Summary Table of Study Protocol

Title	Risk of Hypertension, Acute Myocardial Infarction, and Stroke in Migraine Patients Treated With Migraine Preventive Medications
Protocol version identifier	20200403, Version 1.0
Date of last version of the protocol	NA
EU Post Authorization Study (PAS) Register No	NA
Active Substance	erenumab-aooe
Medicinal Product	Aimovig® (erenumab-aooe), 70 mg or 140 mg
Device	NA
Product Reference	AMG 334
Procedure Number	BLA 761077
Joint PASS	No
Research Question and Objectives	(1) Describe baseline characteristics of four cohorts of migraine patients initiating a migraine preventive treatment: erenumab-aooe, other monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway, selected standard of care (SOC) antiepileptic preventive medications, and onabotulinumtoxinA. (2) Estimate the risk (cumulative incidence) of three cardiovascular outcomes (hypertension, acute myocardial infarction [MI], and stroke) among new users of erenumab-aooe, other mAbs targeting the CGRP pathway, selected SOC antiepileptic preventive medications, and onabotulinumtoxinA. (3) Assess comparability of migraine patients treated with erenumab-aooe to migraine patients treated with (1) other mAbs targeting the CGRP pathway, (2) selected SOC antiepileptic preventive medications, and 3) onabotulinumtoxinA, with respect to baseline confounders and risk factors for cardiovascular disease. (4) GATED – If appropriate based on comparability analyses, separately compare the risk of acute MI and stroke in patients treated with erenumab-aooe to the risk in each of the other three medication cohorts.

Country of Study	**United States**
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Marketing Authorization Holder

Marketing authorization holder(s)	Amgen, Inc. Thousand Oaks, CA 91320
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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

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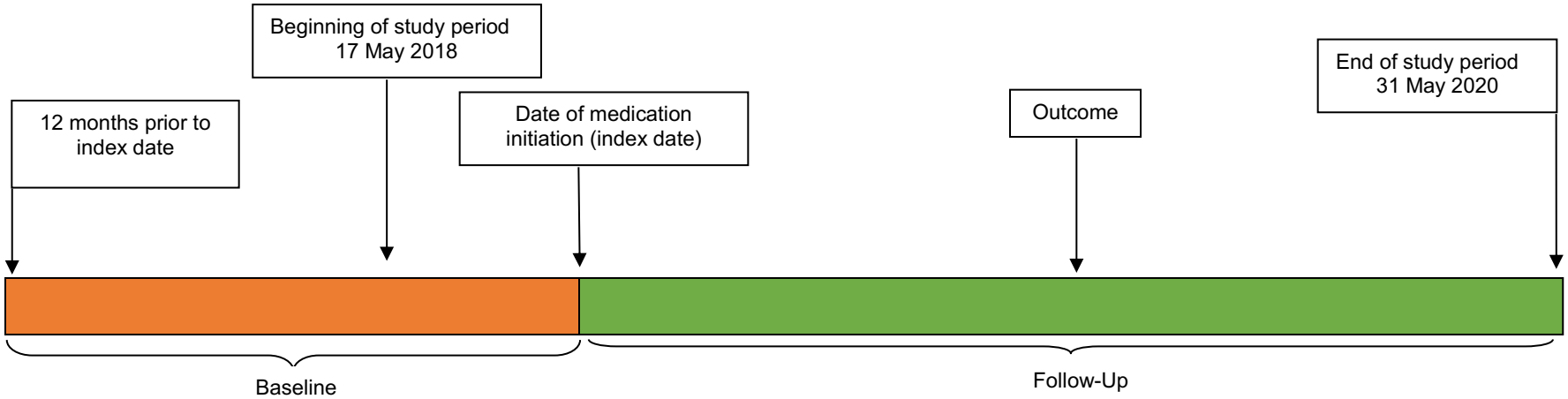
Study Design Schema: Retrospective Cohort Study



Medication Cohorts
Four new user cohorts of patients treated with:
- Erenumab-aooe
- Other mAbs targeting the CGRP pathway
- Selected SOC migraine preventives (anti-epileptics)
- OnabotulinumtoxinA

Study Period
- May 17, 2018 – May 31, 2020 (or most recent date available)

Inclusion Criteria
- 18+ years of age
- One year of continuous enrollment prior to the index date (the baseline period)
- Diagnosis of migraine during the baseline period

Exclusion Criteria
- Prior use of study meds, and prior use of medications targeting the CGRP pathway

Migraine Definition
Occurrence of one of the following during the one-year baseline period:
- ≥ 1 migraine diagnosis claim from a "non-emergency" inpatient visit; OR
- ≥ 1 migraine diagnosis claim from an emergency room visit; OR
- ≥ 1 migraine diagnosis claim from an outpatient visit associated with a neurologist visit; OR
- ≥ 1 outpatient migraine diagnosis claim (regardless of provider specialty) PLUS ≥ 1 acute migraine-specific drug (triptan or ergot-derivative) prescription claim within 365 days of each other; OR
- ≥ 2 outpatient migraine diagnosis claims (regardless of provider specialty) between 7 and 365 days apart; OR
- ≥ 2 acute migraine-specific drug (triptan or ergot-derivative) prescription claims between 7 and 365 days apart

Study Outcomes
- Hypertension
- Acute Myocardial Infarction
- Stroke (Ischemic and Hemorrhagic)

Covariates
Assessed during the 12-month baseline period
- Demographics
- *A priori* defined covariates of interest, including comorbidities and risk factors for the outcomes
- Cohort descriptors identified empirically from the most prevalent diagnoses, procedures, and prescriptions during the baseline period.

