PASS Information

Title	Prospective Non-Interventional Study Evaluating the Long-term Safety of Odevixibat in Patients with Alagille Syndrome (ALGS)
Protocol version identifier	Protocol CLIN-60240-034 V3.0
Date of last version of protocol	20 November 2025
European Union electronic register of post-authorisation studies (HMA-EMA Catalogue of Real-World Data (RWD) Studies) number	To be registered once the final protocol is approved
Active substance	Odevixibat Pharmacotherapeutic group: Selective inhibitor of the ileal bile acid transporter (IBAT) ATC code: A05AX05
Medicinal product	Kayfanda® (odevixibat)
Product reference	IPN60240
Procedure number	EMEA/H/C/006462
Marketing authorisation holder (MAH)	Ipsen Pharma SAS
Joint PASS	No
Research question and objectives	The aim of this study is to assess the long-term real-world safety profile of odevixibat treatment in participants with ALGS, using data collected prospectively. **Primary Objective:** • To evaluate the incidence of adverse events (AEs) and serious adverse events (SAEs) in participants with ALGS chronically treated with odevixibat. **Secondary Objectives:** • To evaluate the incidence of severe diarrhoea events, bloody diarrhoea events, diarrhoea events with concurrent dehydration, and diarrhoea events treated with oral or intravenous (IV) rehydration in participants with ALGS chronically treated with odevixibat. • To evaluate the changes in fat-soluble vitamin (FSV) levels, the incidence of FSV deficiencies, and their clinical manifestations (e.g., bleeding, rickets, osteopenia) in participants with ALGS chronically treated with odevixibat. • To evaluate the incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment. • To evaluate the incidence of clinical manifestations of hepatotoxicity, and changes in liver function tests. • To assess risks in pregnancy, maternal complications, and adverse effects on the developing foetus, neonate, and infant among individuals exposed to odevixibat during pregnancy and/or lactation. • To evaluate the incidence of biliary diversion surgery, liver transplantation, and all-cause mortality in participants with ALGS chronically treated with odevixibat.
Country(ies) of study	European Union (EU)/European Economic Area (EEA)
Author	PPD Ipsen Pharma SAS 70 rue Balard, 75015 Paris France

Marketing Authorisation Holder(s)

MAH	Ipsen Pharma SAS 70 rue Balard, 75015 Paris France
MAH contact person	PPD

*Persons supplied with this information must understand that it is **strictly confidential**. Information contained herein cannot be disclosed, submitted for publication or used for any purpose other than that contemplated herein without the sponsor's prior written authorisation.*

PROTOCOL SIGNATURES

Investigator Signature

I have read and agree to the post authorisation safety study (PASS) protocol N° CLIN-60240-034 entitled "Prospective Non-Interventional Study of the Long-Term 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 (GEP/GPP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: _____

TITLE: (Principal) Investigator: SIGNATURE: _____

DATE: _____

OFFICE: _____

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

On behalf of the Sponsor:

NAME: PPD

TITLE: SIGNATURE: PPD

DATE: 24-Nov-2025

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LIST OF TABLES

2 LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
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
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FSV	Fat-Soluble Vitamin
GGT	Gamma-glutamyl Transferase
GMPC	Global Medical Publications and Communications
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HMA	Heads of Medicines Agencies
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
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Studies
PASS	Post Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee

PT	Preferred Term
RSI	Reference Safety Information
RWD	Real-Word Data
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Service Provider
UDCA	Ursodeoxycholic Acid

3 RESPONSIBLE PARTIES

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

4 ABSTRACT

Title	
Study Title:	Prospective Non-Interventional Study Evaluating the Long-term Safety of Odevixibat in Patients with Alagille Syndrome (ALGS)
Brief Title	A Study to Observe the Long-term Safety of Odevixibat in Patients With Alagille Syndrome (ALGS) Who Are Receiving Ongoing Treatment
Protocol Version N°:	3.0
Date of the Last Version of the Protocol:	20 November 2025
Author:	PPD Ipsen Pharma SAS 70 rue Balard, 75015 Paris France

Rationale and Background

Odevixibat is a medicinal treatment for Alagille Syndrome (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 (IBAT), an integral brush border membrane glycoprotein that co-transports sodium and bile acids and appears to be a major regulator of the bile acid pool.

On 19 September 2024, the European Commission approved odevixibat (Kayfanda®) for the treatment of cholestatic pruritus in ALGS patients aged 6 months or older in the European Union (EU); the centralized marketing authorisation is valid in all EU and European Economic Area (EEA) states (Iceland, Norway, and Liechtenstein).

This will be a long-term, observational, and voluntary participation study designed to examine the real-world safety of odevixibat usage in the chronic treatment of ALGS, using prospectively collected data. The study will be based on the primary data collection.

Research Question and Objectives

The aim of this study is to assess the long-term, real-world safety profile of odevixibat treatment in participants with ALGS, using the data collected prospectively.

Primary objective:

- To evaluate the incidence of adverse events (AEs) and serious adverse events (SAEs) in participants with ALGS chronically treated with odevixibat.

Secondary objectives:

- To evaluate the incidence of severe diarrhoea events, bloody diarrhoea events, diarrhoea events with concurrent dehydration, and diarrhoea events treated with oral or intravenous

(IV) rehydration in participants with ALGS chronically treated with odevixibat.

- To evaluate the changes in fat-soluble vitamin (FSV) levels, the incidence of FSV deficiencies, and their clinical manifestations (e.g., bleeding, rickets, osteopenia) in participants with ALGS chronically treated with odevixibat.
- To evaluate the incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment.
- To evaluate the incidence of clinical manifestations of hepatotoxicity, and changes in liver function tests.
- To assess risks in pregnancy, maternal complications, and adverse effects on the developing foetus, neonate, and infant among individuals exposed to odevixibat during pregnancy and/or lactation.
- To evaluate the incidence of biliary diversion surgery, liver transplantation, and all-cause mortality in participants with ALGS chronically treated with odevixibat.

Study Design

This will be a long-term, observational, prospective, open-ended, and voluntary participation study designed to examine the real-world safety of odevixibat usage in the chronic treatment of ALGS, using primary data collection.

The 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 analysed. No additional evaluations are planned.

Brief Summary for Public Disclosure

This study will collect information from patients with ALGS who are using odevixibat in their daily lives. Odevixibat is a medication that helps patients with ALGS, a rare disease that affects the liver and causes itching.

