PASS Protocol	
Drug Substance	Naloxegol
Study Code	D3820R00009
Edition Number	6.1
Date	29 March 2021

An Observational Post-Authorisation Safety Study (PASS) of MOVENTIG® (Naloxegol) Among Patients Aged 18 Years and Older Treated with Opioids Chronically

EU PAS Register Number:	EUPAS12669
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 provide additional data to characterise the safety of naloxegol in the indicated population and within at-risk vulnerable populations identified in the naloxegol RMP by describing type and frequency of identified and potential risks (including bowel perforation, acute myocardial infarction, stroke, cardiovascular-specific mortality, all-cause mortality, hypertension, opioid withdrawal, abdominal pain, diarrhoea, syncope, and change in pain severity) in patients ≥ 18 years of age who were treated with opioids chronically and subsequently treated with naloxegol in routine post-authorisation use.
Countries of Study:	United Kingdom, Germany and the Netherlands
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KYOWA KIRIN SIGNATURE(S)

An Observational Post-Authorisation Safety Study (PASS) of MOVENTIG® (Naloxegol) Among Patients Aged 18 Years and Older Treated with Opioids Chronically

This Clinical Study Protocol has been subjected to an internal Kyowa Kirin review.

I agree to the terms of this study protocol.

Kyowa Kirin Representative

30 MAR 2021

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2. LIST OF ABBREVIATIONS

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

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AZ	AstraZeneca
CI	Confidence interval
CRC	Concurrent reference cohort
CV	Cardiovascular
CYP	Cytochrome P450
CPRD	Clinical Practice Research DataLink
DDD	Defined daily dose
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GePaRD	German Pharmacoepidemiological Research Database
GP	General practitioner
HES	Hospital Episodes Statistics
MI	Myocardial infarction
NIC	Naloxegol inception cohort
OIC	Opioid induced constipation
PAMORA	Peripherally-acting mu-opioid receptor antagonist
PASS	Post-authorisation safety study
PDD	Prescribed daily dose
PRAC	Pharmacovigilance Risk Assessment Committee
Pgp	P-glycoprotein
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAP	Statistical analysis plan
SmPC	Summary of Product Characteristics
THIN	The Health Improvement Network

Abbreviation or special term	Explanation
UK	United Kingdom
ULN	Upper limit of normal
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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

Table 1. List of main responsible parties

Role	Name
Executive VP Medical Affairs	Danie du Plessis

4. ABSTRACT

Title

An Observational Post-Authorisation Safety Study (PASS) Study of MOVENTIG® (Naloxegol) Among Patients Aged 18 Years and Older Treated with Opioids

Edition Number 6.1, 29 March 2021, Kyowa Kirin (KKI)

Rationale and background

AstraZeneca (AZ), the original market authorisation holder [MAH] of Naloxegol, committed to conduct this post-authorisation observational safety study (PASS) to monitor clinically important identified and potential risks as a licensing commitment to augment routine evaluation of the safety profile of naloxegol in clinical practice. The study is an obligation under the terms of the risk management plan (RMP). After acquiring Naloxegol, KKI have taken over the requirements for the market authorisation, including this PASS, from AZ. The study is a cohort study of patients treated with naloxegol, including the occurrence of bowel perforation, acute myocardial infarction (MI), stroke, cardiovascular (CV)-specific mortality, all-cause mortality, hypertension, opioid withdrawal, abdominal pain, diarrhoea, syncope and change in pain severity.

Research question and objectives

The overall research goal for this study is to provide additional data to characterise the safety of naloxegol in the indicated population, grouped by cancer or non-cancer, and within at-risk vulnerable non-cancer populations identified in the naloxegol RMP by describing type and frequency of identified and potential risks (including bowel perforation, acute MI, stroke, CV-specific mortality, all-cause mortality, hypertension, opioid withdrawal, abdominal pain, diarrhoea, syncope and change in pain severity) in patients ≥ 18 years of age who were treated with opioids chronically and subsequently treated with naloxegol in routine post-authorisation use.

The primary objective of the study is to assess the incidence risk of bowel perforation, acute MI, stroke, all-cause mortality, and hypertension in patients treated with naloxegol (Naloxegol Inception Cohort, [NIC]) grouped by cancer or non-cancer, a Concurrent Reference Cohort (CRC) grouped by cancer or non-cancer, and by pre-specified non-cancer sub-populations that include patients aged ≥ 65 years, pregnant patients, patients with prior CV risk, patients with prior renal or hepatic impairment, patients with concurrent methadone use, and patients with concurrent use of cytochrome P450 (CYP) 3A inhibitors/inducer or P-glycoprotein (Pgp) modulators.

An exploratory objective of the study is to assess the incidence risk of CV-specific mortality, opioid withdrawal, abdominal pain, diarrhoea, syncope, and change in pain severity in patients treated with naloxegol (NIC) grouped by cancer or non-cancer, a CRC grouped by cancer or non-cancer, and by pre-specified non-cancer sub-populations that include patients aged ≥ 65 years, pregnant patients, patients with prior CV risk, patients with prior renal or hepatic

impairment, patients with concurrent methadone use, and patients with concurrent use of CYP3A inhibitors/inducer or Pgp modulators.

Study design

This PASS will utilise a retrospective new users cohort design (Schneeweiss 2010). All recipients of naloxegol who will be followed in this study will have received the marketed drug in the course of ordinary clinical practice after authorisation of the drug (the NIC). The study period will begin from the launch date of naloxegol within the given country. The planned end of this PASS will occur when the minimal target sample size of exposure to naloxegol (and separately in concurrent reference laxative treatments) within separate groups of cancer and non-cancer patients is accrued across all study data sources. For non-cancer, at least 5000 patients and at least 5000 patient-years of exposure to naloxegol are required. Separately, for cancer, at least 1000 patients and at least 1000 patient-years of exposure to naloxegol are required. A cohort of patients initiating a new prescribed laxative (excluding peripherally-acting mu-opioid receptor antagonists [PAMORAs]) while chronically exposed to opioids will be used as a Concurrent Reference Cohort (CRC). The CRC will also be grouped by cancer or non-cancer. The CRC will be used to put the results into clinical perspective. Patients in the CRC will be matched 1:1 on propensity score, which will be based on covariates observed in patients' medical history. Given the 1:1 matching, the CRC sample size will be at least 5000 patients for non-cancer and 1000 patients for cancer. The main outcome measure in this study is an incidence risk for health outcomes related to identified and potential risks listed in the naloxegol RMP. No formal comparison between the treatment groups will be performed.

Population

Patients will be taken from the targeted countries (United Kingdom [UK] [2015 onwards], Germany [2015 onwards, the database will start contributing results to the study in 2022] and the Netherlands [Product launch Second half 2017; the database will be added to the study database once the number of patients taking naloxegol is deemed sufficiently high]) . Patients who receive prescriptions for naloxegol will be identified for inclusion in the NIC, while patients in these countries who receive a prescription for a non-PAMORA laxative will be identified for inclusion in the CRC. All patients in this study will be ≥ 18 years of age; have ≥ 1 year of continuous data available; have exposure to current, regular opioid use; and have no prior exposure to PAMORA laxatives alvimopan, methylnaltrexone, or naloxone + opioid combination (including fixed-dose combinations). Patients will be grouped by cancer or non-cancer for the analysis.

Variables

The health outcomes of interest include bowel perforation, acute MI, stroke, CV-specific mortality, all-cause mortality, hypertension, opioid withdrawal, abdominal pain, diarrhoea, syncope and change in pain severity. Exposure and covariates (i.e., risk factors for a given outcome of interest or predictors of exposure) will also be assessed. It should be noted that due to the nature of data collected in GePaRD, the database will not contain information on

the exploratory endpoint change in pain severity, and will only contain partial information on the exploratory endpoints CV-specific mortality and abdominal pain.

Data sources

The data sources initially targeted for this study include The Health Improvement Network (THIN) in the UK, and the PHARMO Database Network in the Netherlands. As the number of naloxegol users was lower than anticipated in these countries in Q3 2017, the German Pharmacoepidemiological Research Database (GePaRD) in Germany has been added to the study. The GePaRD data will be included in the study from 2022 due to anticipated project-specific authorisation from the Statutory Health Insurance providers and official approval from the governing authority, and subsequent analysis. Additional countries/data sources could be added throughout the study, and an assessment of study feasibility based on updated patient counts was provided in the 2019 progress report.

Study size

With an objective of reporting both incidence risks and exposure-adjusted incidence rates, the study will continue to accrue patients until accumulation of naloxegol exposure across all countries participating in the protocol reaches both 5000 patients and 5000 patient-years of exposure in the non-cancer population and 1000 patients and 1000 patient-years of exposure in the cancer population. Additionally, the study will accrue, across all countries participating in this protocol, at least 5000 patients and 5000 patient-years of concurrent reference laxative exposure in the non-cancer population and 1000 patients and 1000 patient-years of concurrent reference laxative exposure in the cancer population.

Data analysis

All analyses for this study will be descriptive. Demographic, clinical and treatment characteristics will be summarised for both NIC and CRC overall, grouped by cancer or non-cancer, and within sub-populations of interest across all countries and at the country level. Each of the health outcomes of interest will be analysed separately. Event rates and 95% confidence intervals (CIs) for pre-specified health outcomes of interest will be reported as both incidence risks (i.e., percent of patients) and exposure-adjusted incidence rates. The exposure-adjusted incidence rate for an exposure group will be calculated as the number of first occurrences of each type of health outcome of interest (i.e., unique patients) divided by the total aggregate person-time accrued by all patients in that exposure group in the current database dataset. Incidence and exposure-adjusted incidence rates for health outcomes of interest will be generated for patients on naloxegol and concurrent reference laxative treatments that are matched 1:1 on propensity scores with successful balance of underlying covariates that predict the specific outcomes.