End of Follow-up, Earliest of:
- Health plan disenrollment
- Discontinuation of study medication
- Switching to alternate medication
- Occurrence of the outcome of interest
- Administrative end of study (31 May 2020, or most recent date available)

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2. List of Abbreviations

Abbreviation/Acronym	
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence Interval
CPT	Current Procedure Terminology
ER	Emergency Room
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
HCPCS	Healthcare Common Procedure Coding System
ICD-10-CM	International Classification of Disease, Tenth Revision, Clinical Modification
IP	Inpatient
IPCW	Inverse Probability of Censoring Weights
IPTW	Inverse Probability of Treatment Weights
NDC	National Drug Code
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
mAb	Monoclonal Antibody
MI	Myocardial Infarction
OP	Outpatient
PPV	Positive Predictive Value
PS	Propensity Score
RR	Risk Ratio
SOC	Standard of Care
US	United States
USPI	United States Prescribing Information

3. Responsible Parties

Study Sponsor

PPD , PhD

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4. Abstract

- Study Title

  Risk of Hypertension, Acute Myocardial Infarction, and Stroke in Migraine Patients Treated with Migraine Preventive Medications

- Study Background and Rationale

- Erenumab-aooe was approved by the United States (US) Food and Drug Administration (FDA) on 17 May 2018, followed by other monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway (fremanezumab-vfrm on 14 September 2018, galcanezumab-gnlm on 27 September 2018, and eptinezumab-jjmr on 21 February 2020), for the prevention of migraine in adults. On 30 April 2020, new onset hypertension and exacerbation of existing hypertension were added to the Warning and Precautions section of the United States Prescribing Information (USPI) for erenumab-aooe. Regulatory agencies have requested routine post-marketing surveillance data on acute MI and stroke, have required descriptive observational studies on CV outcomes, or have requested additional information for major adverse CV events and hypertension related to use of mAbs targeting the CGRP pathway. In this study, the risk of hypertension, acute MI, and stroke will be estimated in the following four new user cohorts: erenumab-aooe, other mAbs targeting the CGRP pathway, select SOC antiepileptic medications used for migraine prevention, and onabotulinumtoxinA used for migraine prevention. Also, if appropriate based on comparability analyses, gated analyses estimating the relative risk (RR) of acute MI and stroke will be separately conducted for the following three comparisons: (1) erenumab-aooe vs. other mAbs targeting the CGRP pathway, (2) erenumab-aooe vs. selected standard of care (SOC) migraine preventive medications (anti-epileptics), and (3) erenumab-aooe vs. onabotulinumtoxinA.

- Study Feasibility

  In a recent internal Amgen study of the MarketScan® Early View database, a total of 15 212 erenumab-aooe users, 17 239 users of other mAbs targeting the CGRP pathway, and 9242 users of Botox® (onabotulinumtoxinA) were identified from May 2018 through January 2020. Assuming a conservative 3-month growth rate of 15%, the expected number of users of prophylactic migraine medications in the MarketScan® database during the study period (17 May 2018 – 31 May 2020) will be ~20 000 new users of erenumab-aooe, ~23 000 new users of other mAbs targeting the CGRP pathway, and ~13 000 new users of onabotulinumtoxinA.

- Research Question and Objective(s)

Objectives	Endpoints
Primary	
• To describe baseline characteristics of four cohorts of migraine patients initiating a migraine preventive treatment: erenumab-aooe, other mAbs targeting the CGRP pathway, selected SOC migraine preventive medications (anti-epileptics), and onabotulinumtoxinA.	• Not applicable.
• To estimate the cumulative incidence of hypertension, acute MI, and stroke in migraine patients treated with erenumab-aooe, other mAbs targeting the CGRP pathway, selected SOC migraine preventive medications (anti-epileptics), and onabotulinumtoxinA.	• Hypertension • Acute MI • Stroke
• To assess comparability of migraine patients treated with erenumab-aooe to migraine patients treated with (1) other mAbs targeting the CGRP pathway, (2) selected SOC migraine preventive medications (anti-epileptics), and 3) onabotulinumtoxinA, with respect to baseline confounders and risk factors for cardiovascular disease, using propensity score (PS) analyses and evaluation of the standardized mean difference for all variables included in the PS model (see Section 8.7.2.4).	• Not applicable
• To assess comparability, separately compare the cumulative incidence of select negative control outcomes among migraine patients treated with erenumab-aooe to migraine patients treated with (1) other mAbs targeting the CGRP pathway, (2) selected SOC migraine preventive medications (anti-epileptics), and 3) onabotulinumtoxinA.	• Negative Control Outcomes (see sub-section on negative control outcomes in Section 8.7.2.4)
• [GATED ANALYSES] If the cohorts are comparable, separately compare the cumulative incidence of acute MI and stroke among migraine patients treated with erenumab-aooe to migraine patients treated with (1) other mAbs targeting the CGRP pathway, (2) selected SOC migraine preventive medications (anti-epileptics), and 3) onabotulinumtoxinA.	• Acute MI • Stroke

- Hypotheses/Estimation
  We will: (1) estimate the cumulative incidence (95% confidence interval [CI]) of hypertension, acute MI, and stroke (ischemic and hemorrhagic) in initiators of erenumab-aooe, other mAbs targeting the CGRP pathway, selected SOC migraine preventive medications (anti-epileptics), and onabotulinumtoxinA; and, (2) if the cohorts are comparable, we will separately evaluate the null hypothesis of no association between erenumab-aooe versus each of the other new user cohorts on the cumulative incidence (ie, risk) of acute MI and stroke.
- Study Design/Type

  Observational retrospective cohort study design.

- Study Population or Data Resource

  This analysis will utilize data from the MarketScan® Commercial and Medicare Supplemental medical claims database, which represents the medical experience of insured employees and their dependents for active employees, early retirees, individuals who continue their insurance coverage under the Consolidated Omnibus Budget Reconciliation Act, and Medicare-eligible retirees with employer-sponsored medical supplemental plans. The underlying insured population from which the data are drawn is geographically diverse across the US (47% - South, 18% - North, 17% - West, 20% - North Central), 52% of plan participants are male, and 89% are enrolled in fee-for-service plans.

