PASS Protocol	
Drug Substance	Naloxegol
Study Code	D3820R00009
Edition Number	02
Date	31 July 2015

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

EU PAS Register Number:	ENCEPP/SDPP/12669
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 characterize 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, diarrhea, syncope, and change in pain severity) in patients ≥18 years of age diagnosed with non-cancer pain who were treated with opioids chronically and subsequently treated with naloxegol in routine post-authorization use.
Countries of Study:	United Kingdom and the Netherlands
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This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative

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1. TABLE OF CONTENTS PAGE

TITLE PAGE 1
1. TABLE OF CONTENTS 6
2. LIST OF ABBREVIATIONS 8
3. RESPONSIBLE PARTIES 9
4. ABSTRACT 9
5. AMENDMENTS AND UPDATES 11
6. MILESTONES 12
7. RATIONALE AND BACKGROUND 12
8. RESEARCH QUESTION AND OBJECTIVES 14
9. RESEARCH METHODS 14
9.1 Study design 14
9.2 Setting 15
9.2.1 Inclusion criteria 16
9.2.2 Exclusion criteria 16
9.2.3 Follow-up 17
9.3 Variables 18
9.3.1 Exposure 18
9.3.2 Outcomes 19
9.3.3 Covariates 21
9.3.4 Sub-populations 23
9.4 Data sources 24
9.4.1 The Health Improvement Network: United Kingdom 25
9.4.2 PHARMO Database Network: The Netherlands 25
9.5 Study size 26
9.6 Data management 29
9.7 Data analysis 29
9.7.1 Analysis 29
9.7.2 Minimization of bias 30
9.8 Quality control 31
9.9 Limitations of the research methods 31
9.10 Other aspects 32
10. PROTECTION OF HUMAN PATIENTS 32

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 33
11.1 Definitions....33
11.1.1 Definition of adverse events 33
11.1.2 Definition of serious adverse event....33
11.1.3 Definition of adverse drug reactions....34
11.2 Collection of adverse events 34
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 34
13. REFERENCES 35

LIST OF TABLES

Table 1 List of main responsible parties....9
Table 2 List of milestones or planned dates 12
Table 3 Patient characteristics prior to and at index date 21
Table 4 Estimated 95% CI of exposure-adjusted incidence rate with increasing exposure to naloxegol 26
Table 5 Estimated 95% CI of incidence (ie, percentage of patients with an event) with increasing naloxegol sample size 27
Table 6 Probability of observing patients with events with increasing naloxegol sample size....28

LIST OF FIGURES

Figure 1 Example of the continuous drug exposure algorithm....19

LIST OF ANNEXES

Annex A ENCePP checklist for study protocols

Annex B Further description of the PHARMO database network

2. LIST OF ABBREVIATIONS

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

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AZ	AstraZeneca
CI	Confidence interval
CRC	Concurrent reference cohort
CV	Cardiovascular
CYP	Cytochrome P450
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
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-authorization safety study
Pgp	P-glycoprotein
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAP	Statistical analysis plan
THIN	The Health Improvement Network
UK	United Kingdom
ULN	Upper limit of normal

3. RESPONSIBLE PARTIES

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

Table 1 List of main responsible parties

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

4. ABSTRACT

Title

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

Edition Number 02, 31 July 2015, AstraZeneca (AZ)

Rationale and background

AZ agreed to conduct this post-authorization observational safety study (PASS) to monitor clinically important identified and potential risks within a cohort 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, diarrhea, syncope, and change in pain severity. This study is part of a broader post-marketing commitment to augment routine evaluation of the safety profile of naloxegol in clinical practice.