Milestones

The earliest possible index date for a patient is on launch of naloxegol in a given country. Data collection began in September 2016 and will continue across all study data sources, until the minimum target sample size of patients and patient-years of exposure to naloxegol and

concurrent reference laxative treatments (separately) are accrued in cancer and non-cancer populations of interest (anticipated by first half of 2022). Registration in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) occurred in February 2016. Study progress reports will be provided annually, beginning in the second half of 2016 (study progress report 2 will contain the first report of results on cancer patients). Study progress report 5 (delayed from second half 2020 to 30 July 2021) will contain an interim analysis that will include the addition of individual event rate point estimates for pre-specified safety outcomes of interest among all naloxegol-treated patients recruited at the point of database lock for this analysis. The final report of study results is anticipated in Q4 2023.

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	*03 February 2016*	9.2.2 *and* 9.2.3	*Removal of exclusion criterion for presence of cancer prior to naloxegol exposure which results in an inclusion of cancer patients as a population of interest under this study.*	*Execution of a separate PASS protocol proposal studying safety of naloxegol in cancer patients utilising a primary data collection study design was stopped due to study feasibility assessments from potential study sites indicating patient recruitment potential being very low. Only 1.5% of 133 sites were eligible for inclusion. As a result, time to deliver a sample size needed for robust analysis could not be achieved in the proposed timeline (which was already noted by PRAC to be long). As such, a design utilising electronic healthcare databases is preferred as was alignment to this PASS protocol for safety in non-cancer patients treated with naloxegol.*

Number	Date	Section of study protocol	Amendment or update	Reason
2	*03 February 2016*	6 *and* 12	*Inclusion of a footnote in Section 6 identifying cancer data will first be reported in 2017 with progress report 2. A sentence on this point was added to Section 12.*	*The current PASS protocol will be in-progress with our current research partners during PRAC review of this amendment. Given the expected timing of PRAC response in May 2016, AZ and the Research Partners will not have enough time to amend contracts and implement changes in the SAP and statistical programs to achieve a first progress report milestone in first half of 2016.*
3	*03 February 2016*	9.2.3	*Exclusion of prior cancer in non-cancer patients.*	*This exclusion within non-cancer is highlighted to maintain mutually exclusive groups (cancer and non-cancer) for analysis and also to retain the originally proposed population of interest for non-cancer.*
4	*03 February 2016*	9.3.3	*Inclusion of cancer-specific covariates, which include cancer-related clinical and biochemical measurement, medications, treatments and procedures.*	*Given the inclusion of cancer patients, cancer-specific covariates will need to be captured for generation of propensity scores in the analyses specific to cancer patients.*
5	*03 February 2016*	9.3.4	*Enhanced the definition for identifying renal impairment to include the use of serum creatinine where diagnosis codes or creatinine clearance are not present.*	*This improves identification of patients with renal impairment.*

Number	Date	Section of study protocol	Amendment or update	Reason
6	*03 February 2016*	9.3.5	*Highlighting that sub-populations of interest (eg, renal or hepatic impairment) will not be identified and analysed within cancer patients but only in non-cancer patients.*	*This is highlighted to maintain consistency with the originally proposed non-cancer safety PASS where the purpose was to provide additional safety information in at-risk vulnerable sub-populations listed in the RMP.*
7	*03 February 2016*	9.5.2	*Inclusion of a minimum target sample size for the cancer population of interest. The target is 1000 patients and 1000 patient-years of exposure to naloxegol within cancer patients.*	*Since cancer patients will be analysed separately, a target sample size, using background event rates in a cancer population, was required to generate confidence in the precision around event rates for the health outcomes of interest.*
8	*03 February 2016*	9.7.1	*Inclusion of a sensitivity analysis for cancer patients that incorporates an intent-to-treat approach when defining exposure to naloxegol or the concurrent reference exposure.*	*This was included to account for a limitation where patients with cancer may be more likely (than non-cancer) to enter the hospital setting for extended periods of time resulting in a scenario where exposure to naloxegol or the concurrent reference exposure cannot be observed due to limitations of most databases.*
9	*20 July 2017*	*N/A*	*Change of sponsor from AZ to Kyowa Kirin Pharmaceutical Development Limited (KKPD)*	*Kyowa Kirin Limited (part of Kyowa Kirin International plc (KKI)) acquired the MA from AZ and took on the associated post-marketing commitments.* *(NOTE: KKI is the holding company for the sponsor KKPD and the MAH (at time of transfer) Kyowa Kirin Limited)*

Number	Date	Section of study protocol	Amendment or update	Reason
10	*April 2018*	9.4.3	*Inclusion of the German database GePaRD in the study.*	*Patient uptake of naloxegol in the UK and the Netherlands has been lower than expected so an additional data source has been added from another country, with a large reference population and expectation of increased number of naloxegol users to reach the target study size. It should be noted that due to the nature of data collected in GePaRD, the database will not contain information on the exploratory endpoint change in pain severity, and will only contain partial information on the exploratory endpoints CV-specific mortality (this can be partially inferred) and abdominal pain (which can be described based on diagnoses rather than symptoms).*
11.	*September 2018*	9.4; 9.9	*Further information on THIN-HES and GePaRD, including strengths and limitations, have been added.*	*Added on request from the PRAC for the MAH to explain whether HES linkage would be conducted, and to describe the limitations of the GePaRD database.*
12	*September 2018*	9.3.3	*The categorisation of pain codes has been expanded from one to two categories: pain according to location has been added to pain according to origin.*	*Added on request from the PRAC to include pain according to location; the MAH has retained the category of pain according to origin because it allows for a more comprehensive categorisation of pain codes, particularly those that may not indicate pain in a specific location.*

Number	Date	Section of study protocol	Amendment or update	Reason
13	*September 2018*	9.3.1, 9.3.4	*Details regarding the calculation of drug exposure in the absence of prescribed doses have been added*	*Added on request from the PRAC because Protocol Version 5.0 did not contain a detailed description regarding the estimation of drug exposure periods, particularly in the absence of a prescribed daily dose.*
14	*September 2018*	Title page	*Change in MAH*	*MA was transferred from Kyowa Kirin Limited to Kyowa Kirin Holdings B.V. in July 2018*
15	*March 2021*	Person, Abstract, 6.	*Change in timelines for delivery of Study progress report 5 and inclusion of data from GePaRD data source*	*Delays in analysis and delivery of the Study progress report 5*[a]
16	*March 2021*	Title page, signature page, Section 3	*Change in author, Kyowa Kirin representative, and MAH contact person*	*Product responsibilities have changed*

AZ, AstraZeneca; GePaRd, German Pharmacoepidemiological Research Database; PASS, post-authorisation safety study; PRAC, Pharmacovigilance Risk Assessment Committee; RMP, Risk Management Plan; SAP, statistical analysis plan; UK, United Kingdom

[a] In the course of performing the analyses for the interim report (due 31 December 2020) and actioning the associated quality checks, a need for adjustment to the UK Statistical Analysis Plan (SAP) was identified to allow the UK analyses to meet the respective study objectives. Modifications made to the UK SAP are expected to have some implications for the SAPs for other country data to ensure alignment.
The impact of the COVID-19 pandemic has also affected the study teams within the UK research partner through team absence and limited team availability, and caused additional delays.

6. MILESTONES

Any completed or planned study milestones are listed in Table 2.

Table 2. List of delivered milestones and planned delivery dates

Milestone	Planned date
Start of data collection	September 2016
End of data collection[a]	Second half of 2022
Study progress report 1	Second half of 2016
Study progress report 2[b]	Second half of 2017
Study progress report 3	Second half of 2018
Study progress report 4	Second half of 2019
Study progress report 5[c]	30 July 2021
Study progress report 6	Second half of 2021
Study progress report 7	Second half of 2022
Registration in the ENCePP register	February 2016
Final report of study results[a]	Q4 2023

[a] The end of data collection will be dependent upon uptake of product and, therefore, patient enrolment. The planned end of this study will occur when accumulation of naloxegol exposure across all countries participating in the protocol reaches both 5000 patients and 5000 patient-years of exposure in the non-cancer population and 1000 patients and 1000 patient-years of exposure in the cancer population. The final report of study results is expected to be available in Q4 2023 due to a lag in data collection.

[b] Study progress report 2 will contain the first report of results on cancer patients, which will include similar information as presented in progress report 1 which contained only non-cancer patients. See Section 12 for details on content of this report.

[c] Study progress report 5 will contain an interim analysis that will include similar information as presented in previous progress reports with the addition of individual event rate point estimates for pre-specified safety outcomes of interest among all naloxegol-treated patients recruited at the point of database lock for this analysis. See Section 5 for rationale for the delay in the delivery of the Study progress report 5. See Section 12 for details on content of this report.

ENCePP, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

7. RATIONALE AND BACKGROUND

MOVENTIG® (naloxegol) has been approved in the European Union (EU) for the treatment of opioid induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).

Naloxegol is a novel oral PAMORA and as such it targets the underlying pathophysiology of OIC, i.e., the blockage of the mu-opioid receptors in the gut. It is mainly the pharmacokinetic properties that differentiate drugs within this class, rendering them more or less suitable for treatment of OIC. In particular, they exert their mode of action and subsequently affect gut motility, gut secretion, and sphincter function to alleviate constipation symptoms (Poulsen et al 2014).

Naloxegol, which is administered orally, is a PEGylated derivative of naloxone, another mu-opioid receptor antagonist. Naloxone has a high affinity to opioid receptors and is widely used to treat opioid overdose, administered intravenously or by intramuscular injection. However, in order for naloxone to be clinically applicable, increased bioavailability and particularly peripheral restriction is warranted (Eldon et al 2007).

Naloxone's PEGylation, effectively the naloxegol compound, conferred increased oral bioavailability and peripheral selectivity to the naloxone moiety by a reduction in passive permeability across the blood-brain barrier. Naloxegol is also a substrate of the Pgp transporter, which promotes efflux of naloxegol and serves to further restrict its entry into the central nervous system (Poulsen et al 2014, Webster et al 2014).

