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US PMR Protocol (Final)

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United States Post-Marketing Observational Cardiovascular Safety Study in Patients taking Naloxegol

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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
CMS	US Center for Medicare and Medicaid Services
FDA	US Food and Drug Administration
HIRD	HealthCore Integrated Research Database
ICD-10	International Classification of Diseases, 10th Revision
ICD-9	International Classification of Diseases, 9th Revision
MACE	Major adverse cardiovascular events
MEQ	Morphine equivalent units
MI	Myocardial infarction
NDI	US National Death Index
NNPAMORA	Non-naloxegol peripherally acting mu-opioid antagonist
OIC	Opioid-induced constipation
OTC	Over the counter
PAMORA	Peripherally acting mu-opioid antagonist
PDC	Proportion of days covered
PS	Propensity score
RP	Research Partner
SAP	Statistical analysis plan
SCC	Study Coordinating Center
VA	US Veterans Administration
VHA	US Veterans Health Administration

3. RESPONSIBLE PARTIES

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

Table 1 List of main responsible parties

Role	Name
Sponsor Epidemiologist	[redacted]
Sponsor Biostatistician	[redacted]
Sponsor Medical Science Director	[redacted]
Coordinating Investigator (HealthCore)	[redacted]
Coordinating Investigator (Baylor Scott & White/Central Texas Veterans Administration)	[redacted]
Coordinating Investigator (Veterans Health Administration)	[redacted]

4. ABSTRACT

4.1 Title

Naloxegol Post-Marketing Observational Safety Study

4.2 Rationale and background

Naloxegol (MOVANTIK™; AstraZeneca) was approved by the US Food and Drug Administration (FDA) for treatment of opioid-induced constipation (OIC) in patients with chronic non-cancer pain on 16 September 2014 and will be available in the United States in the second quarter of 2015.

Under Section 505 (o) of the Federal Food, Drug, and Cosmetic Act, FDA required that AstraZeneca conduct the following:

> A post-marketing, observational epidemiologic study comparing MOVANTIK™ (naloxegol) to other treatments of opioid-induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Specify concise case definitions and validation algorithms for the primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to MOVANTIK™ (naloxegol)-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, MACE risk among MOVANTIK™ (naloxegol) users relative to comparator(s) considering important potential confounders including lifestyle risk factors and over the counter (OTC) medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. For the MOVANTIK™ (naloxegol)-exposed and comparator(s), clearly define the

new user clean period, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least 12 months of MOVANTIK™ (naloxegol) exposure at the end of the study.

4.3 Research question and objectives

The overall research goal for this study is to provide additional data to characterize the safety of naloxegol in patients aged 18 years and older who do not have a diagnosis of cancer and who are treated with opioids chronically.

The primary objective is to assess the overall risk of major adverse cardiovascular events (MACE) among naloxegol-treated patients compared to that among patients on prescription non-peripherally acting mu-opioid antagonist (PAMORA) OIC treatment. The corresponding analysis is of a new-user cohort study that captures the occurrence of MACE in persons receiving naloxegol or comparison medications. The study takes place in actual-use settings in the US in which existing electronic data captures patient diagnoses, health care, and treatment. The occurrence of MACE in naloxegol-treated patients will be compared to the occurrence of MACE in medically-similar new users of other prescription-only treatments for OIC in the same settings, with both naloxegol-treated and comparison medication-treated patients being followed for as long as they continue on therapy.

In further pursuit of the primary objective, there will be a self-controlled study that follows all members of the new-user cohorts, including both new naloxegol users and new users of comparator products, for as long as data are available as the patients may go on or off treatment. A self-controlled study offers a complementary approach to the statistical control for the possible confounding effects of personal characteristics. Using the same data sources, this self-controlled design follows individuals from the time they finish their first course of treatment as new users for as long as the study continues. Patient treatment statuses are continuously updated since the treatment choices exercised by patients and their caregivers create extended periods of study time on and off naloxegol and possibly on and off other therapies for OIC. Comparisons of the occurrence of MACE occur within individuals and so are unaffected by differences between individuals, as in a crossover trial.

The first secondary objective is to assess the potential confounding effects of lifestyle risk factors on relative risk of MACE among naloxegol-treated patients compared with that among patients on other prescription non-PAMORA OIC treatment. The corresponding analysis is of a case-control study nested within the primary study population. All of the MACE "cases" will be matched to other members of the cohorts ("controls"). In cases and controls, the outpatient medical record will be abstracted for information on lifestyle risk factors. The case-control analysis will provide information on the presence and effect of lifestyle confounding factors that may be identifiable only by chart review.

Further secondary analyses will investigate the relative risks analyzed under an intent-to-treat paradigm over fixed time periods of membership in the naloxegol and comparator cohorts, relative risks for specific components of MACE, relative risks associated with new oral PAMORA agents other than naloxegol (non-naloxegol oral PAMORAs [NNPAMORAs]) that

may come onto the US market during the course of the study, and an exploration of the possible variations in risk associated with variations in the dose and timing of naloxegol dispensing in the case-control study.

4.4 Study design

4.4.1 Primary analysis – New-user cohort

This study will utilize a retrospective, new-user cohort design (Schneeweiss 2010). Although the study is planned into the future, it is "retrospective" in the sense that data collection always looks backward in time, using routinely generated medical records. The study period will start with the first use of naloxegol in each of the participating health systems. The Naloxegol Inception Cohort will consist of persons who are new recipients of naloxegol while chronically exposed to opioids, without a diagnosis of cancer and without prior use of methylnaltrexone bromide for subcutaneous injection (Relistor™). They will have received marketed drug in the course of ordinary clinical practice after authorization of the drug. A cohort of patients initiating lubiprostone or linaclotide with the same inclusion and exclusion criteria as the naloxegol patients will be used as a Concurrent Comparison Drug Cohort (the Concurrent Comparison Drug Cohort). Patients in the Concurrent Comparison Drug Cohort will be frequency-matched 1:1 to the patients in the Naloxegol Inception Cohort with the matching based on covariates recorded in the patient medical histories as summarized in deciles of a propensity score (PS). If oral NNPAMORAs will begin to be used in the health systems participating in this research, otherwise-eligible users of those agents will be included as separate new-user cohort members. The patients will remain under observation for the primary analysis for as long as they are on treatment with the study drug, have not experienced an outcome, and do not receive another study drug or a PAMORA. The main outcome measure will be the relative incidence of MACE in the naloxegol versus comparison cohorts. MACE cases themselves will be followed for as long as the data permit so that they can be fully characterized. The planned end of data accrual is in 2020.

As a method to control for individual characteristics that may confound the comparison of naloxegol with comparison therapies, a self-controlled analysis will be undertaken for all members of the new-user cohort. Observation will continue beyond the end of the first course of treatment. Each individual's observation time will be categorized on the basis of recorded drug dispensings into mutually exclusive exposure periods (naloxegol, no treatment, comparison drugs, oral NNPAMORAs); the MACE are associated with the exposure period during which each event occurs. Comparisons between treatments will be done within individuals so that no fixed personal characteristics that differ between individuals confound the treatment comparisons. The product of a self-controlled analysis is a relative incidence estimate very similar to that produced by a cohort-based proportional hazards analysis.

Cohort members to whom methylnatrexone bromide for subcutaneous injection is dispensed after entry into the new-user cohort study will be censored from both the cohort study and the self-controlled analysis at the date of first dispensing.

4.4.2 Secondary analysis – Nested case-control study for confounder assessment

A nested case-control study will include all cases of MACE (from the primary analysis) and a sample of the study population matched on follow-up and decile of baseline PS as controls. Classification of exposure to study drugs in the case-control study will correspond directly to that in the primary analysis so that the individuals in the cohort and case-control studies have the same exposure status as of the date of case occurrence for each case and for each case's matched controls. The medical records of cases and controls will be reviewed for lifestyle factors and use of over the counter (OTC) drugs. The analysis of the case-control data will follow the cohort analysis (MACE in association with naloxegol versus comparison drugs) with the addition of covariate adjustment for factors identified from chart review. There will be an exploratory analysis in the case-control study that examines timing and dose.

4.4.3 Secondary analysis – Relative risk in different components of MACE

In the new-user cohort study, secondary analyses will substitute individual MACE components (myocardial infarction [MI], stroke and cardiovascular death) for MACE overall as an endpoint.

4.4.4 Secondary analysis – Sensitivity analysis for fixed follow-up periods in an intent-to-treat analysis

Follow-up in members of the new-user cohort will be assessed over fixed follow-up periods without concern for discontinuation of study medications or switching between them. Censoring will occur only at a pre-defined calendar date for close of follow-up or because the cohort member has left the health system providing data. The fixed follow-up times to be considered are 1, 2, 4, 6, and 8 months.

4.4.5 Secondary analysis – Relative risk of MACE in users of NNPAMORAs

Oral PAMORAs other than naloxegol may be marketed in the US during the study period. If so, they will be added to the new-user cohort analysis as a separate exposure group.

4.5 Population

All patients in this study will be 18 years of age or older, and they will have had at least 6 months of continuous data available before they enter one of the new-user cohorts. During the 6-month baseline period before cohort entry, they will have received at least 90 daysof dispensed opioidsdispensed of opioids, of which in the 60 days before cohort entry there were at least 30 days of opioids dispensed at an average of at least 30 morphine equivalent units (MEQ) per day. Patients will have no evidence of active cancer; they will have no evidence in the electronic record of MACE; they will not have received methylnatrexone bromide for subcutaneous injection. At the time of the index dispensing of naloxegol or comparison drug, cohort members will furthermore be current users of a dispensed opioid. (Since diagnostic codes for OIC may not be consistently available, the receipt of opioids at least 30 MEQ per day and a prescribed treatment for constipation is in effect the operational definition of OIC for this study.)

4.6 Variables

MACE includes acute MI, stroke, and cardiovascular death. For each event and at each site, investigators will apply a screening definition for MACE based on diagnoses associated with hospitalizations and deaths in order to determine which records should be abstracted. An Adjudication Committee will specify in advance what information is to be identified in the medical records and will determine case status using medical record extracts and information from the US National Death Index (NDI) or other mortality registries. The Adjudication Committee will be blind to treatment status and operate independently under a Charter.

