AstraZeneca

PASS Protocol	
Drug Substance	Naloxegol
Study Code	D3820R00006
Edition Number	03
Date	21 January 2016

An Observational Post-Authorization Safety Study (PASS) of MOVENTIG® (Naloxegol) Drug Utilization in Selected European Populations

EU PAS Register Number:	ENCEPP/SDPP/12598
Active Substance:	Naloxegol
Medicinal Product:	MOVENTIG
Product Reference:	H2810
Procedure Number:	EMEA/H/C/002810
Joint PASS:	No
Research Question and Objectives:	This study is designed to describe the characteristics of patients prescribed naloxegol at time of first prescription, including the use of naloxegol in non-indicated populations, and treatment patterns of naloxegol in follow-up
Countries of Study:	United Kingdom, Norway, and Sweden
Marketing Authorization Holder (s):	AstraZeneca AB
MAH Contact Person	Ulrika Tjärnbro European Regulatory Lead AstraZeneca AB SE-151 85 Södertälje Sweden T: +46 8 553 235 31 M. +46 767 844 612 F: +46 8 553 269 04 ulrika.tjarnbro@astrazeneca.com
Sponsor:	AstraZeneca
Author:	Robert J. LoCasale, PhD, MS Group Director of Quality, Design & Analytics One MedImmune Way Mailstop: 101ORD-2104A Gaithersburg, MD 20878 T: (301) 398-0295 M: (302) 358-8064 Robert.locasale@astrazeneca.com

ASTRAZENECA SIGNATURE(S)

An Observational Post-Authorization Safety Study (PASS) of MOVENTIG® (Naloxegol) Drug Utilization in Selected European Populations

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative

Robert J. LoCasale, PhD, MS Group Director of Quality, Design & Analytics One MedImmune Way Mailstop: 101ORD-2104A Gaithersburg, MD 20878 T: (301) 398-0295 M: (302) 358-8064 Robert.locasale@astrazeneca.com	Date (Day Month Year)

ASTRAZENECA SIGNATURE(S)

An Observational Post-Authorization Safety Study (PASS) of MOVENTIG™ (Naloxegol) Among Patients Aged 18 years and Older Diagnosed with Cancer Pain and Treated with Opioids Chronically

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AstraZeneca Research and Development site representative

Bruce Berger, MD Clinical Project Leader Global Medicines Development One MedImmune Way Mailstop: 200ORD 1112 Gaithersburg, MD 20878 T: (301) 398-3442 M: (203) 921-8429 bruce.berger@astrazeneca.com	Date (Day Month Year)

ASTRAZENECA SIGNATURE(S)

An Observational Post-Authorization Safety Study (PASS) of MOVENTIG™ (Naloxegol) Among Patients Aged 18 years and Older Diagnosed with Cancer Pain and Treated with Opioids Chronically

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AstraZeneca Research and Development site representative

Charlie Liss
Senior Statistician
One MedImmune Way
Mailstop: 200ORD-2107F
Gaithersburg, MD 20878
T: (301) 398-0322
Charlie.Liss@astrazeneca.com

Date
(Day Month Year)

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2. LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this post-authorization safety study (PASS) protocol.

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AZ	AstraZeneca
CI	Confidence interval
CV	Cardiovascular
CYP	Cytochrome P450
DUS	Drug utilization study
EU	European Union
GP	General practitioner
NPR	National Patient Register
OIC	Opioid-induced constipation
PAMORA	Peripherally-acting mu-opioid receptor antagonist
PASS	Post-authorization safety study
PDR	Prescribed Drug Register
Pgp	P-glycoprotein
PSUR	Periodic Safety Update Report
SAP	Statistical analysis plan
THIN	The Health Improvement Network
ULN	Upper limit of normal
UK	United Kingdom
Q4	4th Quarter

3. RESPONSIBLE PARTIES

The main responsible parties for this study are listed in Table 1.

Table 1 List of main responsible parties

Role	Name
Epidemiologist	Robert LoCasale
Biostatistician	Charlie Liss
Study Deliver Lead	Alecka Sveréus
Clinical Project Leader	Bruce Berger

4. ABSTRACT

Title

An Observational Post-Authorization Safety Study (PASS) Study of MOVENTIG® (Naloxegol) Drug Utilization in Selected European Populations

Edition Number 03, 21 January 2016, AstraZeneca (AZ)

Rationale and background

AZ agreed to conduct this post-authorization observational safety study to determine the characteristics of patients prescribed naloxegol at time of first prescription and treatment patterns of naloxegol in follow-up in the United Kingdom (UK), Norway, and Sweden. This study is part of a broader post-marketing commitment to augment routine evaluation of the safety profile of naloxegol in clinical practice.

Research question and objectives

The overall research questions for this study are: 1) What are the demographic, clinical, and treatment characteristics (including dose) at baseline of patients prescribed naloxegol in real-world practice (including the use of naloxegol in non-indicated populations)? and 2) What are the treatment patterns of naloxegol utilization during follow-up?

Primary objectives:

1 To describe the characteristics of patients prescribed naloxegol at time of first prescription (demographics, targeted comorbidities, targeted comedications, provider characteristics, and indication characteristics).

2 To describe any of the following treatment patterns:

- Discontinuation of naloxegol (permanently during the observation period)
- Switching from naloxegol to other drug(s) potentially used by patients with opioid induced constipation (OIC)

- Prescription of other drug(s) potentially used by patients with OIC in the same period when naloxegol is prescribed (augmentation)
- Restart in the prescription of naloxegol (after temporary discontinuation or treatment holiday)
- Continuous treatment with naloxegol during the study period
- Change in dosing

Exploratory objective:

1. To identify predictors of length of naloxegol use

Study design

This is a drug utilization study that will use observational data from multiple countries: the UK, Norway, and Sweden. It will utilize a retrospective cohort (patients newly prescribed naloxegol) study design in each of the countries.

Population

Patients in the targeted countries who are newly prescribed naloxegol will be identified for inclusion. Patients analyzed in this study will be those who have at least 12 months of continuous data available prior to first prescription. The number of patients who do not have at least 12 months of prior data will be reported for completeness.

