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STUDY PROTOCOL

Study Title:

Linaclotide Utilisation Study in Selected European Populations

Study Protocol Code: EVM-13108

Medicinal Product: Linaclotide, Guanylate cyclase-C agonist

Phase of development: **Post-Authorisation**

Protocol version identifier: 4.2

Date of last version of protocol: 26/01/2017

PROTOCOL SIGNATURES

Protocol Code: EVM-13108

Protocol Title: Linaclotide Utilisation Study in Selected European Populations

Protocol Final Version date: 26/01/2017 for Version 4.2

The individuals signing this study protocol EVM-13108 are responsible for the trial and agree to conduct it in adherence to the present document, any amendments, to International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and to local regulatory requirements wherever to be performed.

[redacted]

Date

[redacted]

Date

Allergan Pharmaceuticals International Limited

[redacted]

Date

[redacted]

Date

Database Investigators

Signature *Date*

Signature *Date*

Signature *Date*

Note: Additional research teams may participate based on the actual use of linaclotide in countries with databases.

Drug Utilisation Study (DUS) information

Title	Linaclotide Utilisation Study in Selected European Populations
Protocol version identifier	4.2
Date of last version of protocol	26 January, 2017
EU PAS register number	ENCEPP/SDPP/12839
Active substance	Linaclotide ATC code: A06AX04
Medicinal product	Constella 290 µg hard capsules
Product reference	EMEA/H/C/002490
Procedure number	MA number: EU/1/12/801/001-004
Marketing authorisation holder(s)	Allergan Pharmaceuticals International Limited.
Joint PASS	No
Research question and objectives	What are the characteristics of patients prescribed linaclotide? What is the extent of off-label use of linaclotide? What are the linaclotide prescription patterns?
Country(-ies) of study	United Kingdom, Spain, Sweden
Author	[redacted]

Abbreviations: ATC=Anatomical Therapeutic Chemical; EU=European Union; MA=marketing authorisation; PAS=post-authorisation study; PASS=post-authorisation safety study;

Marketing authorisation holder(s) (MAH)

Marketing authorisation holder(s)	Allergan Pharmaceuticals International Limited Clonshaugh Industrial Estate Coolock Dublin 17 Ireland
MAH contact person	[redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-HT4	5-Hydroxytryptamine 4
AE	Adverse event
AEMPS	Agencia Española del Medicamento y Productos Sanitarios
ATC	Anatomical therapeutic chemicals
BIFAP	Base de datos para la investigación Farmacoepidemiológica en Atención Primaria
CD-ROM	Compact disk-read only memory
CPRD	Clinical Practice Research Datalink
CSD	Cegedim Strategic Data
DUS	Drug utilisation study
DVD	Digital versatile disk
EMA	European Medicines Agency
EMR	Electronic medical records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GP	General practitioner
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
IACS	Instituto Aragonés de Ciencias de la Salud
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IBS-C	IBS predominately with constipation
IBS-D	IBS predominately with diarrhoea
IBS-M	IBS predominately with mixed bowel habits
ICD-10	International Classification of Diseases and Related Health Problems (10th revision)
ICD-9	International Classification of Diseases and Related Health Problems (9th revision)
ICD-9-CM	International Classification of Diseases and Related Health Problems (9th revision) Clinical Modification
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ISPE	International Society for Pharmacoepidemiology
IT	Information Technology
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not applicable
NOS	Not otherwise specified (or unspecified)
OPCS	Operating procedure code supplement
OTC	Over the counter
PAS	Post-authorisation study
PASS	Post-authorisation safety study
PCP	Primary care physician

Abbreviation	Definition
PDR	Prescribed Drug Register
PSUR	Periodic Safety Update Report
QPPV	Qualified person for Pharmacovigilance
R&D	Research & Development
RMP	Risk management plan
STROBE	Strengthening the reporting of observational studies in epidemiology
TBD	To be determined
THIN	The Health Information Network
UK	United Kingdom
UTS	Up to standard
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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4. ABSTRACT

4.1. Title

Linaclotide Utilisation Study in Selected European Populations

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), with approximately one third of IBS patients having each type.

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).

This study plans to describe the characteristics of patients newly prescribed linaclotide, especially in certain population subgroups for which the use of linaclotide was not sufficiently documented in the clinical programme (including the elderly, males, pregnant or breast-feeding women, and patients with specific comorbidities or taking other medications), and in groups with potential off-label use and patients with potential for abuse/excessive use. Linaclotide treatment patterns will be also described.

4.3. Research Question and Objectives

The specific research objectives for this study are to:

- Describe the characteristics of patients prescribed linaclotide at time of first prescription, overall and by specific subgroups of interest
- Describe the extent of linaclotide off-label use
- Describe the proportion and characteristics of patients prescribed linaclotide (overall, and by alleged indication [IBS-C vs. other indications] who experience discontinuation of linaclotide or switching from linaclotide to other drugs potentially used by patients with IBS-C
- Describe the duration of linaclotide treatment until discontinuation or switching

4.4. Study Design

Retrospective cohort (patients newly prescribed linaclotide).

4.5. **Population**

New users of linaclotide with at least 12 months of previous enrolment in the database (baseline period) before the date of first prescription or dispensation of linaclotide (index date) from three different countries: the UK, Spain, and Sweden. One cohort per country will be extracted.

4.6. **Variables**

The variables assessed will be age, gender, diagnosis of IBS and type (when available), pregnancy and breast-feeding (when available), diagnosis of chronic constipation, mechanical gastrointestinal obstruction or Inflammatory Bowel Disease (IBD), comorbidities, concomitant medications in addition to linaclotide, history of digestive surgery (especially history of cholecystectomy), visits/referrals to gastroenterology clinic, and bacterial/viral/parasite lab information.

All variables will be identified from electronic medical records using a pre-specified list of diagnostic, procedure, and drug codes.

4.7. **Data Sources**

The feasibility of conducting this utilisation study was assessed in the countries of interest and the most suitable databases identified that will be used in this study are the following three:

1. UK: the Clinical Practice Research Datalink (CPRD)

   It contains information recorded by general practitioners (GPs) as part of their routine clinical practice and covers approximately 8% 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) and hospital tests and hospital procedures by operating procedure code supplement (OPCS) codes. The data available in the 2014, 12/14 static version of the database, included 474 research quality (acceptable) patients with at least one prescription for linaclotide.
2. Spain: SIDIAP

   It is a primary care database that collects longitudinal data from electronic medical records (EMR) from 274 primary care centres in Catalonia since 2006, representing approximately 12% of the Spanish population. Data from primary and specialised care, hospital, and pharmacy are available, as well as patient characteristics, such as gender, 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 diagnoses, death date, and pregnancy information. GP diagnoses are coded following the ICD-10 codes, and hospital admissions following the International Statistical Classification of Diseases and Related Health Problems, ninth revision (ICD-9).
3. Sweden: the National Patient Registry (NPR) and Prescription Drug Registry (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**

Based on projected post-authorisation usage information provided by Almirall [MAH of linaclotide at the time of development of this protocol] in the linaclotide risk management plan (RMP), sales data and additional assumptions on the distribution of patients and treatment discontinuation, we estimated that by December 2016, roughly 2,674 patients using linaclotide could be captured by the proposed database in the UK, 2,407 in Spain, and 4,584 in Sweden. Overall, this represents over 9,650 patients who would have been exposed to linaclotide in the three target databases), assuming Almirall [MAH of linaclotide at the time of development of this protocol] sales forecasts are correct, and a combined exposure of approximately 4,572 patient-years. 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.

The extended time frame is considered adequate to achieve the estimated sample to conduct the linaclotide DUS and to allow for sufficient follow-up to assess long-term use of linaclotide and use by subgroups of interest.

4.9. **Data Analyses**

All analyses will be first performed separately in each of the study countries. In addition, for the primary study objectives, aggregated analyses with data from all three countries will be performed.

Baseline analyses will be conducted to characterise linaclotide users, and socio-demographic and clinical variables will be described for all users and for those subgroups of patients who were not sufficiently documented in the clinical development programme. The number and percentage of patients using linaclotide off-label will be also described.

Further, linaclotide treatment patterns will be described from index date to end of study period for linaclotide utilisation. Kaplan-Meier estimates will be used to describe time to discontinuation in the prescription or dispensation of linaclotide; and to describe switching from linaclotide to another drug used in IBS-C (laxatives, antispasmodics, prokinetics, or antidepressants). To better assess differences in time to event by the alleged reason for linaclotide prescription (IBS-C or other condition), Cox regression analysis will be employed if the proportional hazards assumption holds; if not, more complex models will be proposed, including predictor variable interactions with time.

Statistical analyses will be conducted using SAS® statistical software.

4.10. **Milestones**

The start of data collection was February 2013 in Sweden, May 2013 in the UK, and September 2014 in Spain, and the end of data collection has been extended to December 2017. Study progress reports will be issued when the Linaclotide Periodic Safety Update Reports (PSURs) are due (every six months for the first two years and yearly thereafter). No interim report is planned for this study, and a final report of study results is planned for December 2018.