Treatment with a study drug (naloxegol or any comparison drug) is determined from pharmacy dispensing records. If there is a new dispensing for a different study drug, exposure to the previously dispensed drug stops as of the day of the new dispensing.

Covariates identified in the 6 months preceding cohort entry and used to form the PS will include at least all patient diagnoses that represent risk factors for the occurrence of MACE, duration and intensity of opioid use, diagnoses of constipation and its prescription treatments, and demographic factors.

Covariates abstracted from outpatient records in the case-control study will include lifestyle-related factors and OTC drug utilization as can be found in the outpatient records.

4.7 Data sources

The study is conducted in collaboration with 2 organizations with access to suitable populations for study and with demonstrated capacity in large-scale pharmacoepidemiologic safety research. The organizations are HealthCore, a unit of Anthem Blue Cross Blue Shield with data on large commercially insured populations in the US, and the US Veterans Health Administration (VHA), a large integrated health care system consisting of medical centers, ambulatory care, and community-based outpatient clinics for US veterans. These are referred to as “Research Partners” (RP) throughout the protocol. The RP will provide full scientific as well as technical and administrative staffing to carry out the research in their respective sites.

4.8 Study size

The non-inferiority hypothesis for this study is that the risk for MACE associated with current exposure naloxegol is less than 2 times the risk for MACE associated with current exposure to lubiprostone and linaclotide taken together as a group. A study comparing naloxegol-treated patients to an equal number of comparison drug recipients would require 88 MACE events to have a power of 90% to exclude a hypothesis that users of naloxegol experienced twice the incidence of MACE seen in the comparison drug users. Extrapolation from the past experience of chronic opioid users who have not received naloxegol suggests an expected MACE incidence rate of 1 per 100 person-years. The power requirements and the estimate of MACE incidence mean that a study with 4400 person-years of naloxegol use and 4400 person-years of comparison drug treatment would be required.

The RP have identified approximately 550,000 chronic opioid users without active cancer in 2013. The study is moving forward under the assumption that these data resources will be large enough and that chronic opioid use will continue to be common enough that they will provide information on the health experience of the required numbers of naloxegol users and comparison drugs by the end of 2020.

4.9 Analyses

Analyses for this study will be both descriptive and comparative. Demographic, clinical, and treatment characteristics will be summarized for both Naloxegol and Concurrent Comparison Drug Cohorts.

The primary endpoint is the relative incidence of MACE associated with naloxegol use as compared to use of lubiprostone or linaclotide and will be estimated by a proportional hazards regression in the new-user cohorts.

The self-controlled analyses of ongoing exposure patterns and the occurrence of MACE in members of the new-user cohorts are conducted using a conditional Poisson regression. The within-individual matching assures control for all patient features that are stable personal characteristics.

The case-control analyses consist of conditional logistic regression of the relative incidence of MACE as obtained from comparison of the MACE cases to their matched controls. The predictors are exposure to naloxegol or comparator, defined as in the primary analysis, and covariates drawn from medical record review. The case-control results provide information on whether the relative incidence estimate for primary endpoint is subject to confounding bias from lifestyle factors or the use of OTC drugs. The case-control results are not in themselves an endpoint.

The secondary new-user cohort analysis with fixed follow-up times will be carried out using a proportional hazards regression.

The secondary new-user cohort analysis including oral NNPAMORAs will be carried out using a proportional hazards regression.

The secondary new-user cohort for individual MACE endpoints (MI, stroke, cardiovascular death) will be carried out using a proportional hazards regression.

The exploratory case-control analysis of naloxegol dose and timing will use conditional logistic regression.

4.10 Milestones

The earliest possible index date for a patient could occur after the acceptance of naloxegol into the formularies of the health systems covered by the RP, likely to be in late 2015 or early 2016. The study will start when naloxegol is available for prescription and reimbursement within their respective health systems.

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Study milestones are listed in Table 2.

Table 2 List of study milestones and planned dates

Milestone	Planned date
Start of data collection	December 2015
End of data collection[a]	First half of 2022
Interim report of study progress report to FDA	First half of 2018
Final report of study results to FDA	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 88 MACE have occurred. The anticipated end of follow-up is in December 2020. The final report of study results to FDA is expected to be available in Q4 2023 due to a lag in chart abstraction and adjudication and in NDI linkage.

FDA – US Food and Drug Administration; MACE – Major adverse cardiovascular events; NDI – US National Death Index.

7. RATIONALE AND BACKGROUND

Naloxegol (MOVANTIK™; AstraZeneca) has been approved by the FDA for treatment of OIC in patients with chronic non-cancer pain and will be available in the US in the second quarter of 2015.

In addition to the routine pharmacovigilance activities (which include regular analysis of spontaneously reported post-marketing safety data), AstraZeneca has agreed to conduct this post-authorization observational safety study in response to an FDA request that it monitor the occurrence of certain events in users of naloxegol.

8. RESEARCH OBJECTIVES AND QUESTIONS

The overall research goal for this study is to provide additional data to characterize the safety of naloxegol in patients 18 years of age or older without a diagnosis of cancer who are treated with opioids chronically. The investigation will capture the occurrence of MACE in persons newly receiving naloxegol in actual-use settings in which there are electronic data on patient diagnoses, health care, and drug treatment. What is observed in naloxegol-treated patients will be compared to the occurrence of MACE in medically-similar persons treated with lubiprostone or linaclotide in the same settings followed for similar amounts of time. The criteria for similarity used to construct the compared groups will include diagnoses that

correspond to cardiovascular risk factors, laboratory data when available, the duration and intensity of opioid use, records of constipation and its treatments, and demographic factors.

Users of oral NNPAMORAs will be included in the study as the drugs come on to the US market. The inclusion of oral PAMORAs other than naloxegol may help elucidate possible class effects of PAMORAs. Persons with a dispensing of the injectable PAMORA methylnaltrexone bromide in the 183 days prior to cohort entry will be excluded from the new-user cohorts, and persons who receive methylnaltrexone for subcutaneous injection after cohort entry will be censored on the day of dispensing.

Chronic opioid use and use of prescription laxatives rather than OIC is taken as an entry criterion for the cohorts because OIC itself may not be consistently recorded in the data sources available for the study.

To achieve statistical power to reject a hypothetical doubling of risk for MACE in current naloxegol users when compared to current users of comparison products (the non-inferiority hypothesis), the study will enroll a sufficient number of patients and observe them long enough to provide 4400 person-years of observed naloxegol treatment. There will be a similar amount of observation time in patients treated with either lubiprostone or linaclotide. The study will moreover target at least 1000 naloxegol users with at least 12 months each of observed naloxegol treatment time.

8.1 Primary objective

Primary objective: To assess the relative risk of MACE among naloxegol-treated patients compared with that among patients on prescription non-PAMORA OIC treatment.

Cohort designs are ideally suited for generating safety data in a prospective way within a single study for multiple outcomes of interest, given their ability to collect large sample sizes of longitudinal patient data within electronic health records. Utilization of prescribed medications, such as opioids, naloxegol and comparison drugs, is well captured, as are the endpoints. A new-user design coupled with use of a Concurrent Comparison Drug Cohort allows for adjustment of risk factors for outcome or predictors of treatment prior to drug initiation. The new-user design establishes a clear index date for a treated patient without introducing factors related to surviving after treatment initiation and allows for more efficient production of safety information on a given product in the post-market setting.

In further pursuit of the primary objective, there will be a self-controlled study that follows all members of the new-user cohort for as long as data are available during which time the patients may go on or off treatment with any of the study drugs. A self-controlled study offers a complementary approach to the statistical control for the possible confounding effects of personal characteristics. Using the same data sources, this self-controlled design follows individuals from the time they exit the new-user cohort for as long as the observation time continues. Patient treatment statuses are continuously updated since the treatment choices exercised by patients and their caregivers create extended periods of study time on and off naloxegol and possibly on and off other therapies for OIC. Comparisons of the occurrence of

MACE occur within individuals and so remove the effects of inter-individual differences, as in a crossover trial.

8.2 Secondary objectives

8.2.1 Case-control study to assess the impact of lifestyle factors

The first secondary objective is to assess the potential confounding effects of lifestyle risk factors and OTC medications on the relative risk of MACE among naloxegol-treated patients compared with that among patients on other prescription non-PAMORA OIC treatment.

There will be a secondary case-control study nested within the primary study cohorts. All of the MACE observed in the new-user cohorts will be the cases, and matched controls will be chosen from persons under observation at the time since cohort entry that each case occurs. In both cases and controls, the outpatient medical record will be abstracted for the required supplementary information.

The case-control data will also permit an exploratory analysis of the dose and timing of naloxegol versus comparison drug exposure in relation to the occurrence of MACE.

8.2.2 Relative risk for individual MACE components

In the new-user cohort, the risk of each component of MACE (ie, cardiovascular death, MI, and stroke) among naloxegol-treated patients will be compared with that among patients on prescription non-PAMORA OIC treatment.

8.2.3 Sensitivity analyses for fixed follow-up periods

Follow-up in members of the new-user cohort will be assessed over fixed follow-up periods without concern for discontinuation of or switching between study medications. Censoring will occur only because of a pre-defined calendar date for close of follow-up or because the cohort member has left the health system providing data. The fixed follow-up times to be considered are 1, 2, 4, 6, and 8 months.

8.2.4 Relative risk of MACE in users of NNPAMORAs

Oral PAMORAs other than naloxegol may be marketed in the US during the study period. If dispensings for any oral NNPAMORAs appear in any of the participating health systems, those drugs will be added to the new-user cohort analysis as a single separate exposure group.