Variables

Variables in this drug utilization study include demographic, targeted comorbidities, targeted comedications, medical history, health provider characteristics, and naloxegol exposure and treatment outcomes (discontinuation, switching, augmentation, restart of naloxegol after temporary discontinuation, and continuous treatment with naloxegol).

Data sources

The data sources targeted for this study include The Health Improvement Network (THIN) in the UK, the Norwegian Prescription Database in Norway, and the Swedish Prescribed Drug Register in Sweden.

Study size

The end of data collection is currently planned for 3 years post-launch in each participating country and the target sample size is 3000 patients across all participating county's data sources.

Data analysis

All analyses for this study will be descriptive and performed in each of the study countries separately if possible and for all patients combined (where possible for common data elements). Demographic characteristics and naloxegol treatment outcomes will be

summarized for the subpopulation of patients treated according to the approved indication (ie, on-label).

Milestones

Data collection will begin in December 2015 and continue at least until 2018. The earliest possible index date in a given country will be the date of naloxegol launch, which can occur as early as third quarter 2015. Registration in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register is planned for February 2016. Study progress reports will be provided annually, beginning the first half of 2016, and the final report of study results will be provided in 2020.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Any planned study milestones are listed in Table 2.

Table 2 List of milestones and planned dates

Milestone	Planned date
Start of data collection[a]	December 2015
End of data collection[b]	December 2018
Study progress report 1	First half of 2016
Study progress report 2	First half of 2017
Study progress report 3	First half of 2018
Study progress report 4	First half of 2019
Registration in the ENCePP register	February 2016
Final report of study results[c]	2020

[a] The start of data collection is the earliest possible index date in a given country which will be the date of product launch. The proposed date for start of data collection is the estimated date of naloxegol launch in the first target country. Additional countries will follow and all the start of data collection planned dates will be modified to reflect the actual launch date in each target country.

[b] The targeted observation period is to include 3 years of post-market data collection of naloxegol in a given country.

[c] The final report of study results is expected to be available in the first half of 2020 due to a lag in data availability after data collection in some data sources.

7. RATIONALE AND BACKGROUND

In addition to the routine pharmacovigilance activities (which include regular analysis of spontaneously reported post-marketing safety data), AZ agreed to conduct this post-authorization observational study to describe the utilization of naloxegol (drug utilization study or DUS) within a cohort of patients treated with naloxegol. The aim of the DUS is to describe the demographic, clinical, and treatment characteristics of naloxegol users and to investigate real-world use of naloxegol, the extent of off-label use, and use in vulnerable/special populations (ie, patients aged ≥65 years, pregnant patients, patients with prior cardiovascular (CV) disease, patients with prior renal or hepatic impairment, patients with concurrent methadone use, and patients with concurrent use of cytochrome P450 [CYP] 3A inhibitors/inducers or P-glycoprotein [Pgp] modulators). The European Medicines Agency requested that the DUS be conducted in more than 1 member state in order to ensure that the data collected are generalizable and reflective of naloxegol use throughout the EU.

This study is part of a broader post-marketing commitment to augment routine evaluation of the safety profile of naloxegol in clinical practice. In addition to this DUS study, this broad commitment includes a post-authorization observational safety study to monitor clinically important identified and potential risks within a cohort of patients treated with naloxegol in non-cancer pain and an independent prospective safety and effectiveness study of naloxegol use in cancer pain patients conducted via prospective primary data collection.

8. RESEARCH QUESTION AND OBJECTIVES

This study will address the following research questions:

What are the demographic, clinical, and treatment characteristics (including dose) at baseline of patients prescribed naloxegol in real-world practice (including the use of naloxegol in non-indicated populations)?

What are the treatment patterns of naloxegol utilization during follow-up (including dosing and the use of naloxegol in non-indicated populations and in vulnerable/special populations)?

The objectives of the proposed study are as follows:

Primary objectives:

1. To describe the characteristics of patients prescribed naloxegol at time of first prescription (demographics, targeted comorbidities, targeted comedications, provider characteristics, and indication characteristics).

2. To describe any of the following treatment patterns:

   – Discontinuation of naloxegol (permanently during the observation period)

- Switching from naloxegol to other drug(s) potentially used by patients with OIC
- Prescription of other drug(s) potentially used by patients with OIC in the same period when naloxegol is prescribed (augmentation)
- Restart in the prescription of naloxegol (after temporary discontinuation or treatment holiday)
- Continuous treatment with naloxegol during the study period
- Change in dosing

There are no pre-specified hypotheses.

Exploratory objective:

- To identify predictors of length of naloxegol use

9. RESEARCH METHODS

9.1 Study design

This is a drug utilization study that will use observational data from multiple countries. The study will utilize a retrospective new users cohort (patients newly prescribed naloxegol) study design in each of the countries.

The study will include data collected over a 3 year period post-market and will target a sample size of 3000 patients across all data sources (refer to Section 9.5). Naloxegol patient accrual will be assessed annually. In the event the patient accrual is slow, additional candidate countries' data sources satisfying the protocol requirements and drivers for selection will be incorporated, in consultation with the regulatory agency, into the study.

9.2 Setting

9.2.1 Study population

The expected launch dates for naloxegol will differ depending on country. The source population for the naloxegol drug utilization study will be patients from the UK, Norway, and Sweden. A description of the data sources within these respective countries is provided in Section 9.4. Each data source is expected to be a representative sample of the opioid using and naloxegol-exposed patient population in those countries. The main drivers for selection of these data sources were:

1. Ability to capture patient's exposure to naloxegol, including dose, and diagnoses.
2. Ability to define pre-specified subpopulations of interest using demographic and diagnostic data.
3. Ability to contribute data from early product launch countries.

Data sources from additional countries (eg, Germany and Spain) could be added to the study, in advance of the first annual naloxegol progress report, when meeting protocol requirements and drivers for selection.