- Summary of Eligibility Criteria

  Patients must be 18-64 years of age on the index date, have one year of continuous medical and pharmacy eligibility prior to and including the index date (ie, the baseline period), and have a diagnosis of migraine during the baseline period. Patients will be excluded from the study if there is any use of a medication targeting the CGRP pathway during the baseline period. In addition, for the SOC migraine preventive medications (anti-epileptics) and onabotulinumtoxinA new user cohorts, patients will be excluded if there was any prior use of the cohort defining medication during the baseline period.

- Follow-up

  Follow-up will be evaluated in two ways. With an 'intention-to-treat' analysis, patients will be followed for all available time after they initiate a medication, irrespective of whether they discontinue the medication or not, or whether they switch to an alternate medication or not. Follow-up begins the day after the index date and ends at first occurrence of: (a) the outcome of interest, (b) disenrollment from a health plan, or (c) end of study period. With a 'per-protocol analysis' patients are followed for as long as they are actively taking the medication of interest during the follow-up period. Follow-up begins the day after the index date and ends at first occurrence of: (a) the outcome of interest (each outcome will be assessed independently), (b) disenrollment from the health plan, (c) discontinuation of study medication, (d) switching to an alternate medication, or (e) administrative end of study. For the erenumab-aooe and other mAbs targeting the CGRP cohorts, switching occurs when any preventive or acute medication other than the index medication targeting the CGRP pathway is initiated during the follow-up period. For the SOC migraine preventive medications (anti-epileptics) and onabotulinumtoxinA cohorts, switching occurs at initiation of any preventive or acute medication that targets the CGRP pathway during the follow-up period.

- Variables
  - Outcome Variables
    The outcomes of interest are hypertension, acute MI, and stroke, which will be identified using ICD-10-CM diagnosis codes.
    (1) Hypertension – occurrence of one inpatient (IP) diagnosis, one emergency room (ER) diagnosis, or one outpatient (OP) diagnosis during the follow-up period.
    (2) Acute MI – occurrence of one diagnosis in the IP setting during the follow-up period.

(3) Stroke, including both ischemic stroke and hemorrhagic stroke – occurrence of one diagnosis in the IP setting during the follow-up period.

- Exposure Variables
  New users of:
  (1) erenumab-aooe,
  (2) other mAbs targeting the CGRP pathway (fremanezumab-vfrm, galcanezumab-gnlm, eptinezumab-jjmr),
  (3) selected SOC migraine preventive medications (anti-epileptics) (topiramate, valproic acid, divalproex sodium) which are approved by the Food and Drug Administration (FDA) for the prevention of migraine, and
  (4) OnabotulinumtoxinA, which is also approved by the FDA for the prevention of migraine.
- Other Covariates
  We will assess the following variables during the baseline period: demographics, *a priori* defined covariates of interest, including comorbidities, concomitant medications, and risk factors for the outcomes, and cohort descriptors identified empirically from the most prevalent diagnoses, procedures, and prescriptions.

- Study Sample Size

  In a recent study of the MarketScan® Early View database, a total of 15 212 erenumab-aooe users, 17 239 users of other mAbs targeting the CGRP pathway, and 9242 users of onabotulinumtoxinA were identified from May 2018 through January 2020. Assuming a conservative 3-month growth rate of 15%, the expected number of new users during the study period (17 May 2018 – 31 May 2020) will be ~20 000 new users of erenumab-aooe, ~23 000 new users of other mAbs targeting the CGRP pathway, and ~13 000 new users of onabotulinumtoxinA.

  Based on these sample size estimates, the 95% CIs for a cumulative incidence for stroke of 0.50% are (0.40%, 0.60%) for erenumab-aooe, (0.41%, 0.59%) for other mAbs targeting the CGRP pathway, and (0.38%, 0.62%) for onabotulinumtoxinA medication users. The 95% CIs and half-widths of the CIs were estimated across a range of cumulative incidence values, assuming varying population sizes, for all three cardiovascular outcomes of interest (hypertension, acute MI, and stroke).

  If a comparative analysis is conducted (assuming 20 000 patients in the erenumab-aooe cohort and 20,000 patients in the comparator cohort, a background rate for stroke of 0.60 per 100 person-years (PYs), and an alpha-level of 0.05), a risk ratio of 1.46 would be detected with 80% power. Detectable risk ratios, assuming different population sizes and background rates, were estimated for acute MI and stroke.

- Data Analysis

  Baseline characteristics, including the most prevalent diagnoses, procedures, and medication class prescriptions will be summarized for the four study cohorts. Descriptive statistics using mean and standard deviation or median and $25^{th}/75^{th}$ percentile estimates for continuous variables and number and percentages (n, %) for categorical variables will be used to examine patient characteristics.

The naïve, unadjusted cumulative incidence (ie, risk) of hypertension, acute MI, and stroke will be estimated in the following new user cohorts: 1) erenumab-aooe , 2) other mAbs targeting the CGRP pathway, (2) select SOC migraine preventive medications (anti-epileptics), and (3) onabotulinumtoxinA.

Next, the overlap of the propensity score across treatment groups will be evaluated, the mean standardized difference for all variables included in the propensity score model will be assessed, and a determination will be made on whether null findings are or are not estimated for the negative control outcomes chosen for the study. Comparability between erenumab-aooe and each of the other treatment cohorts will be evaluated separately and each of the comparative analyses will be gated. Specifically, the decision to move forward with the comparative analyses for either the acute MI or the stroke outcome will be made after assessment of covariate balance across treatment groups, whether the negative control outcomes showed treatment associations within the accepted bounds around the null, and sufficient sample size to detect a risk ratio of 2.0 or greater. Analyses will proceed only in the treatment pairs where comparability and sufficient sample size are achieved, and not in others.