5. AMENDMENTS AND UPDATES

Version	Date	Section of study protocol	Amendment or update	Reason
4.0	28 Apr 2015	N/A	Protocol version approved by PRAC	N/A
4.1	07 Jun 2016	Marketing Authorisation Holder	Change from Almirall to Allergan.	Change in MAH responsible for linaclotide
4.2	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

In this version 4.2, the timelines for the study milestones have been updated to reflect one more year of data collection. The updated timelines are provided in Table 1 in the Milestones section below.

6. MILESTONES

Table 1. Milestones

Milestone	Date
Start of data collection	May 2013 (UK) September 2014 (Spain) February 2013 (Sweden)
End of data collection	Data collected up to December 2017 Effective date when data up to December 2017 can be accessed: UK: March 2018 Spain: June 2018 Sweden: August 2018 (NPR) and January 2018 (PDR)
Registration in the EU PAS register	March 2016
Study progress reports	With each PSUR
Interim reports	No
Final report of study results	December 2018

Abbreviations: EU=European Union; PAS=post-authorisation study; PSUR=periodic safety update report; UK=United Kingdom; NPR=National Patient Registry; PDR=Prescribed Drug Registry

7. RATIONALE AND BACKGROUND

IBS is a chronic, relapsing gastrointestinal condition characterised by abdominal pain, bloating, and changes in bowel habits. The first presentation of patients with IBS symptoms to a physician is usually in the 30 to 50-year age group, and there is a decrease in reporting frequency among older subjects (Drossman et al., 2002; IBS Global, 2009). Typically, women are diagnosed with IBS two or three times as often as men in most studies and all population-based studies have reported a female predominance (Keeling & Fielding, 1975; Thompson, 1984; 1997; Saito et al., 2002). Moreover, women make up 80% of the population with severe IBS (Longstreth & Wolde-Tsadik, 1993). Prevalence estimations vary with the diagnostic criteria used, and in the UK were estimated between 9.5% and 22% (Spiller et al., 2007).

IBS can be classified according to Rome III criteria, on the basis of the stool's characteristics: IBS-D; IBS-C; and IBS-M. Patients can transition among these subgroups (IBS Global, 2009). Approximately one third of IBS corresponds to IBS-D, one third to IBS-C and one third to IBS-M (Tillisch et al., 2005). When there is insufficient abnormality of stool consistency to meet the criteria for any of the above, IBS is said to be unsubtyped (Longstreth et al., 2006).

Prior IBS treatments were limited to lifestyle modifications, psychological interventions, and symptomatic treatments (e.g., laxatives, anti-diarrhoeals, and anti-spasmodic agents), or drugs unauthorised for this indication in some of the countries. In a recent review, current IBS-C treatment options showed limited efficacy, and the risk-benefit profile of early 5-Hydroxytryptamine 4 (5-HT4) agonists restricts clinical use (Fortea et al., 2013).

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).

Use of linaclotide in certain population groups is not considered to be sufficiently documented in the linaclotide clinical development programme. Therefore, the use of linaclotide in the routine clinical care setting will also be investigated in specific subgroups, including the elderly population, males, pregnant or breast-feeding women, patients with specific comorbidities, and patients taking other medications. The use of linaclotide in groups with potential off-label use and with potential for abuse/excessive use is of special interest.

The proposed study will describe linaclotide utilisation among patients from three selected European countries: UK, Spain, and Sweden. This study is descriptive and we do not have an *a priori* hypothesis.

8. RESEARCH QUESTIONS AND OBJECTIVES

8.1. Research Questions

This study will address the following primary research questions:

- What are the characteristics of patients prescribed linaclotide?
- What is the extent of linaclotide off-label use with regards to its indication?

A secondary research question will be:

- What are the linaclotide prescription patterns?

All research questions will be assessed in three different countries: the UK, Spain, and Sweden.

8.2. Operational Objectives

- To describe the characteristics of patients prescribed linaclotide at time of first prescription (defined as socio-demographics, comorbidities (up to 15), co-medications (up to 15), and other potential variables of interest (up to 10)
- To also describe characteristics of patients by specific subgroups of interest (e.g., paediatric population, elderly population patients with diabetes, hypertension, or cardiovascular disease diagnostic codes, patients with codes for constipation only)
- To estimate the number and percentage of patients with the potential for linaclotide off-label use in the following groups: off-label/abuse/excessive use as a laxative due to the pharmacology of linaclotide within patients with eating disorders; off-label use in other types of constipation disorders distinct from IBS-C, particularly in the elderly population; and potential for off-label use in the paediatric population for chronic constipation.
- To describe the proportion and characteristics of patients prescribed linaclotide (overall and by alleged indication) who experience any of the following:
    - Discontinuation of linaclotide (permanently during the observation period)
    - Switching from linaclotide to drugs potentially also used by patients with IBS-C moderate to severe: laxatives, antispasmodics, prokinetics, or antidepressants (Hugin, 2003)
- To describe the duration of linaclotide treatment until discontinuation or switching

- To describe the effect of the indication (IBS-C diagnosis versus other) on the time from initiation of linaclotide to discontinuation or switching

9. RESEARCH METHODS

9.1. Study Design

This study will use observational data from three different countries: the UK, Spain, and Sweden. It will be a retrospective cohort (patients prescribed linaclotide) study design.

9.2. Setting

9.2.1. Study Population

The source population for the utilisation study will be:

- UK: patients registered with a GP practice participating in the CPRD
- Spain: patients registered with a GP practice participating in the SIDIAP
- Sweden: patients registered in the NPR linked to the PDR

9.2.2. Study Cohort

The study cohort will consist of new users of linaclotide (individuals newly prescribed or dispensed linaclotide) with at least 12 months of previous enrolment in the database (baseline period) before the date of first prescription or dispensation of linaclotide (index date).

9.2.2.1 Inclusion/Exclusion Criteria

Patients in the study will be required to meet the following inclusion criteria:

- The patient has at least one prescription of linaclotide in his/her medical records anytime during the study period in the UK; for Spain and Sweden, inclusion will be determined by at least one dispensation of linaclotide).
- Patient has at least 12 months of computerised records prior to the first use of linaclotide (index date).
- Patient is active (i.e., alive and permanently registered) at index date.

The following exclusion criteria will apply:

- Patient has no follow-up time (for example, transfers out or dies on the date of the first linaclotide prescription).

Additionally, in the UK two additional exclusion criteria will be applied:

- Patient who does not meet the CPRD ‘acceptable’ criteria (patient is permanently registered at the practice and has a valid year of birth and gender) at index date (or equivalent for other database)
- The practice’s up-to-standard (UTS) date in CPRD is later than the index date (practices meeting pre-defined quality control standards for completeness, continuity, and plausibility are registered as UTS since the date those standards are met), or equivalent for other database

No additional exclusion criteria will be applied in Spain or Sweden since all records are considered of sufficient quality to conduct research studies.

9.2.2.2 Time Periods and Dates

The study period is determined by the launch date of linaclotide and subsequent uptake. The study period starts on the date of linaclotide commercialisation in each of the countries: in UK in May 2013, in Spain in September 2014, and in Sweden in February 2013.

The end of the study period is defined by the last day of patient records in the available data cut, currently planned for 31 December 2017, to allow for sufficient follow-up time (long-term use) to have

the opportunity to accrue a sizable number of subjects for descriptive purposes, and for subpopulations of interest (those with potential off-label use and potential for abuse/excessive use). Please refer to the Study Size and Data Analysis sections below.