9.2.2 Study cohort

The study cohort will consist of new users of naloxegol (individuals newly prescribed naloxegol) in real-world practice. This study design enables the assessment of subpopulation-defining characteristics before treatment initiation and facilitates adjusting for predictors of treatment (Schneeweiss 2010).

Since data will be extracted from electronic medical record databases, the study cohort will consist of multiple retrospective incident user cohorts, one from each target country: the UK, Norway, and Sweden. The start of the data collection (earliest possible index date) in a given country will be the date of product launch.

All patients receiving naloxegol will be accounted for in the proposed data sources and reported. Only patients with at least 12 months of previous enrolment in the database (baseline period) before the date of first prescription of naloxegol (index date) will be characterized. This approach will improve the likelihood of reported incidence rates for endpoints of interest to be reflective of the real incidence rates (Lewis et al 2005). The number of patients who do not have at least 12 months of prior data will be reported for completeness.

9.2.2.1 Inclusion criteria

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

1. The patient has at least 1 prescription of naloxegol in his/her medical record anytime during the study period.

2. The patient has at least 12 months of computerized records prior to the first prescription of naloxegol (index date).

9.2.2.2 Exclusion criteria

No exclusion criteria will be applied.

9.2.2.3 Follow-up

The study period starts on the date of naloxegol launch in each of the countries since the earliest possible index date in a given country will be the date of product launch.

Index date for each patient (or patient entry date to the naloxegol cohort) will be defined as date of the first prescription of naloxegol. Baseline period for each patient will be the 12-month period before index date.

The naloxegol drug utilization study end is characterized by two elements:

1. The calendar date of data collection conclusion accounting for 3 years from naloxegol launch in a given country.

2. A target sample size of 3000 exposed patients accrued over the study period across all data sources. Please refer to Section 9.5 and Section 9.6.

The follow-up period for each patient will be the time from the index date to the earliest of the following dates (end of follow-up date):

End of naloxegol exposure

End of the study period

Disenrollment from the database

Date of last data collection

Death

Study enrollment will end 6 months prior to the end of the study's observation window (eg, 30 June 2018) within a given country's data source in order to ensure a minimum of 6 months of follow-up in patients prescribed naloxegol. If the target sample size of 3000 patients across all participating data sources is not reached by end of 2018 then the study will continue to enroll patients for an additional year and will apply the same criteria for ending enrollment 6 months prior to year end. This will continue annually until the target sample size is achieved.

The database's lag time for the most recent collected data in each research partner's database could range from 1 to 12 months. As such, the expectation is that data for 2018 for all data sources will be available for analyses in 2019.

9.3 Variables

9.3.1 Naloxegol exposure

The naloxegol exposure information is characterized by the naloxegol days of supply derived from the prescribed quantity and dose. Days of supply will be ascertained from the prescription information recorded in the databases and the recommended daily dose (1 tablet of naloxegol taken once per day). Days of supply will be calculated by dividing the prescription quantity by the recommended daily dose. The marketed doses for naloxegol are 25 mg and 12.5 mg. First prescribed dose and dosing schedule will be captured as will changes in dose or dosing schedule over the course of follow-up.

9.3.2 Naloxegol treatment outcomes

Naloxegol prescription patterns of interest are as follows:

Discontinuation of naloxegol: defined as no prescription of naloxegol in the period of twice the number of days of supply of the last naloxegol prescription following its expiry date (Peterson et al 2007, Sikka et al 2005). For example, for a 28-day prescription, no new prescription in the 28*2=56 days after the expiry date of the prescription supply (allowable gap). The logic for using 2 as multiplier is based on the recommended daily dose for naloxegol being 1 tablet taken once a day while accounting for potential refill barriers or non-adherent historical "as needed" laxative taking behaviors. The date of discontinuation is the day after the date of expiry of the last naloxegol prescription (eg, for a patient with a last prescription of 28 days and a subsequent period of 56 days without new prescription the date of discontinuation is Day 29). Time to discontinuation (or persistence on naloxegol) is the interval between the date of the first naloxegol prescription and the date of first discontinuation. Permanent discontinuation is defined as a discontinuation with no subsequent naloxegol treatment (see also definition of restart of naloxegol below). Discontinuation will be reported separately for those who permanently discontinue during the study period and for those who discontinue temporarily and subsequently restart (see restart of naloxegol).

Switching from naloxegol to other drug(s) potentially used by patients with OIC, including but not limited to fiber supplements/bulk-forming laxatives, stool softeners, osmotic laxatives, saline laxatives, oral stimulant laxatives, peripherally-acting mu-opioid receptor antagonists (PAMORAs, such as methylnaltrexone bromide, alvimopan, oxycodone/naloxone), lubiprostone, linaclotide, or prucalopride, is defined by a prescription of any of the other drugs in the previous list that starts while on treatment with naloxegol or during the allowable gap (for example, for a 28-day prescription, up to 28*2=56 days after the expiry of the naloxegol prescription supply) and continues after the date of the naloxegol discontinuation. The date of switching is the date when the prescription of the new drug is issued. Time to switching is the interval between the date of the first naloxegol prescription and the date of switching. Switching from naloxegol requires discontinuation in the prescription of naloxegol, therefore switchers will be considered a subgroup of those who discontinue.

Augmentation of Naloxegol with other drug(s) potentially used by patients with OIC, including but not limited to fiber supplements/bulk-forming laxatives, stool softeners, osmotic laxatives, saline laxatives, oral stimulant laxatives, PAMORA (such as methylnaltrexone bromide, alvimopan, oxycodone/naloxone), lubiprostone, linaclotide, or prucalopride, is the prescription of any of the drugs in the previous list on or after the date of Naloxegol prescription that is followed by at least 1 other Naloxegol prescription in the future (overlapping prescriptions of naloxegol and the new drug). An example for augmentation using a 28-day naloxegol prescription: if, in the period between the naloxegol prescription and up to 28*2=56 days after the expiry of the naloxegol prescription supply, there is a prescription for any of the listed drugs followed by at least another prescription of naloxegol in the same period. The date of augmentation is the date when the new prescription of any of drugs in

the list above is issued. Time to augmentation is the interval between the date of first naloxegol prescription and the date of augmentation. Patients who discontinue naloxegol could have had an augmentation before discontinuation.