Based on the comparability analyses and sample size considerations, the risk of acute MI and the risk of stroke will be separately compared across the following three exposure contrasts: (1) erenumab-aooe vs other mAbs targeting the CGRP pathway, (2) erenumab-aooe vs select SOC migraine preventive medications (anti-epileptics), and (3) erenumab-aooe vs. onabotulinumtoxinA. For these gated analyses, we will utilize inverse probability of treatment weights to account for confounding and inverse probability of censoring weights to account for informative censoring.

5. Amendments and Updates

None.

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Migraine is a common, disabling neurologic disease characterized by recurrent episodes of head pain associated with neurological, gastrointestinal, and/or autonomic symptoms (Kurth et al, 2009). The headache is usually located unilaterally, of pulsating quality and moderate to severe in intensity, and aggravated by physical activity (Dodick, 2018; Schürks et al, 2010). Approximately one-third of migraineurs experience migraine aura (MA), which is comprised of transient neurological symptoms (typically visual, sensory, and/or speech/language), prior to or at the onset of the migraine attack (Goadsby et al, 2002). The lifetime prevalence of migraine in the United States has been stable over time, ranging from 10% to 20% depending on the case definition and on the age and sex distribution of the study population (Lipton and Bigal, 2005; Bigal et al, 2004). The prevalence of migraine is three to four times higher in women than men (Lipton and

Bigal, 2005), and reaches a peak in the late 30s and early 40s (Sacco et al, 2014), with approximately 90% of all patients having their first migraine attack before the age of 50 years (Lipton and Bigal, 2005; Rasmussen et al, 1991).

There is growing evidence of a link between migraine and vascular events, but the biologic mechanisms remain unclear. This is because the pathophysiology of migraine is complex and incompletely understood, likely involving activation of the trigeminovascular system (Lantz et al, 2017; Silberstein, 2004; Ferrari et al, 2015) which is, in turn, caused by a dysfunction in the modulation of pain, sensory processing, and autonomic vascular control (Bigal et al, 2009; Goadsby, 1995; Bahra et al, 2001). Cortical spreading depression, which is characterized as a wave of synchronized depression of electrical activity followed by a decrease in cerebral blood flow, has been linked to the aura seen in many migraine patients (Kurth et al, 2012). In the epidemiology literature, four meta-analyses have suggested that migraine aura is a risk factor for ischemic stroke (Etminan et al, 2005; Schurks et al, 2009; Spector et al, 2010; Hu et al, 2017). With respect to other vascular events, including hemorrhagic stroke, transient ischemic attack, myocardial infarction, and unstable angina, there is also evidence of increased risk in migraine patients, when compared to patients without migraine (Sacco and Kurth, 2014).

Previous prophylactic treatment options for migraine have included anti-hypertensive drugs (eg, beta blockers and calcium channel blockers), anti-depressants (eg, tricyclics [TCAs], serotonin norepinephrine reuptake inhibitors [SNRIs], and selective serotonin reuptake inhibitors [SSRIs]), anti-epileptic medications (eg, topiramate), and botulinum toxins (indicated for the prevention of chronic migraine) (American Migraine Foundation, 2019; Estemalik et al, 2013; D'Amico and Tepper, 2008). All of these medications were originally developed for diseases other than migraine, but, more recently, two different classes of drugs blocking the calcitonin gene-related peptide (CGRP) pathway have been developed specifically for migraine: small molecule CGRP receptor antagonists (gepants) and monoclonal antibodies (mAbs), which either inhibit the canonical CGRP receptor or work by binding to the CGRP ligand (Deen et al, 2017).

The following four mAbs targeting the CGRP pathway have been approved for the prevention of migraine by the United States (US) Food and Drug Administration (FDA): erenumab-aooe (Aimovig®), fremanezumab-vfrm (Ajovy®), galcanezumab-gnlm (Emgality®), and eptinezumab-jjmr (Vyepti™). Erenumab-aooe was approved by the US FDA on 17 May 2018, followed by fremanezumab-vfrm on 14 September 2018,

galcanezumab-gnlm on 27 September 2018, and eptinezumab-jjmr on 21 February 2020.

6.2 Rationale

CGRP is a neuropeptide that is expressed in the central and peripheral nervous systems and has been implicated in migraine pathophysiology. In addition, CGRP can mediate vasodilation (Russell et al, 2014) and, therefore, inhibition of the CGRP pathway might result in cardiovascular effects, such as increased blood pressure; however, vasodilatory pathways are redundant, and the relative importance of the CGRP pathway compared with the other vasodilatory pathways (eg, nitric oxide) has not been established. CGRP and its receptors are also found in blood vessels and in the heart (Favoni et al, 2019). Clinical trials evaluating CGRP mAbs for migraine prevention have shown no imbalance in CV adverse events, including hypertension, between active medication and placebo groups. Moreover, during the development of erenumab-aooe, a number of dedicated clinical and nonclinical studies were conducted to address a theoretical cardiovascular risk, and collectively these studies support the cardiovascular safety of erenumab-aooe (Kudrow et al, 2020).

During the fourth quarter of 2019, the FDA identified hypertension as a potential adverse drug reaction (ADR) for erenumab-aooe. On 30 April 2020, new onset hypertension and exacerbation of existing hypertension were added to the Warning and Precautions section of the USPI for erenumab-aooe. In addition, because the phase 2 and 3 clinical trials for erenumab-aooe had a limited number of subjects (0.5%) enrolled with preexisting cardiovascular (CV) disease (Dodick et al, 2018; Goadsby et al, 2017, Tepper et al, 2017), use of erenumab-aooe in patients with major CV disease (including acute myocardial infarction [MI] and stroke) is classified as missing information in the Core Risk Management Plan for erenumab-aooe. CCI [redacted] In this study, the risk of hypertension, acute MI, and stroke will be estimated in the following four new user cohorts: erenumab-aooe, other mAbs targeting the CGRP pathway, select standard of care (SOC) migraine preventive medications (anti-epileptics), and onabotulinumtoxinA. Also, if appropriate based on comparability analyses, the relative risk (RR) of acute MI and stroke will be separately estimated for the following three comparisons: (1) erenumab-aooe vs. other mAbs

targeting the CGRP pathway, (2) erenumab-aooe vs. select SOC migraine preventive medications (anti-epileptics), and (3) erenumab-aooe vs. onabotulinumtoxinA.