9. RESEARCH METHODS

9.1 Study design

9.1.1 New-user cohort study

9.1.1.1 Overview

This study utilizes a retrospective, new-user cohort design (Schneeweiss 2010). Although the study is planned into the future, it is "retrospective" in the sense that data collection always looks backward in time using routinely generated medical records. All recipients of naloxegol who will be followed in this study (the Naloxegol Inception Cohort) will have received marketed drug in the course of ordinary clinical practice after authorization of the drug. The cohort members will meet entry criteria applied over the preceding 6 months of having chronic opioid use (at least 90 days of opioid dispensed in the preceding 183 days, of which at least 30 days at an average of at least 30 MEQ per day in the preceding 60 days), no active cancer, no evidence for MACE, and no use of methylnaltrexone bromide for subcutaneous injection. At the time of the index dispensing of naloxegol or comparison drug treatment, cohort members will be current users of a dispensed opioid.

If oral NNPAMORAs begin to be used in any of the health systems participating in the study during the time of cohort accrual, new users of oral NNPAMORAs who are otherwise eligible cohort members will be brought into the new-user cohort.

A cohort of patients initiating lubiprostone or linaclotide who also meet the entry criteria will form the Concurrent Comparison Drug Cohort. Patients in the Concurrent Comparison Drug Cohort will be frequency-matched 1:1 based on deciles of a PS that capture the relation between treatment choice and covariates observed in the patient medical histories. Identification of the index prescription date, the definition of "new user," prior drug use and diagnoses, the calculation of duration of continuous exposure for the Concurrent Comparison Drug Cohort, follow-up, and handling of missing or erroneous data will use the same logic as that for the Naloxegol Inception Cohort.

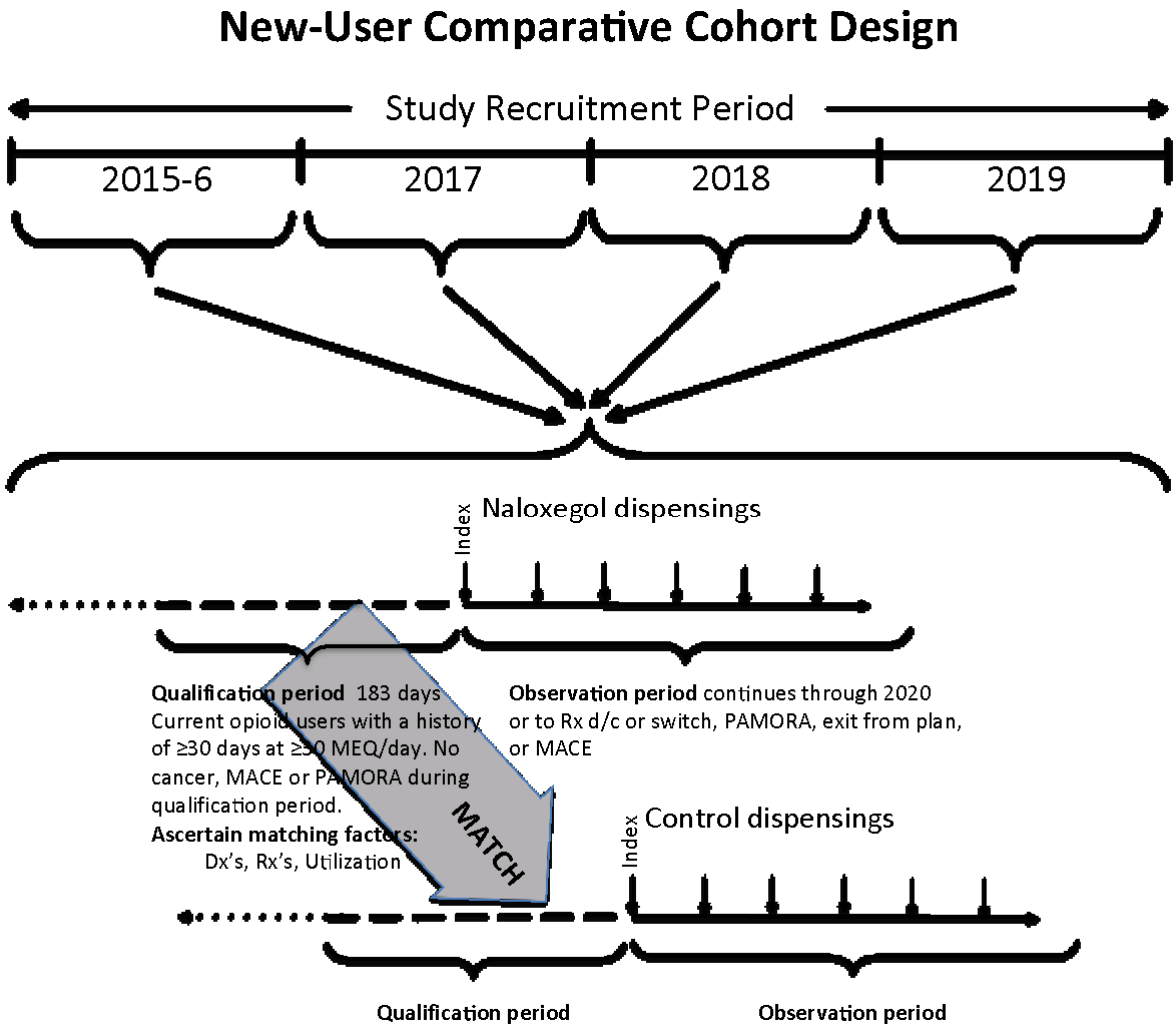
Members of the Naloxegol Inception Cohort and the Concurrent Comparison Drug Cohort will remain under observation for the primary analysis for as long as they are on.treatment with the study drug that led to cohort entry and do not receive another study drug or a PAMORA. Follow-up will extend up to the first occurrence of a specific component for the secondary analyses of individual MACE components.

The study period will begin on the date of first formulary availability of naloxegol within each health system. The study period will extend with each annual refresh of the database. Since this 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. The anticipated end of follow-up is in 2020. The time for case identification, chart reviews for case adjudication as well as for covariate assessment in the case-control study,

adjudication itself, and linkage to the NDI extends retrospective data collection activities into the second half of 2022.

The outcome measure in this study is the occurrence of MACE summarized as the relative incidence on treatment in naloxegol versus comparison drugs estimated from a proportional hazards model. The new-user comparative cohort design is shown in Figure 1.

Figure 1 New-user comparative cohort design



If new users of NNPAMORAs enter the study, they will be followed just as the naloxegol patients are.

9.1.2 Implementation

For naloxegol and the comparison drugs, persons 18 years of age or older with a new dispensing after at least 183 days of membership in the contributing health plan will be identified. To qualify as a new dispensing, there will have been no prior dispensing of the same drug during the preceding 183 days. This is the "index dispensing."

All persons with any of the following conditions in the 183 days preceding the new dispensing will be excluded: (a) a cancer diagnosis associated with medical care; (b) occurrence of conditions meeting the screening criteria for MACE in the electronic record; or (c) dispensing of methylnaltrexone bromide for subcutaneous injection.

For each calendar year of patient accrual, the propensity-matched cohorts will be formed as follows and these annual steps of cohort formation are done as the study progresses in order to permit that accrual reports include the ongoing results of matching and time on treatment:

- Regression analysis to predict treatment (PS model)

  Consider lubiprostone and linaclotide as a single entity, called "comparison drug treatment." Undertake a logistic regression analysis in which the dependent variable is naloxegol versus comparison drug treatment and all of the patient characteristics described in Section 9.3.3 "Covariates for the cohort study" are predictors. These include risk factors for MACE, measures of opioid use duration and intensity, diagnoses related to constipation, and demographic factors. Reduce the model by backwards elimination, retaining variables for which the p-value associated with discarding would be ≤0.1. To facilitate later analyses restricted to persons with no prior use of lubiprostone or linaclotide, retain in the regression the indicator variable for these prior exposures even if it does not qualify through its associated p-value for removal. For the final model, obtain the C-statistic, the Hosmer-Lemeshow goodness-of-fit chi-square (Hosmer and Lemeshow 1980), and the pseudo-R^2. (The pseudo-R^2 is the fractional reduction in the deviance between an intercept-only model and the final model with covariates).

- Matching

  Create 10 matching strata based on the deciles of the distribution of PS distribution in naloxegol initiators. For each stratum so defined, ascertain all initiators of comparator drugs with a PS in that stratum, and select at random a number of comparator-drug initiators equal to the number of naloxegol initiators in that stratum. Study-eligible initiators of lubiprostone or linaclotide are expected to greatly outnumber initiators of naloxegol during the period of the study, and, therefore, it should be possible to obtain an equal number of matched comparators in all strata. If there were unexpectedly a deficit of comparators in a stratum, the stratified analyses proposed remain valid.

- Inclusion of new oral NNPAMORAs

  NNPAMORAs were not on the US market at the time of protocol preparation so their representation in the new-user cohort study will be initially zero. At least at first, after market numbers will be too small to permit calculation of an NNPAMORA-PS.

As oral NNPAMORAs come onto the market and while the cumulative numbers of eligible NNPAMORA recipients across all centers total fewer than 1000, eligible users will be added to the strata defined by deciles of the naloxegol PS. That score is calculated for NNPAMORA entrants by ascertaining their covariate values for each of the covariates retained in the PS, multiplying the values by the corresponding coefficient from the naloxegol PS, and adding the intercept term from the naloxegol PS. If the patient factors that distinguish oral NNPAMORA use from lubiprostone/linaclotide are similar in the magnitude of their discriminating effect to those that distinguish naloxegol use from lubiprostone/linaclotide, the distribution of these factors will be the same in the oral NNPAMORA users and the naloxegol users. Direct comparisons between naloxegol and oral NNPAMORAs users would therefore not be confounded by any of the identified covariates. Stratification by deciles of the naloxegol PS will provide the same level of confounder control versus lubiprostone/linaclotide as for naloxegol so all two-way comparisons are estimable to the extent that the numbers of users permit.

The distribution of covariates across exposed groups, standardized over the strata, will be checked at the interim and final analyses. The final analysis will add control for covariates shown to be out of balance between oral NNPAMORA initiators and their stratum-matched comparators.

- Assess covariate balance

  Tabulate the prevalence of each patient characteristic in the Naloxegol Initiator Cohort and the Concurrent Comparison Drug Cohort. If the standardized difference of naloxegol versus control is 0.1 or greater, introduce into the propensity model interaction terms between the covariate(s) so identified and each other retained characteristic, and redo the regression, variable reduction, and matching of the preceding section. If imbalances remain for any baseline covariates, these should be noted. Section 9.6.8describes the general procedure for adjusting for residual differences between compared cohorts.