The efficacy of naloxegol in patients with OIC and non-cancer pain was demonstrated in two replicate double-blind, randomised, placebo-controlled Phase 3 trials, each over 12 weeks (Chey et al 2014). The same studies also looked into safety, identifying gastrointestinal adverse events (AEs) (diarrhoea, abdominal pain, nausea and vomiting) in a dose-related manner, rare major adverse CV events, and infrequent drug-withdrawal syndrome (Chey et al 2014). No bowel perforation was reported. Webster 2014, studying safety and efficacy of naloxegol in patients with non-cancer pain and OIC for 52 weeks, reported similar AE findings, including two occurrences of opioid withdrawal AE, albeit both events were attributed to a change in opioid dose (and not to naloxegol; Webster et al 2014)

As a complement to routine pharmacovigilance activities (which include regular analysis of spontaneously reported post-marketing safety data), the MAH is committed to conducting this non-interventional PASS to monitor clinically important identified and potential risks within a cohort of patients treated with naloxegol. The European Medicines Agency requested that the PASS specifically monitor the occurrence of bowel perforation, acute MI, stroke, CV-specific mortality, all-cause mortality, hypertension, opioid withdrawal, abdominal pain, diarrhoea, syncope and change in pain severity. Within the EU RMP for naloxegol, opioid withdrawal syndrome and clinically important gastrointestinal AEs (including abdominal pain and diarrhoea) are identified risks, while gastrointestinal perforation and hemodynamic changes

potentially leading to serious CV events (including effects on blood pressure and syncope) are potential risks.

Additionally, as stated, the efficacy and safety of naloxegol was based on a clinical development programme conducted in patients who had chronic non-cancer pain. However, patients with cancer and specific vulnerable populations with non-cancer were either excluded or provided little data. As such, concerns around the use of naloxegol in patients with cancer or in certain vulnerable populations with non-cancer were raised by the Committee for Medicinal Products for Human Use in the initial marketing application. Therefore, the MAH proposed to include into this PASS an analysis of the safety endpoints within patients with cancer and in pre-specified sub-populations with non-cancer that include patients aged ≥ 65 years, pregnant patients, patients with prior CV risk, patients with prior renal or hepatic impairment, patients with concurrent methadone use, and patients with concurrent use of CYP3A inhibitors/inducer or Pgp modulators.

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 PASS, this broad commitment includes a drug utilisation PASS of any naloxegol use and within pre-identified sub-populations of interest, and an FDA commitment to conduct a post-authorisation observational CV safety study in users of naloxegol.

8. RESEARCH QUESTION AND OBJECTIVES

The overall research goal for this study is to provide additional data to characterise the safety of naloxegol in the indicated population, grouped by cancer or non-cancer, and within at-risk vulnerable non-cancer populations identified in the naloxegol RMP by describing type and frequency of identified and potential risks (including bowel perforation, acute MI, stroke, CV-specific mortality, all-cause mortality, hypertension, opioid withdrawal, abdominal pain, diarrhoea, syncope and change in pain severity) in patients ≥ 18 years of age who were treated with opioids chronically and subsequently treated with naloxegol in routine post-authorisation use.

The primary objective of the study is to assess the incidence risk of bowel perforation, acute MI, stroke, all-cause mortality, and hypertension in patients treated with naloxegol (NIC) grouped by cancer or non-cancer, a CRC grouped by cancer or non-cancer, and by pre-specified non-cancer sub-populations that include patients aged ≥ 65 years, pregnant patients, patients with prior CV risk, patients with prior renal or hepatic impairment, patients with concurrent methadone use, and patients with concurrent use of CYP3A inhibitors/inducer or Pgp modulators.

An exploratory objective of the study is to assess the incidence risk of CV-specific mortality, opioid withdrawal, abdominal pain, diarrhoea, syncope, and change in pain severity in patients treated with naloxegol (NIC) grouped by cancer or non-cancer, a CRC grouped by cancer or non-cancer, and by pre-specified non-cancer sub-populations that include patients aged

≥ 65 years, pregnant patients, patients with prior CV risk, patients with prior renal or hepatic impairment, patients with concurrent methadone use, and patients with concurrent use of CYP3A inhibitors/inducer or Pgp modulators.

There are no pre-specified hypotheses.

9. RESEARCH METHODS

9.1 Study design

This PASS will utilise a retrospective new users cohort design (Schneeweiss 2010) for the purposes of conducting analyses of safety data related to naloxegol when the product is used in the post-authorisation period under conditions of usual care use. Of note, this safety study does not involve active administration of naloxegol by the MAH. All recipients of naloxegol who will be followed in this study will have received the marketed drug in the course of ordinary clinical practice after authorisation of the drug. Detailed information on recommended dosages can be found in the prescribing information.

The study period will begin from the launch date of naloxegol within the given country. The study period may be extended with each annual refresh of the country databases. The planned end of this PASS will occur when accumulation of naloxegol exposure (and separately in concurrent reference laxative treatments) across all study data sources reaches both 5000 patients and 5000 patient-years of exposure in non-cancer and 1000 patients and 1000 patient-years of exposure in cancer. The safety study of naloxegol will begin immediately following launch of naloxegol. Since the safety study is observational and follows the outcome of routinely administered patient care, the duration of the study will depend upon the size of the cohort to which naloxegol is prescribed and the general uptake of naloxegol in adult patients diagnosed with cancer and non-cancer pain.

Chronic opioid-using patients with cancer or non-cancer pain initiating a new prescribed laxative (excluding PAMORAs[1]) while exposed to opioids will be used as a CRC. The CRC will be used to put the results into clinical perspective. Patients in the CRC will be first grouped by cancer or non-cancer then matched 1:1 (grouped by cancer and non-cancer) with the NIC on propensity score which will be based on covariates observed in the patients' medical history. Identification of the index prescription date, definition of "new user," prior laxative use, calculation of duration of continuous exposure for the CRC, follow-up, and handling of missing or erroneous data will follow the same logic described for the NIC.

The outcome measure in this study is an incidence risk for health outcomes related to identified and potential risks listed in the naloxegol RMP. The same rate will be generated

[1] Given the safety objective for this study, it is appropriate to remove any potential class effect of PAMORA laxatives for the outcomes of interest from the reference treatment group.

independently for the matched CRC. No formal comparison between the cohorts will be performed.

Cohort designs are ideally suited for generating safety data in a prospective way within a single study for multiple outcomes of interest, given the ability to collect large sample sizes of longitudinal patient data within electronic health records and country-based patient registries. Drug utilisation of prescribed medications, such as opioid and naloxegol, is well captured, as are many of the endpoints, whether it be via a direct diagnosis or a reasonable proxy measure. A new user design coupled with use of a CRC allows for adjustment of risk factors for outcome or predictors of treatment prior to drug-initiation (i.e., not consequences of treatment) while reducing chances for immortal time bias (Suissa 2008). This will establish a clear index date for a treated patient without introducing factors related to survival after treatment initiation and allow for more efficient production of safety information on a given product in the post-market setting.

9.2 Setting

The expected launch dates for naloxegol will differ depending on the country. In order to maximise data capture from three countries, this protocol will target THIN in the UK, the GePaRD database in Germany and the PHARMO database network in the Netherlands. These three countries maintain repositories of longitudinal patient data that allow for capture of exposure and outcomes among populations that are utilisers of opioids. Specifically, the main drivers for selection of these data sources were:

1. Ability to capture exposure to naloxegol and other prescribed non-PAMORA laxatives. Patients with prescribed non-PAMORA laxatives are likely to have a more similar ‘health profile’ with respect to chronic pain, OIC and potentially medication taking behaviours than those utilising over-the-counter laxatives given the fact that they were prescribed a laxative.
2. Ability to capture the outcomes of interest for the primary objective in any healthcare setting through diagnostic codes or a death indicator.
3. Ability to define the pre-specified non-cancer sub-populations of interest using demographic, prescription and diagnosis data.
4. To satisfy drivers 2 and 3, for a given patient, ability to link care across both primary and secondary healthcare settings for a more comprehensive view of the patient’s healthcare interactions.

It should be noted that the content of all the databases included is not exactly the same, therefore, the availability of certain data items (including some endpoints) may vary between data sources. Projections on target sample size goals will be assessed annually based on actual naloxegol uptake and, where necessary and in consultation with a regulatory agency, additional countries/data sources will be added if the data sources in those respective countries satisfy the protocol requirements and drivers for selection above. After an assessment of the study progress in 2017, it was decided to add the GePaRD database (from Germany), starting data access activities in 2018. Additional countries/data sources could be added in the future.

An assessment of study feasibility based on updated patient counts will be conducted as part of the 2019 progress report (submitted H2 2019), and the MAH will consider whether additional data sources are needed at that point.

For both the NIC and the CRC, the date that each patient meets all of the inclusion criteria and none of the exclusion criteria will be his/her cohort entry date (i.e., index date).

9.2.1 Inclusion criteria

This PASS will first identify patients in a given country's data source who meet the following criterion for inclusion:

1. Patient receives a new prescription for naloxegol or a non-PAMORA laxative (Note: only non-PAMORA laxatives that are approved/marketed in the EU at the time naloxegol is authorised are permitted).

9.2.2 Exclusion criteria

Patients will be excluded from either the NIC or CRC if they meet any of the following criteria:

1. Patients < 18 years of age on cohort entry date.

2. Patients with < 1 year of continuous data available prior to cohort entry date.

3. Patients without exposure to current regular opioid use (current regular opioid use defined by > 30[2] days of opioid exposure within the 180 days prior to and inclusive of the cohort entry date).

4. Exposure to PAMORA laxatives, alvimopan, methylnaltrexone, or naloxone + opioid combination (including fixed-dose combinations) prior to cohort entry date.

9.2.3 Cancer and non-cancer populations of interest

All eligible patients will be grouped into two mutually exclusive populations of interest based on the presence of a cancer indicator occurring within the one year of continuous data available prior to cohort entry date.