Research question and objectives

The overall research goal for this study is to provide additional data to characterize the safety of naloxegol in the indicated population and within at-risk vulnerable populations identified in the naloxegol risk management plan (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, diarrhea, syncope, and change in pain severity) in patients ≥18 years of age diagnosed with non-cancer pain who were treated with opioids chronically and subsequently treated with naloxegol in routine post-authorization 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)), a Concurrent Reference Cohort (CRC), and by pre-specified sub-populations that include patients aged ≥65 years, pregnant patients, patients with prior cardiovascular 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, diarrhea, syncope, and change in pain severity in patients treated with naloxegol (NIC), a CRC, and by pre-specified sub-populations that include patients aged ≥65 years, pregnant patients, patients with prior cardiovascular 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 utilize a retrospective new users cohort design (Schneeweiss 2010). All recipients of naloxegol who will be followed in this study will have received marketed drug in the course of ordinary clinical practice after authorization 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 at least 5000 patients and at least 5000 patient-years of exposure to naloxegol are accrued across all study data sources. A cohort of patients initiating a new prescribed laxative (excluding peripherally-acting mu-opioid receptor antagonists [PAMORAs]) while chronically exposed to opioids for non-cancer pain will be used as a CRC. 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 the patients' medical history. Given the 1:1 matching, the CRC sample size will be at least 5000 patients. 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 in the targeted countries (currently the United Kingdom [UK] and the Netherlands) 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; have no evidence of cancer indicators; and have no prior exposure to PAMORA laxatives alvimopan, methylnaltrexone, or naloxone + opioid combination (including fixed-dose combinations).

Variables

The health outcomes of interest include bowel perforation, acute MI, stroke, CV-specific mortality, all-cause mortality, hypertension, opioid withdrawal, abdominal pain, diarrhea, syncope, and change in pain severity. Exposure and covariates (ie, risk factors for a given outcome of interest or predictors of exposure) will also be assessed.

Data sources

The data sources currently targeted for this study include The Health Improvement Network (THIN) in the UK, and the PHARMO Database Network in the Netherlands. Additional countries/data sources could be added in advance of first annual assessment or throughout the course of the study.

Study size

With an objective of reporting both incidence risks and exposure-adjusted incidence rates, the study will continue to accrue patients until both 5000 patients and 5000 patient-years of exposure with naloxegol in non-cancer pain are accumulated across all countries participating in this protocol. 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.

Data analysis

All analyses for this study will be descriptive. Demographic, clinical, and treatment characteristics will be summarized for both NIC and CRC overall, and within sub-populations of interest across all countries and at the country level. Each of the health outcomes of interest will be analyzed separately. Event rates and 95% confidence intervals (CIs) for pre-specified health outcomes of interest will be reported as both incidence risks (ie, 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 (ie, 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 will begin in December 2015 and continue until at least 5000 patients and at least 5000 patient-years of exposure to naloxegol and concurrent reference laxative treatments (separately) are accrued across all study data sources (anticipated first half of 2022). Registration in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register is planned for fourth quarter 2015. Study progress reports will be provided annually, beginning in first half 2016, and the final report of study results will be provided in Q4 2023.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Any planned study milestones are listed in Table 2.

Table 2 List of milestones or planned dates

Milestone	Planned date
Start of data collection	December 2015
End of data collection[a]	First half of 2022
Study progress report 1	First half 2016
Study progress report 2	First half 2017
Study progress report 3	First half 2018
Study progress report 4 [b]	First half 2019
Study progress report 5	First half 2020
Study progress report 6	First half 2021
Study progress report 7	First half 2022
Registration in the ENCePP register	Q4 2015
Final report of study results[a]	Q4 2023

[a] The end of data collection will be dependent upon uptake of product and, therefore, patient enrollment. The planned end of this study will occur when at least 5000 patients and at least 5000 patient-years of exposure to naloxegol are accrued across all study data sources. 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 4 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 12 for details on content of this report.

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 ie, 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, **Error! Reference source not found.**).

The efficacy of naloxegol in patients with OIC and non-cancer pain was demonstrated in two replicate double-blind, randomized, placebo-controlled Phase 3 trials, each over 12 weeks (**Error! Reference source not found.**). The same studies also looked into safety, identifying gastrointestinal adverse events (AEs) (diarrhea, abdominal pain, nausea, vomiting) in a dose-related manner, rare major adverse cardiovascular events, and infrequent drug-withdrawal syndrome (**Error! Reference source not found.**). 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 2 occurrences of opioid withdrawal AE, albeit both events were attributed to a change in opioid dose (and not to naloxegol; **Error! Reference source not found.**)

