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4 ABSTRACT

4.1 TITLE

Linaclotide Safety Study for the Assessment of Diarrhoea-Complications and Associated Risk Factors in Selected European Populations with IBS-C.

4.2 RATIONALE AND BACKGROUND

Irritable bowel syndrome (IBS) is a chronic, relapsing gastrointestinal condition characterised by abdominal pain, bloating, and changes in bowel habits. Prevalence estimations vary with the diagnostic criteria used, and in the United Kingdom (UK) were estimated between 9.5% and 22%. IBS can be classified according to Rome III criteria on the basis of the stool's characteristics: IBS predominantly with diarrhoea (IBS-D); IBS predominantly with constipation (IBS-C); and IBS with mixed bowel habits (IBS-M). Approximately one-third of IBS patients have each type of the disease.

The commercialisation of linaclotide (Constella®), a guanylate cyclase-C receptor agonist with visceral analgesic and secretory activities, was approved as the first medicine authorised for the symptomatic treatment of moderate-to-severe IBS-C in adults in the European Union (EU).

Therefore, this study is planned to assess the safety of linaclotide in terms of the risk of severe complications of diarrhoea (SCD) during treatment and other risk factors among patients with IBS-C.

4.3 RESEARCH QUESTION AND OBJECTIVES

The specific research questions and objectives for this study are to:

- Estimate the risk (case-control odds ratio [OR]) of SCD (case) among patients with IBS-C (source population) who received linaclotide prescriptions vs those who did not, controlling for other potential SCD risk factors (socio-demographics, comorbidities [up to 15], co-medications [up to 15] and other potential variables of interest [up to 10])
- Investigate potential risk factors associated to SCD in patients with IBS-C
- Describe the crude incidence of diarrhoea among patients with IBS-C

If allowed by the results of the cases and controls validation as discussed below, two additional objectives will be addressed:

- Describe the crude incidence of SCD among patients with IBS-C (source population) prescribed linaclotide (first-time users)

- Describe the crude incidence of SCD among patients with IBS-C (source population) prescribed linaclotide (first-time users) who are at increased risk of SCD:
    - Patients ≥ 65 years
    - Patients with hypertension, diabetes, or cardiovascular disease diagnostic codes

4.4 STUDY DESIGN

4.5 RETROSPECTIVE CASE-CONTROL NESTED IN A COHORT OF PATIENTS WITH IBS-C (CASES WILL BE PATIENTS SUFFERING FROM SCD) POPULATION

This study will use observational data from three different countries: the UK, Sweden, and Spain. The study population will be a cohort of IBS-C patients. Patients with less than 12 months of computerised records prior to IBS-C cohort entry date or no follow-up time will not be included.

4.6 VARIABLES

The outcomes of interest are severe complications of diarrhoea including dehydration that requires intravenous rehydration, dehydration that requires oral rehydration with solutions of electrolytes, electrolyte imbalance (potassium and sodium), oliguria, anuria, new onset-thromboembolism, new-onset orthostatic hypotension, new-onset syncope, new-onset dizziness, new-onset vertigo, acute renal failure, hypovolemic shock, hospitalisation due to diarrhoea, stupor, coma, or death.

All variables will be identified using diagnostic and procedure codes from general practitioner (GP) electronic medical records. IBS type and safety outcomes will be validated through a questionnaire to physicians treating the cases and controls included in the study.

4.7 DATA SOURCES

The feasibility of conducting the utilisation and safety study has been assessed in the countries of interest, and the most suitable databases identified are as follows:

- In the UK, the Clinical Practice Research Datalink (CPRD) contains information recorded by GPs as part of their routine clinical practice. As of August 2023, CPRD Aurum covers approximately 20% of the UK population and CPRD GOLD covers about 4.5% covers approximately 4.5% of the UK population. Core data include information on socio-demographic characteristics, diagnoses, symptoms, referrals, tests ordered, some test results, prescriptions issued, and additional clinical information. Prescriptions as prescribed by the primary care physician (PCP) or GP have fields for strength and dose. Medical data are coded using the Read coding system and, when linked to secondary care data from the Hospital Episode Statistics (HES), hospitalisation reasons for admission are coded by the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10); hospital tests and hospital procedures are coded by operating procedure code supplement (OPCS) codes. GPs can be contacted by researchers to request details beyond what can be found in the computerised records or to confirm details of patient conditions and treatments. The latest data currently available correspond to 2014, the 12/14 static version of the database, with 474 research-quality (acceptable) patients with at least one prescription for linaclotide.
- For Spain, the Information System for the Development of Research in Primary Care (SIDIAP) is a primary care database that collects longitudinal data from electronic medical records (EMRs) from 274 primary care centres in Catalonia since 2006, representing approximately 12% of the Spanish population. Data from primary care, specialised care, hospitals, and pharmacies are available, as well as patient characteristics like gender and date of birth, GP-diagnosed conditions, GP prescriptions, prescription dosing and size, date of prescription and dispensation, laboratory test results, other procedures, specialist referrals and diagnosis, hospital referrals, hospital procedures and discharge diagnosis, death date, and