The main aim of this study is to observe the long-term, everyday safety of the drug odevixibat in patients with ALGS who are receiving ongoing treatment.

Population

The population will comprise participants with ALGS enrolled into the Ipsen odevixibat ALGS study. Participants with ALGS who have been prescribed odevixibat by their treating physician will be eligible.

Inclusion criteria:

To be included in the 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.

(4) Aged 6 months or older at the time of consent.

Exclusion criteria:

Participants will not be included in the 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.

Variables

The study is strictly observational. Only data that are routinely documented in participants' medical records as part of usual care will be collected and analysed. No additional laboratory tests or assessments will be required as part of this 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) 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], 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
- 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
- Pregnancy and breastfeeding status

Periodic Data Collection:

- Odevixibat dose (if changed/discontinued, provide date and reason)
- Rate of switchers from odevixibat to maralixibat
- Concomitant medication
- Concomitant vitamin supplementation
- Concomitant surgery

- AEs and Special Situations (including, but not limited to, use during pregnancy and breastfeeding)

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, which should be properly documented in the participant's medical records

- Weight and height
- FSV deficiency questionnaire
- Death (date and cause)
- Laboratory parameters, including AST, ALT, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, serum bile acid levels, and FSV 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

Data Sources

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

Study 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 study, but the goal will be to enrol approximately 30 participants with ALGS in the EU/EEA based on current estimates.

Data Analysis

The following populations will be used for all the statistical analyses:

Enrolled Population: all participants who signed the informed consent form (ICF) (and/or their parents/legally authorised representatives).

Safety Population: all participants who have taken the odevixibat treatment at least once.

A statistical analysis plan will provide full details of analyses and will be finalized prior to the first data analysis.

Analyses will be primarily descriptive.

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

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

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

Evaluation of Primary Endpoints

The primary analyses and summary tables of safety data will be based on the Safety Population.

An overall summary table of AEs during the treatment period (up to 180 days after the last dose) including SAEs, AEs, AEs leading to dose modification (interruption, reduction), AEs leading to death and AEs leading to permanent discontinuation will be presented with the number and proportion of participants and the number of events.

All treatment emergent AEs (TEAEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA primary system organ class (SOC) and preferred term (PT). The incidence of all TEAEs, SAEs, targeted AEs, TEAEs leading to dose modification (interruption, reduction), AEs leading to death and AEs leading to permanent discontinuation will be tabulated by primary SOC and PT. In addition, summary tables by maximum intensity and drug relationship will be presented.

AE listings will be presented by participant, primary SOC and PT.

The sponsor will review safety data on an ongoing basis. Regular updates will be provided in the Periodic Safety Update Reports.

Evaluation of Secondary Endpoints

The incidence of severe diarrhoea events, bloody diarrhoea events, diarrhoea events with concurrent dehydration, diarrhoea events treated with oral or IV rehydration, change in FSV levels, incidence of FSV deficiency, incidence of clinical manifestations of FSV deficiency (e.g., bleeding, rickets, osteopenia), incidence of suspected hepatotoxicity requiring odevixibat interruption, incidence of clinical manifestations related to hepatotoxicity, changes in liver function tests (ALT/AST/GGT, blood bilirubin, INR), incidence of hospitalisations and treatment discontinuations due to diarrhoea, hepatotoxicity, FSV deficiency, incidence of pregnant participants treated with odevixibat and maternal complications, incidence of adverse effects in the developing foetus, neonate, and infant exposed to odevixibat during pregnancy and/or lactation, rate of switchers from odevixibat to maralixibat will be assessed using descriptive statistics.

Changes from baseline in FSV levels will be summarised using descriptive statistics. Signs and symptoms of FSV deficiency will be summarised 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 summarised by a shift table.

Changes in liver function tests (e.g., ALT, AST, GGT, bilirubin, INR) from baseline will be summarised using descriptive statistics. The change from baseline by visit and the last assessment during treatment will be summarised.

The incidence of biliary diversion surgery, liver transplantation, or death will be assessed using descriptive statistics. Depending on the data available, event free survival will be summarised 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.

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 summarised.

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

Milestones

Start of Data Collection

- Once odevixibat is either commercially available in the respective country of study or available through an Early Access Program (EAP), and the first site is approved to enrol (Planned in September 2026)

End of Data Collection

- N/A (open-ended study)

Final Report

- N/A (open-ended study)

5 AMENDMENTS AND UPDATES

The current version of the protocol was released on 20 November 2025 and includes Amendment #2.

	DOCUMENT HISTORY		
Document	**Version**	**Date**	**Status**
Amendment 2	*3.0*	*20 November 2025*	*Effective*
Amendment 1	*2.0*	*07 July 2025*	*Replaced by V3.0 Amendment 2*
Original Protocol	*1.0*	*12 March 2025*	*Replaced by V2.0 Amendment 1*

Amendment 2 (20 November 2025)

Overall Rationale for the Amendment:

The change in the protocol amendment is based on request from the Pharmacovigilance Risk Assessment Committee (PRAC):

- Inclusion of "systematic documentation of all medications initiated within 180 days after odevixibat discontinuation, including maralixibat, and the commitment to report the rate of switchers to maralixibat as a predefined outcome to the study protocol".

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, 07 JULY 2025)	IS (Version 3.0, 20 NOVEMBER 2025)	Rationale
Abstract (Variables)	*Periodic Data Collection:* • Odevixibat dose (if changed/discontinued, provide date and reason)	*Periodic Data Collection:* • Odevixibat dose (if changed/discontinued, provide date and reason) • **Rate of switchers from odevixibat to maralixibat**	Update following PRAC request
Abstract (Data Analysis) and Section 9.7.3.5	[…] FSV deficiency incidence of pregnant participants treated with odevixibat	[…] FSV deficiency incidence of pregnant participants treated with odevixibat **and maternal complications**	Inclusion of maternal complications to align with objectives and endpoints
Abstract (Data Analysis) and Section 9.7.3.5	[…] incidence of ~~potential embryofoetal toxicity report~~s will be assessed using descriptive statistics	[…] incidence of **adverse effects in the developing foetus, neonate, and infant exposed to odevixibat during pregnancy and/or lactation,** **rate of switchers from odevixibat to maralixibat** will be assessed using descriptive statistics	Inclusion of lactation period to align with objectives **and clarification of embryofetal exposure** Update following PRAC request
Abstract (Milestones)	**Start of Data Collection** • Once odevixibat is either commercially available in the respective country of study or available through an Early Access Program (EAP), and the first site is approved to enrol (Planned in ~~Q1~~ 2026)	**Start of Data Collection** • Once odevixibat is either commercially available in the respective country of study or available through an Early Access Program (EAP), and the first site is approved to enrol (Planned in **September** 2026)	Update due to shift of data collection start
Section 6	Start of data collection: ~~Q1~~ 2026 End of data collection: N/A (open-ended study)	Start of data collection: **September** 2026 End of data collection: N/A (open-ended study)	Update due to shift of data collection start