As a complement to routine pharmacovigilance activities (which include regular analysis of spontaneously reported post-marketing safety data), AZ agreed to conduct 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, diarrhea, syncope, and change in pain severity. Within the EU RMP for naloxegol, opioid withdrawal syndrome and clinically important gastrointestinal AEs (including abdominal pain and diarrhea) 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 program conducted in patients who had chronic non-cancer pain. However, specific vulnerable populations were either excluded or provided little data. As such, concerns around use of naloxegol in certain vulnerable populations were raised by the Committee for Medicinal Products for Human Use in the initial marketing application. Therefore, AZ proposed to include into this PASS an analysis of the safety endpoints within pre-specified sub-populations that include patients aged ≥65 years, pregnant patients, patients with prior cardiovascular 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 utilization study of any naloxegol use and within pre-identified sub-populations of interest, and an independent observational prospective safety and effectiveness study of naloxegol use in cancer pain patients conducted via primary data collection.

8. RESEARCH QUESTION AND OBJECTIVES

The overall research goal for this study is to provide additional data to characterize 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 MI, stroke, CV-specific mortality, all-cause mortality, hypertension, opioid withdrawal, abdominal pain, diarrhea, syncope, and change in pain severity) in patients ≥18 years of age diagnosed with non-cancer pain who were treated with opioids chronically and subsequently treated with naloxegol in routine post-authorization 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), a CRC, and by pre-specified sub-populations that include patients aged ≥65 years, pregnant patients, patients with prior cardiovascular 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, diarrhea, syncope, and change in pain severity in patients treated with naloxegol (NIC), a CRC, and by pre-specified sub-populations that include patients aged ≥65 years, pregnant patients, patients with prior cardiovascular 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 utilize 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-authorization period under conditions of usual care use. Of note, this safety study does not involve active administration of naloxegol by AZ. All recipients of naloxegol who will be followed in this study will have received marketed drug in the course of ordinary clinical practice after authorization of the drug. Detailed information on recommended dosages can be found in the product circular.

The study period will begin from the launch date of naloxegol within the given country. The study period will extend with each annual refresh of the database. The planned end of this PASS will occur when at least 5000 patients and at least 5000 patient-years of exposure to naloxegol and concurrent reference laxative treatments (separately) are accrued across all study data sources. 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 non-cancer pain.

Chronic opioid-using patients with 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 matched 1:1 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 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 utilization 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 (ie, 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 country. In order to maximize data capture from two countries with high-quality data, this protocol will target THIN in the UK and the PHARMO database network in the Netherlands. These 2 countries maintain high quality repositories of longitudinal patient data that allow for good capture of exposure and outcome among populations that are utilizers of opioids. Specifically, the main drivers for selection of these data sources where:

[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.

1. Ability to capture exposure to naloxegol and other prescribed non-PAMORA laxatives for non-cancer pain. 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 behaviors than those utilizing 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 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.

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. Additional countries/data sources could be added in advance of the first annual assessment when meeting protocol requirements and drivers for selection.

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 (ie, 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 authorized 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 defined by >30[2] days of opioid exposure within the 180 days prior to and inclusive of the cohort entry date

[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.

4. Patients with evidence of a cancer indicator (diagnosis or treatment) prior to cohort entry date
5. Exposure to PAMORA laxatives, alvimopan, methylnaltrexone, or naloxone + opioid combination (including fixed-dose combinations) prior to cohort entry date

9.2.3 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, cardiovascular 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