pregnancy information. GP diagnoses are coded following the ICD-10 codes, and hospital admissions are classified following the International Statistical Classification of Diseases and Related Health Problems, Ninth Revision (ICD-9). Since 2018, SIDIAP no longer allows the possibility to contact physicians for extracting extended additional information on the patient through long questionnaires. However, there is the possibility of a text review of the primary care records. This text review can be used to validate cases of interest and it would be conducted by IDIAP's clinical researchers. For this study, it is recommended by the data custodians that a review of free-text in the patient's medical records is conducted to improve the validity of the actual study, in place of the previously planned validation strategy using questionnaires to GPs. This free-text review will be made after an anonymisation process of the clinical records and a natural language processing of the text.

- For Sweden, the National Patient Registry (NPR) and Prescribed Drug Register (PDR):
  Information on diagnoses will be obtained from the Swedish NPR, which covers all public inpatient care since 1987 and all outpatient visits since 2001. The medical data include main and up to 21 secondary diagnoses and up to 30 surgical procedures from public and private service providers (National Board of Health and Welfare (Sweden), 2012). Diagnoses are coded using ICD-10 codes and surgical procedures with the Nordic Classification of Surgical Procedures. Primary care is not yet covered in the NPR. At present, the NPR is updated once a year.
  Information about treatment use will be obtained from the Swedish PDR. Its coverage is close to 100% of all prescribed medicines from both primary health care centres and outpatient specialists dispensed to the Swedish population, and information is available since July 2005 (Wettermark et al., 2007). The register contains data on the substance, brand name, formulation, and package, dispensed amount, dosage, expenditure, and reimbursement as well as date of dispensing. Dispensation of over-the-counter (OTC) medications is not included.

4.8 STUDY SIZE

The sample size expected by 2016 in the three countries (available for analysis two to six months later) was at least 200,000 patients with IBS-C (cohort). Based on projected post-authorisation usage data provided by Almirall [MAH of linaclotide at the time of development of this protocol] in the linaclotide risk management plan (RMP), it was expected that roughly 9,665 patients using linaclotide could be captured by the proposed databases in the UK, Spain, and Sweden over the first four years of commercialisation, assuming Almirall [MAH of linaclotide at the time of development of this protocol] sales forecasts were correct, or approximately 5% of all patients with IBS-C would have been exposed to linaclotide. In the progress report for 2016, users of linaclotide included in each of the study database were reported to be below the targeted numbers. Following the recommendation of the PRAC rapporteur, the end of the data collection was then extended by one year until December 2017.

Within the IBS-C cohort, we expect to accrue a non-trivial number of cases (e.g., 94 cases of SCD with an incidence of 0.05% among IBS-C patients) and the same number (or larger) of controls (e.g., that would provide 80% power [or greater] to detect an OR = 4 [or larger] associating SCD with a risk factor present in 5% of controls [notice that we expect exposure to linaclotide in approximately 5% of the cohort]).

4.9 DATA ANALYSES

Country-specific analyses will be conducted, and the heterogeneity of the results will be tested. If heterogeneity is not confirmed, then a pooled analysis aggregating data for all three countries will be conducted and country effect will not be assessed.

Patient characteristics at cohort entry date will be described for the full cohort of patients with IBS-C, as well as incidence rate of diarrhoea.

If the results of the validation of cases and controls are satisfactory positive predictive value of EMRs in the UK and Spain ≥ 95% and negative predictive value ≥ 99%, then information from the whole cohort will be used to estimate incidence and incidence density rates for those groups of patients with IBS-C prescribed linaclotide and those who are potentially at increased risk of SCD and prescribed linaclotide. The crude incidence of diarrhoea and of severe complications of diarrhoea will be described by calculating the proportion of patients with IBS-C experiencing diarrhoea and SCD, respectively, and their associated 95% confidence intervals (CIs). Crude incidence density rates of SCD will be also calculated.

Additionally, the hazard ratios of SCD and the exposures of interest (mainly prescription of linaclotide) will be estimated using Cox proportional hazard models. ORs of SCD and the same exposures of interest will be estimated using data from cases and matched controls by applying conditional logistic regression analysis.

If the results of the validation of cases and controls in the UK and Spain are not satisfactory (positive predictive value of our outcome algorithm in the UK and Spain < 95% or negative predictive value < 99%), only the nested case-control study will be performed and ORs of SCD and the same exposures of interest will be estimated using data from cases and matched controls by applying conditional logistic regression analysis.

