

1 SYNOPSIS

Registry Title:	Prospective Study Evaluating the Effectiveness and Safety of Odevixibat in Participants with Alagille Syndrome (ALGS)
Rationale and Background:	Odevixibat is a medical treatment for ALGS, a rare, multisystem disorder. Approximately 95% of patients with ALGS present with chronic cholestasis, usually within the first 3 months of life. A substantial proportion (45% to 88%) of patients with ALGS present with severe, intractable pruritus, which can be disabling. Odevixibat acts as a potent, selective inhibitor of the human ileal bile acid transporter, an integral brush border membrane glycoprotein that co-transporters sodium and bile acids and appears to be a major regulator of the bile acids pool. Odevixibat is authorized for the treatment of cholestatic pruritus in patients with ALGS ≥ 12 months of age by the United States Food and Drug Administration on 13 June 2023. This is a long-term, observational, and voluntary participation study designed to examine the real-world usage of odevixibat in the chronic treatment of ALGS using prospectively collected data.
Research Questions and Objectives:	The aim of this study is to assess real-world safety data and to describe the effectiveness of odevixibat treatment in participants with ALGS. Primary objective: To evaluate the incidence of biliary diversion surgery, liver transplantation, and all-cause mortality in participants with ALGS chronically treated with odevixibat. Secondary objectives: • To evaluate the growth and development of participants with ALGS treated with odevixibat. • To evaluate the incidence of fat-soluble vitamin (FSV) deficiencies and their possible sequelae in participants with ALGS treated with odevixibat. • To evaluate the incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment. • To evaluate the incidence of bleeding events in participants with ALGS treated with odevixibat. • To assess real-world safety data of odevixibat in participants with ALGS.
Study Design:	This is a long-term, observational, prospective, and voluntary participation registry-based study designed to examine the real-world usage of odevixibat for the chronic treatment of ALGS. The study recruits participants with ALGS treated with odevixibat as prescribed by their treating physician. Data typically collected during the routinely indicated medical visits are captured and analyzed. No additional evaluations are planned.
Study Duration:	The duration of this study is approximately 5 years. Following enrolment, participants continue to participate in the study for ≥ 2 years or until the time point of withdrawal of consent, for up to 180 days after

	last dose of odevixibat (in case of treatment discontinuation), death, the end of data collection, or the sponsor decides to discontinue the study.
Study Population:	The population comprises 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. <u>Inclusion criteria:</u> To be included in the study the participants should fulfil the following 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. <u>Exclusion criteria:</u> Participants are not 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. (4) Had liver transplant before enrolment.
Study Treatment:	This is an observational study. Odevixibat is prescribed according to clinical routine. The assignment of the participant to a particular therapeutic strategy is not decided in advance by this protocol, but falls within current practice, and the prescription of the medicine is independent from the willingness of the participant to be included in the study.
Sample Size:	No formal sample size calculation was performed. Enrolment is based on the number of participants prescribed odevixibat and their willingness to participate in the study, but the goal is to enroll approximately 30 to 45 participants with ALGS based on current estimates.
Variables:	This study is strictly observational. Only data that are routinely documented in participants' medical records as part of usual care are collected. No additional laboratory tests or assessments are 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 are captured in the eCRF by the investigator. These data are transmitted to the sponsor for analysis. Data transmitted are pseudonymized and are identified by