Restart of naloxegol (after temporary discontinuation or treatment holiday): a gap of at least twice the number of days of the last naloxegol prescription supply plus 1 additional day after the date of expiry of the last naloxegol prescription and subsequent restart of naloxegol prescriptions over the follow-up period (for example, for a 28-day prescription, no additional naloxegol prescription up to 28*2=56 days after the expiry of the naloxegol prescription supply and subsequently another naloxegol prescription starting on Day 85 since the last naloxegol prescription). The date of restart is the date when the new naloxegol prescription is issued after discontinuation or switching. Time to restart is the interval between the date of discontinuation and the date of restart in the prescription of naloxegol.

Continuous treatment with naloxegol during the study period: defined as patients who did not discontinue treatment. Continuous treatment allows for patients to stay on the same dose over the treatment period, increase their initially prescribed dose, or experience a dose reduction.

Change in dosing: first prescribed dose and dosing schedule will be captured where available, as will changes in dose or dosing schedule over the course of follow-up.

Time to discontinuation, switching, or augmentation will also be assessed in this naloxegol utilization study. To be able to define the treatment pattern outcomes, it is necessary for a given patient to have enough follow-up time after the expiry of the last naloxegol prescription, corresponding to the gap tolerated between prescriptions (allowable gap). There are implications for the interpretation of naloxegol treatment duration in patients that do not have the required length of follow-up because the outcome would be conditioned by the study length.

9.3.3 Naloxegol off-label utilization

Naloxegol has been approved in the EU for the treatment of OIC in adult patients who have had an inadequate response to laxative(s). Patients with the proposed indication who are prescribed naloxegol will be identified among adult patients with a current prescription for opioids and codes suggestive of constipation, a prior prescription for laxatives, or any reference to the use of over the counter laxatives.

Patients prescribed naloxegol will be described as treated off-label when any of the following criteria are met:

Younger than 18 years

No history of current, regular opioid use defined by >30[1] days of opioid exposure within the 180 days prior to and inclusive of the cohort entry date

No record of laxative use within 180 days prior to and inclusive of the cohort entry day (this includes either prescription laxatives or record of over the counter laxatives)

No diagnostic code or laxative treatment suggestive of constipation (eg, fiber supplements/bulk-forming laxatives, stool softeners, osmotic laxatives, saline laxatives, oral stimulant laxatives, PAMORA [methylnaltrexone bromide, alvimopan, oxycodone/naloxone], lubiprostone, linaclotide, or prucalopride)

9.3.4 Baseline variables of interest

Patients included in the drug utilization study will be described according to their characteristics at index date and data from the baseline period which include diagnoses, procedures, and prescription information from each data source.

Covariates included in the study are those determined to be potential risk factors for a given treatment outcome (See Section 9.3.2). Covariates will be assessed prior to index date to be used for descriptive analyses. The covariate list is presented in Section 9.3.4.1 and the list of codes for all diagnoses, medications, labs, and procedures used to define these covariates will be included in the statistical analysis plan (SAP).

9.3.4.1 Index date

Demographic characteristics:

Age (as continuous variable and categorical: <65 or ≥65 years)

Gender

Body mass index

Smoking status

Geographic indicator

Time characteristics:

Time since naloxegol launch at index date (categorical: ≤6 months, >6 months to ≤1 year, >1 year to ≤2 years, or >2 years)

Calendar year of index date

[1] Thirty days of opioid exposure within the prior 180 days is used to establish some measure of chronicity to the use of the medication for chronic pain. The use does not need to be continuous but cumulative exposure must exceed 30 days within that timeframe. Additionally, 30 days of opioid exposure is aligned with inclusion critiria for Naloxegol Phase 3 trials.

Total baseline time (time from start of observation to index date)

9.3.4.2 Baseline period

It is possible that indicators of chronic conditions may be recorded only once in the patient's medical history; therefore, the patient's available medical history will be taken into consideration for assessing current or prior morbidity at index date. The following list represents items included in the medical history that are of interest to this study within this patient population:

Type, dose, and length of prior opioid use: 0-6 months, >6 up to 12 months, >1 year to ≤2 years, >2 years to ≤3 years, >3 years

Prior constipation diagnosis or symptom (yes/no)

Type, dose, and length of prior laxative use (prescribed or over the counter): No prior use, prior laxative use within 3 months of index date, prior laxative use >3 months of index date

Comorbidities, including any of those listed in Table 3

Table 3 Comorbidities

Prior conditions	Diagnoses
Cardiovascular	Atherosclerotic cardiovascular disease; Arrhythmia; Conduction disorder; Congestive heart failure; Hypertensive cardiovascular disease; Peripheral vascular disease; Lipid disorders; Valvular disorder
Pulmonary	Chronic obstructive pulmonary disease; Reactive airway disease; Respiratory infections
Neurologic	Cerebrovascular disease including stroke; Cognitive disorders; Degenerative neurologic diseases; Inflammatory neurologic disease; Movement disorders; Multiple sclerosis; Seizure disorders; Transient ischemic attack
Gastrointestinal	Acid reflux disease; Anal fissures, strictures, hemorrhoids; Bowel obstruction; Colon diseases; Constipation; Chronic liver disease; Gastrointestinal perforation; Irritable bowel disease; Inflammatory bowel disease;
Endocrine	Diabetes; Diabetic complications; Hyperthyroidism; Hyperparathyroidism; Hypothyroidism; Osteoporosis
Rheumatologic	Inflammatory arthropathy; Osteoarthritis; Rheumatoid arthritis; Other autoimmune diseases
Psychiatric	Anxiety disorders; Bipolar disorder; Substance abuse; Schizophrenia; Other psychiatric disorders; Depression
Renal Disease	Chronic renal failure; Chronic renal insufficiency; Renal/Urinary tract infections
Hepatic disease	Chronic hepatic impairment

Cancer	Any systemic malignancy
Pain conditions	Chronic back pain; Extremities pain; Neuropathic pain
Miscellaneous	Gout; Hyperkalemia; Hypercalcemia; Injury (fractures and falls); Morbid obesity; Smoking; Obesity

Medications: the most common prescribed medication groups, including those listed in **Error! Reference source not found.**. Mapping of specific drugs to these groups will be defined prior to study analyses and detailed in the SAP.