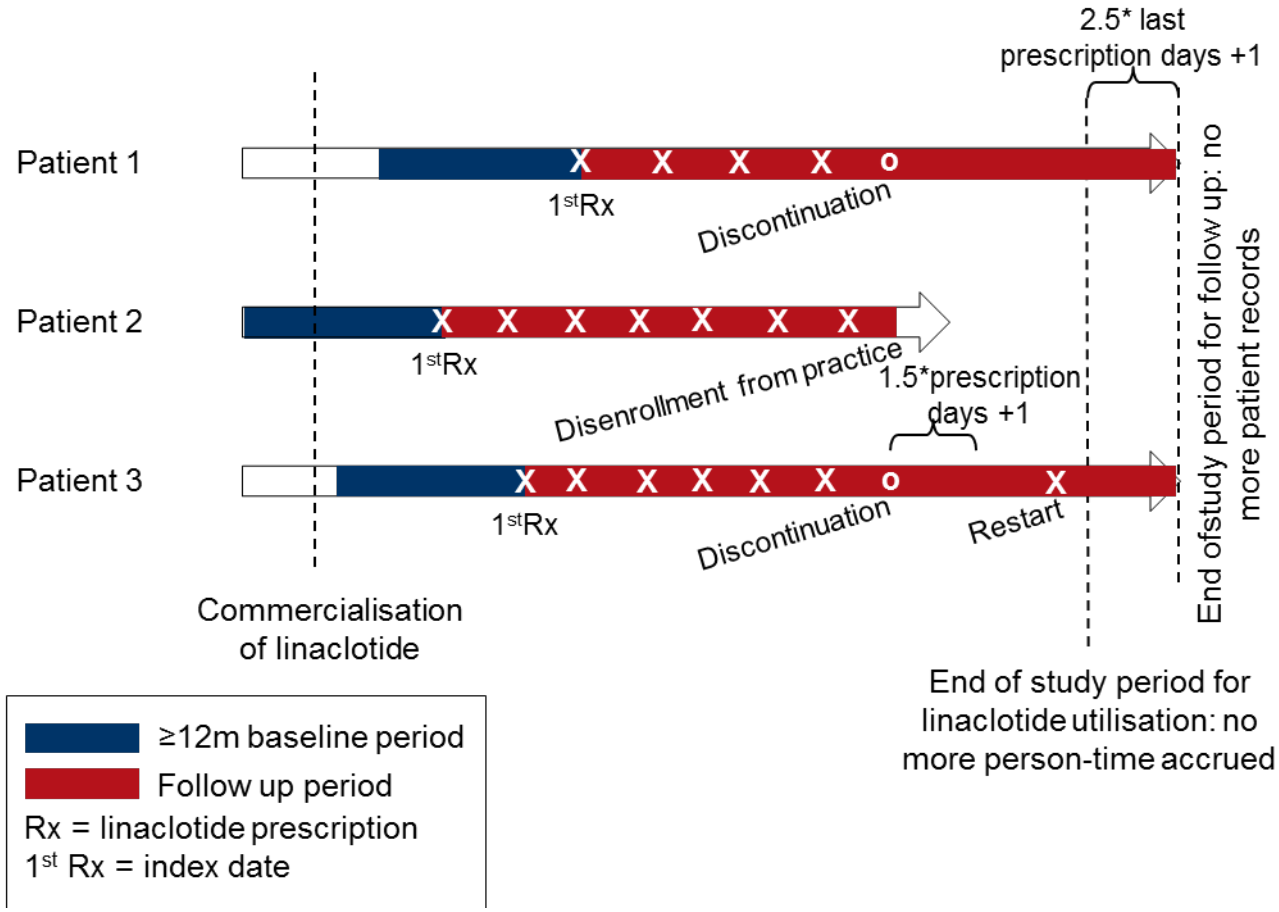
Additionally, the database's lag time (for collected data to be available in each database, estimated as up to 8 months) needs to be factored in to determine when data will be available.

Index date (or cohort entry date) will be defined as date of the first prescription (UK) or dispensation of linaclotide (Spain and Sweden). Baseline period will be the ≥12-month period before index date.

The follow-up period for each study subject will be the time from the index date to the earliest of the following dates (end of follow-up date; one day is the minimum follow-up; Figure 1):

- End of the study period for follow-up
- Disenrollment from the database (date of transfer out of the practice)
- Date of last data collection
- Death
- 1.5 times the number of days of linaclotide supply after the expiry of the last linaclotide prescription during the study period (for a total of 2.5 times the last prescription duration) plus one additional day when a potential discontinuation could be assessed (please refer to section 9.3.3 Linaclotide Treatment Outcomes below)

Figure 1. Study Periods Linaclotide DUS



9.3. **Variables**

9.3.1. Variables to Identify Subgroups of Interest

In order to identify the subgroups of patients of interest, the following variables will be used:

- Age
- Gender
- Pregnancy and breast-feeding (when available)
- Diagnosis of IBS and type
- Chronic constipation
- Mechanical gastrointestinal obstruction or IBD
- Hepatic impairment, chronic kidney disease or chronic renal failure
- Cardiovascular disorders or risk factors—i.e., cerebrovascular disease, coronary artery disease, angina, myocardial infarction, heart failure, arrhythmias, use of antiarrhythmic drugs, hyperlipidaemia, or use of lipid-lowering drugs
- Hypertension or use of antihypertensive drugs
- Diabetes
- Obesity and eating disorders (anorexia nervosa, bulimia) that are suspected conditions related to potential for abuse or excessive use—e.g., use for weight loss or as laxative

9.3.2. Variables at Baseline

Patients included in the DUS will be described according to their characteristics at index date, using data from the baseline period, from diagnoses, procedures and prescription information from each data source:

- Age (as continuous variable and categories <18,18-65, ≥65 years)
- Gender
- Diagnosis of IBS and type [1]
- Comorbidities:
    - Cardiovascular disorders or risk factors—i.e., cerebrovascular disease, coronary artery disease, angina, myocardial infarction, heart failure, arrhythmias, use of antiarrhythmic drugs, hyperlipidaemia, or use of lipid-lowering drugs
    - Hypertension or use of antihypertensive drugs
    - Diabetes
    - Hepatic impairment
    - Chronic kidney disease or chronic renal failure
    - Inflammatory bowel conditions (i.e., Crohn's disease, ulcerative colitis, microscopic colitis)
    - Mechanical gastrointestinal obstruction
    - Any psychiatric disorder, as well as:
        - Depression diagnosis
        - Anxiety diagnosis
    - Food intolerance (e.g., lactose)
    - Celiac disease
    - Cancer (e.g., colon)
    - Bile salt malabsorption
    - Immunodeficiency

[1] When possible, proportion of IBS-C.

- Obesity and eating disorders (anorexia nervosa, bulimia)

- Medications: the three most commonly prescribed medication groups in addition to the following, if not included (Only about half of IBS-C patients are expected to be on prescribed medication, but the majority of patients are expected to be self-treated [Wilson et al., 2004].):
  - Laxatives (i.e., bulk-forming laxatives, stimulant laxatives, faecal softeners, and osmotic laxatives) (Concomitant use of laxatives was described among one-third of the antispasmodic mebeverine users and it was associated with increased odds of hospitalisation [Goettsch WG, 2004].)
  - Antispasmodics (i.e., anti-muscarinic agents and direct-action smooth muscle relaxants)
  - Prokinetic drugs
  - Antidepressants (i.e., tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors)
  - Antibiotics
  - Calcium and aluminium-containing antacids
  - Magnesium-containing antacids
  - H2 blockers
  - Proton pump inhibitors
  - Analgesic drug classes:
    - Non-steroidal anti-inflammatory drugs
    - Opioids
    - Other analgesics

- Other variables:
  - History of digestive surgery (especially history of cholecystectomy)
  - Gastroenterology clinic visit (Spain and Sweden) or referral (UK)
  - Bacterial/viral/parasite lab information, when available (positive versus negative or no information)

For prevalence of chronic comorbidities, prior diagnoses, or history of digestive surgery at index date, the patient's entire medical history will be explored.

9.3.3. Linaclotide Treatment Outcomes

Secondary outcomes of this study will be linaclotide treatment patterns. The linaclotide exposure information is characterised by the linaclotide days of supply. Days of supply will be ascertained from the prescription/dispensation information recorded in the databases and the recommended dose (one capsule of linaclotide 290 μg taken once per day) and calculated by dividing the quantity prescribed/dispensed by the daily dose. Days of supply of one prescription/dispensation are expected to be around 28 days since the 28-capsule pack will be the most widely used package size. If package size is unknown, then the median duration for patients with this information will be used (and if no median can be estimated then 28 days will be used).

Linaclotide prescription patterns of interest are:

- Discontinuation of linaclotide: defined as no prescription of linaclotide in the period of 1.5 times the number of days of supply of the last linaclotide prescription following its expiry date (Sikka et al., 2005; Peterson et al., 2007): for example, for a 28-day prescription, no new prescription in the 43 days after the expiry date of the prescription supply. The date of discontinuation is the day after the date of expiry of the last linaclotide prescription. Time to discontinuation (permanently during the study period or temporarily) is the interval between the date of the first linaclotide prescription and the date of discontinuation. Discontinuation

will be reported separately for those who permanently discontinue during the study period and for those who discontinue temporarily and subsequently restart on linaclotide (see below).

- Switching from linaclotide to laxatives, antispasmodics, prokinetics, or antidepressants without prescription of linaclotide: defined as a prescription of laxatives, antispasmodics, prokinetics, or antidepressants that starts while on treatment with linaclotide and continues after the date of the linaclotide discontinuation. The date of switching is the date when the new prescription of laxatives, antispasmodics, prokinetics, or antidepressants is issued followed by linaclotide discontinuation. Time to switching is the interval between the date of the first linaclotide prescription and the date of switching.

To be able to define linaclotide discontinuation and switching at the end of the study period, it is necessary to have enough study period for follow-up after the expiry of the last linaclotide prescription. This time at the end of the study corresponds to the gap tolerated between prescriptions that could occur if the patient is on treatment but also hospitalized or travelling. This grace period is defined as 2.5 times the number of days of supply of the last linaclotide prescription (the prescription duration in addition to 1.5 times the number of days of supply of the last linaclotide prescription following its expiry date) plus one additional day when a potential discontinuation (or switching) could be assessed. Patients who continue taking linaclotide will be censored at the end date of the study period for linaclotide utilisation. This has implications for the interpretation of linaclotide treatment duration because it is conditioned by the study length.

Switching from linaclotide requires discontinuation in the prescription of linaclotide but these patterns will be considered exclusive events and patients experiencing switching immediately after discontinuation will be allocated to switching. Time to discontinuation and time to switching to another drug are secondary endpoints for the linaclotide utilisation study.

9.3.4. IBS Diagnosis and Severity Definition

The target indication of linaclotide is the treatment of moderate to severe IBS-C in adults. There are several Read, ICD-9 or ICD-10 codes related to IBS, but none are specific to IBS-C. In order to identify potential cases of IBS-C patients using codes, a combination of an IBS code with a code for constipation will be used. Table 4, Table 5 and Table 6 in Annex 3 include a broad list of Read codes, ICD-10 and ICD-9 codes for the identification of patients with IBS with different level of specificity, and codes for constipation to be used in combination.