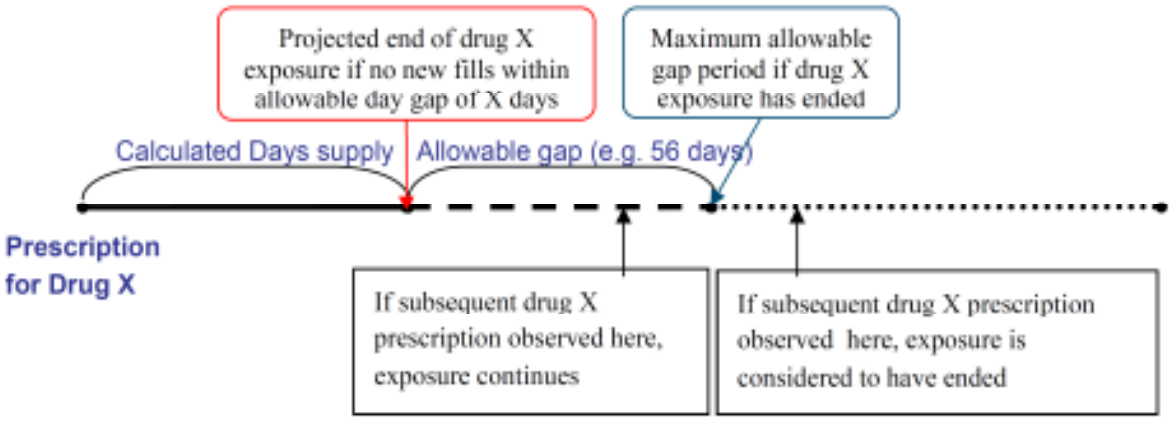
Exposure to naloxegol or the concurrent reference laxative will start with the index prescription date.

The exposure end date is calculated by an algorithm used to derive continuous exposure. The algorithm will utilize quantity (naloxegol strength and number of tablets) and dosing instructions[3] (when available) to calculate days supply for each prescription and combine this 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 behaviors. 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 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 supply is equal to 28 days. If no new prescription for naloxegol is observed within 56 days (28 days*2) after the expiry date of the 1st 28-day prescription supply, then the end of exposure date will be on the 28th day in follow-up (see Figure 1).

[3] Dosing instructions and timing of subsequent refills are expected to account for different strengths prescribed in the event a 12.5 mg or 25 mg tablet is prescribed more than the recommended once a day dose; otherwise daily dose will be assumed to be 1 tablet.

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. 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 supply if no new fills are observed within the allowable gap. In the previous example, this would be the 28th day. The second risk window will be based on patient exposure to drug ending at the projected days 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, diarrhea, syncope, and change in pain severity. Each outcome will be assessed individually, therefore, a patient can experience multiple outcomes. The hierarchy of endpoints (ie, 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, diarrhea, syncope, and change in pain severity are considered secondary outcomes, because they are not recorded in every base data source (eg, CV-specific mortality), are not identified through a clear diagnosis code or algorithm (eg, opioid

withdrawal), require a proxy definition (eg, 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 utilizing 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 (eg, International Classification of Diseases, 10th revision, Read), or combination of codes and/or conditions (eg, hospitalization) 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 hemorrhage 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 cardiovascular 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. Diarrhea: 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, dose, and length of prior opioid use		
Type, dose, and length 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 ischemic attack	
Gastrointestinal	Acid reflux disease; Anal fissures, strictures, hemorrhoids; Bowel obstruction; Colon diseases; Constipation; Chronic liver disease; Gastrointestinal perforation; Irritable bowel disease; Inflammatory bowel disease	
Endocrine	Diabetes; Diabetic complications; Hyperthyroidism; Hyperparathyroidism; Hypothyroidism; Osteoporosis	
Rheumatologic	Inflammatory arthropathy; Osteoarthritis; Rheumatoid arthritis; Other autoimmune diseases	

Psychiatric	Anxiety disorders; Bipolar disorder; Substance abuse; Schizophrenia; Other psychiatric disorders; Depression
Renal Disease	Chronic renal failure; Chronic renal insufficiency; Renal/Urinary tract infections
Hepatic disease	Chronic hepatic impairment
Cancer	Any systemic malignancy
Pain conditions	Chronic back pain; Extremities pain; Neuropathic pain
Miscellaneous	Gout; Hyperkalemia; Hypercalcemia; Injury (fractures and falls); Morbid obesity; Smoking; Obesity; Charlson Comorbidity index (Quan et al 2011, Khan et al 2010)

Clinical and biochemical measurements (where available)		
Glycated hemoglobin (HbA1c)	Alanine aminotransferase	Serum creatinine
Aspartate aminotransferase	Creatinine	Serum bilirubin

Pre-existing and concomitant medications

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

Genito Urinary System medications and Sex Hormones

Blood and Blood Forming Organ medications

Respiratory System medications

Anti-infectives for Systemic Use

Other disease indicated medications

Opioids

Non-opioid analgesics

CYP3A inducer[a]

CYP3A inhibitor[b]

Pgp modulator[c]

Healthcare resource utilization

Total number of hospitalizations

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.

