ABSTRACT

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Family Product Name: Bylvay

International Non-proprietary Names: Odevixibat

Other Names: IPN60240, A4250

Title: Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Subjects with Progressive Familial Intrahepatic Cholestasis (PFIC)

Study Number: A4250-019

Rationale and Background:

Odevixibat (Bylvay) is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older. PFIC is a group of rare genetic disorders that results from defects in bile secretion and presents with intrahepatic cholestasis. Odevixibat acts as a potent, selective inhibitor of the human ileal bile acid transporter (IBAT), an integral brush border membrane glycoprotein that co-transports sodium and bile acids and appears to be a major regulator of the bile acids pool in animals and humans.

Long term follow-up information is needed to provide comprehensive safety data, including clinically significant or severe diarrhoea leading to dehydration and/or electrolyte imbalance, fat-soluble vitamin deficiencies, interaction with fat-soluble drugs and hepatotoxicity.

This registry-based safety study aims to evaluate the long-term safety profile in patients with PFIC receiving odevixibat treatment relative to control patients.

Research Question and Objectives:

The aim of this study is to assess the long-term, real-world safety profile of odevixibat treatment in subjects with PFIC compared to subjects not receiving odevixibat (IBAT inhibitor untreated subjects (control cohort)). The overall objectives of this registry-based study are:

- To evaluate the impact of odevixibat treatment on occurrence of severe diarrhoea.
- To evaluate the impact of odevixibat treatment on the clinical manifestations of fat-soluble vitamin deficiency.
- To evaluate the impact of odevixibat treatment on the effectiveness of fat-soluble drugs.
- To evaluate the impact of odevixibat treatment on nutritional status and growth parameters.
- To evaluate the impact of odevixibat treatment on hepatic function and signs of hepatotoxicity.

Study Design:

This post authorisation safety study (PASS) represents a registry-based secondary use of data study. This is a long-term non interventional, observational and voluntary participation registry-based safety study designed to examine the real-world usage of odevixibat for the treatment of PFIC using data prospectively collected in the Treating patients with Familial Intrahepatic Cholestasis (TreatFIC) registry.

The results presented in this annual report are a secondary use of data provided by the University Medical Center of Groningen (UMCG) who has the ownership of the registry.

The TreatFIC registry is a disease registry that is open to enrolment for all patients with PFIC who are either treated with odevixibat or not treated with an IBAT inhibitor. There is no cut-off date for enrolment or cap on the number of subjects to be enrolled.

This registry-based study has the intent to follow subjects for a minimum of 3 years. Subject participation is assessed annually for the study. Enrolment and length of time for duration of follow-up periods are adjusted, if needed, to ensure that the study provides meaningful data.

This report is the first annual report wherein the safety evaluation of odevixibat in patients enrolled in the TreatFIC registry until the data extract date of 01 June 2024 is presented.

Setting and Study Population:

The TreatFIC registry is initiated by UMCG and is a prospective registry managed by a Steering Committee of global PFIC experts based in Europe. Upon entering the registry, the clinical (including medical history, concomitant medications and odevixibat treatment information), biochemical, genetic and, if applicable, surgical data are retrospectively collected from subjects diagnosed with the indicated form of PFIC disease, followed by prospective collection from that moment onwards.

The retrospective data collection is aligned with that of the retrospective NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion (NAPPED) registry. The aim of NAPPED is to characterise the natural course of disease in PFIC1 and PFIC2, determine associations between genotype and phenotype, assess effects of surgical biliary diversion on native liver survival and identify an early surrogate marker for long-term native liver survival.

The study population comprises of patients with PFIC (all types) enrolled into the TreatFIC registry. Patients who are homozygous for a known, disease-causing mutation of the PFIC family (any type), compound homozygous for two disease-causing mutations or heterozygous for one disease-causing mutation in combination with the clinical phenotype of intrahepatic cholestasis are eligible. Patients treated with odevixibat as well as those not treated with IBAT inhibitors are eligible for this study. There are no exclusion criteria.

Patients and study size, including dropouts:

No formal sample size calculation was performed. The data collected by following 50 patients for a minimum of 3 years is expected to be sufficient for meaningful analyses and interpretation of the results. Overall, this registry-based safety study will target a total of approximately 50 patients with PFIC treated with odevixibat and approximately 50 patients with PFIC in the untreated control cohort.