	Interim results 1 with annual marketing authorisation reassessment ~~November 2026~~ Interim results 2 with annual marketing authorisation reassessment ~~November 2027~~ Interim results 3 with annual marketing authorisation reassessment ~~November 2028~~ Interim results 4 with annual marketing authorisation reassessment ~~November 2029~~ Interim report ~~November 2030~~	Interim results 1 with annual marketing authorisation reassessment **October 2027** Interim results 2 with annual marketing authorisation reassessment **October 2028** Interim results 3 with annual marketing authorisation reassessment **October 2029** Interim results 4 with annual marketing authorisation reassessment **October 2030** Interim report **October 2031**	
Section 9.2.6	[Table 1] b In case of treatment discontinuation, the last Follow-up Visit is recommended to happen onsite approximately 180 days after last dose of odevixibat	[Table 1] b In case of treatment discontinuation, the last Follow-up Visit is recommended to happen onsite approximately 180 days after last dose of odevixibat **and all medications initiated within 180 days after odevixibat discontinuation are to be systematically documented, including maralixibat, and the rate of switchers to maralixibat should be reported as a predefined outcome to the study protocol**	Update following PRAC request
Section 9.2.9	[…] 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.	[…] 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. **Moreover, all medications initiated within 180 days after odevixibat discontinuation are to be systematically**	Update following PRAC request

		documented, including maralixibat, and the rate of switchers to maralixibat should be reported as a predefined outcome to the study protocol.	
Section 9.3.1.2	• Incidence of adverse effects on the developing foetus, neonate, and infant.	• Incidence of adverse effects on the developing foetus, neonate, and infant **exposed to odevixibat during pregnancy and/or lactation**.	Inclusion of lactation period to align with objectives and clarification of embryofetal exposure
Section 9.3.1.2	[…] • Incidence of biliary diversion surgery, liver transplantation, or death.	[…] • Incidence of biliary diversion surgery, liver transplantation, or death. • Rate of switchers from odevixibat to maralixibat.	Update following PRAC request
Section 9.3.2.7	The 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)	The 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) • **Rate of switchers from odevixibat to maralixibat**	Update following PRAC request

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 ☐

6 MILESTONES

Milestone	Planned date
Start of data collection	September 2026
End of data collection	N/A (open-ended study)
Interim results 1 with annual marketing authorisation reassessment	October 2027
Interim results 2 with annual marketing authorisation reassessment	October 2028
Interim results 3 with annual marketing authorisation reassessment	October 2029
Interim results 4 with annual marketing authorisation reassessment	October 2030
Interim report	October 2031
Registration in the HMA-EMA Catalogue of RWD Studies	To be done once the final protocol is approved
Final report of study results	N/A (open-ended study)

7 RATIONALE AND BACKGROUND

7.1 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 signalling pathway, most commonly due to mutations in JAG1, in about 90% of the patients [1-3]. A small number of patients with ALGS have mutations in the gene for the NOTCH2 receptor [4]. 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 [2; 5].

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 [2]. 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 characterised by one or more of the following organ manifestations [2; 6]:

- 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 [5]. The clinical presentation of ALGS is extremely variable and even patients from the same family with the same genetic mutation may have different presentations [7].

Approximately 95% of patients with ALGS present with chronic cholestasis, usually within the first 3 months of life [8]. 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

A substantial proportion (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 [3].

7.2 Treatment Background

Patients with cholestatic liver diseases suffer from excessive serum and intrahepatic bile acid resulting in pruritus and tissue damage to the liver. Attempts at managing cholestatic pruritus are made by including ursodeoxycholic acid (UDCA), cholestyramine, rifampicin, ondansetron, and/or naltrexone in the patient's treatment regimen; these agents are at best partially effective [4]. Biliary diversion surgery is occasionally used to treat intractable pruritus with some success [8; 9]. 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 [10]. 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% [11].

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 [12;13]. Therefore, IBAT is a key regulator of the bile acid pool and a key element in enterohepatic circulation [14].

Odevixibat is orally administered and acts locally in the gut where it binds reversibly to the IBAT to decrease the reuptake of bile acids into the liver, increasing the clearance of bile acids through the colon and lowering hepatic bile acid load and serum bile acid levels.

On 19 September, odevixibat (Kayfanda®) has been approved for the treatment of cholestatic pruritus in ALGS patients aged 6 months and older in the European Union (EU); the centralized marketing authorisation is valid in all EU and European Economic Area (EEA) states (Iceland, Norway, and Liechtenstein). Livmarli® (maralixibat), another IBAT inhibitor, is also approved in the EU for the treatment of cholestatic pruritus in patients with ALGS from 2 months of age.

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, and its long-term, open-label extension study CCI [redacted]. In the Phase 3 study, odevixibat treatment resulted in statistically significant improvements in pruritus when compared with placebo, which were maintained for over more than 72 weeks.

7.3 Study Rationale

This study aims to collect the long-term real-world safety of odevixibat usage in the chronic treatment of ALGS, using prospectively collected data. The study will be based on the primary data collection.

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. On 19 September 2024, the European Commission approved odevixibat (Kayfanda®) for the treatment of cholestatic pruritus in ALGS patients aged 6 months or older; long-term follow-up information is needed to provide comprehensive safety data.

This study is a post-authorisation safety study (PASS) included in odevixibat's EU Risk Management Plan (RMP) as a category 2 (i.e. an imposed mandatory additional pharmacovigilance activity which is a Specific Obligations in the context of Kayfanda®'s marketing authorisation under exceptional circumstances). The study has been requested by the EMA as a post-authorisation measure for odevixibat in the treatment of cholestatic pruritus in ALGS to assess and characterize its long-term safety in patients with ALGS.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

The aim of this study is to assess the long-term, real-world safety profile of odevixibat treatment in participants with ALGS, using the data collected prospectively.

