years.	This registry-based study will follow participants for ≥ 2 years. Following enrolment, participants will continue to participate in the study until the time point of withdrawal of consent, **for up to 180 days after last dose of odevixibat (in case of** treatment discontinuation**)**, death, **the end of data collection,** or sponsor decision to stop the study. The duration of the study is approximately 5 years. Enrolment will close 3 years after the	Extension of data collection after treatment discontinuation as requested by the FDA and clarification of the end of study participation

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
		start of the study to ensure participants are followed for ≥ 2 years.	

Synopsis (Variables)	Data will be collected at the Baseline Visit and at each Follow-up Visit (scheduled as per routine clinical practice ~~or as per the locally approved label~~).
	Baseline
	[…]
	• […]
	  • Prior surgical procedures related to ALGS, including but not limited to prior biliary diversion surgery (date and type of surgery)
	• […]
	• Listing for liver transplantation (date ~~of listing~~ and indication
	• Laboratory parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR), albumin, creatinine, sodium, platelet count, serum bile acid levels, and FSV levels. Historical values (most recent values ~~up to~~ 9 months prior to the first odevixibat dose) are also to be provided if available
		Data will be collected at the Baseline Visit and at each Follow-up Visit (scheduled as per routine clinical practice).
		Baseline
		[…]
		• […]
		  • Prior surgical procedures related to ALGS, including but not limited to prior biliary diversion surgery (date and type of surgery) **and liver transplantation (date and donor information)**
		• […]
		• Listing for liver transplantation (**planned** date and indication)
		• Laboratory parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR), albumin, creatinine, sodium, platelet count, serum bile acid levels, and FSV levels. Historical values (**the** most recent values **in the last** 9 months prior to the first odevixibat dose) are also to be provided if available
			Addition of safety endpoints, bullet points remodelling and rewording for better clarity of the data collected.

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
	Periodic Data Collection (odevixibat and concomitant medications): • […] • Concomitant vitamin supplementation […] *Periodic Safety Data Collection* • Adverse events (AEs) and Special Situations • Weight and height • […]	*Periodic Data Collection (odevixibat and concomitant medications **and surgery**):* • […] • Concomitant vitamin supplementation • **Concomitant surgery** […] *Periodic Safety Data Collection* • Adverse events (AEs, **including hepatic-related and bleeding events)** and Special Situations • Weight and heigh • […]	
Synopsis (Endpoints) and Section 7.3.1.2	Secondary Endpoints: • Growth and development in the form of height and weight (standard-deviation scores. • Incidence of AEs associated with FSV deficiencies and their ~~long term~~ sequelae. • All AEs, based on the incidence, severity grade, causality, outcome, action taken, and seriousness.	Secondary Endpoints: • Growth and development in the form of height and weight (standard-deviation scores). • Incidence of AEs associated with FSV deficiencies and their **possible** sequelae. • **Incidence of hepatic-related AEs, including events requiring emergency department care, hospitalization, or blood transfusion.** • **Incidence of bleeding AEs, including events requiring emergency department care, hospitalization, or blood transfusion.** • All AEs, based on the incidence, severity grade, causality, outcome, action taken, and seriousness.	Addition of safety endpoints following FDA request