Table 4 Pre-existing and concomitant medications

CV disease/risk factor-indicated medication
Psychiatric-indicated medications
Neurologic-indicated medications
Musculoskeletal-indicated medications
Laxatives
Alimentary Tract and Metabolism medications
Other gastrointestinal-indicated medications
Genito Urinary System medications and Sex Hormones
Blood and Blood Forming Organ medications
Respiratory System medications
Anti-infectives for Systemic Use
Other disease indicated medications
Opioids
Non-opioid analgesics
CYP3A inducer[a]
CYP3A inhibitor[b]
Pgp modulator[c]

[a] Including efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, and troglitazone.

[b] Including indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone, telithromycin, aprepitant, erythromycin, fluconazole, verapamil, diltiazem, cimetidine, amiodarone, chloramphenicol, boceprevir, ciprofloxacin, delavirdine, diethyl-dithiocarbamate, fluvoxamine, gestodene, imatinib, mibefradil, mifepristone, norfloxacin, norfluoxetine, telaprevir, and voriconazole.

[c] Including itraconazole, lopinavir, clarithromycin, ritonavir, ketoconazole, indinavir, conivaptan, verapamil, erythromycin, diltiazem, dronedarone, quinidine, ranolazine, amiodarone, felodipine, azithromycin, LY335979, nelfinavir, saquinavir, tacrolimus, valspodar (PSC833), elacridar (GF120918, GG 918), reserpine, captopril,

conivaptan, cyclosporine quercetin carvedilol, ranolazine, avasimibe, carbamazepine, phenytoin, rifampin, and tipranavir.

CV Cardiovascular, CYP Cytochrome P450, Pgp P-glycoprotein.

9.3.4.3 Other variables:

History of gastrointestinal surgery (especially history of cholecystectomy, yes/no)

History of gastroenterology clinic referral (yes/no)

Number of hospitalizations per year prior to index date

Additionally, the health care provider's specialty prescribing naloxegol will be collected at index date.

9.3.5 Subpopulations

In order to identify the subpopulations of patients of interest, the following variables will be used. Lists of codes for all diagnoses will be included in the SAP.

Patients aged ≥65 years at index date.

Current pregnancy as defined by being an adult female between 18 and 44 years of age with presence of a pregnancy marker <280 days AND no presence of a pregnancy outcome prior to index date. Pregnancy markers include coded diagnoses, labs, or procedures indicative of an ongoing pregnancy such as positive pregnancy test, alpha-fetoprotein test, obstetric ultrasound, amniocentesis, Rhesus factor screen, chorionic villus sampling, Aschheim-Zondek test, pregnancy visit indicator (eg, antenatal care), pregnancy diagnosis, multi-fetal pregnancy diagnosis, pregnancy complication, labor or pre-delivery, threatened abortion, abortion referral, or obstetric hospitalization. Pregnancy outcomes include diagnoses or procedures indicating an end of pregnancy such as elective terminations, fetal death, hydatidiform moles/blighted ova, live births or stillborn, unclear delivery outcomes, or delivery bookings (Hardy 2004).

Concurrent CYP3A inhibitor, inducer use or Pgp modulator use as defined by presence of a CYP3A inhibitor, inducer or Pgp modulator prescription at or prior to index date where the projected continuous exposure of CYP3A inhibitor, inducer or Pgp modulator is expected to overlap with index naloxegol. Projections of continuous CYP3A inhibitor, inducer or Pgp modulator exposure will follow similar logic as described in Section 9.3.2 with an allowable gap based on a multiplier of 1 before being considered a discontinuation. Below is a list of CYP3A inhibitors, inducers and Pgp modulators.

- CYP3A inhibitor: Indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone, telithromycin, aprepitant, erythromycin, fluconazole, verapamil, diltiazem, cimetidine, amiodarone,

chloramphenicol, boceprevir, ciprofloxacin, delavirdine, diethyl-dithiocarbamate, fluvoxamine, gestodene, imatinib, mibefradil, mifepristone, norfloxacin, norfluoxetine, telaprevir, and voriconazole
- CYP3A inducer: Efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, Phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, troglitazone
- Pgp modulator: itraconazole, lopinavir, clarithromycin, ritonavir, ketoconazole, indinavir, conivaptan, ticagrelor, verapamil, erythromycin, diltiazem, dronedarone, quinidine, ranolazine, amiodarone, felodipine, azithromycin, LY335979, nelfinavir, saquinavir, tacrolimus, valspodar (PSC833), elacridar (GF120918, GG 918), reserpine, captopril, cyclosporine, quercetin, carvedilol, avasimibe, carbamazepine, phenytoin, rifampin, St. John's Wort and tipranavir.

Concurrent methadone use as defined by presence of a methadone prescription at or prior to index date where the projected continuous exposure of methadone is expected to overlap with index naloxegol. Projection of continuous methadone exposure will follow similar logic as described in Section 9.3.2 with an allowable gap based on a multiplier of 1 before being considered a discontinuation. Use of methadone will be assumed for pain control in the absence of a code for addiction. Patients with a code for addiction will be reported separately.

Prior hepatic impairment as defined by a diagnosis indicating hepatic impairment or prior hepatic abnormality defined by the presence of a lab result for serum alanine aminotransferase or aspartate aminotransferase >2.5 x upper limit of normal (ULN) and/or direct serum bilirubin >1.2 x ULN prior to index date.

Prior renal impairment as defined by a diagnosis indicating renal impairment or the presence of two consecutive lab results for creatinine clearance <60 mL/min prior to index date.

Prior CV disease (yes/no), defined as presence of a CV disease diagnosis in the patient's history prior to index date.