  If either the pseudo-R^2 or the C-statistic exceeds 0.85, reexamine the covariates in the PS for terms that may be administrative predictors of treatment and that are unlikely to be predictors of MACE. Remove these from the model, and repeat the steps of model-fitting, matching, and assessment.

9.1.3 Nested case-control study for confounder assessment

For each adjudicated MACE, the RP will calculate the number of days elapsed from cohort entry until the occurrence of MACE. To serve as controls, there will be 4 members of the compared cohorts combined (Naloxegol Inception Cohort plus the Concurrent Comparison Drug Cohort) who entered the study in the same year as the MACE case, who were under observation on the same follow-up day, and who furthermore had a PS in the same decile group as the case. Among persons meeting these criteria, 4 will be selected at random to serve as matched. If there are only 3, 2, or 1 available, all will be taken. If no matching controls are

available, the unmatched case will be retained for separate presentation of his/her exposure and covariate status.

The outpatient medical records of cases and controls will be abstracted for the preceding 183 days for lifestyle factors and use of OTC drugs.

9.1.4 Self-controlled design

As a complementary method to control for confounding factors, a self-controlled analysis (Maclure et al 2012; Whitaker et al 2006) will be undertaken for members of the new-user cohort with observation beginning at the time of exit from the new-user cohort.

The present self-controlled analysis is right-censored at the time of the first MACE event and avoids the reverse-causality bias that can be of concern in self-controlled designs that include post-event exposures. Eligible time begins at a definite moment that is observable in all persons (exit from the new-user cohort), thus avoiding immortal person-time bias when observation reaches back into periods before cohort entry. Late naloxegol use in persons who were originally in the new-user cohorts as comparator is included. Since all the person-time in the analysis occurs after the conclusion of participation in the new-user cohort, estimates of relative risks for study drugs derived from the self-controlled study are entirely complementary to those derived from the new-user cohort.

The elements of the complementary analysis that are distinct from the primary analysis are as follows:

1. All available follow-up time is included.

   In the primary analysis, the new-user cohort members are under observation for as long as they remain on treatment provided that they do not receive another study drug or methylnaltrexone bromide for subcutaneous injection and do not experience MACE. In the self-controlled secondary analysis, patients remain under observation for as long as data are available. With continued follow-up after discontinuation of the initial treatment regimen in the self-controlled analysis, subjects may remain off of study drugs altogether, or they may reinstitute or switch therapy for possibly many distinct time periods. The time in each treatment state, (naloxegol, lubiprostone/linaclotide, or an oral NNPAMORA) is monitored throughout.

2. For the purposes of analysis, there is a stratification of the study data at the level of the individual.

   Conducting the analysis with stratification at the level of the individual means that

   a. All comparisons between treatments are done within individuals.

   b. No fixed characteristics that differ between individuals confound the treatment comparisons.

c. Individuals for whom there turns out to be no change in treatment status over follow-up time effectively drop out of the estimates because there are no possible within-person treatment comparisons.

d. Individuals who do not experience MACE during follow-up effectively drop out of the estimates because all treatments within individual have the same zero risk.

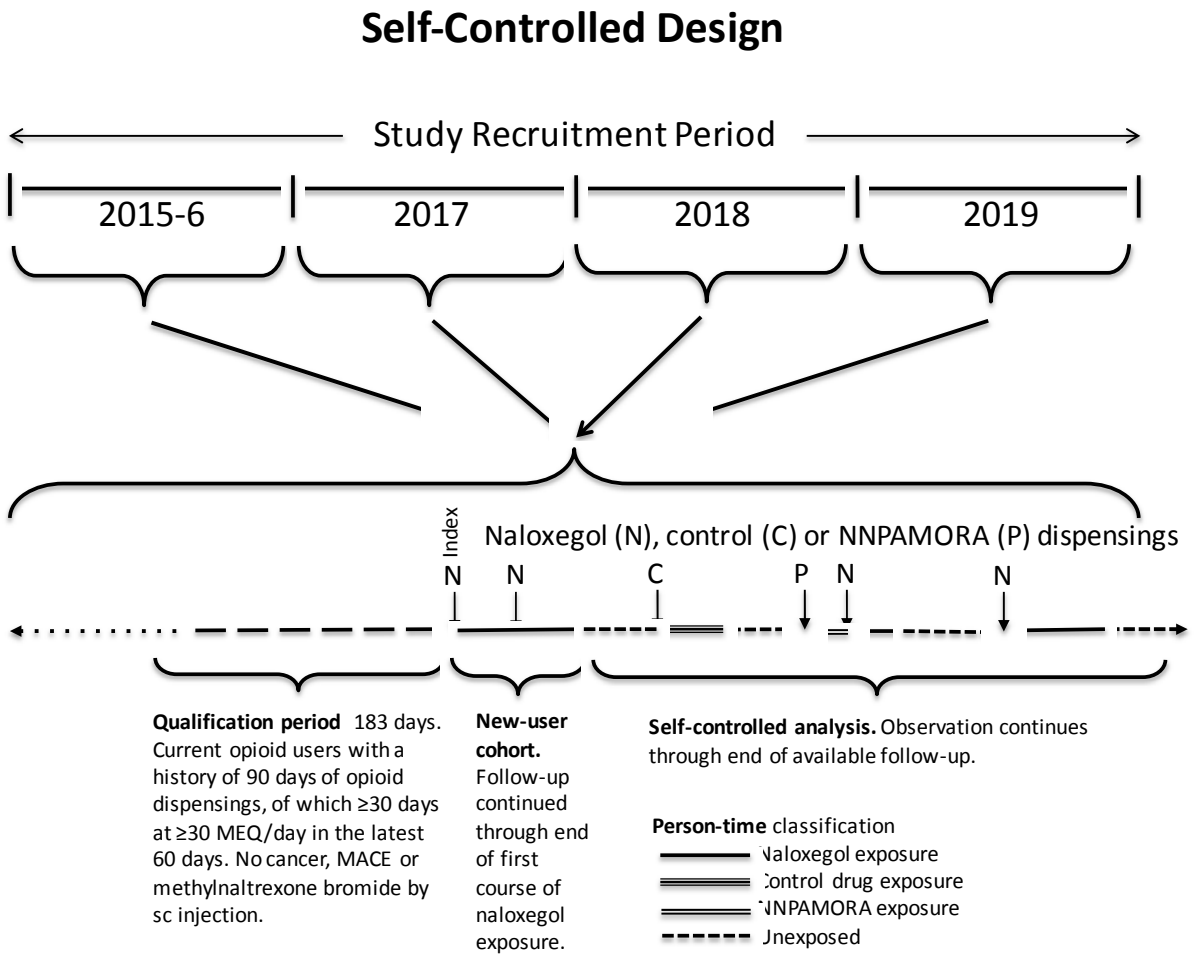
The analysis is "self-controlled" because of consideration 2a above, and it is often referred to as a "case series" because of consideration 2d above. Self-controlled designs are particularly robust in the face of unmeasured differences in risk factors between individuals.

The product of a self-controlled analysis is a relative incidence estimate very similar to that produced by a cohort-based proportional hazards analysis. A distinction is that the estimate is based only on persons with variable exposure and on those who eventually develop the outcome under study. If there is variation in the underlying risk over the population, those who participate in the analysis will come on average from the higher risk strata.

When outcome events terminate follow-up, as they do in this study, the self-controlled analysis described here is closely related to a case-crossover study in which the last day of observation in persons experiencing an event is taken as the "case" window, and each preceding day of observation is a separate "control" window. The self-controlled design is shown in Figure 2 for an illustrative patient. Follow-up for the self-controlled study begins after the patient, in this example a naloxegol user, exits the new-user cohort. After concluding naloxegol exposure, per section 9.3.1, the person illustrated enters the self-controlled analysis with a period of non-exposure followed by use of a comparator drug, non-use of any study drug, use of an NNPAMORA, and further use of naloxegol, which is itself intermittent.

In general and outside of this example, use of any of the study drugs might follow exit from the new-user cohort, and the exposures or non-exposure could occur in any sequence.

Figure 2 Self-controlled design



9.2 Setting

This protocol will be implemented at HealthCore and the US Veterans Administration (VA). These 2 resources maintain high quality repositories of longitudinal patient data that allow for good capture of exposure and outcome among populations that are utilizers of opioids. The expected launch dates for naloxegol will depend on the health system. Assessment of target sample size goals and progress toward these goals will be assessed annually based on actual naloxegol uptake.

For both the Naloxegol Inception Cohort and the Concurrent Comparison Drug Cohort, the date that each patient meets all of the inclusion criteria and none of the exclusion criteria will be his/her index date.

9.2.1 Inclusion criteria

Patients who enter 1 of the study cohorts must meet the following inclusion criteria:

1. Patient receives a new dispensing of naloxegol, lubiprostone/linaclotide, or an oral NNPAMORA.[1] A new dispensing is one that occurs with no dispensing for the same drug having occurred in the preceding 182 days. A patient only qualifies once under this criterion for any drug.

2. Patients 18 years of age or older at the index date

3. Continuous availability of data for at least 183 days immediately before and including the index date

4. 90 days of opioid dispensed in the 183 days before and including the index date of which at least 30 days of opioid dispensed at at least 30 MEQ/day in the 60 days before and including index date

5. Current users of a dispensed opioid, meaning that the interval between index study drug dispensing and at least 1 prior opioid dispensing is less than the days supply associated with the opioid dispensing

9.2.2 Exclusion criteria

Patients will be excluded from either the Naloxegol Inception or Concurrent Comparison Drug Cohorts if they meet any of the following criteria:

1. Any medical care associated with a diagnosis of cancer in the 183 days before and including the index date; a diagnosis of cancer for this purpose is any diagnostic code of International Classification of Diseases, 9th revision (ICD-9) in the range 140-208 “Malignant neoplasms …” or of the 10th revision (ICD-10) in the range C00-C96, “Malignant neoplasms”

2. Dispensing of methylnaltrexone for subcutaneous injection in the 183 days before and including the index date

3. Indication in the electronic records of the occurrence of MACE in the 183 days before and including the index date; see Section 9.3.2 “MACE” for screening criteria

[1] Lubiprostone is indicated for the treatment of OIC. Linaclotide, a guanylate cyclase-C agonist indicated for the treatment of constipation-predominant irritable bowel syndrome and chronic idiopathic constipation, may be used off-label for OIC. Other prescription products that have been suggested for the off-label treatment of OIC include lactulose, colchicine, misoprostol, Orlistat, and polyethylene glycol. Use of these products will be noted in as covariates to be balanced in cohort formation. If other treatments become standard therapy for OIC during the period of this study, the definition of the comparator group may need to be amended.