CV Cardiovascular, CYP Cytochrome P450, OIC Opioid induced constipation.

9.3.4 Sub-populations

Pre-specified 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.

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

9.4 Data sources

As described in Section 9.2, the proposed data sources were those deemed to have sufficient level of key data elements to successfully conduct the study and capable of delivering insights from the study in a reasonable timeframe which includes consideration of data lag, naloxegol launch dates, and lag due to administrative issues. 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 computerized 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 (eg, year of birth, gender, registration dates), medical history (eg, event dates, diagnosis, symptoms, risk factors, comorbidities, referrals), prescription (eg, prescription dates, therapeutic class, molecule, dosage, posology, duration), and clinical data (eg, height, weight, blood pressure, immunizations, life habits).

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 AZ with a count of 383000 patients receiving opioid dispensing between October 2008 and September 2009.

For additional data capture, THIN primary care data can be linked to the National Health Service Hospital Episodes Statistics (HES) database. These HES data include both inpatient and outpatient episodes. The use of HES data does come with a data lag since the National Health Service has a delay on the release of their HES data updates such that the April 2013 to March 2014 HES data is only released in January 2015. Despite the data lag, the GP referral to secondary care is relatively well recorded/coded and would provide reasonable indicators for events prior to verification via HES. Through the linkage, HES data is available for around 2.3 million patients registered with 158 practices in England.

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 1 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, hospitalization, clinical laboratory, general practitioner, and cancer registry. The Out-patient Pharmacy Database and the Hospitalization 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 the proposed databases can be found in Annex B.

9.5 Study size

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

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%**
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 (ie, percentage of patients with an event) with increasing naloxegol sample size

Number of patients (N)	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] 2-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 a 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. As an example, utilizing 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 (N)	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] 2-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.

9.6 Data management

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

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

9.7 Data analysis

A global statistical analysis plan (SAP) will be developed to describe analysis approaches applicable across countries. 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 analyzing the data source. These will include, but are not limited to, differences in the presence and/or naming conventions for specific data elements of interest when defining exposure, outcomes, covariates, and sub-populations of interest.

9.7.1 Analysis

All analyses for this study will be descriptive. Demographic, clinical, and treatment characteristics captured in the patients' medical history for both NIC and CRC overall and within sub-populations of interest (as defined in Section 9.3.4) will be summarized across all countries and at the country level.

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, incident (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 (ie, unique patients) divided by the total number of patients. The 95% confidence intervals 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 (ie, 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 (ie, 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 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 summarized 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.

The time to an onset of a given outcome of interest will also be described (eg, appropriate quantiles) using the Kaplan-Meier method to account for censoring. Cumulative incidence estimates and corresponding 95% CI will also be provided for each outcome of interest at relevant time-points (eg, 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 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 Minimization 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. 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 modeled 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 standardized 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 analyzing 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 utilized 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. Channeling bias: Channeling 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 (eg, channeling 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 utilization.

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 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 (ie, beyond the allowed gap between prescriptions).

5. Matching on propensity score may limit generalizability 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.

6. 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.

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 the fourth quarter of 2015.

The study will comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/European Commission and its refinement provided in Chapter I.7 Section 1 of Volume 9A of the Rules Governing Medicinal Products in the EU: Guidelines on Pharmacovigilance for Medicinal Products for Human Use (European Commission 2008), and referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use's Pharmacovigilance Planning (ICH 2004) and the Guideline on Good Pharmacovigilance Practices, Module VIII—Post-Authorisation Safety Studies (EMA 2012).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Definitions

11.1.1 Definition of adverse events

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

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

11.1.2 Definition of serious adverse event

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

- Death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

11.1.3 Definition of adverse drug reactions

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

- the use of a medicinal product within the terms of the marketing authorisation

- the use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse, and medication errors