9.3.6 Additional variables data collection

Not applicable.

9.4 Data sources

The proposed data sources were those deemed to have sufficient level of key data elements to successfully conduct the study and capable of delivering insights from the study in a reasonable timeframe which includes consideration of data lag, naloxegol launch dates, and lag due to administrative issues. Selected data sources are as follows:

UK: patients registered with one of the almost 600 general practitioner (GP) practices voluntarily participating in THIN, which includes more than 5.6% of the UK

population or 3.6 million active patients and contains information on the prescriptions issued by the GP or the nurse.

Norway: Norwegian Institute of Public Health, allowing linkage of the Norwegian Prescription Database (filled prescriptions), the Hospital Discharge Registry, the Norwegian Causes of Death Registry, the Norwegian Cancer Registry, and registries holding socio-demographic data. The databases cover the complete population of 4.9 million inhabitants.

Sweden: Swedish patient register, Swedish prescribed drug register, causes of death register, and medical birth register. The Swedish databases cover the complete population of 9.5 million inhabitants.

Additional details on the proposed databases can be found in Annex B.

9.5 Study size

The end of data collection is currently planned for 3 years post-launch in each participating country. However, if necessary, the study observation window will be extended annually until a target sample size of 3000 patients across all participating county's data sources is achieved. Annual progress reports will inform on status of naloxegol patient accrual during this period and whether additional data sources will be required to successfully achieve target sample size.

The proportion of patients having a specific characteristic (eg, age, gender) or treatment pattern (eg, treatment discontinuation) among those prescribed naloxegol is of particular interest. In general, precision around estimates for proportions decreases as the estimate tends towards 50% and increases as the sample size increase. Precision around estimates with sample sizes of 100 to 3000 patients are provided for a wide range of estimated proportions in

Table 5. As an example, in the open-label long term safety Study D3820C00008 of naloxegol against usual care, the patient population was made up of 11% who were at least 65 years old and 66% who were female. Among the naloxegol treated patients in the same study, the treatment discontinuation rates at 3 months, 6 months, and 12 months were approximately 20%, 27% and 38%, respectively.

Table 5 Estimated proportions, number of patients with characteristics, and associated 2-sided 95% CIs for a sample size of 100 to 3000

Estimated proportion	Observed number of patients with characteristics 2-sided 95% CI over varying sample size (N)				
	N=100	N=250	N=500	N=1000	N=3000
5%	5 (2.15, 11.18)	12 (2.77, 8.20)	25 (3.41, 7.28)	50 (3.81, 6.53)	150 (4.28, 5.84)
10%	10 (5.52, 17.44)	25 (6.87, 14.35)	50 (7.67, 12.94)	100 (8.29, 12.02)	300 (8.98, 11.13)
15%	15 (9.31, 23.28)	38 (11.28, 20.17)	75 (12.14, 18.40)	150 (12.92, 17.35)	450 (13.77, 16.32)
20%	20 (13.34, 28.88)	50 (15.51, 25.40)	100 (16.73, 23.73)	200 (17.64, 22.59)	600 (18.61, 21.47)
25%	25 (17.55, 34.30)	62 (19.86, 30.51)	125 (21.40, 28.98)	250 (22.42, 27.78)	750 (23.48, 26.58)
30%	30 (21.89, 39.58)	75 (24.66, 35.95)	150 (26.15, 34.16)	300 (27.24, 32.91)	900 (28.39, 31.66)
35%	35 (26.36, 44.75)	88 (29.54, 41.30)	175 (30.95, 39.28)	350 (32.11, 38.01)	1050 (33.31, 36.72)
40%	40 (30.94, 49.80)	100 (34.12, 46.18)	200 (35.80, 44.35)	400 (37.01, 43.07)	1200 (38.26, 41.76)
45%	45 (35.61, 54.76)	112 (38.76, 51.00)	225 (40.69, 49.38)	450 (41.94, 48.10)	1350 (43.23, 46.79)
50%	50 (40.38, 59.62)	125 (43.85, 56.15)	250 (45.63, 54.37)	500 (46.91, 53.09)	1500 (48.21, 51.79)

Note: 95% CI is based on the Wilson Score method.
CI Confidence interval

9.6 Data management

Each data source custodian will collect its corresponding electronic primary care patient records and comply with procedures that include checking electronic files, maintaining security and data confidentiality, following analyses plans, and performing quality checks for all programs.

Each database custodian will maintain any patient-identifying information securely on site according to up-to-date standard operating procedures. They will also maintain appropriate data storage, and archiving procedures will be followed with periodic backup of files.

9.7 Data analysis

All analyses for this study will be descriptive and performed in each of the study countries separately, and if possible overall for all patients combined (where possible for common data elements). Additionally, demographic characteristics and naloxegol treatment outcomes will be summarized for the subpopulation of patients treated according to the approved indication (ie, on-label).

9.7.1 Baseline variables of interest

At naloxegol new user cohort entry date or index date, all baseline characteristics as described previously will be assessed by reviewing data for a minimum of 12 months prior to that date (see Section 9.3). Summary statistics (ie, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables and number and proportion/percentage will be presented for categorical ones. The number and proportion of patients with missing data will be reported for each of the variables of interest. The 95% confidence interval (CI) for the proportion of patients having a specific characteristic will be presented using the Wilson Score method.

Given that all new users of naloxegol will be identified, the number of patients with less than 12 months of data available prior to index date will be reported for completeness.

9.7.2 Naloxegol Exposure

Naloxegol dose and changes in dose will be assessed in the period from index date to the end of follow up (See Section 9.3.1 and Section 9.3.2). The average dose, number and proportion of patients at each dose, and number and proportion of patients who change dose will be reported at relevant time points (eg, 3 month intervals).

9.7.3 Naloxegol treatment outcomes

Naloxegol treatment outcomes (please refer to Section 9.3.2) will be assessed in the period from index date to the end of follow up. In addition to summaries by country, results will also be presented for patients who met the criteria in the approved indication.