There are no Read, ICD-9, or ICD-10 codes to indicate the severity of IBS. The most studied and most commonly used tools for measuring IBS severity involve quality-of-life and patient-reported symptom metrics that are not routinely recorded in the computerised databases selected for this study. Some components like symptoms or number of healthcare visits (part of the Functional Bowel Disorder Severity Index [Drossman et al., 2011]) have been previously used in the development of an IBS severity measure. However, it is not envisaged that this will be done as part of this study.

9.4. **Data Sources**

In the UK, the proposed data source is the CPRD; for Spain, the proposed data source is the SIDIAP; and for Sweden the NPR linked to the PDR. A summary of potential data sources that were evaluated for use in the study can be found in the *Database Feasibility Assessment* section in Annex 3.

9.5. **Study Size**

The study sample size calculations are based on real and projected post-authorisation usage data information provided by Almirall [MAH of linaclotide at the time of development of this protocol]. The estimated patient use by year after the introduction of linaclotide for the three countries of interest is shown in Table 2.

Table 2. Projected Post-authorisation Use of Linaclotide per Year in Countries of Interest (Number of Patients derived from Sales and Projected Sales of Linaclotide Capsules)

Country	2014	2015	2016	2017
Sweden	1,238	2,475	3,263	4,052
Spain	1,889	9,385	16,435	23,073
UK	7,475	14,419	27,619	45,279

Source: Data provided by Almirall [MAH of linaclotide at the time of development of this protocol] on January 2015
Abbreviations: UK=United Kingdom

The end of data collection was initially planned for December 2016 to allow for a minimum of one year of follow-up (long-term use) for approximately 25% of patients enrolled in the study and for subpopulations of interest to have the opportunity to accrue a sizable number of subjects.

To estimate the cumulative number of patients and patient-time use of linaclotide we assumed that:

- Linaclotide prescriptions are evenly distributed across each of the countries
- Each database captures data of a representative sample of the population
- The database patient base is constant over the forecast period and 90% of patients meet inclusion and exclusion criteria
- There is an approximately 40% yearly treatment discontinuation rate and an average treatment duration of 135 days per patient and year (approximately one-third of patients expected to cease medication after one pack of linaclotide or 28 capsules because of unsatisfactory response; one-third of patients expected to use the medication for an average of 150 days out of 365 because of clinically meaningful benefit; approximately one-third expected to use medication almost continuously for an average duration of treatment calculated at 220 days per year)

Based on the above assumptions, the number of patients initially anticipated in each of the countries available for analyses was as described in Table 3.

Table 3. Projected Post-authorisation Cumulative Number of IBS-C Patients using Linaclotide in the CPRD from the UK, PDR from Sweden and SIDIAP from Spain, and Corresponding Number of Patient-years, 2014–2016, Meeting Inclusion and Exclusion Criteria for Linaclotide DUS*

	2014	2015	2016
CPRD: 8% of the UK			
projected number of patients	518	1211	2,674
projected number of patients-years	211	557	1,219
SIDIAP: 12.8% of Spain			
projected number of patients	207	1,108	2,407
projected number of patients-years	76	456	1,122
Sweden National Patient Register: 95% of Sweden			
projected number of patients	1,147	2,766	4,584
projected number of patients-years	506	1,250	2,231
Combined:			
projected number of patients	**1,872**	**5,085**	**9,665**
projected number of patient-years	**794**	**2,263**	**4,572**

*86% in Sweden and Spain, 81% in the UK, of the total number of linaclotide users
Abbreviations: CPRD=clinical practice research datalink; UK=United Kingdom

By the end of 2016 it was estimated that over 9,650 patients would have been exposed to linaclotide

in the three target databases together, for a combined exposure of more than 4,500 patient years. The UK would be contributing approximately 28% of patients, Spain 25%, and Sweden 47%.

For the treatment patterns, a total of approximately 8,800 patients would allow the detection of a hazard ratio of 1.2 or greater for patient characteristics, assuming linaclotide discontinuation or linaclotide switching occur in about 10% the observed sample (users with a specific characteristic) with a probability of 40%, with 90% power and a two-sided type I error rate (alpha) of 5%.

In the progress report for 2016, users of linaclotide included in each of the study databases 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 to allow for the number of users to reach the desired sample size.

9.6. **Data Management**

We will collect electronic primary care patient records from the CPRD in the UK and electronic records on inpatient and outpatient admissions and dispensation of drugs in Sweden from the NPR and PDR. Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programmes. In Spain, SIDIAP will be in charge of the data management.

Each database custodian will maintain any patient-identifying information securely on site according to internal standard operating procedures. [redacted] will maintain the data cuts according to internal procedures.

An [redacted] data analyst will write and review programs to implement the analyses outlined in the Data Analysis section below. The project team will review all data output, including SAS® code as needed. Changes and corrections to programs stemming from the review will be made as appropriate. All programs will be saved and the process documented. Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on compact disk read-only memory [CD-ROM] or digital versatile disk [DVD]) with periodic backup of files to tape. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

9.7. **Data Analysis**

Analyses will be performed in each of the study countries separately.

9.7.1. Patient Characteristics and Medical History

At linaclotide cohort entry date or index date, the socio-demographic characteristics of all linaclotide users, comorbidities, and the most relevant co-medications will be assessed by reviewing data for a minimum of 12-months prior to index date, and summary statistics will be reported with mean and standard deviation for continuous variables and number and percentage for categorical ones. The number and proportion of patients with missing data will be reported for each of the variables of interest.

Baseline characteristics will also be described in the following subgroups of patients, selected because in the clinical development programme, the use of linaclotide in these groups reflected important missing information, potential off-label use, and potential for abuse/excessive use:

- Children and adolescents (younger than 18 years of age)
- Older adult population (65 years or older)
- Pregnant or breast-feeding women

- Male patients
- Non-IBS-C patients with chronic constipation
- Patients with known or suspected mechanical gastrointestinal obstruction or IBD
- Patients with specific comorbidities (i.e., hepatic or renal impairment, cardiovascular diseases and associated risk factors, hypertension, diabetes)
- Patients with potential for abuse/excessive use—e.g., use for weight loss (patients with body mass index <20), use as a laxative (patients with codes for constipation only).

9.7.2. Linaclotide Prescription Patterns

Linaclotide treatment patterns will be assessed in the follow-up period from index date, as defined above.

The numbers and proportions of patients who experience one of the following treatment events will be reported separately:

- Discontinuation in the prescription of linaclotide
- Switching from linaclotide prescription to the prescription of another drug (i.e., laxatives, antispasmodics, prokinetics or antidepressants)

Switching from linaclotide requires discontinuation in the prescription of linaclotide but these patients will be allocated to switching so the two categories will be mutually exclusive. Kaplan-Meier estimates will be used to describe the times to first discontinuation or switching.

To better assess differences in time to event by the alleged reason for linaclotide prescription (IBS-C or other conditions), Cox regression analysis will be employed. Multivariate Cox regression models will be fitted to identify the effects of the indication and various other baseline variables on the time from initiation of linaclotide to first treatment discontinuation or switching. For each of the two outcome variables (time to discontinuation and time to switching), a set of plausible candidate models will be proposed and fitted to the data. Models will be ranked according to Akaike's Information Criterion and the best model will be selected; or, if several models prove to perform well, these will be averaged to produce a final model. Some iteration between choosing candidate models and data analysis will likely be necessary, owing to the need to check that the proportional hazards assumption holds for each candidate model.

Statistical analyses will be conducted using SAS® statistical software.

9.8. **Quality Control**

Standard operating procedures at each research centre will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All work will be subject to quality control and documentation procedures to make certain the final report is accurate and thorough and the analyses can be reproduced. If the data do not permit an analysis as planned (e.g., through insufficient sample size in a subgroup analysis) or if clarifying analyses are required (e.g., an unexpected result that could be explained by a subgroup analysis), [redacted] staff will inform Allergan and include the additional information and results in the report. All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

A quality-assurance audit of this study may be conducted.

9.9. **Limitations of the Research Methods**

Categorisation of patients with IBS into IBS-C, IBS-D, or IBS-M might be challenging. Differentiation between IBS-C and chronic constipation will also be challenging. As a consequence, some degree of misclassification is to be expected.

The use of over-the-counter medications for the treatment of IBS-C-related symptoms, constipation, and diarrhoea is acknowledged as another study limitation (Hungin, 2003). Over-the-counter medications will not be available in the UK or in Sweden. For Spain, we will include over-the-counter medications; however, we expect under-recording of these in the database.