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
Synopsis (Statistical Methods)	Evaluation of Secondary Endpoints Adverse events (AEs) and overall safety, including but not limited to the incidence of FSV deficiencies and their ~~long-term~~ sequelae and growth and development (in the form of change in height and weight from baseline) will be assessed using descriptive statistics. The sponsor will review safety data on an ongoing basis. […]	Evaluation of Secondary Endpoints Adverse events (AEs) and overall safety, including but not limited to the incidence of FSV deficiencies and their **possible** sequelae, **the incidence of hepatic-related and bleeding events (including events requiring emergency department care, hospitalization, or blood transfusion),** and growth and development (in the form of change in height and weight from baseline) will be assessed using descriptive statistics. The sponsor will review safety data on an ongoing basis. […]	Addition of new safety endpoints.
Section 7.1	[…] This registry-based study will collect data at Baseline and at each Follow-up Visit. Follow-up Visits are scheduled as per routine clinical practice (~~recommended~~ ~~t~~o occur at least every ~~3~~ months). The duration of this registry-based study is approximately 5 years. Following enrolment, participants will continue to participate in the study for ≥ 2 years or until the time point of withdrawal of consent, treatment discontinuation, death, or the sponsor decides to discontinue the study. […] The secondary objectives are to evaluate the growth and development, incidence of FSV deficiencies and their ~~long-term~~ sequelae and	[…] This registry-based study will collect data at Baseline and at each Follow-up Visit. Follow-up Visits are scheduled as per routine clinical practice (**expected** to occur at least every **6** months **or more frequently, based on the investigator's judgement**). The duration of this registry-based study is approximately 5 years. Following enrolment, participants will continue to participate in the study for ≥ 2 years or until the time point of withdrawal of consent, **for up to 180 days after last dose of odevixibat (in case of** treatment discontinuation**),** death, **the end of data collection**, or the sponsor decides to discontinue the study. […] The secondary objectives are to evaluate the growth and development, incidence of FSV deficiencies and their **possible** sequelae, **evaluate the incidence of hepatic-related events and bleeding events (including events**	Alignment with the modifications in follow-up visits intervals, study participation duration and the addition of new safety objectives

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
	assess real-world safety data of odevixibat in participants with ALGS.	**requiring emergency department care, hospitalization, or blood transfusion)** and assess real-world safety data of odevixibat in participants with ALGS.	
Section 7.2.6	Assessment/Procedure column • Informed consent~~[b]~~ • Demographic and baseline characteristics~~[c]~~ • Prior ~~and concomitant~~ medications~~[d]~~ • Concomitant vitamin supplementation~~[e]~~ • Biliary diversion surgery ~~(date, type of surgery, and indication)~~ • Liver transplantation ~~(date and indication)~~~~[f]~~ • Clinical symptoms~~[g]~~ • Laboratory parameters~~[h]~~ • AEs and Special Situations~~[i]~~ • Fat-soluble vitamin deficiency questionnaire	*[Table 1 updated]* Footnote [b] added at Follow-up Visit(s) column (in the title and at the level of the Study discontinuation assessment row) Footnote [l] added at assessment/procedure column for Fat-soluble vitamin deficiency questionnaire assessment Assessment/Procedure column • Informed consent**[c]** • Demographic and baseline characteristics**[d]** • Prior medications**[e]** • **Concomitant medications[f]** • Concomitant vitamin supplementation**[g]** • **Planned** Biliary diversion surgery**/Liver transplantation[h]** • **Biliary diversion surgery cancellation/**Liver transplantation **removal from listing** • Clinical symptoms**[i]** • Laboratory parameters**[j]** • AEs and Special Situations**[k]** • Fat-soluble vitamin deficiency questionnaire**[l]**	Updates of table 1 and footnotes to clarify the assessments and procedures (including FSV deficiency questionnaire) for the investigator, define the end of study for participants, and specify that the expected follow-up visits interval is defined by routine clinical care and investigator decision

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
	• Death report ~~form~~ *Visits column* Follow up Visit(s) (as per routine clinical practice) ~~/ End of Study Visit~~[a] *Footnotes* [a] Follow-up Visits are ~~recommended~~ to occur at least every ~~3~~ months or as ~~per the locally approved label~~. ~~[f] At baseline, listing for liver transplantation, including~~ date and indication are to be collected [h] Laboratory parameters include~~, but are not limited to,~~ AST, ALT, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, and	• Death report *Visits column* Follow up Visit(s) (as per routine clinical practice [a, b] *Footnotes* [a] Follow-up Visits are **expected** to occur at least every **6** months **according to routine clinical care or more frequently, based on the investigator's judgement**. **Investigators are encouraged to contact the participants (e.g., text-based reminders or phone calls to caregivers) to ensure follow-up visits are attended and to facilitate rescheduling, if necessary.** [b] **End of study for participants: the last Follow-up Visit as per routine clinical practice before the planned end of data collection (Section 4), withdrawal of consent, lost-to follow up, or 180 days after treatment discontinuation, whichever comes first. In case of treatment discontinuation, the last Follow-up Visit is recommended to happen onsite approximately 180 days after last dose of odevixibat** [h] **Planned** date and indication are to be collected [j] Laboratory parameters include AST, ALT, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, and serum bile acid levels reported	