The number and proportion (and 95% CI based on the Wilson Score method) of patients who experience one of the following treatment events will be reported:

Discontinuation in the prescription of naloxegol

- Permanent discontinuation during the study period
- Restart of the prescription of naloxegol (temporary discontinuation or treatment holiday)

Switching from naloxegol prescription to the prescription of another drug (ie, laxatives, lubiprostone, linaclotide, or prokinetics)

Augmentation (or treatment step-up) of naloxegol with another drug potentially used in OIC therapy (ie, laxatives, lubiprostone, linaclotide, or prokinetics)

Continuous treatment with naloxegol during the study period

Change in dose or dosing schedule (where recorded)

The following time to events will be described using estimates (eg, median) and 95% CI based on the Kaplan-Meier method: any change in treatment (ie, earliest of treatment augmentation, switching, or discontinuation); treatment discontinuation; treatment restart.

- Patients 'at-risk' for a first 'event' of interest in treatment outcomes (ie, a specific change in treatment: discontinuation, switching, or augmentation) are those who are in continuous treatment with naloxegol, have not yet experienced the 'event' of interest and have not been censored. Patients who reach the end of follow-up (ie, study termination, disenrollment, end of data collection, or death; see Section 9.2.2.3) prior to the 'event' will have their time to event censored at the end of patient follow-up not including the allowable gap.

- Patients 'at-risk' for a first 'event' of treatment restart are those who have discontinued treatment with naloxegol, have not restarted treatment and have not been censored. Patients who reach the end of follow-up (ie, study termination, disenrollment, end of data collection, or death; see Section 9.2.2.3) prior to restarting treatment will have their time to event censored at the end of patient follow-up.

Cumulative incidence estimates and corresponding 95% CI will also be provided at relevant time-points (eg, 3 month-intervals) for the following events: any change in treatment (ie, earliest of treatment augmentation, switching, or discontinuation) or treatment discontinuation. The cumulative incidence estimate will account for censoring and will consider death as a competing risk (Gooley et al 1999).

Additionally, sensitivity analyses will be conducted by also describing treatment discontinuation considering a shorter allowable gap (more stringent requirement for continuous treatment).

Additional exploratory analyses of potential predictors of length of naloxegol use may be conducted using appropriate methodology (eg, Cox regression analysis) depending on the observed treatment outcomes. Details of this exploratory analysis will be described in the SAP.

9.8 Quality control

Standard operating procedures at each research center 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. Only research quality data, as defined by the data providers processes, will be used.

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 or if clarifying analyses are required, then the missing or the additional information and results will be included in the report(s) and the corresponding explanation made. All key study documents, such as the protocol, 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

A number of limitations could be encountered in this study:

1. Accurate classification of patients according to OIC diagnosis. Another limitation results from the sensitivity and specificity of the code lists used to identify characteristics of interest. Additionally, some characteristics are based on combinations of codes and lab values, when more specific codes are not available.

2. The use of over the counter medication for the treatment of OIC is a limitation since we can only assess those drugs that were prescribed. Additionally, we will not be able to identify whether those prescriptions were dispensed or not, and if affirmative whether they were actually used by the corresponding patient.

3. The validity of research findings within secondary databases depends on the quality and completeness of data recorded and the method by which it is recorded. For example, in THIN, the identification of comorbidities for a given patient is determined through consultation and recording by their GP.

4. Generalization of the study results to other countries in Europe is limited by the similarities between patient populations and healthcare strategies among those countries.

5. The final sample size and the time required to accrue the sample size can become limitations. Precision of estimates can be reduced by a low sample size. A long recruitment period can result in modified treatment protocols from study initiation to study end and a more heterogeneous patient population.

6. The descriptive results and time to event analyses are susceptible to bias resulting from interval censoring, since the nature of the data does not allow for a precise assessment of the treatment outcomes (ie, 'events' of interest). Only at the time when a new prescription would be due, including allowable gap, is when 'events' of interest will be assigned.

9.10 Other aspects

Not applicable.

10. PROTECTION OF HUMAN PATIENTS

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 Guidelines for Good Pharmacoepidemiology Practices, the ENCePP's Guide on Methodological Standards in Pharmacoepidemiology. The ENCePP Checklist for Study Protocols will be completed.

The study will be registered in the ENCePP Electronic Register of Studies in February 2016.

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 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 (EMA, 2012).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Definitions

11.1.1 Definition of adverse events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs.

11.1.2 Definition of serious adverse event

A serious adverse event corresponds to any untoward medical occurrence that at any dose results in:

- Death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

11.1.3 Definition of adverse drug reactions

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. This includes adverse reactions which arise from:

- the use of a medicinal product within the terms of the marketing authorisation
- the use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse, and medication errors
- occupational exposure

The definition of an ADR implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

11.2 Collection of adverse events

No active collection of AE data will be performed in this study. However any serious ADR that is inadvertently discovered and has an identifiable patient must be reported, including the study number, to the Patient Safety Designated Entry Site by fax, unless the original report was from an AZ-sponsored study. (One or more of the following qualifies a patient as identifiable: sex, age [or category, for example “elderly”], date of birth, initials, hospital, or other identifying number.) In order to be classified as a serious ADR, the serious criteria must be met, and the medical record should clearly indicate that the treating physician considered

there to be a possible causal relationship between the AE and the AZ product. If the medical records do not include a statement regarding causality there is no requirement to report the event.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final, approved protocol will be registered with the ENCePP. As agreed with the regulatory authority, study results will be provided in the form of progress reports starting in 2016 through 2019. Progress reports will be provided as part of periodic safety update report (PSUR) procedures and will include naloxegol patient recruitment status and descriptive statistics on baseline characteristics. A final report will be provided as part of PSUR procedures and will be generated at study end. The final report will contain content provided in the progress reports as well as all treatment pattern, time to event, and predictors of naloxegol use analyses. Results for both progress and final reports will be presented across all countries and by county. Any publication plan resulting from this study will be discussed with the Regulatory Authority and any subsequent publication will be shared with the Regulatory Authority.