9.2.3 Follow-up

For the new-user cohort study, follow-up continues as long as there is continuous time on-treatment (see Section 9.3.1) for the study drug that defined cohort entry, allowing for all lengths of exposure duration to contribute. Follow-up ends at the first occurrence of MACE. Administrative censoring for all analyses occurs at the date of last available data. Last available data may occur because (1) the patient has reached a pre-specified calendar date for end of follow-up or (2) the patient has exited from the RP health system.

In the secondary intent-to-treat analyses with fixed follow-up periods, follow-up continues until the earlier of the end of the follow-up period or date of last available data.

For the secondary analyses of individual MACE components, follow-up will extend up to the first occurrence of each specific MACE component.

For the self-controlled analysis of persons who exit the new-user cohort, observation continues for as long as data are available or until the occurrence of MACE.

9.3 Variables

9.3.1 Exposure

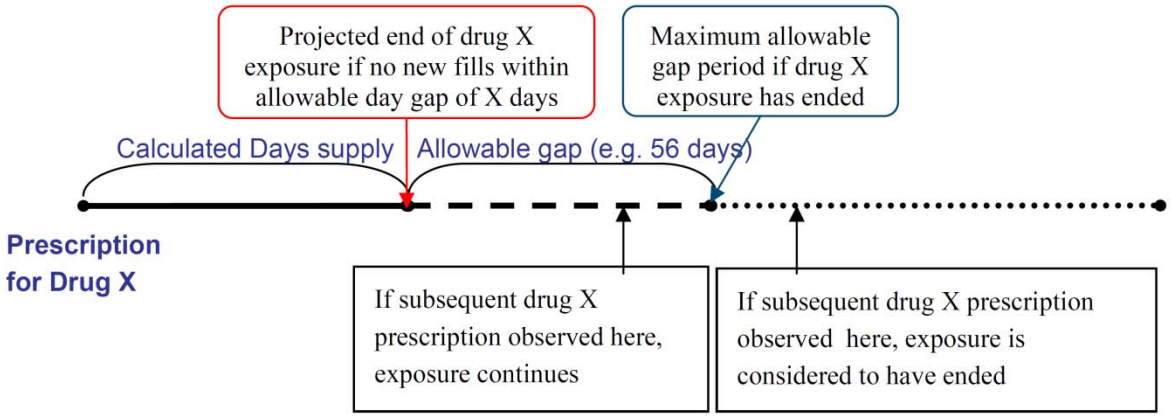
Exposure to naloxegol or the concurrent comparison drug treatment will start with the index dispensing.

Exposure for naloxegol, the concurrent control treatments, and oral NNPAMORAs will continue from the date of dispensing through 3 times the number of days supply available at the dispensing. The number of days supply available at a dispensing is the number of days dispensed plus any unused days dispensed from an earlier dispensing when the new dispensing occurs before the previous dispensing's days supply is exhausted. (The practice of carrying over previous unused medication still available at the time of a new dispensing is accounting for "stockpiling.") The logic for 3-fold multiplier is based on historical as-needed laxative-taking behaviors, which can result in the patient taking drug on the average of every third day to assure a successful bowel movement.

If there is a dispensing of a study drug other than the study drug that defined cohort entry, current exposure ends, and the patient is censored from the corresponding new-user cohort. Patients in the Concurrent Comparison Drug Cohort will be permitted to switch between lubiprostone and linaclotide and remain classified as continuous users.

End of exposure (ie, discontinuation) for naloxegol, the concurrent control treatments, and oral NNPAMORAs will be the date of the end of current exposure. 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 occurs, the end of exposure date will be on the 84th day in follow-up. An example of continuous drug exposure algorithm is shown in Figure 3.

Figure 3 Example of continuous drug exposure algorithm



In the primary analysis, exposure constitutes a single treatment episode after which membership in the new-user cohort is censored. If oral NNPAMORAs are included in the study, they will each similarly be represented by a single treatment episode in the primary analysis.

In secondary, intent-to-treat analyses, the new-user cohorts will be followed for periods of 1, 2, 4, 6, and 8 thirty-day months following cohort entry (30, 60, 120, 180, and 240 days). Subjects will remain in their initially assigned cohort throughout each of the follow-up windows and will not change exposure status as a consequence of discontinuation of the cohort-defining agent or with the initiation of other study drugs. End of available data will be the only reason for censoring.

In the self-controlled analysis, observation continues after the end of the first episode of exposure that defined cohort entry. The patient can enter a drug-specific exposure category at the time of another dispensing with an end date calculated as before on the basis of dispensing date(s) and days' supply. If a dispensing for a different drug occurs during what would be a period of exposure to any drug, the earlier exposure period terminates on the preceding day, and exposure to the new drug begins on the day of dispensing. If there is no current exposure (in the sense defined in Section 9.3.1) to any of the study drugs, the person-time will be classified as "unexposed."

9.3.2 Outcomes – MACE

In its charter, the Adjudication Committee will set criteria for each of the MACE conditions, including inclusion and exclusion factors.

Each year, the RP will abstract records of persons with the code combinations suggesting MACE (given below) in all follow-up time of persons who enter the new user cohorts. Identification of these records is not restricted to the times while individuals are in the primary analysis. Later-occurring events enter into the self-controlled study as well. The RP will transmit the abstracts to the Study Coordinating Center (SCC), which will in turn organize evaluation by the Adjudication Committee. If there are multiple MACE for a subject, the RP

will seek information on all events. Each year, 10% of the records abstracted in the previous year will be abstracted a second time by a different abstractor who will not have reviewed the earlier abstraction. The RP will submit these second abstraction forms to the SCC.

On the basis of abstracted medical records and results from the NDI, the Adjudication Committee will determine that each case

1. Meets its criteria for MACE and, if so, whether the case is MI, stroke, or cardiovascular death.

2. On the basis of sufficient information, does not meet criteria for MACE, or

3. Has insufficient information available for determination.

For cases in categories (1) and (2), the Adjudication Committee will specify which of its criteria are met and not met, and, for cases in category (3), the Adjudication Committee will make a recommendation as to what further records the RP might usefully seek to provide necessary information for adjudication. The Adjudication Committee will determine a date of onset for each case meeting its criteria.

If the Adjudication Committee's assigned status for any re-abstracted case differs from the initially assigned status, the Adjudication Committee, the SCC, and the RP will review together all available information and arrive at an ad hoc adjudication of case status and will determine what aspects of case identification, chart abstraction, and case review need to be adjusted going forward. They will also seek to establish whether proposed changes in procedure would affect any already-adjudicated case.

The screening criteria for selecting records for adjudication are as follows:

- MI

  Electronic records for all cohort members will be examined for the occurrence of ICD-9 hospital discharge codes of 410xx (acute MI) or ICD-10 hospital discharge codes of I21xx (ST elevation and non-ST elevation MI).[2]

- Stroke

  Ischemic stroke will be identified using hospital claims for primary discharge diagnoses indicating potential stroke events (ICD-9-CM codes 433, 434, 436).[3] Following conversion to ICD-10, the codes I63xx (cerebral infarction) will be used.

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[2] Both the MI and cardiovascular death screening definitions here are more inclusive than those proposed by Selby and colleagues for Mini-Sentinel in "A Protocol for Active Surveillance of Acute Myocardial Infarction in Association with Use of Anti-Diabetic Agents. Version 4. January 8, 2014" (www.mini-sentinel.org/work_products/Assessments) in that they do not restrict terminal digits. Medical record review will ensure accuracy.

- Cardiovascular death

  The Mini-Sentinel criterion for cardiovascular deaths will be applied to the RP electronic data. This includes any deaths recorded as having occurred within 1 day of an emergency department encounter for acute ischemic heart disease (ICD-9 codes: 410, 411, 413).

  Note that hospitalizations whose discharge codes meet the screening criteria of MI or stroke and that have a discharge status of death will also have been captured under those screening criteria.

  For cohort members who terminate health plan enrollment at any time, RP will submit identifying information in confidence to the NDI following the NDI's procedure. NDI matching information will be attached to the de-identified study files and returned to the RP.

  The definition of cardiovascular death using results from the NDI will be an extension of criteria originally proposed for insurance claims and death index data by Cecelia Chung and colleagues, working with TennCare, the Tennessee Medicaid program (Chung et al 2010). Chung and colleagues identified ICD-10 categories for the death certificate's underlying cause of death that proved on chart review to correspond to sudden cardiac deaths in non-institutionalized persons.

Deaths from MACE confirmed in the medical record (from Adjudication Committee reviews conducted for MI, stroke, and the criterion based on emergency department use and an ICD code) will be cross-tabulated against NDI-derived MACE events to provide estimates as a metric for the completeness of capture from the NDI for those patients in the study population.

9.3.3 Covariates for the cohort study

Covariates included in the study are potential risk factors for MACE or possible predictors of choice of treatment for OIC. Covariates will be assessed for each new user of naloxegol or a control treatment as of the date of first dispensing and will be used for descriptive analyses and for PS development. Each of the diagnosed conditions below will be represented by the corresponding ICD-9 or ICD-10 codes as appearing in association with health care encounters or as hospital discharge diagnoses. Drugs and drug groups will be derived from drug classification schemes available for each of the RP. Laboratory values as available will be derived from the coding systems in effect with each of the RP. Refer to Table 3 for patient characteristics.