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
	serum bile acid 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] AEs 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).	since the prior data collection. At the Baseline visit, historical (**the** most recent values **in the last** 9 months prior to the first odevixibat dose) values are also to be provided if available. [k] AEs collection begins once the informed consent has been signed and will end **180** 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). [l] **The fat-soluble vitamin deficiency questionnaire will be included in the eCRF and completed by the investigator (Section 7.6.1).**	
Section 7.2.7	Visits will be done in accordance with routine clinical practice (Follow-up Visits are ~~recommended~~ to occur at least every ~~3~~ months). The registry-based study will assess data collected at the Baseline Visit and Follow-up Visits.	Visits will be done in accordance with routine clinical practice (Follow-up Visits are **expected** to occur at least every **6** months **or more frequently, based on the investigator's judgement). Investigators are encouraged to contact the participants (e.g., text-based reminders or phone calls to caregivers) to ensure follow-up visits are attended and to facilitate rescheduling, if necessary.** The registry-based study will assess data collected at the Baseline Visit and Follow-up Visits. **The End of Study for participants will be the last Follow-up Visit as per routine clinical practice performed before the planned end of data collection (approximately 5 years after the start of data collection, see Section 4), withdrawal of consent, lost-to follow up,**	Alignment with the expected interval of routine clinical practice following investigator's feedback, proposal of contacts for visit reminders, and definition of the end of study for participants

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
		or 180 days after treatment discontinuation, whichever comes first.	
Section 7.2.7.1	For this registry-based study, the following variables will be captured from Baseline Visit records as available: • […] • Prior surgical procedures related to ALGS, including but not limited to prior biliary diversion surgery (date and type of surgery) • Prior ~~and concomitant~~ medications o Prior medications refer only to medications related to the treatment of ALGS, including but not limited to rifampicin and/or UDCA taken up to 9 months prior to the first odevixibat dose o Concomitant medications include ALGS and non-ALGS oriented treatments, including but not limited to rifampicin and UDCA • […] • Listing for liver transplantation (date ~~of listing~~ and indication) • Laboratory parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR),	For this registry-based study, the following variables will be captured from Baseline Visit records as available: • […] • Prior surgical procedures related to ALGS, including but not limited to prior biliary diversion surgery (date and type of surgery**) and liver transplantation (date and donor information)** • Prior medications o Prior medications refer only to medications related to the treatment of ALGS, including but not limited to rifampicin and/or UDCA taken up to 9 months prior to the first odevixibat dose • **Concomitant medications** o Concomitant medications include ALGS and non-ALGS oriented treatments, including but not limited to rifampicin and UDCA • […] • Listing for liver transplantation (**planned** date and indication) • Laboratory parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio	Remodelling of bullet points and rewording for better clarity of data collected

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
	albumin, creatinine, sodium, platelet count, serum bile acid levels, and FSV 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.	(INR), albumin, creatinine, sodium, platelet count, serum bile acid levels, and FSV levels. Historical values (**the** most recent values **in the last** 9 months prior to the first odevixibat dose) are also to be provided at baseline if available.	
Section 7.2.7.2	Follow-up Visit(s)/~~End of Study Visit~~ Odevixibat and Concomitant Medications Data Collection: • […] • Concomitant vitamin supplementation Periodic Safety Data Collection: • Adverse events and Special situation • […] Periodic Effectiveness Data Collection: • […] • Biliary diversion surgery (date and indication) • Liver transplantation (date and indication) • […]	Follow-up Visit(s) Odevixibat and Concomitant Medications **and Surgery** Data Collection: • […] • Concomitant vitamin supplementation • **Concomitant surgical procedures (including but not limited to biliary diversion surgery (date, indication, and type of surgery) and liver transplantation (date and donor information))** Periodic Safety Data Collection: • Adverse events **(including hepatic-related and bleeding events)** and Special situation • […] Periodic Effectiveness Data Collection: • […] • **Planned** Biliary diversion surgery (**planned** date and indication) • **Listing for** liver transplantation (**planned** date and indication) • […]	Inclusion of the new safety endpoints and rewording for better clarity of data collected