8.2 Objectives

8.2.1 Primary Objective

- To evaluate the incidence of adverse events (AEs) and serious adverse events (SAEs) in participants with ALGS chronically treated with odevixibat.

8.2.2 Secondary Objectives

- To evaluate the incidence of severe diarrhoea events, bloody diarrhoea events, diarrhoea events with concurrent dehydration, and diarrhoea events treated with oral or intravenous (IV) rehydration in participants with ALGS chronically treated with odevixibat.
- To evaluate the changes in FSV levels, the incidence of FSV deficiencies, and their clinical manifestations (e.g., bleeding, rickets, osteopenia) in participants with ALGS chronically treated with odevixibat.
- To evaluate the incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment.
- To evaluate the incidence of clinical manifestations of hepatotoxicity, and changes in liver function tests.
- To assess risks in pregnancy, maternal complications, and adverse effects on the developing foetus, neonate, and infant among individuals exposed to odevixibat during pregnancy and/or lactation.
- To evaluate the incidence of biliary diversion surgery, liver transplantation, and all-cause mortality in participants with ALGS chronically treated with odevixibat.

9 RESEARCH METHODS

9.1 Study Design

This will be a long-term, observational, prospective, open-ended, and voluntary participation study designed to examine the real-world safety of odevixibat usage in the chronic treatment of ALGS, using primary data collection.

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

As this is an observational study designed to examine 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 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 study. No additional assessments or tests are 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 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).

Following enrolment, participants will continue to participate in the study for ≥ 2 years or until the time point of withdrawal of consent, loss to follow up, 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 study is to evaluate the incidence of overall AEs and SAEs in participants with ALGS treated chronically with odevixibat. Secondary objectives include assessing the incidence of severe diarrhoea events, bloody diarrhoea events, diarrhoea events with concurrent dehydration, and diarrhoea events requiring oral or IV rehydration. Additionally, the study will evaluate changes in FSV levels, the incidence of FSV deficiencies, and their clinical manifestations. The incidence hepatotoxicity and their clinical manifestations, and changes in liver function tests will also be examined. Furthermore, the study aims to assess risks in pregnancy, including maternal complications and potential adverse effects on the developing foetus, neonate, and infant in individuals exposed to odevixibat during pregnancy and/or lactation. Finally, the study will evaluate the incidence of biliary diversion surgery, liver transplantation, and all-cause mortality in participants with ALGS undergoing chronic treatment with odevixibat.

9.2 Setting

9.2.1 Inclusion Criteria

To be included in the 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.

(4) Aged 6 months or older at the time of consent.

9.2.2 Exclusion Criteria

Participants will not be included in the 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.

Individuals who do not meet the criteria for participation in this study (screen failure) or who withdraw their consent may be rescreened. Rescreened participants should be assigned a new participant number. The informed consent process is described in Section 9.13.

9.2.3 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 9.2.1) and none of the exclusion criteria (Section 9.2.2).

It is expected that approximately 30 participants with ALGS in the EU/EEA will be enrolled, however this will be based on the number of participants prescribed odevixibat and their willingness to participate in the study.

9.2.4 Study Duration

This is an open-ended study. Participants will be followed for ≥ 2 years. Following enrolment, participants will continue to participate in the study until the time point of withdrawal of consent, loss to follow up, 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.

9.2.5 Study Place

The study will be implemented in the EU/EEA.

9.2.6 Study Schedule

The schedule of assessments that will be collected during the study is summarised 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	X	-
Inclusion/exclusion criteria	X	-
Demographics and baseline characteristics	X	-
Weight and height	X	X
Prior surgical procedures related to ALGS	X	-
General medical or surgical history	X	-
Prior medications[c]	X	-
Concomitant medications[d]	X	X
Concomitant vitamin supplementation	X	X
Treatment with odevixibat (dates of treatment, dose, and changes/discontinuation)	X	X
Biliary diversion surgery / Liver transplantation[e]	X	X
Laboratory parameters[f]	X	X
Concomitant surgical procedures	X	X
AEs and Special Situations[g]	X	X
Fat-soluble vitamin deficiency questionnaire[h]	X	X
Study discontinuation	-	X[b]

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ALGS=Alagille syndrome; AST=aspartate aminotransferase; eCRF= electronic case report form; FSV= fat-soluble vitamin GGT=gamma-glutamyl transferase; IBAT=ileal bile acid transporter; 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 (Section 6), 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. All medications initiated within 180 days after odevixibat discontinuation are to be systematically documented, including maralixibat.

[c] Prior medications refer only to medications related to the treatment of ALGS, including but not limited to rifampicin, UDCA 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.

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

[e] Including planification and cancellation/removal to be collected.

[f] Laboratory parameters include-AST, ALT, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, serum bile acid levels and FSV 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.

[g] 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 11.1.3).

[h] The FSV deficiency questionnaire will be included in the eCRF and completed by the investigator (Section 9.6.1).

9.2.7 Study Visit(s)

Visits will occur 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 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 conclusion of data collection (as this is an open-ended study, see Section 6), withdrawal of consent, lost-to follow up, or 180 days after treatment discontinuation, whichever comes first.

9.2.7.1 Baseline

Investigators at participating sites will identify participants who fulfil the inclusion and none of the exclusion criteria. Signed informed consent must 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 authorised representative consent will also be required.

For this 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, 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
- 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 questionnaires

- Pregnancy or breastfeeding status

9.2.7.2 Follow-up Visit(s)

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

- 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))
- Adverse events and Special Situation (including, but not limited to, use during pregnancy and breastfeeding)
- Weight and height
- FSV deficiency questionnaire
- Death (date and cause)
- Laboratory parameters, including AST, ALT, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, serum bile acid levels and FSV 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

9.2.8 Study Discontinuation/Withdrawal

The participant can withdraw (or be withdrawn if the participant is a child upon legal representative's decision) from this 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.

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 study if:

- They enrol 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 11.4 for follow-up of AEs and Section 11.1.3.1 for follow-up of pregnancies)

  Note: Participants can remain in the 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.

9.2.9 Treatment Discontinuation

Odevixibat treatment may be discontinued based on the judgement of the treating physician, including in the event of any SAEs, AEs, or Special Situations (see Section 11.1.3 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 11.1.3.1).

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 should ensure that the participant receives appropriate medical follow-up, and document this 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. Moreover, all medications initiated within 180 days after odevixibat discontinuation are to be systematically documented, including maralixibat.