6.3 Feasibility Considerations

In a recent internal Amgen study of the MarketScan® Early View database (Amgen Study 20200218), a total of 15 212 erenumab-aooe users, 17 239 users of other mAbs targeting the CGRP pathway, and 9242 users of onabotulinumtoxinA were identified from May 2018 through January 2020. In the same study, the rate of hypertension in new users of erenumab-aooe was 3.56 (95% confidence interval [CI]: 3.39, 3.73) per 10 PYs. In a separate study evaluating the rate of 19 vascular events in migraine patients, the rate of acute MI was 1.83 (95% CI: 1.78, 1.89) per 1000 PYs, the rate of ischemic stroke was 5.13 (95% CI: 5.04, 5.23) per 1000 PYs, and the rate of hemorrhagic stroke was 1.00 (95% CI: 0.95, 1.04) per 1000 PYs (Gill et al, 2020).

6.4 Statistical Inference

We will: (1) estimate the cumulative incidence (95% confidence interval [CI]) of hypertension, acute MI, and stroke (ischemic and hemorrhagic) in initiators of erenumab-aooe, other mAbs targeting the CGRP pathway, select SOC migraine preventive medications (anti-epileptics), and onabotulinumtoxinA; and, (2) if the cohorts are comparable, we will separately evaluate the null hypothesis of no association between erenumab-aooe versus each of the other new user cohorts on the cumulative incidence (ie, risk) of acute MI and stroke.

7. Research Question and Objectives

7.1 Primary

This study protocol will address the following objectives:

(1) To describe baseline characteristics of four cohorts of migraine patients initiating a migraine preventive treatment: erenumab-aooe, other mAbs targeting the CGRP pathway, selected SOC migraine preventive medications (anti-epileptics), and onabotulinumtoxinA.

(2) To estimate the cumulative incidence of hypertension, acute MI, and stroke in migraine patients treated with erenumab-aooe, other mAbs targeting the CGRP pathway, selected SOC migraine preventive medications (anti-epileptics), and onabotulinumtoxinA.

(3) To assess comparability, as described in Section 8.7.2.4, of migraine patients treated with erenumab-aooe to migraine patients treated with (1) other mAbs targeting the CGRP pathway, (2) selected SOC migraine preventive medications (anti-epileptics), and 3) onabotulinumtoxinA, with respect to baseline confounders and risk factors for cardiovascular disease. Comparability between

medication cohorts will be evaluated with propensity score analyses, evaluation of the standardized mean difference for all variables included in the propensity score model, and negative control outcome analyses.

(4) [GATED ANALYSES] If the cohorts are comparable, separately compare the cumulative incidence of acute MI and stroke among migraine patients treated with erenumab-aooe to migraine patients treated with (1) other mAbs targeting the CGRP pathway, (2) selected SOC migraine preventive medications (anti-epileptics), and 3) onabotulinumtoxinA.

8. Research Methods

8.1 Study Design

This study will utilize an observational retrospective cohort study design, using secondary data from the MarketScan® Commercial and Medicare Supplemental medical claims database. The strength of the cohort study design is the ability to study multiple outcomes in a single study. In this study, the following events that occur during the follow-up period will be evaluated: hypertension, stroke, and acute MI. All outcomes will be identified using International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnosis codes. New user cohorts for erenumab-aooe, other mAbs targeting the CGRP pathway (galcanezumab-gnlm, fremanezumab-vfrm, eptinezumab-jjmr), selected SOC migraine preventive medications (anti-epileptics: topiramate, valproic acid, divalproex sodium) which are approved by the FDA for the prevention of migraine, and , onabotulinumtoxinA, which is also approved by the FDA for the prevention of migraine, will be created based on National Drug Code (NDC) and Healthcare Common Procedure Coding System (HCPCS) codes that occur during the study period. To evaluate the burden of disease, the cumulative incidence (ie, risk) of each outcome, across all four new user cohorts, will be estimated. For the outcomes of acute MI and stroke, the three causal contrasts of interest are the following:

(1) Erenumab-aooe vs other mAbs targeting the CGRP pathway
(2) Erenumab-aooe vs select SOC migraine preventive medications (anti-epileptics)
(3) Erenumab-aooe vs. onabotulinumtoxinA

The measure of effect that will be estimated for the comparative analyses is the RR.

8.2 Setting and Study Population

8.2.1 Study Period

The study period will be from 17 May 2018, which is the date of US FDA approval for erenumab-aooe, to 31 May 2020 (or the latest release date for the MarketScan® claims database).

8.2.2 Patient Eligibility

The following four new user cohorts based on available data in a claims database will be created: (1) erenumab-aooe, (2) other mAbs targeting the CGRP pathway, (3) selected SOC migraine preventive medications (anti-epileptics), and (4) onabotulinumtoxinA. The index date is defined as the date of first claim for each of these group of medications. Use of mAbs targeting the CGRP pathway based on free/discount/coupon programs is not captured in claims data, therefore in the current protocol the term “new users” for these medications refers to the first appearance of a claim for the medication in the claims database and not necessarily the first time the patient has used the medication. Because treatment guidelines recommend inadequate response or intolerance to two SOC migraine preventive medications prior to erenumab initiation, the SOC anti-epileptic preventive medication cohort and the botulinum toxin cohort will be selected from the remaining population of migraine patients after the erenumab and other CGRP mAbs cohorts have been created.