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
Section 7.2.8	[…] The participant will be withdrawn from the registry-based study if: • They enroll 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) Note: Participants can remain in the registry-based study during odevixibat treatment interruptions.	[…] The participant will be withdrawn from the registry-based study if: • They enroll in any interventional clinical trial • The participant is no longer receiving odevixibat **and has completed the last follow-up visit up to 180 days after last dose of odevixibat** (see Section 9.4 for follow-up of AEs and Section 9.1.3.1 for follow-up of pregnancies) Note: Participants can remain in the registry-based study during odevixibat treatment interruptions.	Inclusion of the extended follow-up period after treatment discontinuation
Section 7.2.9	[…] All participants discontinuing odevixibat treatment will be followed up to ~~30~~ days after last odevixibat dose (unless consent is withdrawn).	[…] All participants discontinuing odevixibat treatment will be followed up to **180** days after last odevixibat dose (unless consent is withdrawn) **or until the end of data collection, whichever comes first**.	Extension of the follow-up period after treatment discontinuation and clarification of the end of study for participants discontinuing treatment
Section 7.3.2.1	[…] • Prior surgical procedures related to ALGS including but not limited to prior biliary diversion surgery (date and type of surgery) • Laboratory parameters, including ALT, AST, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, serum bile acid levels, and FSV levels. Historical values (most recent values ~~up to~~ 9 months prior to the first	[…] • Prior surgical procedures related to ALGS including but not limited to prior biliary diversion surgery (date and type of surgery) **and liver transplantation (date and donor information)** • Laboratory parameters, including ALT, AST, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, serum bile acid levels, and FSV levels. Historical values (**the** most recent values **in the last**	Rewording for better clarity of data collected

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
	odevixibat dose) are also to be provided at baseline if available. • […] • Planned biliary diversion surgery (planned date) • Listing for liver transplantation (date ~~of listing~~ and indication)	9 months prior to the first odevixibat dose) are also to be provided at baseline if available • […] • Planned biliary diversion surgery (planned date **and indication**) • Listing for liver transplantation (**planned** date and indication)	
Section 7.3.2.2 and 7.3.2.3	7.3.2.2 Prior ~~and Concomitant~~ Medication ~~and Vitamin Supplementation~~ The registry-based study will assess the use of prior and concomitant medication including 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.~~ Concomitant vitamin supplementation will also be assessed.	7.3.2.2 Prior Medication The registry-based study will assess the use of prior medication including dose, frequency, start and end dates, and reason for prescription at the Baseline Visit. This includes but is not limited to prior/current use of odevixibat, rifampicin, and UDCA. **The reasons for interruption of prior therapies for ALGS will be assessed.** **Section 7.3.2.3 Concomitant Medication and Vitamin Supplementation** The registry-based study will assess the use of concomitant medication including dose, frequency, start and end dates, and reason for prescription at the Follow-up Visits if available. This includes but is not limited to current use of odevixibat, rifampicin, and UDCA. Concomitant vitamin supplementation will also be assessed.	Remodelling of sections to clarify data collection and addition of data collected at Baseline Visit to understand reasons for treatment switch

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
Section 7.3.2.4	~~7.3.2.3~~ Concomitant surgery The registry-based study 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: • […] • Date or surgery	**7.3.2.4** Concomitant surgery The registry-based study 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 Visits if available: • […] • Date or surgery • **Type of surgery (for Biliary diversion surgery)** • **Donor (for Liver transplantation)**	Rewording for better clarity of data collected
Section 7.3.2.5	~~7.3.2.4~~ Weight and Height The registry-based study will assess growth and development (in the form of 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** Weight and Height The registry-based study will assess growth and development (in the form of weight and height) for all participants at the Baseline Visit and at the Follow-up Visits (only if clinic visit) if available	Removal of End of Study Visit as end of study for participants has been defined as the last Follow-up Visit and clarification of weight and height variables.