9.2.10 Early Study Termination

The sponsor can decide at any time to discontinue this 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.

9.3 Endpoints and Variables

9.3.1 Endpoints

9.3.1.1 Primary Endpoints

- Incidence of AEs and SAEs.

9.3.1.2 Secondary Endpoints

- Incidence of severe diarrhoea events, bloody diarrhoea events, diarrhoea events with concurrent dehydration, diarrhoea events treated with oral or IV rehydration.
- Changes in FSV levels.
- Incidence of FSV deficiencies and their clinical manifestations (e.g., bleeding, rickets, osteopenia).
- Incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment.
- Incidence of clinical manifestations related to hepatotoxicity.
- Changes in liver function tests (ALT/AST/GGT, blood bilirubin INR).
- Incidence of hospitalisations due to diarrhoea, FSV deficiency, hepatoxicity.
- Discontinuation of treatment due to diarrhoea, FSV deficiency, hepatoxicity.
- Incidence of pregnancy and maternal complications.
- Incidence of adverse effects on the developing foetus, neonate, and infant exposed to odevixibat during pregnancy and/or lactation.
- Incidence of biliary diversion surgery, liver transplantation, or death.
- Rate of switchers from odevixibat to maralixibat.

9.3.2 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.

9.3.2.1 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
- Pregnancy or breastfeeding status
- Planned biliary diversion surgery (planned date and indication)
- Listing for liver transplantation (planned date and indication)

9.3.2.2 Prior Medication

The 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 any other IBAT inhibitors. If the prior medication involves other IBAT inhibitors, any AEs leading to their discontinuation will be documented, including their resolution.

9.3.2.3 Concomitant Medication and Vitamin Supplementation

The study will assess the use of concomitant medication including dose, frequency, start and end dates, and reason for prescription at the Baseline Visit and 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.

9.3.2.4 Concomitant Surgery

The study will assess the following data on concomitant surgery 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)

9.3.2.5 Weight and Height

The study will assess growth and development (in the form of weight and height) for all participants at the Follow-up Visits if available.

9.3.2.6 Study Variables

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

- AEs and Special Situations (including, but not limited to, pregnancy or breastfeeding status; Section 11.1.3) 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

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.

- FSV 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 9.6.1 for details on Data Collection)
- Death (date and cause), irrespective of causality, including date and cause of death
- 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

9.3.2.7 Treatment Variables

The 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
- Rate of switchers from odevixibat to maralixibat

9.4 Data Sources

Source data include prospectively collected data as part of routine medical care which will be captured in an eCRF by the investigator and transmitted to the sponsor for analysis. For validity and quality control data, please refer to Section 9.8.

9.5 Study Size

No formal sample size calculations have been performed for this 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 enrol approximately 30 participants with ALGS in the EU/EEA based on current estimates.

9.6 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.

9.6.1 Data Collection

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

All relevant data collected as part of routine medical care will be captured using the eCRF by the investigator and transmitted to the sponsor. If some assessments included in the protocol

are not routinely performed by the investigator, the corresponding sections in the eCRF do not need to be completed.

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

Each site is required to have a computer and internet connection available for site entry of clinical data. Data entry in the eCRF will be performed by the investigator or by the designated person from their team and to ensure confidentiality and security of the data, all entries into the eCRF will be made under the electronic signature (e-signature) of the person performing the action (username and password). Only sponsor-authorised users will be given access to the eCRF as appropriate for their 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 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.

9.6.2 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.

9.7 Data Analysis

9.7.1 Analyses Population Definitions

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

9.7.2 Sample Size Determination

This is a descriptive non interventional study therefore no formal sample size calculations have been performed for this study. The aim is to enrol as many participants as possible and according to feasibility assessment and previous studies, the goal is to enrol approximately 30 participants in the EU/EEA.

9.7.3 Statistical and Analytical Methods

9.7.3.1 Statistical Analyses

A SAP describing the planned statistical analysis in detail with table, figure, and listing templates will be developed as a separate document.

The following populations will be used for all the statistical analyses:

Enrolled Population: all participants who signed the assent/ ICF (and/or their parents/legally authorised representatives).

Safety Population: all enrolled participants who have taken the treatment at least once.

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 summarised.

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

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

9.7.3.2 Demographic and Other Baseline Characteristics

Descriptive statistics of demographic and baseline data will be presented. Previous/concomitant medications will be summarised by drug categories.

Data on medical history, coded using MedDRA will be summarised.

9.7.3.3 Patient Disposition and Withdrawals

The numbers and percentages of participants included in the analysis populations will be tabulated overall and by country and site. The reasons for participant exclusions from each of the populations will also be tabulated.

In addition, the number of participants who ended the treatment, withdrew or completed the study will the presented with the primary reasons for discontinuation.

9.7.3.4 Primary analyses

The primary analyses and summary tables of safety data will be based on the Safety Population.

An overall summary table of AEs during the treatment period (up to 180 days after the last dose) including SAEs, AEs, AEs leading to dose modification (interruption, reduction) or, AEs

leading to death and AEs leading to permanent discontinuation of odevixibat will be presented with the number and proportion of participants and the number of events.

All treatment emergent AEs (TEAEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA primary system organ class (SOC) and preferred term (PT). The incidence of all TEAEs, SAEs, targeted AEs, TEAEs leading to dose modification (interruption, reduction), AEs leading to death and AEs leading to permanent discontinuation of odevixibat will be tabulated by primary SOC and PT. In addition, summary tables by maximum intensity and drug relationship will be presented.

AE listings will be presented by participant, primary SOC and PT.

The sponsor will review safety data on an ongoing basis. Regular updates will be provided in the Periodic Safety Update Reports.

9.7.3.5 Secondary analysis

The incidence of severe diarrhoea events, bloody diarrhoea events, diarrhoea events with concurrent dehydration, diarrhoea events treated with oral or IV rehydration, incidence of FSV deficiency, incidence of clinical manifestations of FSV deficiency (e.g., bleeding, rickets, osteopenia), incidence of suspected hepatotoxicity requiring odevixibat interruption, incidence of clinical manifestations related to hepatotoxicity, incidence of hospitalisations and treatment discontinuations due to diarrhoea, hepatotoxicity, FSV deficiency incidence of pregnant participants treated with odevixibat and maternal complications, incidence of adverse effects on the developing foetus, neonate, and infant exposed to odevixibat during pregnancy and/or lactation, rate of switchers from odevixibat to maralixibat will be summarised using descriptive statistics.