The CPRD provides a large, diverse, and representative sample of UK people using primary care services, which allows for generalizability of the study findings to the broader UK population. The CPRD (and its predecessor General Practice Research Database [GPRD]) have been widely used for observational studies, with over 890 studies published to date in peer-reviewed journals. The SIDIAP database includes information for 90% of the population resident in Catalonia, a region in the north-east of Spain, and resembles the data collected by UK databases. One limitation is that date of prescription is available for only the first prescription and, thereafter, only approximate date of dispensation is available. For Sweden, the NPR and PDR cover the entire Swedish population and have been previously use in observational studies including drug utilisation ones. However, no primary care data will be available, so diagnoses will be those determined by a specialist, which are expected to be required for the variables of interest for this study. The PDR is not complete with regard to drugs used in nursing homes. According to the National Board of Health and Welfare, about 1% of people aged 65−79 years live in nursing homes, and about 20% of people aged 80 or more years live in nursing homes in Sweden [Socialstyrelsen]. This may be reflected in potential lower numbers of elderly patient using linaclotide identified in Sweden.

The validity of research findings based on CPRD data as well as the other databases depends on the quality and completeness of data recorded. We are only able to identify comorbidities for which the patient has consulted their GP. Referrals are not always uniformly coded and may appear as free-hand text or letters within the database.

Interval censoring might have an impact on the precision of the results.

9.10. **Other Aspects**

No further aspects to be considered.

10. PROTECTION OF HUMAN SUBJECTS

Institutional review board approval and/or any other required reviews of the study protocol by specific committees will be obtained in accordance with applicable national and local regulations.

The study will be conducted in accordance with the International Society for Pharmacoepidemiology's (ISPE) Guidelines for Good Pharmacoepidemiology Practices (2007), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance's (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2011a). The ENCePP Checklist for Study Protocols (ENCePP, 2011b) will be completed.

The study will be registered in the ENCePP Electronic Register of Studies (ENCePP, 2010) after regulatory endorsement of the protocol.

The study will comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/European Commission and its refinement provided in Chapter I.7 Section 1 of Volume 9A of the Rules Governing Medicinal Products in the EU: Guidelines on

Pharmacovigilance for Medicinal Products for Human Use (European Commission, 2008), and referred to in the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use's Pharmacovigilance Planning (ICH, 2004) and the Guideline on Good Pharmacovigilance Practices, Module VIII—Post-Authorisation Safety Studies (European Medicines Agency [EMA], 2012a).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS (AE)/ADVERSE REACTIONS

For studies in which the research team uses only data from automated health care databases, the ISPE provides the following guidance:

> *'Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines.'* (ISPE, 2007, Section VI)

The EMA *Guideline on Good Pharmacovigilance Practices, Module VI*, provides the following guidance:

> *'For non-interventional study designs which are based on secondary use of data, such as studies based on medical chart reviews or electronic healthcare records, systematic reviews or meta-analyses, adverse reactions reporting is not required. Reports of adverse events/reactions should only be summarised in the study report, where applicable.'* (EMA, 2012b, Section C.1.2.1)

The linaclotide DUS does not require adverse events (AEs) to be reported in an expedited manner to European authorities.

Procedures for the collection and reporting to Allergan of AEs/reactions identified during the study conduct will be agreed with Allergan and put in place, in accordance with the provisions of *Module VI, Management and Reporting of Adverse Reactions to Medicinal Products*, from the EMA.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Regulatory Communication Plan

Study protocol, study status, and report(s) will be included in regulatory communications in line with the RMP, PSUR, and other regulatory milestones and requirements.

12.2. Publication and Communication Plan

Any publication resulting from the work outlined in this proposal will be discussed with Allergan. will ensure Allergan has adequate time to review and comment on any manuscript or abstract developed. For all publications of project work, adheres to the authorship definitions and requirements as stated in the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* from the International Committee of Medical Journal Editors (ICMJE) 2013, repeated in part, as follows:

- Authorship credit should be based on: 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2 and 3
- All persons designated as authors should qualify for authorship and all those who qualify should be listed
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content

- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship

Study results will be published following guidelines of the ICMJE (2010) and communication in appropriate scientific venues, e.g., ISPE will be considered. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed (STROBE, 2007).

In its *Guidelines for Good Pharmacoepidemiology Practices*, ISPE contends that '*there is an ethical obligation to disseminate findings of potential scientific or public health importance*' (ISPE, 2007, Section V). This would include results pertaining to the safety of a marketed medication. Study results will be published following guidelines, including those for authorship, established by the ICMJE (2010).

The marketing authorisation holder and the investigator have agreed on a publication policy allowing the principal investigator to prepare publications independently based on the study results, irrespective of data ownership. The marketing authorisation holder will be entitled to view the results and interpretations included in the manuscript, and provide comments prior to submission of the manuscript for publication (EMA, 2012a, Section VIII.B.7).

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	SAP version identifier: 1.1	07/06/2016	Linaclotide Utilisation Study in Selected European Populations Statistical Analyses Plan

ANNEX 2. ENCePP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for:				
1.1.1 Start of data collection[2]	☒	☐	☐	11
1.1.2 End of data collection[3]	☒	☐	☐	11
1.1.3 Study progress report(s)	☒	☐	☐	11
1.1.4 Interim progress report(s)	☐	☐	☒	11
1.1.5 Registration in the EU PAS register	☒	☐	☐	3, 11
1.1.6 Final report of study results	☒	☐	☐	11

Comments:

Section 2: Research Question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
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)	☒	☐	☐	11
2.1.2 The objective(s) of the study?	☒	☐	☐	12
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	12, 13
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	12

Comments:

Section 3: Study Design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g., cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	12-14
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	15,16
3.3 Does the protocol describe the measure(s) of effect? (e.g., relative risk, odds ratio, deaths per 1,000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm [NNH] per year)	☒	☐	☐	17, 18

Comments:

Section 4: Source and Study Populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	12,17,36-42
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	13,14

[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 4: Source and Study Populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.2 Age and sex?	☒	☐	☐	19, 20
4.2.3 Country of origin?	☒	☐	☐	12, 18-19
4.2.4 Disease/indication?	☒	☐	☐	17, 19-20
4.2.5 Comorbidity?	☒	☐	☐	19, 20
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	12-14

Comments:

Subgroup analyses will be performed by age, sex, indication, and presence of comorbidities.

Section 5: Exposure Definition and Measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g., operational details for defining and categorising exposure)	☒	☐	☐	16,17
5.2 Does the protocol discuss the validity of exposure measurement? (e.g., precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	21
5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

All patients with at least one prescription / dispensation of linaclotide will be included

Section 6: Endpoint Definition and Measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☒	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Section 7: Confounders and Effect Modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g., collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	14-16
7.2 Does the protocol address known effect modifiers? (e.g., collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	14-16

Comments:

Section 8: Data Sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	36-42
8.1.2 Endpoints? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐ ☒	☐ ☐	☒ ☐	 36-42
8.1.3 Covariates?				
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	36-42
8.2.2 Endpoints? (e.g., date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (e.g., age, sex, clinical and drug use history, comorbidity, co-medications, lifestyle, etc.)	☒	☐	☐	36-42
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g., International Classification of Diseases [ICD-10])	☒	☐	☐	17,33 36-42
8.3.2 Endpoints? (e.g., Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g., World Health organization (WHO) Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	3,15,17,18,36-42
8.4 Is the linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

Analyses in the three countries will be performed separately.

Section 9: Study Size and Power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	18, 19

Comments:

Section 10: Analysis Plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	19-21
10.3 Are descriptive analyses included?	☒	☐	☐	19,20
10.4 Are stratified analyses included?	☐	☒	☐	

Section 10: Analysis Plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	20
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	20

Comments:

Section 11: Data Management and Quality Control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	19
11.2 Does the protocol provide information on data storage? (e.g. software and information technology (IT) environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	19
11.3 Are methods of quality assurance described?	☒	☐	☐	19,21
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	19,21,36-42
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	19,21,23

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒ ☒	☐ ☐	☐ ☐	21 17, 21
12.2 Does the protocol discuss study feasibility? (e.g., sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	18,19
12.3 Does the protocol address other limitations?	☒	☐	☐	21

Comments:

Section 13: Ethical Issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	22, 36-42
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	19,22

Comments:

Section 14: Amendments and Deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	10

Comments:

Section 15: Plans for Communication of Study Results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	23
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	23

Comments:

Name of the main author of the protocol:

Date: 07/June/2016

Signature:

ANNEX 3. ADDITIONAL INFORMATION

A. Lists of Codes to Identify Patients with IBS and IBS Type

Table 4. Read Codes for the Identification of IBS and Constipation

Read Code	Description	Comments
J521000	IBS with diarrhoea	To be used as exclusion criteria
14CF.00	History of irritable bowel syndrome (IBS)	To identify potential prevalent cases
Eu45324	**Psychogenic IBS**	**Unfrequently used, check for constipation**
J521.00	**Irritable colon–IBS**	**Preferred code, check for constipation**
J521.13	**Spastic colon**	**Unfrequently used, check for constipation**
J521.11	**IBS**	**Preferred code, check for constipation**
19C..11	Constipation symptom	Preferred code, combined with IBS
19C..00	Constipation	Preferred code, combined with IBS
19C2.00	Constipated	Unfrequently used, combined with IBS
19CZ.00	Constipation NOS	Unfrequently used, combined with IBS
J520z00	Constipation NOS	Third choice, combined with IBS
J520.00	Constipation – functional	Second choice, combined with IBS
J520100	Chronic constipation with overflow	Unfrequently used, combined with IBS
J520000	Acute constipation	Unfrequently used, combined with IBS
J520200	Chronic constipation without overflow	Unfrequently used, combined with IBS
J520300	Drug induced constipation	Unfrequently used, combined with IBS
E264500	Psychogenic constipation	Unfrequently used, combined with IBS
J520y00	Other specified constipation	Unfrequently used, combined with IBS
1962.00	Colicky abdominal pain	Second choice as code in IBS
1971.00	Central abdominal pain	Third choice as code in IBS
1972.00	Epigastric pain	Third choice as code in IBS
196..00	Type of GIT pain	Unfrequently used
196..11	Abdominal pain type	Unfrequently used
1968.00	Abdominal discomfort	Third choice as code in IBS
1969.00	Abdominal pain	Second choice as code in IBS
197..13	Site of abdominal pain	Unfrequently used
197A.00	Generalised abdominal pain	Second choice as code in IBS
197C.00	Lower abdominal pain	Third choice as code in IBS
197Z.00	Site of GIT pain NOS	Unfrequently used
1963.00	Non-colicky abdominal pain	Unfrequently used
196Z.00	Type of GIT pain NOS	Unfrequently used
196..12	Type of GIT pain - symptom	Unfrequently used
1976.00	Right flank pain	Unfrequently used
1975.00	Left flank pain	Unfrequently used

197..11	Flank pain	Unfrequently used
197..12	Iliac fossa pain	Unfrequently used
1977.00	Right iliac fossa pain	Unfrequently used
1978.00	Left iliac fossa pain	Unfrequently used
197B.00	Upper abdominal pain	Unfrequently used
197D.00	Right upper quadrant pain	Unfrequently used
1974.00	Right subcostal pain	Unfrequently used
197..00	Site of GIT pain	Unfrequently used
197..14	Subcostal pain	Unfrequently used
1973.00	Left subcostal pain	Unfrequently used
197A.11	General abdominal pain symptom	Unfrequently used
R090400	[D] Abdominal cramps	Unfrequently used
R090.00	[D] Abdominal pain	Unfrequently used
R090500	[D] Epigastric pain	Unfrequently used
R09E00	[D] Recurrent acute abdominal pain	Unfrequently used
R090z00	[D] Abdominal pain NOS	Unfrequently used
R090100	[D] Abdominal colic	Unfrequently used
R090700	[D] Hypocondrial pain	Unfrequently used
R090400	[D] Abdominal cramps	Unfrequently used
R090N00	[D] Nonspecific abdominal pain	Unfrequently used
R090J00	[D] Right upper quadrant pain	Unfrequently used
R090H00	[D] Upper abdominal pain	Unfrequently used
R090900	[D] Pain in right iliac fossa	Unfrequently used
R090600	[D] Umbilical pain	Unfrequently used
R090A00	[D] Pain in left iliac fossa	Unfrequently used
R090000	[D] Abdominal tenderness	Unfrequently used
R090K00	[D] Left upper quadrant pain	Unfrequently used
R090y00	[D] Other specified abdominal pain	Unfrequently used
R090L00	[D] Left lower quadrant pain	Unfrequently used
R090311	[D] Right lower quadrant pain	Unfrequently used
1961.00	No abdominal pain	To be used as exclusion criteria
19A..00	*Abdominal distension symptom*	*Second choice as code in IBS*
19A3.00	*Abdomen feels distended*	*Unfrequently used*
19A2.00	*Abdomen feels bloated*	*Unfrequently used*
19AZ.00	*Abd. Distension symptom NOS*	*Unfrequently used*
19A4.00	*Abdomen feels swollen*	*Unfrequently used*
19B..12	*Bloating symptom*	*Second choice as code in IBS*
19B..15	*Wind symptom*	*Unfrequently used*
19B2.00	*Excessive flatulence*	*Unfrequently used*

19B..14	*Flatulence symptom*	*Unfrequently used*
19B..00	*Flatulence/wind*	*Unfrequently used*
19BZ.00	*Wind NOS*	*Unfrequently used*
R073400	*[D] Bloating*	*Third choice as code in IBS*
R073000	*[D]Flatulence*	*Unfrequently used*
R073.00	*[D] Flatulence, eructation, and gas pain*	*Third choice as code in IBS*
R073300	*[D] Abdominal distension, gaseous*	*Unfrequently used*
R073z11	*[D] Wind*	*Unfrequently used*
R073200	*[D] Gas pain (abdominal)*	*Unfrequently used*
R073z00	*[D] Flatulence, eructation and gas pain NOS*	*Unfrequently used*
19EA.00	*Change in bowel habit*	*Unfrequently used*
19EA.11	*Altered bowel habit*	*Unfrequently used*
R078.00	*[D] Change in bowel habit*	*Unfrequently used*
R121200	*[D] Mucus in stool*	*Unfrequently used*
4763.00	*Faeces: mucous present*	*Unfrequently used*
19EH.00	*Mucus in faeces*	*Unfrequently used*
198..00	*Nausea*	*Second choice as code in IBS*
1982.00	*Nausea present*	*Unfrequently used*
198..12	*Nausea symptoms*	*Third choice as code in IBS*
198..11	*C/O - nausea*	*Unfrequently used*
198Z.00	*Nausea NOS*	*Unfrequently used*
R070000	*[D] Nausea*	*Unfrequently used*
R070.00	*[D] Nausea and vomiting*	*Unfrequently used*
R093000	*[D] Abdominal swelling*	*Unfrequently used*
J16y411	*Flatulent dyspepsia*	*Unfrequently used*
19D..12	*Anal symptoms*	*Unfrequently used*
19D..11	*Tenesmus symptom*	*Unfrequently used*
19D..00	*Tenesmus*	*Unfrequently used*
19D2.00	*Tenesmus present*	*Unfrequently used*
19DZ.00	*Tenesmus NOS*	*Unfrequently used*
19E..11	*Faeces symptom*	*Unfrequently used*
19E..12	*Motions – symptom*	*Unfrequently used*
19E..00	*Faeces/motions – symptoms*	*Unfrequently used*
19F..	Diarrhoea symptoms	
19G..00	Diarrhoea and vomiting	
J525.00	Functional diarrhoea	
J43z.	Chronic diarrhoea	
J4z..	Non-infectious diarrhoea	

Abbreviations: IBS=irritable bowel syndrome; IBS-C=IBS predominately with constipation; NOS=unspecified

Patients with IBS will be identified through the following criteria:

- One or more IBS- related codes codes among the following: J521.00, J521.11, J521.13, Eu45324, 14CF.00.
- Alternatively, a combination of a code of abdominal pain or discomfort (in gray background and regular font) and at least two codes among those reported as "second choice as code in IBS", "third choice as code in IBS" or "unfrequently used" (in *italics* and gray background).

Patients with only 14CF.00 will identify as prevalent IBS-C patients since the diagnosis date is uncertain.

Patients with IBS-C will be identified through the following criteria:

- Patient with IBS as specified above an one preferred code including the term "constipation"

Patients with IBS and a code for diarrhoea will be IBS-D. Patients with IBS only or meeting both criteria will be IBS-M.

Table 5. ICD-10 Codes for the Identification of IBS and Constipation

ICD-10 Code	Description	Comments
K58	Irritable bowel syndrome (IBS), irritable colon	Preferred code, check for constipation
K58.0	IBS with diarrhoea	To be used as exclusion criteria
K58.9	IBS without diarrhoea; IBS NOS	Preferred code, check for constipation
K59.9	Functional intestinal disorder, unspecified	Not specific
K59.0*	Constipation	To be used in combination with K58, K58.9, and K59.9 to identify IBS predominantly with constipation (IBS-C

Abbreviations: IBS=irritable bowel syndrome; IBS-C=IBS predominately with constipation ; NOS=unspecified

Patients with IBS will be identified through the following criteria:

- At least one code K58, K58.9 or K59.9 without code K58.0

Patients with IBS-C will be identified through the following criteria:

- Patient with IBS as specified above and code K.59.0

Patients with IBS-D will be identified through the following criteria:

- Patient with code K58.0

Patients with IBS-M will be all others with IBS but no criteria of IBS-C or IBS-D

Table 6. ICD-9 Codes for the Identification of IBS and Constipation

ICD-9 Code	Description	Comments
564.1	Irritable bowel syndrome (IBS); irritable colon; spastic colon	Preferred code, check for constipation
564.0, 564.00, 564.01, 564.09	Constipation	To be used in combination with 564.1 to identify IBS predominantly with constipation (IBS-C)
787.91	Diarrhoea	To be used in combination with 564.1 to identify IBS predominantly with constipation (IBS-D)

Abbreviations: IBS=irritable bowel syndrome; IBS-C=IBS predominately with constipation; IBS-D=IBS predominantly with diarrhoea

Patients with IBS-M will be identified through the following criteria:

- Code 564.1 without codes for constipation or codes for diarrhoea.

B. Database Feasibility Assessment

This section includes a summary of the databases assessed for use in the linaclotide studies, planned to be implemented in the UK, Spain, and Sweden. The feasibility assessment in Italy as a candidate country is also reported, although the coverage of the data sources investigated was not large enough to accrue sufficient sample size for this study. All databases identified were explored for feasibility and data content, as well as interest and availability in conducting the studies. This section contains the information provided by the candidate data sources contacted for this purpose.