Study Endpoints and Evaluations:

Patients are stratified based upon whether or not they receive odevixibat treatment and PFIC type. The safety of odevixibat treatment is evaluated using the following safety endpoints:

- Adverse event (AE) data, including but not limited to
  - Episodes of diarrhoea lasting more than 3 days, bloody diarrhoea, or diarrhoea leading to dehydration or electrolyte imbalance and any treatment.
  - Episodes of fat-soluble vitamin deficiencies, including symptoms and treatment.
  - Episodes of hepatotoxicity.
  - Incidence of hospitalisation due to diarrhoea, fat-soluble vitamin deficiency and hepatotoxicity.
- Changes from baseline in laboratory data, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, serum bile acids (sBA), total bilirubin, international normalised ratio (INR) and fat-soluble vitamin levels.
- Changes in growth parameters (height, weight, body mass index (BMI)) and their corresponding sex/age z-scores.
- Incidence of reports of ineffectiveness of fat-soluble drugs that were previously effective.
- Incidence of reports of new nutritional interventions (special diets, nasogastric feeding, gastrostomy, parenteral nutrition).
- Incidence of clinical manifestations related to hepatotoxicity.
- Discontinuation of treatment due to diarrhoea, fat-soluble vitamin deficiency, hepatotoxicity (only for treated patients).

Statistical Methods:

Continuous data are summarised using the number of observations available, mean, standard deviation (SD), median, minimum and maximum. Categorical and ordinal data are summarised using the count and percentage of patients.

Full analysis set (FAS) includes all subjects enrolled and matching the eligibility criteria.

The following two cohorts in TreatFIC are considered.

- Odevixibat cohort: Subjects with PFIC who receive odevixibat at any time before or during the study. A distinction is made depending on time of start of odevixibat:
  - Odevixibat prevalent users: subjects who receive odevixibat before enrolment in the TreatFIC registry.
  - Odevixibat incident users: subjects who receive odevixibat when enrolled in the TreatFIC registry.
- Control subjects: Subjects with PFIC diagnosed from 2005 who have never received odevixibat when enrolled in TreatFIC registry.

Baseline is defined as the last available value on Day 1. Day 1 for the odevixibat cohort is the date of enrolment for prevalent users and date of first dose of odevixibat for incident users. Day 1 for the control cohort is the date of enrolment.

The expected intercurrent events in this study are liver transplant and death. The hypothetical strategy is implemented by excluding data after an intercurrent event.

Two time periods are defined to distinguish between subjects who are transferring from being in the control cohort to entering the odevixibat cohort, i.e. receiving odevixibat after enrolling in TreatFIC registry.

- Period 1 is from enrolment to last day before the first dose of odevixibat.
- Period 2 is after the first dose of odevixibat.

If an event occurs in Period 1, it is counted in the control cohort. If an event occurs in Period 2, it will be counted in the odevixibat cohort.

Subject Disposition

Enrolment and disposition are summarised (number and percentages) in the FAS by odevixibat cohort: overall and by incidence and prevalent cohorts and control cohort.

Demographics, Baseline Characteristics, Prior or Current Medication

Summaries of subject demographics are tabulated in the FAS for each cohort: by odevixibat cohort: overall and by incidence and prevalent cohorts and control cohort.

Treatment Duration and Study Duration

The number and percentage of subjects using odevixibat are tabulated.

Safety Evaluation

For the safety endpoint, the number of events and incident rates are calculated. Descriptive analyses (mean (SD), median (interquartile range (IQR)), minimum and maximum values) are conducted for safety endpoints. No formal statistical significance testing is performed.

Adverse events:

Summaries of the incidences of any AEs (number of subjects with any events and number of events) as well as each AEs are tabulated for each cohort in FAS. If a subject receives odevixibat after Day 1, they are counted in both cohorts. If an AE occurs on or after Day 1 but prior to the first dose of odevixibat, this AE is counted in the control cohort. If an AE occurs on or after the first dose of odevixibat, this AE is counted in the odevixibat cohort.

Hospitalisation:

The incidence rate and incidence rate per 100 subject years for hospitalisations are provided for each cohort. For subjects who receive odevixibat during the study, the method described for AEs are applied for all and affected subjects.

Results:

The results of the safety endpoints as of 01 June 2024 are summarised for the control cohort which includes 14 subjects and the odevixibat cohort which includes of 12 prevalent users. There are no incident users of odevixibat available indicating no subjects initiated odevixibat treatment upon enrolment.

While participating in the registry, PPD

The reason for liver transplantation was intractable pruritus.

One prevalent user experienced at least one event of diarrhoea lasting >3 days. No deaths were reported in any of the two cohorts. No subject had undergone surgical biliary diversion during follow-up. With regards to clinical laboratory and growth parameter evaluations, at 6 and 12 months, due to few subjects (one or two) or none in the cohorts at these timepoints, no meaningful interpretation can be made for the change from baseline (increase or decrease) at this stage. No other safety signals were observed.
Discussion: Due to the small number of subjects (less than 50 subjects) and small number of sites (3), no comprehensive analysis of safety evaluation between the control and odevixibat-treated PFIC subjects is possible for this annual report.
Date of Report: 19 August 2024