	a participant number. Data are collected at the Baseline Visit and at each Follow-up Visit (scheduled as per routine clinical practice). This study only collects variables related to the objectives and is dependent on the availability and routine assessment of data, including: <i>Baseline:</i> • Age, sex, weight, height, ALGS genetic variant, date of birth (MM/YYYY), and date of ALGS diagnosis • General medical and surgical history • Prior surgical procedures related to ALGS, including but not limited to prior biliary diversion surgery (date and type of surgery) and liver transplantation (date and donor information) • Prior medications refer only to medications related to the treatment of ALGS, including but not limited to rifampicin, ursodeoxycholic acid [UDCA], and/or other IBAT inhibitors, taken up to 9 months prior to the first odevixibat dose • Concomitant medications (include ALGS and non-ALGS oriented treatments, including but not limited to rifampicin and UDCA) • Concomitant vitamin supplementation • Odevixibat treatment dose and start date • Clinical symptoms: pruritus and sleep disturbance, if (semi-) objective scoring data are available. For non-naïve participants: most recent values prior to the first odevixibat dose are to be collected. • Planned biliary diversion surgery (planned date and indication) • Listing for liver transplantation (planned date and indication) • Laboratory parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR), albumin, creatinine, sodium, platelet count, serum bile acid levels, and FSV levels. Historical values (the most recent values in the last 9 months prior to the first odevixibat dose) are also to be provided if available. • FSV deficiency questionnaire <i>Periodic Data Collection (odevixibat and concomitant medications and surgery):</i> • Odevixibat dose (if changed/discontinued, provide date and reason) • Concomitant medication • Concomitant vitamin supplementation • Concomitant surgery
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	<i>Periodic Effectiveness Data Collection:</i> • Laboratory parameters, including AST, ALT, ALP, total bilirubin, direct bilirubin, GGT, INR, albumin, creatinine, sodium, platelet count, and serum bile acid levels reported since the prior data collection • Biliary diversion surgery • Liver transplantation • Cancellation of planned biliary diversion surgery and reason for cancellation • Removal from listing for liver transplantation and reason for removal from the list • Clinical symptoms: pruritus and sleep disturbance, if (semi-) objective scoring data are available <i>Periodic Safety Data Collection:</i> • Adverse events ([AEs] including suspected hepatotoxicity requiring interruption of odeixibat treatment and bleeding events) and Special Situations • Weight and height • Fat-soluble vitamin levels and FSV deficiency questionnaire • Death (date and cause) If AEs or their sequelae, whether or not causally related, persist after the date of odeixibat discontinuation, the investigator must ensure that the participant receives appropriate medical follow-up and this should be properly documented in the participant's medical records.
Endpoints:	Primary Endpoints: • Incidence of biliary diversion surgery, liver transplantation, or death in participants with ALGS chronically treated with odeixibat. • Surgical biliary diversion-free survival, defined as time from the start of odeixibat treatment to the first occurrence of surgical biliary diversion or death. • Liver transplant-free survival, defined as time from the start of odeixibat treatment to the first occurrence of liver transplant or death. • Overall survival, defined as time from the start of odeixibat treatment to death. Secondary Endpoints: • Growth and development in the form of height and weight (standard-deviation scores). • Incidence of AEs associated with FSV deficiencies and their possible sequelae.

	• Incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment. • Incidence of bleeding AEs, including events requiring emergency department care, hospitalization, or blood transfusion. • All AEs, based on the incidence, severity grade, causality, outcome, action taken, and seriousness.
Statistical Methods:	A statistical analysis plan provides full details of analyses and was finalized prior to the first data analysis. Descriptive summaries of continuous variables 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 include frequencies and percentages. Percentages are based on the number of non-missing observations. Missing data are also summarized. The number and relative frequency of participants who prematurely discontinue participation in the study and reasons for discontinuation are tabulated. Demographic and baseline characteristics of participants are summarized using descriptive statistics. Evaluation of Primary Endpoints The incidence of biliary diversion surgery, liver transplantation, or death is assessed using descriptive statistics. Depending on the data available, event free survival endpoints are summarized using the Kaplan-Meier method. Median time to event with 2-sided 95% CIs and the first and third quartiles are reported. Survival curves are 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 are reported. Evaluation of Secondary Endpoints AEs and overall safety, including but not limited to the incidence of FSV deficiencies and their possible sequelae, the incidence of suspected hepatotoxicity requiring interruption of odevixibat treatment and bleeding events (including events requiring emergency department care, hospitalization, or blood transfusion), and growth and development (in the form of change in height and weight from baseline) are assessed using descriptive statistics. The sponsor reviews safety data on an ongoing basis. There are regular updates in the Periodic Benefit-Risk Evaluation Reports and Periodic Safety Update Reports. Interim analyses are performed annually and/or for sponsor decision making purposes.
Milestones:	Start of Data Collection • Once odevixibat is commercially available and first site approved to enroll (Planned November 2024) End of Data Collection • Approximately 5 years following start of data collection (Planned November 2029)

	Final Report Planned May 2030
Results	Baseline: At the cut-off date of the interim report, only two (2) participants were included in the study. They started odeixibat treatment prior to study inclusion. Primary endpoint analysis: At the cut-off date of 03 October 2025, no biliary diversion surgery, liver transplantation, or death occurred in the two (2) participants included in the study. Secondary endpoint analysis: At the cut-off date of 03 October 2025, only one (1) participant performed Follow up Visit 1. No significant changes in height and weight were observed for this participant with ALGS treated with odeixibat. FSV deficiency questionnaires results reported no sequelae in any of the participants. No events describing hepatotoxicity or bleeding were reported by any of the participants. Conclusion: Due to the small participants number and limited follow-up, it is difficult to draw any conclusions on the long-term effectiveness and safety of odeixibat in participants with ALGS.