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[3] See "A Protocol for Assessment of Dabigatran. Version 2. March 18, 2014" (www.mini-sentinel.org/work_products/Assessments). Mini-Sentinel investigators assert that more restrictive versions of these codes that limit the 5th digit have a positive predictive value of 83%.

Table 3 Patient characteristics for matching and description ascertained in 6 months leading up to cohort entry or at the time of cohort entry

Demographic characteristics		
Gender	Age	Geographic indicator
Time characteristics		
Total prior time in health system (time from start of data to index date)		
Calendar year of cohort entry		
Prior OIC diagnoses and treatment and prior opioids		
Constipation diagnosis and procedures for treatment of constipation		
Any dispensing of lubiprostone or linaclotide (yes/no)		
Days dispensed of lubiprostone, linaclotide		
Days dispensed of lactulose, colchicine, misoprostol, Orlistat, and polyethylene glycol.		
Days dispensed of opioids		
Average MEQ/day opioids		
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; Chronic liver disease; 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, dissociative and somatoform disorders; Adjustment reactions; Bipolar disorder; Substance abuse; Schizophrenia; Other psychiatric disorders; Depression	
Renal Disease	Chronic renal failure; Chronic renal insufficiency; Renal/Urinary tract infections	

Table 3 Patient characteristics for matching and description ascertained in 6 months leading up to cohort entry or at the time of cohort entry

Pain conditions	Arthritis, Back pain, Fractures; Headaches; Musculoskeletal; Neuropathies; Wounds/Injury	
Miscellaneous	Gout; Hyperkalemia; Hypercalcemia; Morbid obesity; Smoking; Obesity; Charlson comorbidity index	
Clinical and biochemical measurements (where available)		
HbA1c	High density lipoprotein	Low density lipoprotein
C-reactive protein	Triglycerides	
Medication		
All drug classes appearing in at least 10% of the population and not otherwise listed in this table[a]		
Control treatment (lubiprostone or linaclotide) in the baseline period		
CYP3A inducer[b]		
CYP3A inhibitor[c]		
P-gp modulator[d]		
Healthcare resource utilization		
Number of hospitalizations		
Number of emergency department visits		
Number of outpatient physician visits		
Number of laboratory tests		

[a] Based on preliminary tabulations from the RP, these are likely to include at least: HMG CoA reductase inhibitors, proton pump inhibitors, antidepressants (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors), anticonvulsants, antibiotics (azithromycin, aminopenicillins, cephalosporins, fluoroquinolones), hypnotics, antihypertensives (ACE inhibitors, cardio-selective beta blockers, calcium channel blockers), non-salicylate NSAIDs, benzodiazepines, oral hypoglycemic agents, thiazide diuretics.

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

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

[d] Including amiodarone, azithromycin, captopril, clarithromycin, cyclosporine, piperine, quercetin, quinidine, quinine, reserpine, ritonavir, tariquidar, and verapamil.

ACE – Angiotensin converting enzyme; CYP3A – Cytochrome P 3A; HbA1c – Glycated hemoglobin; HMG CoA – 3-hydroxy-3-methyl-glutaryl-CoA; MEQ – Morphine equivalent units; NSAID – Non-steroidal anti-inflammatory drug; OIC - Opioid-induced constipation; P-gp - P-glycoprotein.

9.3.4 Covariates for the nested case-control study

For each MACE event, 4 members of the compared cohorts (Naloxegol Initiator Cohort plus the Concurrent Comparison Drug Cohort) under observation on the same follow-up day and

with the closest PS will be selected, and the outpatient medical record will be abstracted for the preceding 183 days.

Items to be abstracted will include

- Smoking status (most recent typical number of cigarettes smoked per day, approximate time since last regular smoking if not currently smoking, and duration of smoking).
- Body mass index (most recent, including qualitative descriptions if neither BMI nor height and weight are recorded).
- Reported activity level.
- Reported use of aspirin either for MI prophylaxis or as a supplementary medication for chronic pain.
- Use of analgesics obtained without a prescription, including OTC products and prescription or illicit opiates obtained from non-pharmacy sources.

To the extent consonant with the study goals, abstraction will use already developed and validated instruments. Existing instruments may be adapted to the available data, and new elements may be developed. These will be tested for replicability in the RP data, but will not be further validated.

9.4 Data sources

The populations from which the study cohorts are drawn will consist of persons served by HealthCore (Anthem Blue Cross/Blue Shield) or the VHA during the years 2015 through 2020.

9.4.1 HealthCore

HealthCore conducts industry-sponsored research in safety, health economic outcomes, comparative effectiveness, and epidemiology.

The HealthCore Integrated Research Database (HIRD) is a large administrative healthcare database maintained by HealthCore. The HIRD contains medical and pharmacy claims data from members of Anthem Blue Cross/Blue Shield health plans across the US. Member enrollment, medical care (professional and facility claims), outpatient prescription drug use, outpatient laboratory test results, and health care utilization may be tracked back to January 2006. The HealthCore Integrated Research Environment has the ability to link the claims data in the HIRD to inpatient and outpatient medical records, national vital statistics records, cancer and vaccine registries (state-by-state), disease and device registries, member and provider surveys, and point of care clinical data. Using these resources, HealthCore conducts retrospective database studies, medical record review studies, cross-sectional and longitudinal patient and provider surveys, and prospective site-based studies.

US commercial health insurers, such as Anthem Blue Cross/Blue Shield, keep transactional information that falls into the following broad categories:

1. Population descriptors

   Eligibility files provide dates of enrollment and exit from coverage and basic demographic information. These files also have personal identifying information that can be used, with appropriate permission, for linkage to external data sources.

2. Drug exposures

   Claims for reimbursement of all drugs dispensed include date of dispensing; the name, dose and form of the product dispensed; and the quantity dispensed.

3. Health Outcomes

   Hospitals and health care centers use the US Center for Medicare and Medicaid Services (CMS)-1450 form, previously known as the US Healthcare Financing Administration-1450 claim form or Uniform/Universal Billing form 92, when submitting bills to Medicare and third-party payers. Relevant fields on the CMS-1450 are patient and provider identifiers, patient characteristics, dates of service, a principal and other discharge diagnoses codes, procedures, admission diagnosis, and discharge status.

   All outpatient services are captured with billed diagnoses. Laboratory services do not have associated diagnoses.

4. Deaths

   In-hospital deaths are captured with great reliability on the CMS-1450 as 1 of the possible discharge status values. Out-of-hospital deaths may often be inferred from patterns of services (an ambulance service on the same day as an emergency visit with charges for resuscitation and the absence of further claims, for example). Full ascertainment of deaths is possible because the data resources retain full identifying information, which can be linked to the NDI.

9.4.2 Veterans Health Administration

The VA established the Center for Medication Safety in October 2003 to improve the safety of drug prescribing practices and medication administration. Its primary goals are to identify, track, and reduce preventable adverse drug events with an emphasis on active surveillance.

The VHA is a large, integrated health care system consisting of medical centers, ambulatory care, community-based outpatient clinics, extended care facilities, and several comprehensive home care programs. There is a VHA automated electronic health record as well as the National Patient Care Database that consists of the medical and clinical databases for all patients treated in the VHA.

The VHA's National Patient Care Database holds demographic data, hospitalizations, and outpatient visits and encounters that occur within the VA system. These include inpatient and outpatient information, medications, test results, and full text notes. All records of prescription drugs dispensed in the VA are captured. Laboratory test results are available as are the date and cause of death.

Prescription databases and disease coding have been extensively evaluated in VA for accuracy and quality. Medical charts are readily available to validate outcomes to confirm diagnosis when needed. The datasets are readily accessible and are used on a daily basis as part of the Center for Medication Safety efforts.

The VA's mortality files (Vital Status File and the Beneficiary Identification Records Locator System) will be used to identify deceased patients and the NDI will be used to obtain detailed death statistics.

9.4.3 US National Death Index

The NDI [4] is a computerized index of death records in the United States. The National Center for Health Statistics established the NDI as a resource to aid researchers with their mortality ascertainment activities. Records that provide the date, place, and causes of death, including both primary and underlying causes, are available upon application for statistical research in medicine and public health.

A national file of identifying death record information (beginning with 1979 deaths) is compiled each year from computer files submitted by vital statistics offices of the individual states. The NDI seeks to make these files available in the first half of the second year following deaths as they occur. Deaths from 2020 required to complete the planned reports should be in hand in 2022.

To obtain matching records, the user submits to the NDI a file containing all available elements of the identifying information for the individuals whose records are to be sought in the NDI. The NDI matches the identifying data to its death records and calculates a score that summarizes the quality of the match between a submitted record and records in the NDI files.

Tests of the NDI have consistently shown sensitivity in excess of 90% and nearly 100% specificity for identification of the deaths of US residents for whom Social Security Number and other identifying information are available (Boyle and Decouflé 1990; Fujita et al 2004; LaVeist et al 1996; Rich-Edwards et al 1994; Stampfer et al 1984; Williams et al 1992)

9.5 Study size

The non-inferiority hypothesis for this study is that the risk for MACE associated with current naloxegol exposure is less than 2 times the risk for MACE associated with current exposure to the comparison drugs, lubiprostone and linaclotide, taken as a group. With an objective of excluding a hazard ratio of 2, the study will continue until at least 88 MACE events have been

[4] See http://www.cdc.gov/nchs/ndi.htm for more information.

observed in the matched cohorts for the primary treated comparison. Schoenfeld's asymptotic power formula for a 2-sample log-rank test in a follow-up with proportional hazards and equal censoring in the compared cohorts is (Schoenfeld 1981)

$$D=(Z_{1-\alpha/2}+Z_{1-\beta})^2/[(\ln\rho)^2 P_1 P_0]$$

where D is the number of events that needs to be observed to produce a power of 1-β for a test with a rejection region of size α against an alternative hypothesis that the hazard ratio is ρ, assuming that treatments have been allocated in proportions P_1 and P_0.