Database Identification

The starting point for the feasibility assessment was the data sources previously identified in the outline protocol included in the RMP prepared in August 2012. This document included relevant information on one proposed data source per country, but no contact with the data custodians was established at that point and information on availability of the key variables and an interest in collaboration in this study had not been initiated. For each of the three countries of interest, additional data sources were explored in order to be able to select the databases that were more informative, available and complete for the study purposes.

Data sources were identified through a targeted literature search in Embase and PubMed on the patient population of interest, with key words to cover all IBS references. Following the search, abstracts of interest or full articles, when available, were retrieved and reviewed to identify potential data sources. Additional national and regional databases were found through a desktop search and through [redacted] prior experience in reviewing data sources. Finally, key global websites, such as PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium), ENCePP and ISPOR (International Society for Pharmacoeconomics and Outcomes Research) were accessed in order to identify further sources.

For all data sources identified in Table 7, general background information was explored and some of the data sources were excluded. For those potentially interesting, a contact was established to further discuss content and verify the feasibility of implementing the drug use and safety study.

Database Assessment

For the three countries considered in this study, the following candidate data sources were explored:

Table 7. Summary of Data Sources Explored

Country	Data Source Name	Feasibility Assessment
UK	CPRD* THIN	Proposed Alternative
Spain	SIDIAP Aragón* BIFAP IASIST	Proposed Alternative Excluded Excluded
Sweden	NPR PDR	Proposed Proposed
Italy	Health Search Database Local Health Units Cegedim Longitudinal Patient Database Friuli Venezia Giulia (FVG)	Potential Alternative Potential Alternative Potential Alternative Excluded

Abbreviations: BIFAP=Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria; CPRD=Clinical Practice Research Datalink; THIN=The Health Improvement Network;
* Included in the RMP protocol outline

UK

In the UK, the two candidate data sources identified are very similar in content. The CPRD is the one proposed since it has a larger population base and the possibility to link primary and secondary records for the majority of patients. CPRD has also the possibility to request additional information of all of their patients through questionnaires sent to physicians.

Proposed Data Source: CRPD
CRPD, formerly known as the GPRD, contains the information recorded by GPs as part of their routine clinical practice in the UK (http://www.cprd.com). The database covers approximately 8% of the UK population and has approximately 5.1 million active users who are alive and currently contribute data to the database. Patients are representative of the whole UK population in terms of age and gender. Core data include information on socio-demographic characteristics, diagnoses, symptoms, referrals, tests ordered, some test results, prescriptions issued, and additional clinical information. These data are linkable, at least partially—through the CPRD Division of the UK Medicines and Health Care Products Regulatory Agency (MHRA)—with other healthcare datasets (e.g., hospitalisation records, national mortality data, census data) via the patient's National Health Service (NHS) number, gender, date of birth, and postal code. The type of data collected is strictly longitudinal from EMRs of patients attending a GP practice, with an average of 10 years of follow-up.

Medical data are coded using the Read system, which is very granular and is updated regularly in response to user (physician) requests. It includes several codes for IBS and also for constipation, diarrhoea, and general gastrointestinal symptoms (e.g., bloating). Prescriptions as prescribed by the GP have fields for strength and dose. Drugs are classified following the British National Formulary. If records are linked to secondary care data using the HES, hospitalisation reasons for admission are coded by the ICD-10 and hospital tests and hospital procedures by OPCS codes.

CPRD data can be accessed by external researchers. It is available in SAS format and the time between the purchase and the receipt of data in 90% of studies is approximately three months. GPs can also 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. Additionally, CPRD has an internal research team with expertise in pharmacoepidemiology, pharmacoeconomics and risk-benefit that can support this type of research. Finally, it is possible to select the exact cohort of patients from CPRD's main primary care database (CPRD GOLD) and from linked databases when necessary.

The CPRD characteristics would make it suitable for the study, on linaclotide utilisation, and the second study, on linaclotide safety.

The study objectives were discussed with CPRD researchers and the DUS was confirmed to be fairly straightforward to complete. Pharmacy data, as prescribed from the GP, are readily available. The safety study will also be feasible to conduct, since severe complications are more likely to be recorded in full than milder complications, and the former are the safety outcome of interest. Prior research on IBS has been done based on CPRD data, which has also been extensively published in peer-reviewed journals, with up to 11 research articles on IBS from 1999 to 2012.

The latest data currently available corresponds to 2014, 12/14 static version of the CPRD, with 474 research quality (acceptable) patients with at least 1 prescription for linaclotide.

Some limitations of the database content include lack of detailed information on secondary care (only all-cause hospitalisations can be identified) and the current unavailability of data on specialist visits and secondary care. CPRD does not include unique codes for clearly distinguishing IBS patients with constipation from those with diarrhoea, but patients can be classified based on code combinations.

Alternative Candidate Database: The Health Information Network (THIN)
THIN contains computerised and anonymised medical records from 559 PCPs covering 6% of the UK population. THIN contains information on more than 3.8 million active patients, with 11.3 million patients in total, resulting in over 77 million years of research into quality patient follow-up. Most of the contributing practices have recorded more than 15 years of data on their system and it is, therefore, representative of the non-institutionalised UK population. Core data includes information on diagnoses, symptoms, referrals, tests ordered, some test results, prescriptions issued by the GP and additional clinical information. From the summer 2012, THIN patient longitudinal data can also be linked to the HES data for England, although the number of practices with linked HES records is limited and available only for a fraction of them.

Medical data are coded using the Read coding system and when linked to HES, hospitalisation records are coded by the ICD-10. Similarly, GP prescriptions are coded by Multilex codes following the British National Formulary.

THIN data can be accessed by external researchers and have been extensively published in peer-reviewed journals; however, no publications focused on IBS were identified. To access the data, a short version of the protocol needs to be approved by the Scientific Review Committee and by the Research Ethics Committee.

THIN could be a good alternative database for this study because it has the same characteristics and data content as the CPRD and data extraction can be achieved with a quick turnaround of approximately one or two weeks. However, it covers a smaller number of practices and, therefore, a smaller proportion of the UK population, so recruitment of the same sample size as CPRD could take longer. The proportion of practices that can be linked to hospitalisation data from HES is smaller and around 50% of the GP practices participate in extra data collection.

Spain

Nationwide data sources for Spain could not provide the necessary information to perform this study, so the proposed data source and alternative candidate are each representative from one of its regions.

Proposed Data Source: SIDIAP
SIDIAP is a primary care database launched in 2010, following the steps of CPRD or THIN in the UK, that collects longitudinal data from EMR from 274 primary care centres in Catalonia since 2006. Catalonia is a region with a total of 5.8 million patients who represent approximately 12% of the Spanish population (4% of the Spanish population in SIDIAP-Q with higher quality indicators). Data is updated once a year and there are several scientific publications using this data source and reporting validation study results. The date of the latest available data is December 2013, and 2014 data will be made available by May−June 2015.

Data from primary and specialised care, hospital and pharmacy data are available, as well as patient characteristics such as 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 rate, and pregnancy information. GP diagnoses are coded following the ICD-10 codes, and hospital admissions following the ICD-9.

SIDIAP does not transfer data to private entities, but it can carry out quality investigation projects (Bolivar et al., 2012) and submit on their completion the corresponding reports on results, which will be agreed upon with the funding body in the design stage of the study. It also allows the possibility to contact physicians (currently a group that includes 10% of the total) for extracting additional information on the patient through a questionnaire.

SIDIAP is considered to be an appropriate source of data for the execution of this as the vast majority of its patients have two and three or more years of follow-up and the database itself can link with the Drug Dispensation databases (and additionally with the Mortality Registry for Death Cause); both characteristics are relevant for the proposed linaclotide study. The objectives were reviewed by their research team who are confident about the utilisation study. They identified some challenges for the safety study, and recommended performing a preliminary descriptive and exploratory study to confirm feasibility of conducting the study and to improve the validity of the actual study results.

Some of the challenges mentioned for the safety study were that the exact date of the prescription is only available for the first prescription. For subsequent prescriptions, only the month when it was dispensed by the pharmacy will be available. Identification of complication outcomes based on codes might be incomplete due to inconsistent recording and could be difficult to relate an episode of diarrhoea to potential complications. However, these challenges could be overcome by the use of questionnaires to a sample of physicians or the use of free text in the medical records of patients.

Alternative Candidate: Instituto Aragones de Ciencias de la Salud (IACS)
The Public Health and Health Services Research at the IACS in the Spanish region of Aragón, has the possibility to link different electronic medical and administrative databases in the region for research purposes. With data covering 126,838 patients from six urban health centres in one Health Sector of Zaragoza, IACS covers a small percentage of the Spanish population (0.27%). When linked, these different databases provide administrative and clinical information from outpatient clinics (primary care health centres), administrative and clinical information from specialty clinics, emergency room diagnoses and care, hospital procedures and discharge diagnoses, and pharmacy prescription data.