A cancer indicator is defined as the presence of a cancer specific diagnosis, treatment or procedure. Non-melanoma skin cancers are excluded from the definition of eligible cancer diagnoses. A list of codes for all eligible cancer diagnoses, procedures and medications to identify a cancer indicator will be included in the statistical analysis plan.

Separately, in the event a cancer indicator is not present in the one year prior to cohort entry date, the patient would then be considered eligible for the non-cancer population of interest.

[2] 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 criteria for naloxegol Phase 3 trials.

Prior to inclusion into the non-cancer population, all patient data available prior to cohort entry will be reviewed and the presence of any cancer indicator any time in the patients' history, defined as presence of a cancer-specific diagnosis, treatment or procedure, will exclude a given patient from the non-cancer population eligible for study. The resulting eligible non-cancer population will only include patients that have no record of a cancer indicator in the patient's medical history as recorded in the database.

9.2.4 Follow-up

Follow-up for each patient will be based on exposure status of the respective treatment group plus a pre-specified risk window of 30 days. The risk window would capture the identified and potential risks of interest since they are acute events (eg, CV endpoints and bowel perforation) and it would also account for naloxegol's half-life once exposure has ended. Follow-up will begin on index date and continue until the first occurrence of either the exposure has ended (plus pre-specified risk window), disenrolls/transfers out of the research partner's data source, death or end of study period. Follow-up in the pre-specified risk window will end if either a NIC or CRC patient receives a prescription for a PAMORA; if a NIC patient receives a prescription for a concurrent reference laxative; or if a CRC patient receives a prescription for naloxegol during the risk window. The end of the risk window will occur on the date of that new written prescription.

9.3 Variables

9.3.1 Exposure

Exposure to naloxegol or the concurrent reference laxative will start with the index prescription date.

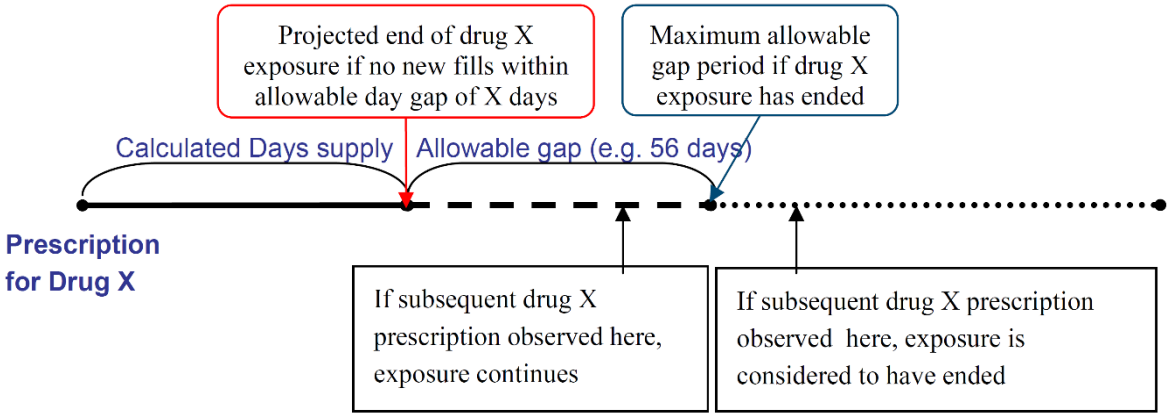
The exposure end date is calculated by an algorithm used to derive continuous exposure. The algorithm will utilise quantity (naloxegol strength and number of tablets) and dosing instructions (when available). Where dosing instructions are not available, days of supply of naloxegol will be estimated using the recommended daily dose (corresponding to the World Health Organization (WHO) defined daily dose (DDD) (WHO 2018) and the recommended daily dose in the Summary of Product Characteristics (SmPC) (SmPC, 2018). The rationale for using the recommended daily dose is that naloxegol is only available in two strengths, and the dosing instructions are simple and not expected to vary between patients; this means that this approach should give an accurate estimate of dosing in the majority of patients. Patients prescribed naloxegol 25mg will be expected to take one tablet per day. Patients prescribed naloxegol 12.5mg are expected to be prescribed at a reduced dose (12.5mg daily) due to evidence of renal impairment or concomitant use of CYP34A inhibitors, as per the SmPC; therefore, they will also be assumed to take one tablet per day. If the package size or strength is unknown, the median size or strength from patients with this information available will be used to impute an expected pack size or pack strength.

Days of supply will be combined with the refill sequence of successive prescriptions to calculate duration of continuous exposure, average daily dose and cumulative dose over the study period. An allowable gap between successive prescriptions in calculating continuous

exposure will be defined according to a pre-determined multiplier of the previous prescriptions days supply. The multiplier for both naloxegol and the concurrent reference laxative exposures will be 2 (Peterson et al 2007, Sikka et al 2005). This 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 behaviours. To account for switching in the continuous exposure definition, patients in the CRC will be permitted to switch between non-PAMORA laxatives and remain classified as continuous users given the switch occurs with the allowable gap permitted by a multiplier of 2. Multipliers for other exposures used to define pre-specified sub-populations in this study will be set at 1.

End of exposure due to discontinuation for any observed medication in this study will be the date of the projected end of a given medication's days of supply in the event a new prescription is not observed within the allowable gap. For example, patient 1 gets a single prescription for naloxegol where the calculated days of supply is equal to 28 days. If no new prescription for naloxegol is observed within 56 days (28 days x 2) after the expiry date of the first 28-day prescription supply, then the end of exposure date will be on the 28th day in follow-up (see Figure 1).

Figure 1. Example of the continuous drug exposure algorithm



End of exposure due to switching or augmentation will occur when a NIC patient receives a prescription for a concurrent reference laxative during the naloxegol exposure window or a CRC patient receives a prescription for naloxegol during use of the concurrent reference laxative exposure (or any patient receives a prescription for a PAMORA laxative as indicated in Section 9.2.4). End of exposure will occur on the date of that new written prescription. Finally, patients from the NIC will not be eligible to enter the CRC nor can patients in the CRC enter the NIC. Censoring in cases of switching or augmentation and sensitivity analyses pertaining to exposure definitions are discussed in Section 9.7.1.

With respect to follow-up for outcomes of interest, two exposure windows will be created for observing an event. The primary exposure window will be based on patient exposure to drug ending at the projected days of supply if no new fills are observed within the allowable gap. In

the previous example, this would be the 28th day. The second exposure window will be based on patient exposure to the drug ending at the projected days of supply plus the maximum allowable gap. Therefore, using the same example, observation of outcome would occur for up to an additional 56 days (Day 84 in follow-up) after the end of exposure occurring on the 28th day. As described previously, a pre-specified risk window of 30 days will be added to the derived end of exposure windows to account for metabolic clearance of the exposure to be completed or to account for any latent, acute outcomes of the exposure.

9.3.2 Outcomes

The health outcomes of interest include bowel perforation, acute MI, stroke, CV-specific mortality, all-cause mortality, hypertension, opioid withdrawal, abdominal pain, diarrhoea, syncope and change in pain severity. Each outcome will be assessed individually, therefore, a patient can experience multiple outcomes. The hierarchy of endpoints (i.e., primary and secondary) is based on the limitations of data sources. Bowel perforation, acute MI, stroke, all-cause mortality, and hypertension are considered primary outcomes because they are endpoints that can be reliably and consistently identified in the base data sources of our research partners through pre-specified coding algorithms. CV-specific mortality, opioid withdrawal, abdominal pain, diarrhoea, syncope and change in pain severity are considered secondary outcomes because they are not recorded in every base data source (e.g., CV-specific mortality), are not identified through a clear diagnosis code or algorithm (e.g., opioid withdrawal), require a proxy definition (e.g., change in pain), or are a symptom and not reliably and consistently recorded in the base data source. No additional review of cases is planned for this study.

Health outcomes of interest for the study will be defined according to coding algorithms developed through a systematic process utilising previously published literature, medical coding expertise, and expert opinion from practicing clinicians. A coding algorithm is defined as a single diagnosis, procedure, drug or lab value code (e.g., International Classification of Diseases, 10th revision, Read), or combination of codes and/or conditions (e.g., hospitalisation) that could be applied to identify a specific outcome of interest.

Specifically, health outcomes of interest will be defined as follows. Lists of codes for all diagnoses will be included in the statistical analysis plan.

1. Bowel perforation: Presence of a diagnostic or procedure code

2. Acute MI: Presence of a diagnostic code for acute MI or a diagnostic code for electrocardiogram supportive of MI or cardiac enzyme lab tests with positive results (Avillach et al 2013, Delaney et al 2007, Khan et al 2010)

3. Stroke: Presence of a diagnostic code for cerebral or cerebellar haemorrhage or infarction, cerebral embolism, stroke or cerebrovascular accident (Gulliford et al 2009, Khan et al 2010)

4. CV-specific mortality: Record of death with an indicator due to a CV event

5. All-cause mortality: Record of death

6. Hypertension: Presence of a hypertension diagnostic code where no record of hypertension or treatment for hypertension is observed in the baseline or no record of change in hypertension treatment type or dose from baseline is observed (van der Linden et al 2009)

7. Opioid withdrawal: Presence of a diagnosis or symptom code

8. Abdominal pain: Presence of a diagnosis or symptom code

9. Diarrhoea: Presence of a diagnosis or symptom code

10. Syncope: Presence of a diagnosis code

11. Change in pain severity: Increase in opioid dose/type based on the morphine equivalent unit from baseline

9.3.3 Covariates

Covariates included in the study are those determined to be potential risk factors for a given outcome of interest or predictors of exposure. Covariates will be assessed prior to index date to be used for descriptive analyses and for propensity score development. The covariate list is presented in Table 3, and the list of codes for all diagnoses, medications, labs and procedures used to define these covariates will be found in the statistical analysis plan.