Changes from baseline in FSV levels will be summarised using descriptive statistics. Signs and symptoms of FSV deficiency will be summarised 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 summarised by a shift table.

Changes in liver function tests (e.g., ALT, AST, GGT, bilirubin, INR) from baseline will be summarised using descriptive statistics. The change from baseline by visit and the last assessment during treatment will be summarised.

The incidence of biliary diversion surgery, liver transplantation, or death will be assessed 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.

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 summarised.

9.7.4 Subgroup Analyses

Subgroup analyses may be defined in the SAP, particularly for liver-transplanted participants at baseline.

9.7.5 Interim Analyses

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

9.8 Quality Control

9.8.1 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 [15], 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 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 enrolment of the participants listed in the participant screening log, to remind the sites to propose the 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 Follow the included participants and avoid/limit the drop out of participants
- Answer any questions related to the completion of the eCRF

9.8.2 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.

9.8.3 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 study
- The date on which informed consent (and assent, if applicable) was obtained prior to participation in the study
- The identity of the 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 authorised representative (if the participant is not an adult) must have consented to their medical records being viewed by sponsor authorised personnel, and by local, and possibly foreign, CA. This information is included in the ICF.

9.8.4 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.

9.9 Limitations of the Research Methods

This is an observational, prospective 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 is an inherent limitation of the observational design, of this study, expected in the context of real-world data collection. Nevertheless, missing data on the primary and secondary endpoints are expected to be minimal, considering that the study is based on primary data collection and conducted prospectively. To further mitigate the risk of missing critical data, onsite or remote monitoring visits are planned as part of the study oversight.

Information bias is also expected to be limited, as data collection relies on objective information from medical records and regularly scheduled clinical visits every six months, rather than on patient-reported outcomes. Most variables, including relevant medical history and treatments, are routinely documented in medical records, further reducing the risk of bias.

Finally, to mitigate the risk of selection bias, the study includes a wide range of participating centers, both public and private, covering adult and paediatric populations across several European countries, and by broad inclusion criteria that reflect routine clinical practice.

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

9.10 Other Aspects

None

9.11 Regulatory Approval

The SP and/or sponsor will ensure that all legal and regulatory aspects are covered, including submitting the protocol to the EMA and 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/favourable 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.

9.12 Compliance with Good Pharmacoepidemiology Practice and Ethical Considerations

This study will be conducted in accordance with the principles of the World Medical Association Declaration of Helsinki [16], and all subsequent amendments], International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the International Ethical Guidelines for Epidemiological Studies, Council for International Organizations of Medical Sciences [17].

This study is observational and falls outside the scope of European Commission European Union (EU) Directive 2005/28/EC [18] and Regulation (EU) 536/2014 [19].

This study complies with Regulation (EU) 2016/679 [20] 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 study will also follow the recommendations of the International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research [21], the International Society for Pharmacoepidemiology Guidelines for GPP [15], the EMA Guideline on GVP [22; 23] (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 [24].

This 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 [25], Ipsen's Code of Ethical Conduct, and any other applicable local regulations.

9.13 Informed Consent

Prior to participant's enrolment in this 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 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.

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 study.

For participants already enrolled in the study, eligibility must be reconfirmed, 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.

10 PROTECTION OF HUMAN SUBJECTS

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

Any data transmitted will be 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.

10.2 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.

10.3 Insurance

Insurance may be contracted according to local regulatory requirements.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

11.1 Definition

11.1.1 Adverse Event

AE Definition
An Adverse Event (AE) is any untoward medical occurrence in a patient/participant, administered a medicinal product [Kayfanda® in this study] 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. ECG, 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 intensity 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 include: The signs, symptoms, and/or clinical sequelae resulting from lack of effectiveness will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of effectiveness" or "failure of expected pharmacological action" also constitutes 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 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.

11.1.2 Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. 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.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other important medical event: Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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 for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

g. Is a suspected transmission of any infectious agent via an authorised medicinal product.

11.1.3 "Special Situations"

Special situation (SS) is any incidence of drug exposure during pregnancy (i.e. drug exposure to a foetus in utero, whether the foetus is exposed via the mother taking the product or transmission via semen following paternal exposure) or breastfeeding, overdose, off-label use, medication errors, occupational exposure, abuse, misuse 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.

11.1.3.1 Pregnancy or Breastfeeding

Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the medicinal 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 to be related to interference by the medicinal 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. The Investigator is to report to the Sponsor if they become aware of a pregnancy occurring in the partner of a participant participating in the study. If the female partner gives her consent, the pregnancy outcome should be followed up and reported.

Information regarding any pregnancies must be collected on the AE eCRF and the Ipsen Adverse Event and Special Situations Reporting Form for Non-Interventional Studies (134232-FOR), including those with normal progress and throughout the Drug exposure for Pregnancy form (080479-FOR).

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

The Investigator must instruct all female participants to inform them immediately should they become pregnant whilst using the study medication.

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

Breastfeeding

Any use of an IPSEN product during lactation/ breastfeeding must be collected on the AE eCRF **and** the Ipsen Adverse Event and Special Situations Reporting Form for Non-Interventional Studies (134232-FOR).

11.1.3.2 Overdose, Off-label Use, Misuse, Abuse, Occupational Exposure, and Medication Error

Overdose

Any dose higher than the maximum recommended dose in local label/SmPC, or in the protocol is defined as an overdose. For products which require gradual titration, any dose (initial or maintenance) which is higher than the recommended regime in the protocol, or labeling text

will be assessed as 'overdose'. Overdoses should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All overdoses should be reported to Ipsen within 7 calendar days using the Ipsen Adverse Event and Special Situations Reporting Form for Non-Interventional Studies (134232-FOR).

Off-label Use

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

Off-label uses should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All Off-label uses should be reported to Ipsen within 7 calendar days using the Ipsen Adverse Event and Special Situations Reporting Form for Non-Interventional Studies (134232-FOR).

Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation in the respective country.

Misuse should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All misuse should be reported to Ipsen within 7 calendar days using the Ipsen Adverse Event and Special Situations Reporting Form for Non-Interventional Studies (134232-FOR).

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 as AEs in the AE eCRF page whether or not they were associated with a clinical event. All abuse should be reported to Ipsen within 7 calendar days using the Ipsen Adverse Event and Special Situations Reporting Form for Non-Interventional Studies (134232-FOR).