8.2.2.1 Inclusion Criteria

Patients must meet the following inclusion criteria:

1. 18-64 years of age on the index date.
2. One year of continuous enrollment (ie, complete medical and pharmacy coverage) prior to and including the index date, which defines the baseline period.
3. A diagnosis of migraine during the baseline period, based on one of the following criteria:
    a) ≥1 inpatient claim with a diagnosis of migraine (ICD-10-CM) diagnosis code of G43.xxx).
    b) ≥1 outpatient evaluation and management claim with a diagnosis of migraine and a specialty code of 260 (neurologist).
    c) ≥1 claim for emergency room visit with a diagnosis of migraine.
    d) ≥1 outpatient evaluation and management claim with a diagnosis of migraine PLUS ≥1 pharmacy fill for a migraine-specific triptan or an ergotamine class medication within 365 days of each other
    e) ≥2 outpatient evaluation and management claims with a diagnosis of migraine between 7 and 365 days apart.
    f) ≥2 pharmacy fills for migraine-specific triptans or ergotamine class medications between 7 and 365 days apart.

8.2.2.2 Exclusion Criteria

(1) For the new user cohorts of mAbs targeting the CGRP pathway, no use of any medication targeting the CGRP pathway (erenumab-aooe, galcanezumab-gnlm, fremanezumab-vfrm, eptinezumab-jjmr, ubrogepant, rimegepant) in the year prior to the index date.

(2) For the SOC migraine preventive medications (anti-epileptics) new user cohort, no use of any of the migraine preventive anti-epileptics: (topiramate, valproic acid, divalproex sodium), or any medication targeting the CGRP pathway in the year prior to the index date.

(3) For the onabotulinumtoxinA new user cohort, no use of any onabotulinumtoxinA or any medication targeting the CGRP pathway in the year prior to the index date.

8.2.3 Matching

Matching will not be undertaken in this study.

8.2.4 Baseline Period

The index date for all medication cohorts is the earliest prescription claim date for a given medication occurring during the study period that satisfies the inclusion/exclusion criteria. The 365 days of continuous enrollment (ie, complete medical and pharmacy coverage) prior to and including the index date will be the baseline period.

8.2.5 Study Follow-up

Follow-up will be evaluated in two ways. With an 'intention-to-treat' analysis, patients will be followed for all available time after they initiate a medication, irrespective of whether they discontinue the medication or not, or whether they switch to an alternate medication or not. Follow-up begins the day after the index date and ends at first occurrence of: (a) the outcome of interest, (b) disenrollment from a health plan, or (c) end of study period.

With a 'per-protocol analysis' patients are followed for as long as they are actively taking the medication of interest during the follow-up period. Follow-up begins the day after the index date and ends at first occurrence of: (a) the outcome of interest, (b) disenrollment from the health plan, (c) discontinuation of study medication, (d) switching to the alternate medication, or (e) administrative end of study. When a gap greater than the allowable gap of 30 days is encountered, discontinuation of study medication occurs at the end of the last prescription which includes the days supply (+60 day extension). Censoring due to switching will occur for the new user cohorts in this study when the following conditions are met:

(1) For new users of erenumab-aooe, initiation of any other medication targeting the CGRP pathway (galcanezumab-gnlm, fremanezumab-vfrm, eptinezumab-jjmr, ubrogepant, rimegepant) during the follow-up period.

(2) For new users of other mAbs targeting the CGRP pathway, initiation of erenumab-aooe, ubrogepant, or rimegepant during the follow-up period.

(3) For new users of the SOC migraine preventive medications (anti-epileptics), initiation of any medication targeting the CGRP pathway (erenumab-aooe, galcanezumab-gnlm, fremanezumab-vfrm, eptinezumab-jjmr, ubrogepant, rimegepant) during the follow-up period.

(4) For new users of onabotulinumtoxinA, initiation of any medication targeting the CGRP pathway (erenumab-aooe, galcanezumab-gnlm, fremanezumab-vfrm, eptinezumab-jjmr, ubrogepant, rimegepant) during the follow-up period.

8.3 Variables

8.3.1 Exposure Assessment

The cohorts of erenumab-aooe, other mAbs targeting the CGRP pathway (galcanezumab-gnlm, fremanezumab-vfrm, eptinezumab-jjmr), select SOC migraine preventive medications (anti-epileptics: topiramate, valproic acid, divalproex sodium), and onabotulinumtoxinA initiators will be identified as described in Section 8.2. New use of medications will be based on NDCs or HCPCS codes as captured in the pharmacy tables within the MarketScan® claims database. The list of NDCs and HCPCS codes that will be used for cohort identification is provided in Appendix C.

8.3.2 Outcome Assessment

The outcomes of interest are hypertension, acute MI, and stroke, which will be identified within the MarketScan® claims database using ICD-10-CM diagnosis codes. The following algorithms will be used for each of the outcomes:

(1) Hypertension – occurrence of one inpatient (IP) diagnosis, one emergency room (ER) diagnosis, or one outpatient (OP) diagnosis during the follow-up period.

(2) Acute MI – occurrence of one diagnosis in the IP setting during the follow-up period.

(3) Stroke, including both ischemic stroke and hemorrhagic stroke – occurrence of one diagnosis in the IP setting during the follow-up period.

All outcomes will be assessed separately starting from the index date through the end of follow-up as described in Section 8.2.5. Only the first (incident) event for each outcome will be included in the analysis. The ICD-10-CM diagnosis codes for hypertension acute MI, and stroke are provided in Appendix C. The validation studies supporting the algorithms and ICD-10-CM diagnosis codes for the outcomes evaluated in this study are

provided in Section 8.3.4. The negative control outcomes that will be used to evaluate exchangeability between study cohorts for the comparative analyses are described in Section 8.7.2.4.

8.3.3 Covariate Assessment

Table 1 below provides categorization of a set of baseline covariates that will be used to describe the study population.