Section 7.3.2.6	~~7.3.2.5~~ Safety Variables
	The registry-based study will assess the following safety data from the signing of the informed consent form (ICF):
	• Adverse Events and Special Situations (including pregnancy or breastfeeding status; Section 9.1.3) until ~~30~~ days after the last dose of odevixibat
	  ○ Note: any change in laboratory values deemed as clinically significant by the investigator will be reported as an AE
	• Fat-soluble vitamin levels
	• […]
		7.3.2.6 Safety Variables
		The registry-based study will assess the following safety data from the signing of the informed consent form (ICF):
		• Adverse Events **(including hepatic-related and bleeding events)** and Special Situations (including pregnancy or breastfeeding status; Section 9.1.3) until **180** days after the last dose of odevixibat
		  ○ Note: any change in laboratory values deemed as clinically significant by the investigator will be reported as an AE
		• Fat-soluble vitamin levels **and FSV deficiency questionnaire**
			Alignment with new safety objectives/endpoints, the duration of data collection, and clarification that specific manifestations of FSV deficiency will be assessed by the investigator and collected through the FSV deficiency questionnaire

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
		○ **Note: the questionnaire will assess FSV deficiencies and possible sequelae of FSV deficiency, including whether participants are refractory to clinically recommended vitamin supplementation. The FSV questionnaire will be included in the eCRF and completed by the investigator (See Section 7.6.1 for details on Data Collection)** • […]	
7.3.2.8	~~7.3.2.7~~ Treatment Variables The registry-based study will collect the following data on odevixibat treatment at the Baseline Visit and at the Follow-up~~/End of Study~~ Visits if available	**7.3.2.8** Treatment Variables The registry-based study will collect the following data on odevixibat treatment at the Baseline Visit and at the Follow-up Visits if available	Removal of end of study visit as end of study for participants has been defined as the last follow-up visit
7.6.1	[…] Once the signed informed consent (and assent, if applicable) has been obtained, the eCRF will provide a numeric participant identifier to pseudonymize 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 pseudonymized 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.	[…] Once the signed informed consent (and assent, if applicable) has been obtained, the eCRF will provide a numeric participant identifier to pseudonymize the data from each participant. Data for each participant must be entered into the eCRF within 5 days of the participant's enrolment **and** each Follow-Up Visit. Data transmitted will be pseudonymized 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.	Removal of end of study visit as end of study for participants has been defined as the last follow-up visit

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
Section 7.7.2.2	Safety data, including but not limited to the incidence of FSV deficiencies and their ~~long-term~~ sequelae and growth and development (in the form of change in height and weight from baseline) will be collected, and descriptive statistics will be presented. […] In addition, the incidence of all AEs associated with FSV deficiencies will be tabulated. […]	Safety data, including but not limited to the incidence of FSV deficiencies and their **possible** sequelae**, the incidence of hepatic-related and bleeding events (including events requiring emergency department care, hospitalization, or blood transfusion),** and growth and development (in the form of change in height and weight from baseline) will be collected, and descriptive statistics will be presented. […] In addition, the incidence of all AEs associated with FSV deficiencies**, and the incidence of all hepatic-related events and bleeding AEs (including events requiring emergency department care, hospitalization, or blood transfusion)** will be tabulated. […]	Inclusion of new safety objectives/endpoints
Section 7.7.3	~~No subgroup analyses are planned.~~	**Subgroup analyses may be defined in the SAP.**	Rewording to allow the possibility of defining subgroup analyses
Section 9.2.1	All AEs will be collected in the eCRF from the signing of the ICF until ~~30~~ days after last dose of odevixibat or until consent is withdrawn.	All AEs will be collected in the eCRF from the signing of the ICF until **180** days after last dose of odevixibat or until consent is withdrawn.	Extension of the follow-up period after treatment discontinuation
Section 9.4	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	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	Extension of the follow-up period after treatment discontinuation

Section	WAS (Version 1.0, 08 FEBRUARY 2024)	IS (Version 2.0, 23 JULY 2024)	Rationale
	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.	participant is lost to follow-up, or up to **180** days after last dose of odevixibat. Further information on follow-up procedures is provided below.	
Section 9.6	The expectedness of an AE shall be determined by the sponsor according to the ~~locally approved label~~. ~~The reference document for assessing expectedness of AEs/events in this study will be the current approved United States Prescribing Information~~ for odevixibat.	The expectedness of an AE shall be determined by the sponsor according to the **Reference Safety Information (RSI) contained within the Company Core Data Sheet (CCDS).**	Clarification of the safety reference document used for assessing expectedness of AEs/events.