For the present study with α=0.05, 1-β=0.90, ρ=2, and $P_1=P_0=0.5$,

$$D=88.$$

While 88 MACE events is the target and minimum number of events required to achieve 90% power, there will likely be more than 88 events in the final analysis database. Due to administrative time lags, some candidate MACE events may still be awaiting adjudication when the full complement of 88 adjudicated MACE events has been observed. Any potential cases that are in process when the study meets its recruitment goals will still be adjudicated and included in the analysis dataset if accepted as MACE.

There is no hypothesis test of a naloxegol effect planned for the analysis of individual MACE components and the case-control analysis.

Extrapolation from the past experience of chronic opioid users who have not received naloxegol suggests an expected MACE incidence rate of 1 per 100 person-years (Carman et al 2011). The power requirements and the estimate of MACE incidence mean that is expected in a study with 4400 person-years of naloxegol use and 4400 person-years of comparison drug treatment is adequate to produce the required number of cases.

The RP have identified approximately 550,000 chronic opioid users without active cancer in 2013. The study is moving forward under the assumption that these data resources will be large enough and that chronic opioid use will continue to be common enough that they will provide information on the health experience of the required numbers of naloxegol users and comparison drug users by the end of 2020.

9.6 Data analysis

The RP will submit to the SCC a de-identified analytic data set in an agreed format.

9.6.1 Statistical Analysis Plan

A global statistical analysis plan (SAP) will be developed to describe analysis approaches applicable across RP. The RP will develop detailed local SAPs to execute the analyses. The local SAPs address health-system-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. The RP will share their local SAPs with one another and with the SCC, which will hold them for possible review or audit by the Scientific Steering Committee and AstraZeneca.

9.6.2 General methods

All data analyses are based on all available information. All analyses will be stratified by RP.

For continuous variables, the number of observations, mean, standard deviation, median, interquartile range, and range will be presented; for categorical variables, the number and percentages of patients in each category will be presented.

9.6.3 Disposition

The number of subjects included in the database will be summarized for each treatment group and overall. The reasons for study discontinuation (ie, administrative censoring at the end of observation, discontinuation from participation in RP health system, MACE, or other death) will be tabulated.

9.6.4 Demographics and baseline characteristics

Demographic characteristics, diagnoses, drug dispensing, and health services as captured in the baseline period for the Naloxegol Inception Cohort and the Concurrent Comparison Drug Cohort will be summarized descriptively by year, by RP, and overall. Demographic characteristics include age, gender, and geographic region. Baseline clinical characteristics include all covariates identified in the PS calculations. See Section 9.1 for details.

9.6.5 Exposure

Exposure to naloxegol and comparison drugs will be summarized for each study year, each RP, and overall. Duration on and adherence to initial treatment and adherence during periods after initial treatment will be used to quantify exposure. For naloxegol and comparison drugs (treated as a single agent), duration on initial treatment extends from the first day through the last day of the on-treatment period. The adherence to treatment will be defined by proportion of days covered (PDC) over the course of (a) initial treatment and (b) succeeding calendar quarters for the entire duration of follow-up.

PDC will be calculated for each person as the number of days' supply dispensed divided by the number of eligible days over defined periods. Eligible days in the initial treatment course extend from a cohort member's index day for as long as treatment is uninterrupted. Eligible days for each calendar quarter after exit from initial treatment are days that follow the last day of the initial treatment period through the last day of membership in the RP health system.

Duration of initial treatment and PDC (by initial treatment and by succeeding calendar quarter) will be summarized as continuous variables and in 10 categories approximately equally spaced between 0 and maximum observed values.

9.6.6 Patient new-user eligibility for the primary analyses

Patients enter the analysis only once. Accordingly, an individual will enter the comparative cohort analysis provided that he or she was not earlier matched into the comparative cohort analysis.

9.6.7 Primary analysis – Relative incidence of MACE in the new-user comparative cohorts

The primary effect estimate is the relative incidence of MACE during naloxegol exposure as compared to during comparison drug treatment. The analysis of MACE is based on the Cox proportional hazards model with an indicator for naloxegol versus comparison drug treatment as a predictor, a non-specified baseline hazard with stratification by calendar year of cohort entry, and decile of PS. In addition to treatment status, the predictors will include covariates that are not balanced by the PS (see Section 9.1).

For each subject, the time to event used in the primary analysis will extend from the start of the index treatment until the first occurrence of a MACE or a censoring event. Censoring events are (1) end of study, (2) disenrollment from RP health system, (2) death for reasons other than MACE, (3) treatment discontinuation, (4) switch to a drug in the other treatment group, or (5) treatment with another PAMORA.

A self-controlled study design offers a complementary approach to the statistical control for the possible confounding effects of personal characteristics. The self-controlled design assesses the occurrence of MACE in relation to the duration of time each subject spends in each possible exposure category. Analysis is by conditional log-linear Poisson regression with MACE as the endpoint and indicator variables for exposure status at each possible level (naloxegol, oral NNPAMORA, and no drug exposure taken against lubiprostone/linaclotide as a common reference). The natural logarithm of time at each exposure level is the offset. The conditional regression absorbs coefficients corresponding to individuals, which are nuisance parameters (Farrington et al 2010). The hazard ratio estimates resulting from this analysis are adjusted by matching for all individual characteristics that do not change appreciably over the course of observation. The estimates include events that occur after the end of the first treatment regimen and provide an alternative, adjusted assessment of the relation between MACE and naloxegol versus comparison drugs.

9.6.8 Secondary analysis – Case-control analysis for assessment of confounding

An analysis of a subset of all subjects will allow identification of and control for MACE risk factors by using more extensive data collected on a select group of subjects. A case-control analysis will include MACE cases and selected matching subjects from the same cohort who do not experience any MACE event.

A matched set will be created for each adjudicated MACE case and its matched controls. For the cases and their matched controls, the results of medical record abstraction and exposure status will be recorded.

Exposure status is primarily defined so as to correspond to the exposure definition in the primary analysis (c.f. Section 9.3.1 and Figure 3). An individual is counted at exposed to a study drug if it is the study drug most recently dispensed and if the interval between the most recent dispensing and the date of case occurrence for the individual's matched set is less than or equal to 3 times the days supply dispensed at the most recent dispensing.

Descriptive statistics of exposure status and the information abstracted from medical chart review will be presented for cases and for their matched controls from each cohort. Cases and their matched controls will be entered into conditional logistic regression analyses that match cohort analyses, retaining exposure status (naloxegol versus comparison drug) and adding covariates based on medical chart abstraction. The focus of the analysis is the adjusted case-control estimate of the odds ratio between MACE and naloxegol versus comparison drug from the conditional logistic regression, which will be compared to the same estimate from the cohort analysis in order to derive a qualitative estimate of the degree of residual confounding by factors identified on chart review. The odds ratio along with the corresponding confidence interval for each risk factor will also be presented to characterize the relationship between the risk factor and occurrence of MACE.

In the sense described in Section 9.3.1 and illustrated in Figure 3, all persons in the new-user cohort are currently exposed to naloxegol, linaclotide or lubiprostone, or to an oral NNPAMORA. The same is true of the subjects in the case-control study that is nested within the cohort. Further exploratory case-control analyses will explore the effect of recency and continuity of naloxegol exposure. A series of dichotomous temporal exposure measures will be created for naloxegol corresponding to dispensing in the (1) greater than 60 days prior to case date; (2) 31-60 days prior; (3) 30 days prior to and including case date at a dose of 25 mg/day, and (4) 30 days prior to and including case date at a dose of 12.5 mg/day. A fifth dichotomous variable will flag current exposure to an oral NNPAMORA if any have entered into the study. A model containing all 5 predictors will be fit and reduced by backwards elimination with the implicit reference category being use of either lubiprostone or linaclotide. The model will be reduced by backward elimination using $p<0.1$ to retain coefficients. Two-way interactions between retained coefficients will be introduced, and backwards elimination again carried out. The procedure will be repeated with higher-order interactions until none are retained.

9.6.9 Secondary analysis – Relative incidence of individual MACE components

MACE components (MI, stroke, and cardiovascular death) will be tabulated according to treatment group.

For individual components of MACE, a proportional hazards analysis with the same stratification as the primary analysis will be carried out separately. For these analyses, subjects will not be censored when experiencing other MACE events other than death. Otherwise, censoring from the primary analysis will continue to be implemented. The hazard ratios for each of the MACE components along with the corresponding confidence interval will be presented in a forest plot. Any component with treatment effect that differs from the others by an amount inconsistent with chance at a level of $p\leq0.05$ will be explored further.

9.6.10 Secondary analysis – Sensitivity analyses for fixed follow-up periods

Follow-up in members of the new-user cohort will be assessed over fixed follow-up periods without concern for discontinuation of or switching between study medications. Censoring will occur only because of a pre-defined calendar date for close of follow-up or because the cohort member has left the health system providing data. The fixed follow-up times to be considered are 1, 2, 4, 6, and 8 months.

9.6.11 Secondary analysis – Relative incidence of MACE in users of NNPAMORAs

If users of oral NNPAMORAs have entered the study, they will form a single separate cohort. In order to distinguish them from other comparators, the proportional hazards modeling will include a term for membership in the NNPAMORA cohort, but this will not be interpreted as part of the primary analysis.

The secondary analysis is an interpretation of the contrasts of oral NNPAMORAs collectively versus lubiprostone/linaclotide and oral NNPAMORAs versus naloxegol.

9.6.12 Secondary analysis – Relative incidence of MACE in first-line users of prescription drugs for OIC

The proportional hazards analysis described for the new-user cohort (Section 9.6.8) will be repeated for persons with no prior use of lubiprostone or linaclotide (Section 9.3.3, Table 3).

9.7 Data management

Each RP 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 RP 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.

9.7.1 Veterans Health Administration

All data are stored on servers in a locked and secure computer room on the grounds of Hines VA Medical Center, with Hines Police Department on site. Data are backed up to tape nightly, Monday through Friday. Backup tapes are stored off-site in a reputable VA storage facility and on-site in a locked fireproof safe in a secure area. Backup tapes are encrypted using 256 bit AES encryption. Data and all research records will be kept indefinitely until VA's Records Control Schedule guidance and local policy is determined.

Only those authorized project team members of the study will have access to study data files. There are multiple levels of security to insure the integrity and confidentiality of all data stored on the system. The computer system operates entirely within the VA network, which is protected by firewalls maintained by the VA Central Office.