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 as AEs in the AE eCRF. All occupational exposure should be reported to Ipsen within 7 calendar days using the Ipsen Adverse Event and Special Situations Reporting Form for Non-Interventional Studies (134232-FOR).

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. This includes mistakes in prescribing, dispensing, storing, preparing, and administering medications.

Medication error should be reported as AEs in the AE eCRF whether or not they were associated with a clinical event. All medication error should be reported to Ipsen within 7 calendar days using the Ipsen Adverse Event and Special Situations Reporting Form for Non-Interventional Studies (134232-FOR).

11.1.4 Adverse Events of Special Interest

Not applicable

11.2 Time Period and Frequency for Collecting and Reporting AE, SS and SAE Information

11.2.1 Collection of the AEs/SAEs/SSs 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.

11.2.2 Reporting of SAEs, nonserious ADRs and SSs 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:

- All SAEs: related and non-related
- All related nonserious AEs (adverse drug reactions)
- Any Special Situations (see definitions in Section 11.1.3).

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[1]
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

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.

[1] 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 after the pregnancy outcome (in case of live birth).

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 adverse events will be processed by Ipsen according to their relevant Standard Operating Procedures. This includes the follow up of adverse event reports with the Investigator, as required.

If an AE occurs with a "non-Ipsen product", the Investigator should consider informing the competent authority in the Member State where the event occurred or to the marketing authorisation holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

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 for a SAE and within 7 days for a nonserious related AE of awareness for each adverse event:

- 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 adverse event 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 adverse event considered as the foremost untoward medical occurrence from secondary adverse events which occurred as complications. The investigator should also provide the batch number and expiry date of the concerned product wherever possible.

11.3 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs 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 and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

AE and SAE Recording

- When an AE/SAE 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 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.

Assessment of Intensity

The investigator will make an assessment of intensity 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 should 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 Product Information, in his/her 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 his/her 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.

11.4 Follow-up of AEs and SAEs

After the initial AE/SAE/Special Situation report, the investigator shall proactively follow each participant at subsequent visits/contacts. All AEs including SAEs (defined in Section 11.1) and Special Situations (defined in Section 11.1.3) 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 and SAEs
The investigator should perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated 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.

11.5 Regulatory Reporting Requirements for SAEs/related AEs

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

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

11.6 Expectedness of Events

The expectedness of an AE shall be determined according to the Reference Safety Information (RSI) contained within the Company Core Data Sheet (CCDS).

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Study Reports

A report will be prepared for each annual interim analysis. A final report will be prepared once the study is complete.

12.2 Publication Policy

12.2.1 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.

12.2.2 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 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.

12.2.3 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.

12.2.4 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.

12.2.5 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.

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LIST OF APPENDICES

Appendix 1 LIST OF STANDALONE DOCUMENTS

Details of all main responsible parties and full list of Investigators at all participating registry sites (available on request).

Appendix 2 EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE (ENCEPP) CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

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

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

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

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Prospective Non-Interventional Study Evaluating the Long-term Safety of Odevixibat in Patients with Alagille Syndrome (ALGS)

Study reference number:
CLIN-60240-034

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	6
1.1.2 End of data collection[3]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	N/A
1.1.4 Interim report(s)	☒	☐	☐	6, 12.1
1.1.5 Registration in the HMA-EMA Catalogue of RWD studies	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6,12.1

Comments:

The milestones proposed in this protocol are in line with the milestones as defined in the EU Risk Management Plan for Odevixibat version 7.0 (the latest approved version at the time of protocol version 3.0 finalisation), where it is mentioned that interim results and an interim report should be provided yearly with the annual reassessment and within 5 years from study start, respectively. No progress report was requested.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7.3,8.1,8.2, 9.2.3
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.3, 8.1
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	9.2.3
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	N/A

2 Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
3 Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7.2

Comments:

This study will report descriptive results only.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.3.4
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	N/A
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Only descriptive information will be presented, with no measures of association.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.3
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.4
4.2.2 Age and sex	☒	☐	☐	9.2.1
4.2.3 Country of origin	☒	☐	☐	9.2.5
4.2.4 Disease/indication	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up	☒	☐	☐	9.2.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

The study will be conducted in EU/EEA.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	N/A
5.3 Is exposure categorized according to time windows?	☐	☐	☒	N/A
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☒	9.3.2.7
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	N/A
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	N/A

Comments:

This study will report the use of Kayfanda® in a real world setting with descriptive results only.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3, 9.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3, 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	N/A
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☒	☐	N/A

Comments:

Outcomes are collected according to clinical practice.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	N/A
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

It is a descriptive study without a comparator and is conducted in a real-world setting, confounding and covariates do not apply.

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

Comments:

As this is a descriptive study, effect modifiers do not apply.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4, 9.8.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4, 9.8.3
9.1.3 Covariates and other characteristics?	☐	☐	☒	N/A
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3, 9.8.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3, 9.8.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	N/A
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7.3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7.3
9.3.3 Covariates and other characteristics?	☐	☐	☒	N/A
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	N/A

Comments:

As this is a descriptive study, confounding factors and covariates do not apply. Only one data source is considered for this study: primary data collection during routine practice

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☐	☒	☐	N/A
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☒	☐	N/A
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	N/A
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	N/A
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	N/A

Comments:

Due to the rare disease context and the descriptive nature of the study, the sample is

determined based on a feasibility assessment. No stratified analysis is planned, some subgroups analysis will be proposed and detailed in the SAP.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6.2, 10
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6, 9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	11.5

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☐	☒	☐	
12.1.3 Residual/unmeasured confounding?	☐	☐	☒	
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				N/A
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5, 9.1

Comments:

As this is a descriptive study, confounding factors do not apply.

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.11, 11.5
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	N/A
13.3 Have data protection requirements been described?	☒	☐	☐	10.2

Comments:

Not yet submitted.

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

Comments:

This is the ~~first version of~~ amendment 2 of the protocol.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: PPD

Date: dd/Month/year

Signature: _____

Appendix 3 AMENDMENT FORM #1

Amendment 1 (07 July 2025)

Overall Rationale for the Amendment:

The main changes in the protocol amendment are based on requests from the Pharmacovigilance Risk Assessment Committee (PRAC):

- Revision of the milestones to reflect the open-ended nature of the study.
- Addition of the age restriction as an inclusion criterion: aged 6 months or older.
- Wording update to confirm the open-ended design and primary data collection.
- Development of the Limitations section to address potential biases, and clarification of the data sources and their validity.