Table 3. Patient characteristics prior to and at index date

Demographic and physician characteristics		
Gender	Physician specialty	Smoking status
Body mass index	Age	Geographic indicator
Time characteristics		
Total base time (time from start of observation to index date)		
Calendar year of index date		
Time since launch of naloxegol at index date		
OIC characteristics		
Prior constipation diagnosis		
Type and dose of prior opioid use		
Type and dose of prior laxative use		
Pre-existing conditions and 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 ischaemic attack
Gastrointestinal	Acid reflux disease; Anal fissures, strictures, haemorrhoids; Bowel obstruction; Colon diseases; Constipation; Gastrointestinal perforation; Irritable bowel disease; Inflammatory bowel disease, Diarrhoea
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	Acute hepatic impairment, chronic liver disease
Cancer	Any systemic malignancy
Pain conditions	According to presumed pain origin: Neuropathic pain, psychogenic pain, nociceptive somatic pain, nociceptive visceral pain, mixed pain, unknown pain. According to presumed pain location: Chronic back pain, Pain in the extremities, Pain in other locations
Miscellaneous	Gout; Hyperkalaemia; Calcium metabolism alterations; Injury (fractures and falls); Morbid obesity; Smoking; Obesity; Charlson Comorbidity index (Quan et al 2011, Khan et al 2010)

Clinical and biochemical measurements (where available)		
Glycated haemoglobin (HbA1c)	Alanine aminotransferase	Serum creatinine
Aspartate aminotransferase	Serum bilirubin	Histology
Pathology	Tumour specific markers (eg, EGFR, KRAS, BRCA)	

Pre-existing and concomitant medications/treatments and procedures
CV disease/risk factor-indicated medications
Psychiatric-indicated medications
Neurologic-indicated medications
Musculoskeletal-indicated medications
Laxatives
Alimentary tract and metabolism medications
Other gastrointestinal-indicated medications
Blood and blood forming organ medications
Respiratory system medications
Anti-infectives for systemic use
Opioids
Non-opioid analgesics
Antineoplastic and immunomodulating agents
Radiation therapy
CYP3A inducer[a]
CYP3A inhibitor[b]
Pgp modulator[c]
Healthcare resource utilisation
Total number of hospitalisations
Total number of emergency department visits
Total number of specialist referrals
Total number of lab tests
Total number of outpatient physician visits
Total number of prescriptions

[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 amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil, avasimibe, carbamazepine, phenytoin, rifampin, St. John's Wort and tipranavir/ritonavir.

BRCA, breast cancer; CV, cardiovascular; CYP, Cytochrome P450; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog; OIC, opioid induced constipation; Pgp P-glycoprotein

The prescription duration of concomitant medications will be estimated according to standard principles in each of the targeted data sources. In THIN and PHARMO, this relies on prescribed daily doses where available. In GePaRD, this relies on the use of DDD methodology combined with the timing of consecutive prescriptions, which is used to estimate drug exposure periods in the absence of a prescribed daily dose. Specifically, exposure periods in GePaRD will be constructed in a two-step process. First, the duration of a single prescription will be estimated via the DDDs, based on dosing information in the SmPC or by specific algorithms, depending on the characteristics of the drug. GePaRD utilises the German DDDs (WIdO 2018), as these reflect the doses German physicians would prescribe more accurately. To assess whether the estimation of the duration of a single prescription is plausible, gaps and overlaps between prescriptions in patients are consequently examined. In the second step, drug exposure periods are estimated based on the durations of the single prescription, accounting for stockpiling and small gaps in usage.

9.3.4 Sub-populations in the non-cancer population of interest

Pre-specified non-cancer sub-populations of interest include patients aged ≥ 65 years, with prior CV risk, prior renal or hepatic impairment, concurrent methadone use, concurrent use of CYP3A inhibitors or inducers, or concurrent use of Pgp modulators; or patients who are pregnant. Sub-population will be established at index by reviewing all patient history for indicators of a given sub-population being present at index date. Specifically, sub-populations of interest will be defined as follows. Lists of codes for all diagnoses will be included in the statistical analysis plan.

1. Patients aged ≥ 65 years at index date.

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

3. Prior renal impairment as defined by a diagnosis indicating renal impairment or the presence of two consecutive lab result for creatinine clearance <60 mL/min prior to index date. Where a diagnosis or results for creatinine clearance are not present, patients will then be assessed for the presence of two consecutive lab results for serum creatinine >1.5 x the upper limit of normal (ULN).

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

5. 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 or concurrent reference laxative exposure. Projection

of continuous methadone exposure will follow similar logic as described in Section 9.3.1 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. Those with a code for addiction will be reported separately.

6. Concurrent CYP3A inhibitor or inducer use or Pgp modulator use as defined by presence of a CYP3A inhibitor or inducer or Pgp modulator prescription at or prior to index date where the projected continuous exposure of CYP3A inhibitor or inducer or Pgp modulator is expected to overlap with index naloxegol or concurrent reference laxative exposure. Projections of continuous CYP3A inhibitor or inducer or Pgp modulator exposure will follow similar logic as described in Section 9.3.1 with an allowable gap based on a multiplier of 1 before being considered a discontinuation.

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

    - CYP3A inducer: Efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, Phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, troglitazone

    - Pgp modulator: Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil, avasimibe, carbamazepine, phenytoin, rifampin, St. John's Wort, tipranavir/ritonavir

7. 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-foetal pregnancy diagnosis, pregnancy complication, labour or pre-delivery, threatened abortion, abortion referral, or obstetric hospitalisation. Pregnancy outcomes include diagnoses or procedures indicating an end of pregnancy such as elective terminations, foetal death, hydatidiform moles/blighted ova, live births or stillborn, unclear delivery outcomes, or delivery bookings (Hardy et al 2004).

9.3.5 Sub-populations in the cancer population of interest

There are no pre-specified cancer sub-populations of interest defined or analysed in this study.

9.4 Data sources

As described in Section 9.2, the proposed data sources were those deemed to have sufficient levels 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. However, it should be noted that all "real-world" databases also have a number of limitations. Data content and capture is furthermore likely to vary both between data sources and countries. The initial data sources targeted for this protocol include the following:

9.4.1 The Health Improvement Network: United Kingdom

THIN is an observational database containing information collected in computerised primary care records throughout the UK. Software provided by INPS allows unobtrusive anonymous data collection 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 (e.g., year of birth, gender, registration dates), medical history (e.g., event dates, diagnosis, symptoms, risk factors, comorbidities, referrals), prescription (e.g., prescription dates, therapeutic class, molecule, dosage, posology, duration), and clinical data (e.g., height, weight, blood pressure, immunisations, life habits).

General practitioners (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, THIN database 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. THIN provided the MAH with a count of 383000 patients receiving opioid dispensing between October 2008 and September 2009.

A proportion of individuals in THIN can be linked to the Hospital Episode Statistics (HES) database, which covers UK secondary care. However, this linkage is only available for a subset (approximately 30% of practices [Clegg et al 2016]), depending on the study population, and is not available for patients after 1 January 2018. Due to these limitations in coverage, the current study will not include linkage to HES. However, this is not considered a significant limitation given the communication loop from secondary to primary care in the UK health system, ensuring that diagnoses and care in a secondary setting are captured within primary care recording systems. Prior studies investigating the concordance of diagnostic presence within CPRD, a database similar to THIN, and HES have found that the degree of under-recording varies depending on the disease condition, with approximately 94% of cancer

diagnoses in HES also present within CPRD among patients with type II diabetes (Williams et al 2018).

9.4.2 PHARMO Database Network: The Netherlands

The PHARMO Database Network is a population-based network of healthcare databases and combines data from different healthcare settings in the Netherlands. These different data sources are linked on a patient level through validated algorithms. The longitudinal nature of the PHARMO Database Network system enables follow-up of more than 4 million (25%) residents of a well-defined population in the Netherlands for an average of 10 years. PHARMO provided AZ with a count of 393000 patients receiving opioid dispensing since 2009. Data collection period, catchment area and overlap between data sources differ. Therefore, the final cohort size for any study will depend on the data sources included. As data sources are linked on an annual basis, the average lag time of the data is one year. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status and mortality. Other information available is dependent on the data source. Data sources used in this study will include outpatient pharmacy, hospitalisation, clinical laboratory, GP and cancer registry. The Out-patient Pharmacy Database and the Hospitalisation Database have a 100% overlap. The overlap with the Clinical Laboratory Database is approximately 30%, and the overlap with the GP database is approximately 30% to 40%. Additional details on PHARMO can be found in Annex B.

9.4.3 GePaRD – German Pharmacoepidemiological Research Database

In Germany, it is compulsory for anyone who earns less than a certain amount (€57600 p.a. in 2017) to be a member of the government health insurance scheme, which is administered by approximately 118 health insurance companies. Many people earning more than the annual threshold remain voluntary members of the statutory health insurance (SHI) providers and approximately 85% of the German population are covered by one of the SHI providers (Ohlmeier 2015). The Bremen Institute for Prevention Research and Social Medicine (BIPS) has been working with four of the largest SHI providers: AOK Bremen/Bremerhaven, DAK-Gesundheit, hkk Krankenkasse and Teckniker Krankenkasse (TK), to establish the German Pharmacoepidemiological Research Database (GePaRD).

The GePaRD database covers all geographical regions of Germany and includes information on approximately 15 million persons (17% of the total German population). Data has been collected since 2004 and includes information on patient demographics, geographic region, hospitalisations, ambulatory visits, procedures and outpatient prescriptions. Hospital data include admission and discharge dates, diagnoses and procedures performed in the inpatient setting (Fassmer 2016). Outpatient visit information includes diagnoses, treatments and procedures. Treatments include all dispensations of reimbursable drugs and this information can be linked to a pharmaceutical reference database that provides information on the amount of substance prescribed and the DDD, but not the prescribed daily dose (PDD). Diagnoses are based on the German modification of the International Classification of Diseases, 10th revision (ICD-10-GM) and drugs are coded using the Anatomical Therapeutic Chemical (ATC) code. It should be noted that due to the nature of data collected in GePaRD,, the database will not

contain information on the exploratory endpoint change in pain severity, and the database will only contain partial information on the exploratory endpoints CV-specific mortality (this can be partially inferred) and abdominal pain (which can be described based on diagnoses rather than symptoms).