- occupational exposure

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

11.2 Collection of adverse events

No active collection of AE data will be performed in this study. However any serious ADR that is inadvertently discovered and has an identifiable patient must be reported, including the study number, to the Patient Safety Designated Entry Site by fax, unless the original report was from an AZ-sponsored study. (One or more of the following qualifies a patient as identifiable: sex, age [or category, for example “elderly”], date of birth, initials, hospital, or other identifying number.) In order to be classified as a serious ADR, the serious criteria must be met, and the medical record should clearly indicate that the treating physician considered there to be a possible causal relationship between the AE and the AZ product. If the medical records do not include a statement regarding causality there is no requirement to report the event.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final, approved protocol will be registered with the ENCePP. As agreed with the regulatory authority, study results will be provided in the form of progress reports starting in 2016 through 2022.

Progress reports will be provided as part of periodic safety update report (PSUR) procedures and will include for both NIC and CRC patient recruitment status, descriptive statistics on baseline characteristics, and accumulated event counts. 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 submitted in Q4 2019 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. 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-Authorization Safety Study (PASS) of MOVENTIG® (Naloxegol) Among Patients Aged 18 Years and Older Diagnosed with Non Cancer Pain and Treated with Opioids Chronically

Study reference number:

D3820R00009

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[4]	☒	☐	☐	12
1.1.2 End of data collection[5]	☒	☐	☐	12
1.1.3 Study progress report(s)	☒	☐	☐	12
1.1.4 Interim progress report(s)	☒	☐	☐	12
1.1.5 Registration in the EU PAS register	☒	☐	☐	12
1.1.6 Final report of study results.	☒	☐	☐	12

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk	☒	☐	☐	12-14

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
management plan, an emerging safety issue)				
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	14-16
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	14

Comments:

This is a descriptive study with no formal comparisons planned.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	14-15
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	14,19-20
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)	☒	☐	☐	15,26-28

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15-16,25-26
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	12
4.2.2 Age and sex?	☒	☐	☐	16-17
4.2.3 Country of origin?	☒	☐	☐	15-16
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☒	☐	☐	16-17
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)	☒	☐	☐	16-17

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**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	14,15
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	21,22,27
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	15,25

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	18-19
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	29-30

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	19-20
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	20,25-26,47-48

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	21-24
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	21-24

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	15-16,25-26,47-48
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.)	☒	☐	☐	15-16,25-26,47-48
8.1.3 Covariates?	☒	☐	☐	15-16,25-26,47-48
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)	☒	☐	☐	15-16,25-26,47-48
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	15-16,25-26,47-48
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	15-16,25-26,47-48
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	20,25-26,47-48
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory	☒	☐	☐	20,25-

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
Activities (MedDRA) for adverse events) 8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	26,47-48 20,25-26,47-48
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	25-26,47-48

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	26-28

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	29-31
10.3 Are descriptive analyses included?	☒	☐	☐	29-30
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	30-31
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	30-31

Comments:

No stratified analyses, instead exposure groups and sub-populations are considered, and no formal comparisons planned.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	31
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	29
11.3 Are methods of quality assurance described?	☒	☐	☐	31
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	31-32
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	

Comments:

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

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	31-32
12.1.2 Information biases?	☒	☐	☐	31-32
(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)	☒	☐	☐	17,26-28
12.3 Does the protocol address other limitations?	☒	☐	☐	31-32

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	33
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	29-31

Comments:

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

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	35
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	35

Comments:

Name of the main author of the protocol: ____ Robert J LoCasale _____

Date: 31/07/2015

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 Organization (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 dispensings 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 dispensings from the hospital pharmacy given during a hospitalization. The dispensing records include information on type of drug, start and end date of use, strength, dosage regimen, and route of administration. Drug dispensings 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.

Hospitalization Database

The Hospitalization 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 southeastern part of the Netherlands. Trained registry personnel subsequently actively collect onsite data, including cancer diagnosis, tumor staging, comorbidity at diagnosis, and treatment received directly after diagnosis (eg, chemotherapy [yes/no], radiation therapy, and surgery). Staging of cancer is categorized according to the TNM-classification developed and maintained by the Union for International Cancer Control. Tumors 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 subcohort of the PHARMO Database Network (approximately 1.2 million residents). For more information, visit www.netherlandscancerregistry.nl.