The goal is to assess SCD among patients who were treated with linaclotide, were ≥ 65 years old, and had history of hypertension, diabetes or cardiovascular disease diagnostic codes (i.e., SCD occurrence is the outcome variable [yes/no]. and the independent variables of main interest are whether the patient has a prescription for linaclotide, a prescription for laxatives, the patient is ≥ 65 years old, and the patient has hypertension, diabetes, or cardiovascular disease diagnostic codes, all of them at index date, or not, controlling for potential confounders).

Statistical analyses will be conducted using SAS® statistical software.

4.10 MILESTONES

The start of data collection was in February 2013 in Sweden, May 2013 in the UK, and September 2014 in Spain. The end of data collection was to be based on the linaclotide uptake and has been extended to December 2018 in Sweden and Spain, and the most recent HES and CPRD data available by the time of data extraction in 2023 in the UK.

Due to delays on data processing from the Swedish data custodians, data became available for the planned analyses in December 2019. The validation questionnaires to GPs in the UK were eventually available electronically in February 2020. Very low response rate of GPs to questionnaires to validate SCD diagnosis, because of COVID-19 shut down in the UK, motivated a proposal that the validation questionnaires to the GPs in the UK would be sent out again in Q1 2021, aiming to improve the response rate. Continued COVID-19 related shut down in the UK necessitated further postponement of sending the validation questionnaires to GPs in the UK to Q4 2021. When approached on this matter in Q4 2021, the planning manager at CPRD explained that CPRD paused GP questionnaire studies until further notice due to the shortage of primary care clinical staff in the UK to continue focusing their resources on supporting COVID-19 activities. In Q2 2022, CPRD confirmed that they have reopened GP questionnaire services and suggested the study team to resume the validation questionnaires in Q4 2022 given CPRD's resources and current pipeline of work. In the protocol version 12.0, the MAH proposed to reopen the UK validation study in October 2022 until January 2023 with planned study report date in Q3 2023. In response to the MAH's proposal, in the preliminary assessment report for the PASS protocol amendment submission (3rd Oct 2022), PRAC requested the MAH to extend the UK observational period up to the most recent possible date in order to include all available data and to revise the data collection period in the milestones accordingly, without further postponement of the final report (Q3 2023). The MAH contacted CPRD to confirm next steps for data extraction and validation study rerun. CPRD required that the MAH submit a new protocol to the CPRD review committee before

requesting the new datasets and re-running the validation study. This is due to the change of dataset from CRRD GOLD to CPRD GOLD and CPRD Aurum, and the change of the observational period. Of note, most practices have moved from CPRD GOLD to CPRD Aurum in the last few years, which makes the CPRD GOLD dataset much smaller. In parallel the MAH informed the EMA / PRAC Rapporteur on 31st March 2023, of the challenges faced due to the protocol update and the consequential impact to the final PASS CSR deliverable. The process from the submission of the protocol amendment until receiving datasets from CRPD is approximately 3-4 months. The MAH submitted a new protocol to CPRD in April 2023 and expects to receive approval and the new datasets in Q3 2023. The MAH proposes to identify the new SCD cases and controls from the new datasets first and reopen the UK validation study in Q4 2023 - Q1 2024 to validate the new cases and controls.

Study reports will be issued when Periodic Safety Update Reports (PSURs) are due (every six months for the first two years and yearly thereafter). No additional interim report is planned for this study, and the final report of study results will be submitted to PRAC in Q3 2024.

5 AMENDMENTS AND UPDATES

Version	Date	Section of study protocol	Amendment or update	Reason
5.0	17 Jul 2015	N/A	Protocol version approved by PRAC.	N/A
6.0	07 Jun 2016	Marketing Authorisation Holder Annex 3: Physician's Questionnaire	Change from Almirall to Allergan. Change to the proposed questionnaire.	Change in MAH responsible for linaclotide. Improve questionnaire comprehension.
6.1	26 Jan 2017	Several sections in protocol abstract and main text	Timeline extended by one year and agreed with Rapporteur	2016 progress report counts of linaclotide users lower than planned
6.2	08 Jan 2018	Annex 3: Physician's Questionnaire	Language added to introduction paragraph	To ensure physicians only provide information about requested patient
7.0	18 Feb 2019	Several sections in protocol abstract and main text	Timeline extended by six months; change in Spain, from case validation through questionnaires to GP to free-text review of medical records; text added for clarity	The overall timelines are extended due to ongoing delays in data receipt from the Swedish authorities. The Spanish data custodian no longer offers the possibility to conduct validation using questionnaires to GP.