New data are added to the database on an annual basis, but prior to being made available for research the data are pseudonymised and validated – this process can take up to two years, thus, by November 2017 information up to 2015 is available in the database. A limitation of the GePaRD database is that outpatient diagnoses are only recorded on a quarterly basis, so the exact date of diagnosis is not known.

Access to the data is granted to BIPS employees for officially approved research projects only. Project approval is obtained from the SHI providers and the respective governing authorities (www.bips-institute.de). Therefore, BIPS would apply for project specific authorisation from the SHI providers and upon approval would then request official approval from the governing authority. This process can take several weeks or longer.

9.5 Study size

With an objective of reporting both incidence risks (i.e., percent of patients with an event) and exposure-adjusted incidence rates (i.e., rate of events per patient-years of exposure), the study will continue to accrue patients until, across all countries participating in this protocol, accumulation of naloxegol exposure in non-cancer patients reaches both 5000 patients and 5000 patient-years and accumulation of naloxegol exposure in cancer patients reaches both 1000 patients and 1000 patient-years. Given the 1:1 matching, the CRC sample size will be at least 5000 patients and at least 5000 patient-years of exposure for non-cancer and at least 1000 patients and at least 1000 patient-years of exposure for cancer.

9.5.1 Study size for non-cancer population of interest

For the non-cancer population of interest, the associated precision of event rate estimates across varying underlying incidence rates are presented in Table 4 and Table 5. To our knowledge, there is little published observational data describing event rates of our targeted health outcomes of interest among chronic opioid users or users of laxatives. As such, we have selected a target sample size based on a published incidence of 1.0% per patient-year, which was observed for MI among chronic opioid users in a United States administrative claims study (Carman et al 2011). Using this background event rate, 5000 patient-years of naloxegol exposure will yield an incidence estimate with a 95% CI based on the Wilson Score method of approximately ±0.28% (0.74%-1.32%, Table 4 in bold). Event rates for other targeted health outcomes of interest are also expected to be in the range provided in Table 4. It can be seen from the precision presented in this table that the target sample size of 5000 patient-years of exposure will yield a confidence interval with an upper bound that is no greater than double the observed event rate. While no statistical testing will be performed, this level of precision is sufficient when the observed ratio of event rates is at least 2. Also see Table 4, Table 5, and Table 6 for more details on precision of event rates by patient and patient-year.

Table 4. Estimated 95% CI of exposure-adjusted incidence rate with increasing exposure to naloxegol

Exposure (patient-years)	Expected number of patients with events (95% CI for exposure-adjusted incidence rate)[a]				
	Underlying event rates per patient-year				
	0%	0.5%	1.0%	1.5%	2.0%
300	0 (0.00, 1.23)	2 (0.08, 2.41)	3 (0.21, 2.92)	4 (0.36, 3.41)	6 (0.73, 4.35)
500	0 (0.00, 0.74)	2 (0.05, 1.44)	5 (0.32, 2.33)	8 (0.69, 3.15)	10 (0.96, 3.68)
1000	0 (0.00, 0.37)	5 (0.16, 1.17)	10 (0.48, 1.84)	15 (0.84, 2.47)	20 (1.22, 3.09)
5000	0 (0.00, 0.07)	25 (0.32, 0.74)	50 (0.74, 1.32)	75 (1.18, 1.88)	100 (1.63, 2.43)

[a] Exact CIs based on the Poisson distribution for event rate/year.
CI, confidence interval

Table 5. Estimated 95% CI of incidence (i.e., percentage of patients with an event) with increasing naloxegol sample size

Number of patients	Expected number of patients with events (95% CI for incidence)[a]				
	Underlying percentage of patients with event				
	0%	0.5%	1.0%	1.5%	2.0%
300	0 (0.00, 1.26)	2 (0.18, 2.40)	3 (0.34, 2.90)	4 (0.52, 3.38)	6 (0.92, 4.29)
500	0 (0.00, 0.76)	2 (0.11, 1.45)	5 (0.43, 2.32)	8 (0.81, 3.13)	10 (1.09, 3.64)
1000	0 (0.00, 0.38)	5 (0.21, 1.17)	10 (0.54, 1.83)	15 (0.91, 2.46)	20 (1.30, 3.07)
5000	0 (0.00, 0.08)	25 (0.34, 0.74)	50 (0.76, 1.32)	75 (1.20, 1.88)	100 (1.65, 2.43)

[a] Two-sided 95% CIs following Wilson method.
CI, confidence interval

This is a descriptive study with no formal comparisons planned; although the study will provide a well-constructed, matched reference group to put results into context and establish a current background risk. In lieu of power calculations, Table 6 presents the expected probabilities of observing a specific number of events in the NIC under varying underlying

incidence risks. The table indicates that a minimum of 1000 patients will provide an adequate chance of observing even rare events. For any event rate larger than 0.5%, there is at least an 87.6% chance of observing three or more events with a sample size of at least 1000 patients. The probability of observing a minimum number of events increases with the underlying incidence risk. As an example, utilising the same background incidence for MI of 1% as above, 5000 patients in the NIC will provide a 100% chance of observing at least 10 patients with an event.

Table 6. Probability of observing patients with events with increasing naloxegol sample size

Number of patients	Observed patients with events (x)	Incidence estimates[a]		Probability (%) of observing at least x (Pr[X≥x]) patients with events[b] with varying underlying incidence				
		95% CI	Precision	0.01%	0.5%	1.0%	1.5%	2.0%
300	1	(0.06, 1.86)	±0.90	2.96	77.77	95.10	98.93	99.77
	3	(0.34, 2.90)	±1.28	0.00	19.08	57.79	82.85	93.98
	5	(0.71, 3.84)	±1.56	0.00	1.83	18.39	46.86	71.76
	10	(1.82, 6.03)	±2.10	0.00	0.00	0.10	1.63	8.18
	50	(12.88, 21.30)	±4.21	0.00	0.00	0.00	0.00	0.00
500	1	(0.04, 1.12)	±0.54	4.88	91.84	99.34	99.95	100.0
	3	(0.20, 1.75)	±0.78	0.00	45.65	87.66	98.04	99.74
	5	(0.43, 2.32)	±0.94	0.00	10.83	56.04	86.99	97.19
	10	(1.09, 3.64)	±1.27	0.00	0.03	3.11	22.23	54.33
	50	(7.67, 12.94)	±2.63	0.00	0.00	0.00	0.00	0.00
1000	1	(0.02, 0.56)	±0.27	9.52	99.33	100.0	100.0	100.0
	3	(0.10, 0.88)	±0.39	0.02	87.60	99.73	100.0	100.0
	5	(0.21, 1.17)	±0.48	0.00	55.99	97.13	99.92	100.0
	10	(0.54, 1.83)	±0.64	0.00	3.15	54.27	93.16	99.53
	50	(3.81, 6.53)	±1.36	0.00	0.00	0.00	0.00	0.00
5000	1	(0.00, 0.11)	±0.06	39.35	100.0	100.0	100.0	100.0
	3	(0.02, 0.18)	±0.08	1.44	100.0	100.0	100.0	100.0
	5	(0.04, 0.23)	±0.10	0.02	100.0	100.0	100.0	100.0
	10	(0.11, 0.37)	±0.13	0.00	99.98	100.0	100.0	100.0
	50	(0.76, 1.32)	±0.28	0.00	0.00	51.91	99.92	100.0

[a] Two-sided 95% CIs following Wilson method. Precision is calculated as one half the width of the CI.
[b] Probabilities based on the binomial distribution.
CI, confidence interval

9.5.2 Study size for cancer population of interest

Specific to a cancer population, published background exposure-adjusted incidence rates of the following events have been provided and can be used to project the precision of the event rate estimate. Where event rates are expected to be different between naloxegol and reference group, both rates are provided. Where only a single rate is provided, rates are expected to be the same in both groups.

- **MI:** Van Herk-Sukel et al 2013 utilised secondary data sources in the Netherlands to establish rates of MI before and after lung cancer diagnosis compared to cancer-free controls. A rate of 4.5 per 1000 patient-years (or 0.45%) with 1000 patient-years is expected to produce 5 events. The CI of (0.06, 0.94) has precision of ±0.44%.

- **Stroke:** In the same study, Van Herk-Sukel et al 2013 reported that an event rate of 3.8 per 1000 patient-years (or 0.38%) with 1000 patient-years is expected to produce 5 events. The CI of (0.06, 0.94) has precision of ±0.44%.

- **All-cause mortality:** The European Network of Cancer Registries and International Agency for Research on Cancer websites provide 1-year observed survival probabilities by cancer and by country registry. Looking at the tables generated for the UK, Ireland, Germany, Norway and Sweden, the 1-year survival probabilities for men and women between the ages of 55 and 64 between 1995 and 1999 for all cancers sites, excluding other skin, were between 59.3% and 83.1% (Steliarova-Foucher et al 2012). Given this range, the 1-year mortality is estimated to be approximately 40% and can be estimated with 1000 patients with a precision of ±3%.

- **Bowel perforation:** Incidence of bowel perforation in clinical studies for Avastin range from 0.3% to 3.2% (Avastin 2015). This rate increases to 9% in a cohort with biopsy proven GI involvement with lymphoma (Vaidya and Witzig 2014). As such, an expected rate of 2.0% per patient-year with 1000 patient-years is expected to produce 20 events. The CI of (1.12, 2.88) has a precision of ±0.88%.

For other endpoints, published incidence risk estimates have been provided and can be used to project the precision of the incidence risk estimate:

- **Uncontrolled hypertension:** Previously reported prevalence of hypertension among cancer survivors ranges between 20% and 65% (Choi et al 2013). Additionally, chemotherapeutic agents are associated with a higher rate of new or worsening hypertension with an increase ranging from 17% to 80% (Mouhayar and Salahudee 2011). For 1000 patients, the precision of an incidence risk estimate of 20% is ±2.5%.