Access to study directories is based on Active Directory security groups and Access Control Lists. Authorized project team members are assigned an active, individually unique user identification code and password. The accounts and passwords comply with existing VA policies and procedures for computer access. Access to directories and files is limited to particular user identification codes. The Research computer system is accessed via personal computers assigned to authorized investigators.

Authorized project team members will take cyber security awareness training and privacy training annually and will follow HIPPA guidelines for accessing and manipulating patient level data.

9.8 Quality control

Implementation of this protocol will be laid out in a global SAP. Local modifications by the RP will ensure that each local SAP is sufficiently detailed to trace data manipulations from the original database files through study files to final analyses and tabulations. The SAP will be the basis for checking all analytic computer programs by a second team member. Original data files, intermediate files, study files, and the programs that link them will be maintained by each RP in a secure archive for 5 years following submission of the final study report.

Standard operating procedures for each RP 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, SAP, 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. If a quality assurance audit were to be conducted, an auditor will be accompanied by the study team members, and the information needed will be provided by the study team members. An auditor will have no direct access to the data.

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. The primary threat to the usefulness of the proposed analyses lies in the possibility that there may be unmeasured factors predictive of MACE that differ systematically

between the compared groups. This will arise for factors that influence treatment choice, are inadequately represented in the available covariates, and are themselves predictors of mortality even within groups that are homogeneous with respect to all the measured risk factors.

2. The study will not include a concurrent comparison group of persons who do not use prescription-only treatments for OIC. Comparison to non-users of OIC treatments would require the identification of chronic opioid users who were medically similar to new users of naloxegol, but for whom providers did not select treatment with prescription-only therapies for OIC. The untreated comparison patients would be expected to have OIC. Unfortunately, OIC is not defined in the available data sets, nor is the information to define OIC sought in any systematic way in routine medical practice. Thus, existence and severity of OIC could not be demonstrated as comparable between treated and untreated groups and indeed might be considered as implausible since one got treatment and the other did not.

3. 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. Diagnostic codes or laboratory data may lack the specificity needed to determine if an event of interest occurred.

4. 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 this may result in apparent association of increased risk of events of interest in this population. PS 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 comparison drug. Covariates in the PS model will include demographic factors, profile of previous or current therapies, previous medical diagnoses, and measures of healthcare resource utilization.

5. 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.

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.

9.10 Other aspects

9.10.1 Governance

AstraZeneca bears accountability for all aspects of study design and conduct and communicates with regulatory authorities.

RP under contract with AstraZeneca carry out all aspects of study implementation, including local IRB approvals, interactions with the NDI, manipulation of raw data files, formation of intermediate and analyzable data sets following the protocol and the SAP, and chart abstraction. RP maintain audit-ready documentation of all activities. The RP interact on a regular basis with the SCC and meet at least annually in person with the Scientific Steering Committee, AstraZeneca, and the SCC.

A *Scientific Steering Committee* consists of a biostatistician with expertise in non-interventional studies, a clinician with expertise in pain management, and an epidemiologist with expertise in drug safety. The Scientific Steering Committee is retained by AstraZeneca, but operates independently under a charter agreed in advance with AstraZeneca. The Scientific Steering Committee reviews and interprets reports from the RP, and it directs the SCC in its preparation of study reports, which it reviews, modifies as necessary, and ultimately accepts. The Scientific Steering Committee advises AstraZeneca on any changes that may be necessary in study conduct or protocol to meet the study goals in light of emerging information.

A *SCC* retained by and answerable to AstraZeneca handles all aspects of interactions with the RP, writing and revision of the central SAP, and review of RP SAPs. The SCC writes summary reports for AstraZeneca, subject to the review and approval by the Scientific Steering Committee. The SCC meets with the Scientific Steering Committee twice yearly and with each of the RP at least monthly to monitor study progress. The SCC is responsible for monitoring and auditing the RP documentation and quality control activities.

An *Adjudication Committee* consists of clinicians with expertise in cardiovascular health and morbidity. The Adjudication Committee reviews materials provided to it by the RP through the SCC for potential MACE. The Adjudication Committee forms its own charter, laying out criteria for case adjudication and specifying materials to be abstracted from medical records of potential cases.

9.10.2 Timeline for SAP and protocol

Three months following FDA acceptance of this protocol, AstraZeneca will complete and submit to the FDA a global SAP for the study. No study data files will be created before the completion of the global SAP. The RP will receive the global SAP at the same time and prepare local variants to account for particularities of their local data environments. The partners will return the global SAPs to the SCC for verification that they conform in scientific essentials to the global SAP.

Minor amendments to the protocol and the SAPs include changes that do not affect the study objectives or change the comparison groups, nature of covariates, or methodology. Minor amendments include, for example, resolution of previously unnoticed inconsistencies and clarification of procedures or definitions to achieve the study objectives. These will be documented promptly as minor amendments to the protocol, global SAP, and local SAPs.

Proposed major amendments to the protocol and consequently to the SAPs will be communicated to the FDA within one month of AstraZeneca's determination that the amendment may be required. Major amendments will be implemented and documented upon FDA concurrence.

10. PROTECTION OF HUMAN PATIENTS

This non-interventional research is based on the examination of data generated in the course of routine health care.

The SCC will request a waiver of informed consent and privacy board exemption from a common IRB, and each RP IRB.

It would be impractical to receive informed consent retrospectively for a large numbers of patients and impossible for key study subjects since, by definition, all of those who experienced an outcome of cardiac death will be inaccessible. The risks of this research are less than minimal as described above and the benefits strongly outweigh such risks. A waiver of informed consent will not affect the rights and welfare of the research subjects.

Identifying data necessary for patient matching between the RP and the NDI will be kept secure by the RP and not shared other than with the NDI.

The study will be conducted in accordance with the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices.

AstraZeneca will register the study with ClinicalTrials.gov.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Definitions

11.1.1 Definition of adverse events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg, laboratory

findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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 is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient 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 1 of the outcomes listed above

11.1.3 Definition of adverse drug reactions

An adverse drug reaction (ADR) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, suspected to be causally related to the product.

11.2 Collection of adverse events

No active collection of AE data will be performed in this study. However, RP will follow local reporting policies (e.g. for VA, the Hines local AE reporting policy as per Hines IRB Standard Operating Procedures and revised Handbook 1058.01). In addition, any serious ADR that is inadvertently discovered and has an identifiable patient must be reported, including the study number, to the Patient Safety Data Entry Site by fax at +1 (302) 886-4114 or email at AEMailboxClinicalTrialTCS@astrazeneca.com, unless the original report was from an AstraZeneca-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 AstraZeneca product. If the medical records do not include a statement regarding causality, there is no requirement to report the event.

As only the RP will undertake direct review of medical records, it is the obligation of the RP to recognize when a medical record clearly indicates that the treating physician considered there to be a possible causal relationship between the AE and the AstraZeneca product and to report this immediately to AstraZeneca.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

AstraZeneca will register the study with ClinicalTrials.gov.

Results will be provided to AstraZeneca in the form of an interim report in 2018. The interim report will include patient counts of exposure to naloxegol and comparison drugs, descriptive statistics of baseline characteristics in the compared cohorts, numbers of dispensings and dispensed treatment days for all study drugs, time on-study, and accumulated event counts in the compared cohorts.

Results for each exposure cohort will be presented across all RP and by each RP. A final report will be generated at study end in 2023. The final report will contain content provided in the interim report as well as hazard ratios and 95% confidence intervals estimated from matched Naloxegol Inception and Concurrent Comparison Drug Cohorts for the entire study population and by RP.

After submission of study results to regulatory authorities, the Scientific Steering Committee, with the support of the SCC and in conjunction with the RP, will prepare 1 or more manuscripts suitable for publication resulting from this study.

13. REFERENCES

Boyle and Decouflé 1990
Boyle CA, Decouflé P. National sources of vital status information: extent of coverage and possible selectivity in reporting. American Journal of Epidemiology 1990;131(1):160–8.

Carman et al 2011
Carman WJ, Su S, Cook SF, Wurzelmann JI, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. Pharmacoepidemiology and Drug Safety 2011;20:754-62.

Chung et al 2010
Chung CP, Murray KT, Stein M, Hall K, Ray WA. A computer case definition for sudden cardiac death. Pharmacoepidemiology and Drug Safety 2010;19:563–72.

Farrington et al 2010
Farrington CP, Whitaker HJ, Hocine MN. Case series analysis for censored, perturbed, or curtailed post-event exposures. Biostatistics 2009;10(1):3-16.

Fujita et al 2004
Fujita Y, Ito C, Mabuchi K. Surveillance of mortality among atomic bomb survivors living in the United States using the National Death Index. Journal of Epidemiology 2004;14:17-22.

Hosmer and Lemeshow 1980
Hosmer DW, Lemeshow S. A goodness-of-fit test for the multiple logistic regression model. Communications in Statistics 1980;A10:1043-69.

LaVeist et al 1996
LaVeist TA, Diala C, Torres M, Jackson JS. Vital status in the National Panel Survey of Black Americans: a test of the National Death Index among African Americans. Journal of the National Medical Association 1996;88:501–5.

Maclure et al 2012
Maclure M, Fireman B, Nelson JC, Hua W, Shoaibi A, Paredes A, et al. When should case-only designs be used for safety monitoring of medical products? Pharmacoepidemiology and Drug Safety 2012;21(Suppl 1):50-61.

Rich-Edwards et al 1994
Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. American Journal of Epidemiology 1994;140:1016-9.

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

Schoenfeld 1981
Schoenfeld D. The asymptotic properties of nonparametric tests for comparing survival distributions. Biometrika 1981;68(1):316-9.

Stampfer et al 1984
Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, et al. Test of the National Death Index. American Journal of Epidemiology 1984;119:837–9.

Whitaker et al 2006
Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. Statistics in Medicine 2006;25(10):1768-97.

Williams et al 1992
Williams BC, Demitrack LB, Fries BE. The accuracy of the National Death Index when personal identifiers other than Social Security number are used. American Journal of Public Health 1992; 82:1145-47.