Table 1. Baseline Covariates

Variable	Measurement
Demographics	
Patient age (years)	Continuous, and categorized into five categories (18-24, 25-34, 35-44, 45-54, 55-64)
Patient gender	0/1 indicator (female)
Comorbidities	
Diabetes mellitus	0/1 indicator at study entry
Hypercholesterolemia	0/1 indicator at study entry
Hypertension	0/1 indicator at study entry
Liver disease / Cirrhosis	0/1 indicator at study entry
Depression	0/1 indicator at study entry
Chronic Obstructive Pulmonary Disease (COPD)	0/1 indicator at study entry
Renal Disease	0/1 indicator at study entry
Malignancy (Other Than Skin)	0/1 indicator at study entry
Cardiac arrhythmia	0/1 indicator at study entry
Asthma	0/1 indicator at study entry
Human immunodeficiency virus (HIV)	0/1 indicator at study entry
Lupus	0/1 indicator at study entry
Psoriasis	0/1 indicator at study entry
Atopic dermatitis	0/1 indicator at study entry
Rheumatoid arthritis (RA)	0/1 indicator at study entry
Epilepsy/Seizure/Convulsions	0/1 indicator at study entry

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Table 1. Baseline Covariates

Variable	Measurement
Comorbidities (continued)	
Anxiety	0/1 indicator at study entry
Depression	0/1 indicator at study entry
Peripheral Artery Disease	0/1 indicator at study entry
Venous thromboembolism	0/1 indicator at study entry
Critical limb ischemia	0/1 indicator at study entry
Myocardial Ischemia	0/1 indicator at study entry
Congestive heart failure	0/1 indicator at study entry
Acute myocardial infarction	0/1 indicator at study entry
Unstable angina	0/1 indicator at study entry
Prinzmetal angina	0/1 indicator at study entry
Other and unspecified angina pectoris	0/1 indicator at study entry
Acute atrial fibrillation	0/1 indicator at study entry
Paroxysmal atrial fibrillation	0/1 indicator at study entry
Acute ventricular fibrillation	0/1 indicator at study entry
Premature atrial contractions	0/1 indicator at study entry
Acute ventricular tachycardia	0/1 indicator at study entry
Coronary revascularization	0/1 indicator at study entry
Ischemic/hemorrhagic stroke	0/1 indicator at study entry
Sub-arachnoid stroke	0/1 indicator at study entry
Unspecified stroke	0/1 indicator at study entry
Transient ischemic attack	0/1 indicator at study entry
Other acute cerebrovascular events	0/1 indicator at study entry
Other ischemic cerebrovascular events	0/1 indicator at study entry
Migraine Features	
Chronic Migraine (without Aura)	0/1 indicator at study entry
Migraine Aura	0/1 indicator at study entry
Healthcare Utilization	
Number of ambulatory visits	Continuous, and categorized based on distribution
Number of emergency room visits	Continuous, and categorized based on distribution
Number of inpatient hospital stays	Continuous, and categorized based on distribution

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Table 1. Baseline Covariates

Variable	Measurement
Concomitant Medications	
Overall Medication Utilization[a]	
Number of unique generic medications dispensed	Continuous, and categorized based on distribution
Number of unique drug classes dispensed	Continuous, and categorized based on distribution
Preventive Migraine Medications	
Anti-epileptic agents	0/1 indicator at study entry for Carbamazepine, Gabapentin, Levetiracetam, Pregabalin, Topiramate, valproic acid, divalproex sodium, Zonisamide
Anti-hypertensive, beta blockers	0/1 indicator at study entry for Atenolol, Bisoprolol, Metoprolol, Nadolol, Nebivolol, Pindolol, Propranolol, Timolol
Anti-hypertensive, calcium channel blockers	0/1 indicator at study entry for Flunarizine, Verapamil,
Anti-hypertensive, other	0/1 indicator at study entry for Candesartan, Clonidine, Lisinopril
Anti-depressants, serotonin norepinephrine reuptake inhibitors	0/1 indicator at study entry for Duloxetine, Desvenlafaxine, Venlafaxine
Anti-depressants, tri-cyclics	0/1 indicator at study entry for Amitriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline, Protriptyline
Anti-depressants, selective serotonin reuptake inhibitors	0/1 indicator at study entry for Escitalopram, Citalopram, Sertraline
Botulinum toxin	0/1 indicator at study entry for AbobotulinumtoxinA, IncobotulinumtoxinA, OnabotulinumtoxinA, RimabotulinumtoxinB
Other migraine preventive agents	0/1 indicator at study entry for Carisoprodol, Cyproheptadine, Guanfacine, Memantine, Methysergide, Milnacipran, Tizanidine
Acute Migraine Medications	
Ergotamines	0/1 indicator at study entry for Dihydroergotamine mesylate, Ergotamine tartrate, Ergotamine tartrate + caffeine, Ergotamine tartrate + caffeine + belladonna + pentobarbital
Triptans	0/1 indicator at study entry for Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan (with and without naproxen), Zolmitriptan

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Table 1. Baseline Covariates

Variable	Measurement
Acute Migraine Medications (continued)	
NSAIDS	0/1 indicator at study entry for Aspirin, Celecoxib, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Magnesium salicylate, Meclofenamic Acid, Mefanamic Acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Rofecoxib, Salsalate, Sulindac, Tolmetin, Valdecoxib
Opioids	0/1 indicator at study entry for Codeine, Fentanyl, Hydrocodone, Hydromorphone, Morphine Sulfate, Oxycodone, Oxymorphone, Tramadol, Alfentanil, Buprenorphine, Butorphanol tartrate, Dezocine, Dihydrocodeine, Levomethadyl, Levorphanol, Meperidine, Methadone, Nalbuphine, Opium / belladonna alkaloids / opium alkaloids, Pentazocine, Propoxyphene, Remifentanil, Sufentanil, Tapentadol
NonNSAID NonOpioid Analgesics	0/1 indicator at study entry for Acetaminophen, Baclofen, Butalbital, Ziconotide
Other acute migraine treatment	0/1 indicator at study entry for Lasmiditan
Other Medications	
Contraceptives	0/1 indicator at study entry
Anti-hypertensives	
Aldosterone antagonist	0/1 indicator at study entry
Angiotensin receptor blockers	0/1 indicator at study entry
Angiotensin-converting enzyme (ACE) inhibitors	0/1 indicator at study entry
Beta-blockers	0/1 indicator at study entry
Calcium-channel blockers	0/1 indicator at study entry
Diuretics	0/1 indicator at study entry
Other anti-hypertensives	0/1 indicator at study entry
Anti-coagulants	0/1 indicator at study entry
Anti-platelets	0/1 indicator at study entry
Lipid-lowering agents	
Statins	0/1 indicator at study entry
Non-statins	0/1 indicator at study entry