- **Abdominal pain:** For naloxegol-treated patients, the proportion experiencing abdominal pain symptoms has been observed to be approximately 17.8% (Webster et al 2014), which can be estimated using 1000 patients with a precision of ±2.3%. For reference group patients, this proportion has been observed to be 3.3%, which can be estimated using 1000 patients with a precision of ±1.1%.

- **Diarrhoea:** For naloxegol-treated patients, the proportion experiencing diarrhoea has been observed to be approximately 12.9% (Webster et al 2014), which can be estimated using 1000 patients with a precision of ±2.1%. For reference group patients, this proportion has been observed to be 5.9%, which can be estimated using 1000 patients with a precision of ±1.5%.

- **Opioid withdrawal:** For naloxegol-treated patients, the proportion experiencing opioid withdrawal syndrome has been observed to be approximately 0.8% (Chey et al 2014), which can be estimated using 1000 patients with a precision of ±0.55%. For reference group patients, this proportion has been observed to be 0.2%, which can be estimated using 1000 patients with a precision of ±0.28%.

Given the observed event rates reported in the literature, a sample size target of at least 1000 patients and at least 1000 patient years of exposure to naloxegol in cancer patients will provide a sufficient level of precision for describing the exposure-adjusted incidence rate and incidence risk for the health outcomes of interest under study. Additionally, Table 6 indicates that a minimum of 1000 patients will provide an adequate chance of observing even rare events. For any event rate larger than 0.5%, there is at least an 87.6% chance of observing 3 or more events with a sample size of at least 1000 patients. The probability of observing a minimum number of events increases with the underlying incidence risk.

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 programmes.

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

A global statistical analysis plan (SAP) will be developed to describe analysis approaches applicable across countries. No study data files will be created before the completion of the global SAP. Detailed SAPs will be developed locally in collaboration with the research partners selected to execute the analyses within a given country’s database. The local SAPs will address country-specific data differences that may need to be accounted for when analysing the data source. These will include, but are not limited to, covariates that apply to a given population and outcome, as well as, differences in the presence and/or naming conventions for specific data elements of interest when defining exposure, outcomes, covariates, and sub-populations of interest. The final study report will contain a meta-analysis of pre-specified results from individual countries.

9.7.1 Analysis

All analyses for this study will be descriptive. All analyses will be conducted within both cancer and non-cancer populations of interest as well as within both NIC and CRC. All analyses will be conducted within non-cancer sub-populations of interest (as defined in Section 9.3.4). Results will be provided for all countries through a meta-analysis and at the country level.

Demographic, clinical and treatment characteristics captured in the patients' medical history will be described.

Each of the health outcomes of interest will be described separately. Event rates and 95% CIs for pre-specified health outcomes of interest will be reported as both incidence risks and exposure-adjusted incidence rates.

During follow-up, incidents (or first occurrence) of each type of health outcome of interest within each patient will be identified. An event will be attributed to a given exposure if observed during the exposure or in the risk window described in Section 9.3.1.

For a given exposure group, the incidence risks will be calculated as the number of patients with the outcome of interest (i.e., unique patients) divided by the total number of patients. The 95% CIs will be calculated based on the Wilson Score method.

The exposure-adjusted incidence rate for an exposure group will be calculated as the number of first occurrences of each type of health outcome of interest (i.e., unique patients) divided by the total aggregate person-time accrued by all patients in that exposure group. The contribution of each patient to the exposure time will depend on whether the patient reported the health outcome of interest (i.e., the event). Accrued person-time for patients who experience an event is calculated as the total number of days accrued between the index date until the date of the event; whereas, accrued person-time for patients who do NOT experience an event is calculated as the total number of days accrued between the index date until the earliest occurrence of the exposure end date (as determined by the algorithm in Section 9.3.1). For analyses, exposure and follow-up for health outcomes of interest for a given patient in both NIC and CRC will be censored when a patient disenrolls/transfers out of the research partner's data source, initiates treatment with a PAMORA, if a CRC patient initiates treatment with naloxegol, or if a NIC patient initiates treatment with another laxative. Exposure-adjusted incidence rates and associated exact mid-probability CIs based on the Poisson distribution will be calculated for each exposure group and reported per 1000 person-years.

Incidence risks and exposure-adjusted incidence rates for each health outcome of interest will be summarised overall and within the sub-populations of interest for both NIC and CRC. Additionally, rates will be presented across all countries and at the country level. Results from specific sub-populations would be interpreted in light of the results from the overall population. Sensitivity analyses will be conducted to account for different definitions of exposure window or censoring in cases of switching or augmentation. Specifically, in the case of censoring for switching or augmentation, sensitivity analyses will allow for exposure to

continue to the derived end of exposure date plus the pre-specified 30-day risk window. Additionally, for the cancer population of interest, patient may enter the hospital setting for extended periods of time resulting in a scenario where exposure to naloxegol or the concurrent reference exposure cannot be observed due to limitations of most databases. As such, a sensitivity analysis will allow for exposure in both the NIC and CRC to be analysed under an intent-to-treat paradigm for the duration of their follow-up period.

The time to an onset of a given outcome of interest will also be described (e.g., appropriate quantiles) using the Kaplan-Meier method to account for censoring. Cumulative incidence estimates and corresponding 95% CIs will also be provided for each outcome of interest at relevant time-points (e.g., 3 month-intervals) to account for censoring and competing risk (Gooley et al 1999). For all-cause mortality, this is equivalent to the complement of the Kaplan-Meier estimator, where patients who are alive are censored at the exposure end date (as determined by the algorithm in Section 9.3.1). For each of the non-all-cause mortality outcomes, death is considered a competing risk. For these outcomes, patients who discontinue from treatment prior to observing an event are censored at the exposure end date.

9.7.2 Minimisation of bias

The main goal of the study is to estimate the event rates of health outcomes of interest among patients receiving naloxegol. While there is no formal comparison planned, a CRC is defined to provide clinical context to the estimated event rates among the NIC. Incidence risks and exposure-adjusted incidence rates for health outcomes of interest will be generated for patients on naloxegol and reference laxative treatments that are matched 1:1 on propensity scores with successful balance of underlying covariates that predict the specific outcomes. The number of matched pairs will be reported as will incidence and exposure-adjusted incidence rates for unmatched patients. Matching on propensity score will occur during the final analysis after the target sample size of 5000 patients and 5000 patient-years in each cohort is accrued.

The SAP will outline the strategy for modelling propensity scores in more detail. Selection of covariates for inclusion into the propensity score model are listed in Table 3. Covariates include known (as defined by medical or epidemiologic literature) risk factors of the outcome, predictors of exposure, and standard covariates for adjustment which include patient, physician, or time since launch characteristics. All covariates will be modelled as continuous or binary indicators. A single propensity score model will be developed for each country using only patients accrued within that country's data source. The propensity score, defined as the conditional expectation or probability of being exposed given a vector of observed covariates, has been shown to effectively balance covariates across treatment groups (Rosenbaum and Rubin 1983). The primary propensity score approach to balancing covariates will be a 5 to 1-digit matching algorithm (Parsons 2001). The concordance statistic (or c-statistic) will be used to measure the discriminatory power of the predictive model for treatment. Covariate balance will be assessed using average standardised differences. If there are sufficient numbers of patients who are not successfully matched, a sensitivity analysis that includes those patients who were not matched on the propensity score will be conducted. Finally, analytical strategies to address missing data will also be detailed in the analysis plan. At a high-level, for key

variables including study endpoints and those employed in cohort balancing efforts during the final analysis, the impact of missing data will be explored through analysing only complete cases for a given endpoint and separately for propensity score derivation. Sensitivity analysis will be conducted where missing information for key covariates will be imputed.

9.8 Quality control

Standard operating procedures for each research partner 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 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

This study has a number of limitations that potentially affect the validity of findings or the interpretation of the results. The majority of limitations are inherent to the data sources used in the study and are as follows:

1. Ascertainment of health outcomes of interest: Despite the efforts taken to define algorithms specific to each health outcome of interest, some of the data sources utilised in this study are physician-based electronic medical record databases; therefore, under-reporting or misclassification of health outcomes of interest may occur. Events occurring in emergency care only will be missed. Diagnostic codes or laboratory data may lack the specificity needed to determine if an event of interest occurred.

2. Channelling bias: Channelling bias may be introduced through prescribing of treatment based on certain characteristics of a patient such as those whose prior alternative treatment was poorly tolerated or ineffective. These patients may be selectively prescribed the new treatment and may result in apparent association of increased risk of events of interest in this population. For this study, the use of a CRC may be subject to certain biases (e.g., channelling bias) that will have to be considered when interpreting the results. Propensity score matching methodology will be applied to address imbalance among risk factors for outcome and predictors of exposure at first prescription of naloxegol and the concurrent reference laxative. Covariates in the

propensity score model will include demographic factors, profile of previous or current therapies, previous medical diagnoses, and measures of healthcare resource utilisation.

3. Accrual of patients and exposure: Given multiple laxative treatment options, there could be a delay in accrual of patients treated with naloxegol if adoption by physicians is low. In addition, treatment initiation originating in secondary care (especially for cancer patients) may be missed if not recorded in the physician-based data source. Finally, for data where linkage is required, accrual may be delayed where 100% overlap in data sources is not available.

4. The lack of data on exposure in the hospital setting may result in immeasurable time bias (Suissa 2008) where secondary stays are lengthy (i.e., beyond the allowed gap between prescriptions).

5. Length of follow-up (i.e., exposure length) varies due to disease stage (e.g., cancer progressed and patient died), thus exposure of naloxegol may be short in length, and the percentage of patients who had any outcome event may depend on how long the patients stay in the study, rather than treatment effect.

6. Matching on propensity score may limit generalisability of incidence and exposure-adjusted incidence rates in the event a sufficient number of matched pairs are not identified. Incidence and exposure-adjusted incidence rates in unmatched patients will be reported to account for this potential limitation.