Amendments to be implemented in the following documents:

Informed consent form	Yes ☒	No ☐
Case report form (CRF)	Yes ☒	No ☐
Statistical analysis plan (SAP)	Yes ☒	No ☐

Appendix 2 Amendment Form #2

Overall Rationale for the Amendment:

The main changes of the protocol Amendment are linked to requests from the US Food and Drug Administration (FDA):

- Revision of secondary endpoint related to drug-induced liver injury to incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment.
- Additional exclusion criterion: prior liver transplant.

Summary change table from previous version of the protocol

Any new or amended text in the protocol is indicated in bold (IS column). Deletions are marked in strikeout text (WAS column). Minor formatting and editing are not included.

Section	WAS (Version 2.0 23 JULY 2024)	IS (Version 3.0, 03 SEPTEMBER 2024)	Rationale
Cover Page and Protocol Signature Page	Ipsen Group	Ipsen Pharma SAS	Clarification of the sponsor.
Synopsis (Research Questions and Objectives) and Section 6.2.2	Secondary objectives: […] • ~~To evaluate the incidence of hepatic related events in participants with ALGS treated with odevixibat.~~	Secondary objectives: […] • **To evaluate the incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment.**	Revision of secondary objective related to drug-induced liver injury as requested by the FDA.
Synopsis (Study Population) and Section 7.2.2	Exclusion criteria: Participants will not be included in the registry-based study if: (1) Currently participating in a clinical trial with odevixibat. (2) Currently participating in any interventional clinical trial for ALGS. (3) Have any contraindication to odevixibat as per the locally approved label.	Exclusion criteria: Participants will not be included in the registry-based study if: (1) Currently participating in a clinical trial with odevixibat. (2) Currently participating in any interventional clinical trial for ALGS. (3) Have any contraindication to odevixibat as per the locally approved label. **(4) Had liver transplant before enrolment.**	Addition of an exclusion criterion as requested by the FDA.
Synopsis (Variables)	[…] *Periodic Safety Data Collection:* • Adverse events (AEs, including ~~hepatic related~~ and bleeding events) and Special Situations	[…] *Periodic Safety Data Collection:* • Adverse events (AEs, including **suspected hepatotoxicity requiring interruption of odevixibat treatment** and bleeding events) and Special Situations	Revision of variables related to drug-induced liver injury as requested by the FDA.

Synopsis (Endpoints) and Section 7.3.1.2	Secondary Endpoints: • Growth and development in the form of height and weight (standard-deviation scores). • Incidence of AEs associated with FSV deficiencies and their possible sequelae. • ~~Incidence of hepatic-related AEs, including events requiring emergency department care, hospitalization, or blood transfusion.~~ […]	Secondary Endpoints: • Growth and development in the form of height and weight (standard-deviation scores). • Incidence of AEs associated with FSV deficiencies and their possible sequelae. • **Incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment.** […]	Revision of secondary endpoints related to drug-induced liver injury as requested by the FDA.
Synopsis (Statistical Methods)	[…] **Evaluation of Secondary Endpoints** Adverse events (AEs) and overall safety, including but not limited to the incidence of FSV deficiencies and their possible sequelae, the incidence of ~~hepatic related~~ and bleeding events (including events requiring emergency department care, hospitalization, or blood transfusion), and growth and development (in the form of change in height and weight from baseline) will be assessed using descriptive statistics.	[…] **Evaluation of Secondary Endpoints** Adverse events (Aes) and overall safety, including but not limited to the incidence of FSV deficiencies and their possible sequelae, the incidence of **suspected hepatotoxicity requiring interruption of odevixibat treatment** and bleeding events (including events requiring emergency department care, hospitalization, or blood transfusion), and growth and development (in the form of change in height and weight from baseline) will be assessed using descriptive statistics.	Revision of secondary endpoints related to drug-induced liver injury as requested by the FDA.