However, the IACS does not maintain any database and, currently, each of the linkable databases belongs to two different governmental organisations which collect the data, either the Servicio Aragonés de Salud or the Departamento de Sanidad Bienestar Social y Familia. To gain access to these data, it is required to apply to each of the data custodians by presenting a research protocol with the post-authorisation approval. Then an extraction of data would be performed, tailored for each particular study. Managing a study of this kind will require, the participation of one of their researchers as principal investigator, who will be responsible for the good use of the *ad hoc* database created. Information on GP-diagnosed conditions uses the International Classification of Primary Care coding and on GP prescriptions the ATC classification codes.

The Aragón region database, although proposed in the study outline included in the linaclotide RMP, is not recommended as the first choice for this linaclotide since it represents a smaller proportion of the Spanish population and, at the moment, is not maintained as an electronic database nor has it been validated to perform these type of studies.

Data Source Excluded: BIFAP (Base de datos para la investigación Farmacoepidemiológica en Atención Primaria) **Database**
The BIFAP is a population-based database in Spain containing primary care information from about 2,692 primary care physicians (GPs and paediatricians) from 10 different autonomous communities in Spain, and 4,800,207 valid and anonymised medical charts with the following information:

- 76,561,939 records on health problems
- 414,852,056 records on pharmaceutical drugs
- 14,190,861 records on vaccination

- 674,846,412 records with general patient data
- 24,957,871 person-years of follow-up

BIFAP is a project from the Agencia Española del Medicamento y Productos Sanitarios (AEMPS) and has been designed for its use in pharmacoepidemiological studies. It is the largest and most detailed source of information in Spain and several research articles using the BIFAP data have been published, as well as validation studies for incidence and prevalence of certain disease areas, risk factors, and medication use.

BIFAP could not be included in this study since it is not accessible to researchers outside their network.

Data Source Excluded: IASIST
IASIST contains primary and secondary care clinical databases in Spain. The Inpatient Care Dataset accounts for more than 65% of real National Health System discharges, and is built from real data obtained from 170 hospitals from 15 (out of a total of 17) different autonomous communities (regions) in Spain. This database is updated on a yearly basis, with one-year lag time (at the end of year `t' the complete database for year `t-1' is available). Hospitalisations are defined as those episodes with a length of stay greater than zero days (one or more days) or those with length of stay equal to zero and discharge status equal to 'death'.

Fields available within the Inpatient National Database for all hospitals are:

- Patient information including birth date, gender and medical record identifier
- Process information, including episode identifier, date of admission, discharge date and status
- Clinical information including main diagnosis (ICD-9-CM), secondary diagnosis (up to 10 different diagnosis), medical/ surgical procedures (up to 10 different surgical procedures, ICD-9CM)
- Cost information including diagnostic-related group (all patients diagnostic-related groups) and estimated inpatient cost

The primary care database accounts for at least two million people every year. This data source is built entirely from real data and covers 100% of four (out of a total of 17) different autonomous communities (regions) in Spain. Due to confidentiality reasons IASIST cannot provide any further information on the areas that are being covered.

Major limitations for the purposes of this study data are that patients cannot be tracked across different hospitals as patient identification numbers are designated by every region and every year. For the same reason, patients cannot be tracked longitudinally over time. Additionally, primary care data cannot be linked to secondary care given that information is provided to IASIST by each provider separately and patient identification is done separately by each provider. Therefore, this data source was not considered appropriate and was excluded.

Sweden

In Sweden, there exist several registries with high quality data and large coverage of the population. Given that for this study one of the main challenges were related to accrual of sufficient sample size, only national registries were considered. The two registries that have been proposed for this study include diagnosis and medications and could be linked together through a unique patient identifier:

Proposed Data Source: The National Patient Register
The Swedish National Patient Register (NPR) was initiated in 1964, initially covering inpatients in six county councils in Sweden. Since 1987, the register covers all public inpatient care and all outpatient visits since 2001. Data on primary care is not available. The information in NPR can be divided into 4 different groups covering several variables each: 1. Patient data; 2. Geographical data; 3.

Administrative data from inpatient hospital admissions and outpatient visits; and 4. Medical data regarding main and up to 21 secondary diagnosis using the ICD-10 classification, external cause of injury and poisoning, and up to 30 surgical procedures from public and private service providers. A quality control check of the NPR is performed periodically, and in 2007 the main diagnosis was missing from 1.0% of records. At present, the NPR is updated once a year.

Proposed Data Source: The Prescribed Drug Registry
The Swedish Prescribed Drug Register (PDR) has been functioning since July 2005 and contains data on all prescriptions dispensed to the entire Swedish population. Data collection is administered by the National Corporation of Swedish Pharmacies, a state-owned company responsible for the provision of pharmaceutical services to the whole country. Information from all prescriptions dispensed is transferred monthly to the National Board of Health and Welfare, which is responsible for maintaining the PDR.

The register contains the following data on drugs prescribed and dispensed in ambulatory care: dispensed item (substance, brand name, formulation, and package); dispensed amount, dosage, expenditure, and reimbursement; age, sex, and unique identifier (personal registration number) of the patient; place of residence of the patient (county, municipality, and parish); date of prescribing and dispensing; the practice (primary health care centre or hospital clinic) that issued the prescription; and the prescriber's profession (e.g., general practitioner; specialist in internal medicine, psychiatry, or paediatrics). All drugs are classified according to the ATC classification system. The register does not include data on over-the-counter (OTC) medications or drugs administered in hospitals or complete data on drugs that are used in ambulatory care but are administered during day care at hospitals. The register is not complete with regard to drugs used in nursing homes.

Italy

In Italy, data sources have limited reference population size or limited availability of variables relevant for the proposed study. Additionally, linaclotide sales in Italy started in September 2014 hence the sample size contributed by Italy is relatively small.

Excluded Data Source (Potential alternative): Health Search/CSD Longitudinal Patient Database
Health Search was founded in 1998 as a research unit of the Italian College of General Practitioners (SIMG). SIMG is a scientific society aimed to promote the role of General Practice within the National Health System. The main activities are focused on education and research. Research is mainly developed throughout the Health Search network, based on: (1) a school in which PCPs receive training and share the same standards for recording electronic patients' information; (2) a database (Health Search), where PCPs collect patients' information. The group working with HSD data is a multidisciplinary team of epidemiologists, statisticians and IT experts; it provides value-added services to: (1) the PCPs who contribute to the HSD; (2) the stakeholders that are interested in using this research tool. Health Search-SIMG is currently involved in several national and multinational research projects on drug safety and drug utilization, health technology assessment (HTA) and health services research studies.

The HSD collects longitudinal data from approximately 900 active GPs across Italy, with 700 of them selected as most reliable for research purposes. The HSD contains patient demographic information, medical data (e.g., diagnoses, tests and test results, hospitalization, etc.), drug prescription, and prevention information, collected when patients visit PCPs, from approximately 2.4 million patients, and one million active patients currently assisted by the GPs selected for research project participation. The current average length of patient's electronic medical records since inception of the database is approximately 10 years. A unique identification number links all data for an individual patient in an anonymous way and no identifying details are available. The geographical distribution of patients of these PCP is from 16 Italian regions and similar to the general Italian population, without significant

differences both in geographical location and age distribution (Prezioso et al., 2014; Masclee et al., 2013). The latest data currently available for research is data up to 31 December 2013.

The proposed database has been used in previous studies that also included similar European population-based primary care databases such as CPRD (Masclee et al., 2013).

Excluded Data Source: Local Health Units

A Local Health Unit (LHU) is a body assigned by the National Health System in Italy to provide healthcare to a specific geographic area, generally a province. The LHUs in Italy are responsible for assessing the medical needs and providing comprehensive care for a defined population. Each LHU is responsible for the hospital and primary care services in its area as well as for prevention and health promotion activities. LHUs have an information network that measures the expenditure for drug reimbursement for registered patients. LHUs record all claims from pharmacies concerning drugs that are fully or partially reimbursed. The data available include: demographics, hospital admission and discharge diagnoses, specialist visits, drug prescription and dispensation (primary care only), mortality, and costs. A patient's personal health number can be cross-checked with the registry office and hospital database. This allows the information to be connected to the date of birth, gender, and any record of previous hospitalisations. Diagnoses and procedures are recorded based on the International Classification of Diseases (ICD)-9 and ICD-9-CM codes. On average, each LHU covers a total population of 500,000 beneficiaries, and 3 to 5 LHUs have been included by [redacted] in previous studies. The main limitation of this database for our current study is its lack of primary care and specialist diagnosis records.

Excluded Data Source: Cegedim Longitudinal Patient Database

The CSD Medical Research group provides access to European longitudinal patient data using data collected from the electronic medical records entered into a primary care physician's software, including 700 GPs attending over 800,000 patients from Italy. CSD includes information on the patient profile, clinical profile, prescriptions and the prescriber profile, but no information on hospital admissions (date of admission, admission diagnosis, discharge diagnosis, hospital stay duration, accident, or emergency (A&E) visits or discharge status). Data characteristics are similar to those in the proposed database.

Data Source Excluded: Friuli Venezia Giulia Regional Information Health System (FVG)

FVG is in the northeastern part of Italy and has approximately 1.2 million inhabitants. In Italy, all citizens are covered by taxed-based public health insurance. The hospital discharge database of the FVG region of Italy routinely collects data from all hospitals in the region and includes information on patients' sociodemographic characteristics and treatment received during hospitalization. Given that the LHUs can capture the same data, in a larger population, this database was excluded.