13. REFERENCES

EMA 2012
European Medicines Agency. Guideline on Good Pharmacovigilance Practices, Module VIII—Post-Authorisation Safety Studies (Rev 1). EMA/813938/2011 Rev 1. 19 April 2013.

European Commission 2008
European Commission. Rules Governing Medicinal Products in the EU: Guidelines on Pharmacovigilance for Medicinal Products for Human Use. Volume 9A. September 2008.

Gooley et al 1999
Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: New presentations of old estimators. Stat Med 1999;30;18(6):695-706.

Hardy 2004
Hardy JR, Holford TR, Hall GC, Bracken MB. Strategies for identifying pregnancies in the automated medical records of the General Practice Research Database. Pharmacoepidemiol Drug Saf 2004;13:749-59.

ICH 2004
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use's Pharmacovigilance Planning E2E. Current Step 4 version. 18 November 2004.

Lewis et al 2005
Lewis JD, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the General Practice Research Database. Pharmacoepidemiol Drug Safety 2005;14:443-51.

Peterson et al 2007
Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. Value Health 2007;10(1):3-12.

Schneeweiss 2010
Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. Pharmacoepidemiol and Drug Saf 2010;19:858-68.

Sikka et al 2005
Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. Am J Manag Care 2005;11:449-57.

Annex A ENCePP checklist for study protocols

Study title:

An Observational Post-Authorization Safety Study (PASS) of MOVENTIG® (Naloxegol) Drug Utilization in Selected European Populations

Study reference number:

D3820R00006

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]	☒	☐	☐	10
1.1.2 End of data collection[3]	☒	☐	☐	10
1.1.3 Study progress report(s)	☒	☐	☐	10
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	10
1.1.6 Final report of study results.	☒	☐	☐	10

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:	☒	☐	☐	10-11

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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?	☒	☐	☐	12-13,20-21
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☐	☐	☒	
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	11
2.1.5 If applicable, that there is no *a priori* hypothesis?				

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
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	11,14-16
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	12,21
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	10
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	12
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☐	☐	☒	
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)	☒	☐	☐	13

Comments:

The study population are new users of naloxegol without restrictions on sex, disease, comorbidity or seasonality.

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)	☒	☐	☐	14
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy,	☒	☐	☐	21,39-40

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)				
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	14-16
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	14
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Drug response is not studied.

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?	☒	☐	☐	14-16
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)	☒	☐	☐	21,39-40

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)	☒	☐	☐	16-21
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	16-21

Comments:

Predictors of length of naloxegol use will be explored.

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.)	☒	☐	☐	21,39-40
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.)	☒	☐	☐	21,39-40
8.1.3 Covariates?	☒	☐	☐	21,39-40
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)	☒	☐	☐	21,39-40
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	21,39-40

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	21,39-40
8.3 Is a coding system described for: 8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	39-40
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	39-40
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	39-40

Comments:

Endpoints are defined and no coding system is applicable.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	21-22

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?	☒	☐	☐	23-25
10.3 Are descriptive analyses included?	☒	☐	☐	23-25
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	23-25
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	23-25

Comments:

No stratified analyses, instead subgroups are considered.

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?	☒	☐	☐	23,25
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	23,25
11.3 Are methods of quality assurance described?	☒	☐	☐	23,25
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	25
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	

Comments:

Independent review of study results by commissioned research partners, AZ committees and Health Authorities

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	25-26
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)	☒	☐	☐	25-26
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	21-22
12.3 Does the protocol address other limitations?	☒	☐	☐	25-26

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?	☒	☐	☐	26
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	23,39

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)?	☒	☐	☐	28
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	28

Comments:

Name of the main author of the protocol: _____Robert J LoCasale_____

Date: 21/01/2016

Signature: _____

Annex B Further description of the selected data sources

THE HEALTH IMPROVEMENT NETWORK DATA, UK

THIN is an observational database containing information collected in computerized primary care records throughout the UK. Software provided by INPS allows unobtrusive anonymous data collection software for Vision practices that have joined THIN and records the participating physicians' daily patient interactions, with data collected automatically and downloaded electronically each month. Patient metrics included in the data are demographics (eg, year of birth, gender, registration dates), medical history (eg, event dates, diagnosis, symptoms, risk factors, comorbidities, referrals), prescription (eg, prescription dates, therapeutic class, molecule, dosage, posology, duration), and clinical data (eg, height, weight, blood pressure, immunizations, life habits).

GPs in the UK maintain electronic recording for the purpose of patient management during the GP-patient encounters. Since data are collected in a non-interventional way they reflect routine clinical practice in primary care. The panel of GPs maintained in THIN is a representative sample of the GP population in the UK according to age, sex, and geographical distribution. Additionally, the patient population is representative of the respective country population according to age and sex distribution, as provided by national statistic authorities. The THIN database is compliant with European and national regulations of patient data protection.

Currently, the THIN database currently owns around 12 million patient records. The median time of direct follow-up in the database is between 9 and 10 years; with 25% having >15 years follow up.

NORWEGIAN INSTITUTE OF PUBLIC HEALTH, NORWAY

This institution allows linkage of the Norwegian Prescription Database (filled prescriptions), the Hospital Discharge Registry, the Norwegian Causes of Death Registry, the Norwegian Cancer Registry and registries holding socio-demographic data. The Hospital Registry is relatively new in Norway, but since only one year of historic data is required for this study, the study is feasible in Norway. The databases cover the complete population of 4.9 million inhabitants.

SWEDISH REGISTERS, SWEDEN

In Sweden, there exist several registries with high quality data and large coverage of the population. The two main registries that have been proposed for this study include diagnosis and medications and could be linked together through a unique patient identifier. Additionally we propose using data from the Cause of death register, the cancer register, and the medical birth register.

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 International Classification of Diseases, 10th revision, external cause of injury and poisoning, and up to 30 surgical procedures from public and private service providers. 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 center or hospital clinic) that issued the prescription; and the prescriber's profession (e.g., GP; specialist in internal medicine, psychiatry, or pediatrics). All drugs are classified according to the anatomical therapeutic classification system. The register does not include data on over the counter medications, 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.