Section 7.1	[…] The primary objective of this registry-based study is to evaluate the incidence of biliary diversion surgery, liver transplantation, and all-cause mortality in participants with ALGS chronically treated with odevixibat. The secondary objectives are to evaluate the growth and development, incidence of FSV deficiencies and their possible sequelae, evaluate the incidence of ~~hepatic-related events~~ and bleeding events (including events requiring emergency department care, hospitalization, or blood transfusion) and assess real-world safety data of odevixibat in participants with ALGS.	[…] The primary objective of this registry-based study is to evaluate the incidence of biliary diversion surgery, liver transplantation, and all-cause mortality in participants with ALGS chronically treated with odevixibat. The secondary objectives are to evaluate the growth and development, incidence of FSV deficiencies and their possible sequelae, evaluate the incidence of **suspected hepatotoxicity requiring interruption of odevixibat treatment** and bleeding events (including events requiring emergency department care, hospitalization, or blood transfusion) and assess real-world safety data of odevixibat in participants with ALGS.	Revision of secondary objective related to drug-induced liver injury as requested by the FDA.
Section 7.2.7.2	[…] **Periodic Safety Data Collection:** • Adverse events (including ~~hepatic-related~~ and bleeding events) and Special Situation	[…] **Periodic Safety Data Collection:** • Adverse events (including **suspected hepatotoxicity requiring interruption of odevixibat treatment** and bleeding events) and Special Situation	Revision of secondary objective related to drug-induced liver injury as requested by the FDA.

Section 7.3.2.6	The registry-based study will assess the following safety data from the signing of the informed consent form (ICF): • Adverse Events (including ~~hepatic-related~~ and bleeding events) and Special Situations (including pregnancy or breastfeeding status; Section 9.1.3) until 180 days after the last dose of odevixibat ○ Note: any change in laboratory values deemed as clinically significant by the investigator will be reported as an AE.	The registry-based study will assess the following safety data from the signing of the informed consent form (ICF): • Adverse Events (including **suspected hepatotoxicity requiring interruption of odevixibat treatment** and bleeding events) and Special Situations (including pregnancy or breastfeeding status; Section 9.1.3) until 180 days after the last dose of odevixibat ○ Note: any change in laboratory values deemed as clinically significant by the investigator will be reported as an AE.	Revision of safety variables related to drug-induced liver injury as requested by the FDA.

Section 7.7.2.2	Safety data, including but not limited to the incidence of FSV deficiencies and their possible sequelae, the incidence of ~~hepatic-related~~ and bleeding events (including events requiring emergency department care, hospitalization, or blood transfusion), and growth and development (in the form of change in height and weight from baseline) will be collected, and descriptive statistics will be presented. […] In addition, the incidence of all AEs associated with FSV deficiencies, and the incidence of all ~~hepatic-related~~ events and bleeding AEs (including events requiring emergency department care, hospitalization, or blood transfusion) will be tabulated.	Safety data, including but not limited to the incidence of FSV deficiencies and their possible sequelae, the incidence of **suspected hepatotoxicity requiring interruption of odevixibat treatment** and bleeding events (including events requiring emergency department care, hospitalization, or blood transfusion), and growth and development (in the form of change in height and weight from baseline) will be collected, and descriptive statistics will be presented. […] In addition, the incidence of all AEs associated with FSV deficiencies, and the incidence of all **suspected hepatotoxicity requiring interruption of odevixibat treatment** events and bleeding AEs (including events requiring emergency department care, hospitalization, or blood transfusion) will be tabulated.	Revision of safety data collection related to drug-induced liver injury as requested by the FDA.

Amendments to be implemented in the following documents:

Informed consent form	Yes ☐	No ☒
Case report form (CRF)	Yes ☐	No ☒
Statistical analysis plan (SAP)	Yes ☒	No ☐