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, 12 MARCH 2025)	Is (Version 2.0, 07 JULY 2025)	Rationale
Throughout the document	Ipsen Pharma ~~65, quai Georges Gorse~~ ~~92100 Boulogne-Billancourt~~ France	Ipsen Pharma SAS 70 rue Balard, 75015 Paris France	Update of the sponsor's address.
Marketing Authorisation Holder(s) (MAH contact person)	PPD	PPD	Change of the MAH's contact person.
Throughout the document	~~EU PAS register~~	HMA-EMA Catalogue of Real-World Data (RWD) Studies	Change of the study catalogue name.
List of abbreviations		HMA: Heads of Medicines Agencies PRAC: Pharmacovigilance Risk Assessment Committee RWD: Real-Word Data	Adding new abbreviations.
Abstract (Brief Title)		A Study to Observe the Long-term Safety of Odevixibat in Patients With Alagille Syndrome (ALGS) Who Are Receiving Ongoing Treatment	Adding a brief title for public disclosure.
Abstract (Rationale and Background), Section 7.3.	This will be a long-term, observational, and voluntary participation study designed to examine the real-world safety of odevixibat usage in the chronic treatment of ALGS using prospectively collected data.	This will be a long-term, observational, and voluntary participation study designed to examine the real-world safety of odevixibat usage in the chronic treatment of ALGS using prospectively collected data. The study will be based on the primary data collection.	Wording updated to confirm that data collection is primary.
Abstract (Study Design), Section 9.1 and Section 9.2.4	This will be a long-term, observational, prospective, and voluntary participation study designed to examine the real-world safety of odevixibat usage in the chronic treatment of ALGS.	This will be a long-term, observational, prospective, open-ended, and voluntary participation study designed to examine the real-world safety of odevixibat usage in the chronic treatment of ALGS, using primary data collection.	Wording updated to reflect the open-ended nature of the study and/or clarify that data collection is primary.

Abstract (Brief Summary for Public Disclosure)		This study will collect information from patients with ALGS who are using odevixibat in their daily lives. Odevixibat is a medication that helps patients with ALGS, a rare disease that affects the liver and causes itching. The main aim of this study is to observe the long-term, everyday safety of the drug odevixibat in patients with ALGS who are receiving ongoing treatment.	Adding a brief summary for public disclosure.
Abstract (Inclusion criteria) and Section 9.2.1	[…]	[…] (4) Aged 6 months or older at the time of consent.	Addition of one inclusion criterion, as requested by the PRAC.
Abstract (Data Sources) and Section 9.4	Source data include collected data as part of routine medical care which will be captured in an eCRF by the investigator and transmitted to the sponsor for analysis.	Source data include prospectively collected data as part of routine medical care which will be captured in an eCRF by the investigator and transmitted to the sponsor for analysis.	Wording updated to clarify that data collection is primary.
Abstract (Milestones) and Section 6	Start of Data Collection • Once odevixibat is commercially available in the respective country of study ~~and~~ first site approved to enrol (Planned ~~January~~ 2026) End of Data Collection • ~~Approximately 5 years following start of data collection (Planned January 2031)~~ Final Report • ~~Planned July 2031~~	Start of Data Collection • Once odevixibat is either commercially available in the respective country of study or available through an Early Access Program (EAP) and the first site is approved to enrol (Planned in September Q1 2026) End of Data Collection • N/A (open-ended study) Final Report • N/A (open-ended study)	Revision of the milestones to reflect the open-ended nature of the study, as requested by the PRAC, to account for sites where odevixibat may not yet be commercially available but is accessible through an EAP, and to allow for a more flexible timeline for site initiation.
Section 9.1	[…] The duration of this study is approximately 5 years.	[…] ~~The duration of this study is approximately 5 years.~~	Wording deleted to reflect the open-ended nature of the study.

Section 9.2.4	[…] ~~The duration of this 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, loss to follow up, 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.	[…] This is an open-ended study. Participants will be followed for ≥ 2 years. Following enrolment, participants will continue to participate in the study until the time point of withdrawal of consent, loss to follow up, 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.	Wording updated to reflect the open-ended nature of the study.
Section 9.2.6 (Table 1)	[b] End of study for participants: the last Follow-up Visit as per routine clinical practice ~~before the planned end of data collection~~ (Section 6), 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.	[b] End of study for participants: the last Follow-up Visit as per routine clinical practice before the planned end of data collection (Section 6), 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.	Wording updated to reflect the open-ended nature of the study.
Section 9.2.7	[…] 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 6), withdrawal of consent, lost-to follow up, or 180 days after treatment discontinuation, whichever comes first.	[…] The End of Study for participants will be the last Follow-up Visit as per routine clinical practice performed before the conclusion of data collection (as this is an open-ended study, see Section 6), withdrawal of consent, lost-to follow up, or 180 days after treatment discontinuation, whichever comes first.	Wording updated to reflect the open-ended nature of the study.

Section 9.4	Source data include collected data as part of routine medical care which will be captured in an eCRF by the investigator and transmitted to the sponsor for analysis.	Source data include prospectively collected data as part of routine medical care which will be captured in an eCRF by the investigator and transmitted to the sponsor for analysis. For validity and quality control data, please refer to Section 9.8.	Clarification of data source validity, as requested by the PRAC
Section 9.9	[…] 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.	[…] 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 is an inherent limitation of the observational design, of this study, expected in the context of real-world data collection. Nevertheless, missing data on the primary and secondary endpoints are expected to be minimal, considering that the study is based on primary data collection and conducted prospectively. To further mitigate the risk of missing critical data, onsite or remote monitoring visits are planned as part of the study oversight. Information bias is also expected to be limited, as data collection relies on objective information from medical records and regularly scheduled clinical visits every six months, rather than on patient-reported outcomes. Most variables, including relevant medical history and treatments, are routinely documented in medical records, further reducing the risk of bias. Finally, to mitigate the risk of selection bias, the study includes a wide range of participating centers, both public and private, covering adult and paediatric populations across several European countries, and by broad inclusion criteria that reflect routine clinical practice. No formal statistical testing will be performed, and all the analyses will be primarily descriptive in nature.	Development of the Limitations section to address potential biases, as requested by the PRAC;

Appendix 2 (Section 7)			Slight modification to reflect the development of the bias section in the body of the protocol.