7. 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.

8. The GePaRD database does not contain exact dates for outpatient diagnoses, rather these are coded by quarter due to the nature of the reimbursement system in Germany. However, as the reason for this coding is administrative and not related to drug exposure, it is not expected to introduce differential bias within the study. In addition, it is possible to approximate outpatient diagnoses dates by utilising the exact dates of prescriptions available in the database. It is further noted that exact dates on hospitalisations is provided within the database, allowing the most important endpoints to be captured with accurate dates.

9. The estimation of prescription duration may be subject to inaccuracies due to the lack of information on PDDs in GePaRD, or due to missing data or data entry errors within this information in THIN and/or PHARMO. Some of the exploratory endpoints, including changes in pain severity and abdominal pain, will be identified through the use of algorithms.

10. The cause of death, and the exploratory endpoint CV-specific mortality will be identified utilising diagnostic information from hospital stays occurring shortly prior to the date of death.

11. Linkage between HES and THIN is not useful in this study as HES linkage for THIN practices is not available after 2018. This means that the UK data source will be restricted to a primary care database, potentially resulting in under-recording of conditions that are primarily diagnosed or managed within the secondary care setting. However, due to the communication channels between primary and secondary care in the UK, any potential bias is expected to be minimal. Prior studies looking at diagnostic concordance have found that, at least among patients with type II diabetes, there is a high concordance of cancer recordings between HES and the Clinical Practice Research DataLink (CPRD), which is similar in structure to THIN (Williams et al 2018).

9.10 Other aspects

Not applicable.

10. PROTECTION OF HUMAN PATIENTS

Institutional review board approval and/or any other required ethical or scientific 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 and 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 unfavourable 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 AE corresponds to any untoward medical occurrence that at any dose results in:

- Death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- 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 jeopardise 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 AE. An adverse reaction, in contrast to an AE,

is characterised 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 a KKI-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 KKI 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 2022.

Progress reports will be provided as part of periodic safety update report (PSUR) procedures and will include for both NIC and CRC, grouped by cancer and non-cancer, patient recruitment status, descriptive statistics on baseline characteristics, and accumulated health outcome counts. Results specific to the cancer population of interest will begin with the second progress report. Progress reports from a separate study conducted to meet a post-marketing requirement to the FDA will also be included as part of PSUR procedures. Additionally, the progress report no.5 (delayed from second half 2020 to 30 July 2021)will contain an interim analysis that will include similar information as presented in previous progress reports with the addition of individual event rate point estimates for each pre-specified outcome of interest for all naloxegol-treated patients recruited at the point of database lock for this analysis. For both progress reports and the interim analysis, results for each treatment group will be presented across all countries.

A final report will be provided as part of PSUR procedures and will be generated at study end in 2023. The final report will contain content provided in the progress reports as well as estimated incidence risks and exposure-adjusted incidence rates, with their corresponding 95% CIs for pre-specified outcomes of interest based on a matched naloxegol-exposed and concurrent reference exposed population grouped by cancer and non-cancer. Event rates and 95% CIs for each outcome of interest will be presented across all countries and will be presented for individual countries when 1000 patient-years of naloxegol exposure have been accumulated from that country. Event rates and 95% CI for pre-specified health outcomes of

interest for individual sub-populations (combined across countries) will also be presented in the final report. Additionally, all proposed sensitivity analyses as detailed in the statistical analysis plan and corresponding information for unmatched patients will be reported to ensure full transparency. 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.

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Annex A ENCePP checklist for study protocols

Study title:

An Observational Post-Authorisation Safety Study (PASS) of MOVENTIG® (Naloxegol) Among Patients Aged 18 Years and Older Treated with Opioids Chronically

Study reference number:

D3820R00009

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[3]	☒	☐	☐	6; 17
1.1.2 End of data collection[4]	☒	☐	☐	6; 17
1.1.3 Study progress report(s)	☒	☐	☐	6; 17
1.1.4 Interim progress report(s)	☒	☐	☐	6; 17
1.1.5 Registration in the EU PAS register	☒	☐	☐	6; 17
1.1.6 Final report of study results.	☒	☐	☐	6; 17

Comments:

The Study progress report 5 delivery date be moved from the second half of 2020 to the 30th of July 2021.

[3] 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.
[4] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section of protocol; 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)	☒	☐	☐	8; 19-20
2.1.2 The objective(s) of the study?	☒	☐	☐	8; 19-20
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2 21-22
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	N/A
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8; 19-20

Comments:

This is a descriptive study with no formal comparisons planned.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	9.1; 20-21
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	9.1; 20-21, 9.3.2; 25-26

Section 3: Study design	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
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)	☒	☐	☐	9.1; 20-21, 9.5; 33-37

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	9.2.1; 22, 9.4; 31-33
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	6; 17
4.2.2 Age and sex?	☒	☐	☐	9.2; 21-23
4.2.3 Country of origin?	☒	☐	☐	9.2; 21-23
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☒	☐	☐	9.3.3; 26-29
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)	☒	☐	☐	9.2.2; 22

Comments:

Study of patients who receive a new prescription for naloxegol or a non-PAMORA laxative.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	9.3.1; 23-25
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)	☒	☐	☐	9.3.1; 23-25
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.1; 20-21, 9.3.1; 23-25
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1; 23-25
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	9.7.1; 38-39

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	9.3.2; 25-26
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity,				

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.2; 25-26

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Section of protocol; 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)	☒	☐	☐	9.3.3-4; 26-30
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	9.3.3-4; 26-30

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Section of protocol; 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.)	☒	☐	☐	9.2; 21-23, 9.4; 31-33, Annex B; 60-61 9.2; 21-23, 9.4; 31-33,

Section 8: Data sources	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
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.)	☒	☐	☐	Annex B; 60-61
8.1.3 Covariates?	☒	☐	☐	9.2; 21-23, 9.4; 31-33, Annex B; 60-61
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)	☒	☐	☐	9.2; 21-23, 9.4; 31-33, Annex B; 60-61
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.2; 21-23, 9.4; 31-33, Annex B; 60-61
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.2; 21-23, 9.4; 31-33, Annex B; 60-61
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	9.2; 21-23, 9.4; 31-33, Annex B; 60-61
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	9.2; 21-23, 9.4; 31-33, Annex B; 60-61
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.2; 21-23, 9.4; 31-33, Annex B; 60-61

Section 8: Data sources	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
				9.2; 21-23, 9.4; 31-33, Annex B; 60-61
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4; 31-33, Annex B; 60-61

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	9.5; 33-37

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	9.7; 37-40

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1; 38-39
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.2; 39-40
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	9.7.2; 39-40

Comments:

No stratified analyses, instead two mutually exclusive populations of interest will be created (cancer, non-cancer). exposure groups and sub-populations are considered, and no formal comparisons planned.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	9.8; 40
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6; 37
11.3 Are methods of quality assurance described?	☒	☐	☐	9.8; 40
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	9.9; 40-42
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	9.8; 40

Comments:

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

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	9.9; 40-42
12.1.2 Information biases?	☒	☐	☐	9.9; 40-42
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.1; 20-21, 9.5; 33-37
12.3 Does the protocol address other limitations?	☒	☐	☐	9.9; 40-42

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	10; 42
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.8; 40

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	5; 12-16

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section of protocol; Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12; 44-45
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12; 44-45

Comments:

Name of the main author of the protocol: ____ Danie du Plessis _____

Date: 29 March 2021

Signature: _____

Annex B Further description of the PHARMO database network

PHARMO

General Practitioner Database

The General Practitioner (GP) database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists, and healthcare product/drug prescriptions. The prescription records include information on type of product, date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) Classification System. Diagnoses and symptoms are coded according to the International Classification of Primary Care, which can be mapped to International Classification of Diseases (ICD) codes, but can also be entered as free text. GP data cover a catchment area representing 1.9 million residents.

Out-patient Pharmacy Database

The Out-patient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Drug dispensing is are coded according to the WHO ATC Classification System. Out-patient pharmacy data cover a catchment area representing 3.6 million residents.

In-patient Pharmacy Database

The In-patient Pharmacy Database comprises drug dispensing from the hospital pharmacy given during a hospitalisation. The dispensing records include information on type of drug, start and end date of use, strength, dosage regimen and route of administration. Drug dispensing are coded according to the WHO ATC Classification System. In-patient pharmacy data cover a catchment area representing 2.0 million residents.

Clinical Laboratory Database

The Clinical Laboratory Database comprises results of tests performed on clinical specimens. These laboratory tests are requested by GPs and medical specialists in order to get information concerning diagnosis, treatment and prevention of disease. The electronic records include information on date and time of testing, test result, unit of measurement and type of clinical specimen. Laboratory tests are coded according to the Dutch WCIA Coding System. Clinical laboratory data cover a catchment area representing 1.2 million residents.

Hospitalisation Database

The Hospitalisation Database comprises hospital admissions from the Dutch Hospital Data Foundation for more than 24 hours and admissions for less than 24 hours for which a bed is required. The records include information on discharge diagnoses, procedures and hospital

admission and discharge dates. Diagnoses are coded according to the ICD, and procedures are coded according to the Dutch Classification of Procedures.

Cancer Registry

The Eindhoven Cancer Registry is maintained by the Comprehensive Cancer Centre the Netherlands and comprises information on newly diagnosed cancer patients in the south-eastern part of the Netherlands. Trained registry personnel subsequently actively collect onsite data, including cancer diagnosis, tumour staging, comorbidity at diagnosis and treatment received directly after diagnosis (e.g., chemotherapy [yes/no], radiation therapy, and surgery). Staging of cancer is categorised according to the TNM-classification developed and maintained by the Union for International Cancer Control. Tumours are classified based on site (topography) and morphology (histology), according to the WHO International Classification of Diseases for Oncology (ICD-O-3). The ECR overlaps with a sub-cohort of the PHARMO Database Network (approximately 1.2 million residents). For more information, visit www.netherlandscancerregistry.nl.