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Table 1. Baseline Covariates

Variable	Measurement
Other Medications (continued)	
Anti-diabetics	
Insulin	0/1 indicator at study entry
Non-Insulin	0/1 indicator at study entry
Cardiac glycosides	0/1 indicator at study entry
Calcium gluconate	0/1 indicator at study entry
Fludrocortisone/ Midodrine	0/1 indicator at study entry
Weight loss prescriptions	0/1 indicator at study entry
Fludrocortisone/ Midodrine	0/1 indicator at study entry
Hyperpolarization-activated cyclic nucleotide-gated channel blocker	0/1 indicator at study entry

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[a] Health care utilization will also be evaluated as the following time-varying covariate during the follow-up period, evaluated every three months: occurrence of any outpatient visit over the prior three months, occurrence of any ER visit over the prior three months, and occurrence of any inpatient visit over the prior three months. Continuous measures of heath care utilization will also be considered. Medication utilization will be assessed as the number of unique generic medications dispensed during the interval and number of unique drug classes dispensed during the interval.

8.3.4 Validity and Reliability

We will use validated definitions where appropriate to identify the cardiovascular events that are of interest in this study (Sentinel Initiative, 2018; McCormick et al, 2015; Sherman et al, 2013; Cutrona et al, 2013; Tirschwell and Longstreth, 2012; Quan et al, 2009; Roumie et al, 2008; Tu et al, 2007; McCormick et al, 2015).

The primary algorithm, with a positive predictive value (PPV) of 86% (95% CI: 79%, 91%), to identify acute MI requires an ICD-10-CM diagnosis code of I21.xxx or I22.xxx (see Appendix C) in the principal or primary position of facility claims for hospitalization (Cutrona et al, 2013).

As with acute MI, an algorithm to identify ischemic stroke with good PPV (90% [95% CI: 77%, 97%]) also requires an ICD-10-CM diagnosis code (I63.xxx) occurring in the primary position for facility claims for hospitalization (Tirschwell and Longstreth, 2012). In contrast, the algorithms for intracerebral hemorrhage (PPV – 89% [95% CI: 75%, 99%], ICD-10-CM diagnosis code I61.xxx) and subarachnoid hemorrhage (PPV – 94% [95% CI: 83%, 99%], ICD-10-CM diagnosis code I60.xxx) require a diagnosis code for hemorrhage that can occur in any diagnosis position for an inpatient hospitalization (Tirschwell and Longstreth, 2012). All ischemic and hemorrhagic (intracerebral and subarachnoid) stroke events will be combined to identify 'any stroke' for the primary analysis; however, the cumulative incidence of ischemic and hemorrhagic stroke events will also be described separately.

Algorithms that evaluate acute MI, ischemic stroke, and hemorrhagic stroke in either the emergency room (ER) or the inpatient setting will also be considered.

There are a number of algorithms, with varying performance characteristics, to identify clinical hypertension in administrative claims data (Sherman et al, 2013; Quan et al, 2009; Tu et al, 2007) but none to evaluate drug-induced hypertension. As a result, using the hypertension codes listed in Appendix C, we will evaluate new onset hypertension with the following algorithms:

1. 1 IP / 1 ER / 1 OP diagnosis (any position) of hypertension
2. 1 IP / 1ER / 1 OP diagnosis (any position) of hypertension, with a prescription fill for an anti-hypertensive medication within 30 days after the hypertension diagnosis date.
3. 1 IP / 1ER / 1 OP diagnosis of hypertension (any position), and discontinuation of the study medication within 90 days after diagnosis
4. 1 IP / 1 ER / 1 OP diagnosis (any position) of hypertensive crisis
5. 1 IP / 1 ER diagnosis of hypertension in the primary position

New onset hypertension will be the primary hypertension outcome of interest, and the cumulative incidence of this outcome will be evaluated at 1 month, at 2 months, at 3 months, at 6 months, and at 12 months. When evaluating new onset hypertension, individuals with a prior history of hypertension during the baseline period will be excluded. For individuals with baseline hypertension and anti-hypertension medication use, we will also evaluate changes in medication dosage or initiation of new anti-hypertensive medications within 90 days after initiation of the study medication.

In addition, we will evaluate the occurrence of a single diagnosis of elevated blood pressure reading, without diagnosis of hypertension (ICD-10-CM diagnosis code R03.0) occurring in any diagnosis position in the IP, ER, or OP setting.

The algorithm used to identify patients with migraine in this study has not been validated, but a similar algorithm (Kolodner et al, 2004) had high specificity and low sensitivity. Thus, it is possible that some migraine patients will be misclassified as non-migraine patients and will be excluded from this study.

8.4 Data Sources

This analysis will utilize data from the MarketScan® Commercial and Medicare Supplemental medical claims database, which represents the medical experience of insured employees and their dependents for active employees, early retirees, individuals who continue their insurance coverage under the Consolidated Omnibus Budget

Reconciliation Act, and Medicare-eligible retirees with employer-sponsored medical supplemental plans. The underlying insured population from which the data are drawn is geographically diverse across the US (47% - South, 18% - North, 17% - West, 20% - North Central), 52% of plan participants are male, and 89% are enrolled in fee-for-service plans. These databases are Health Insurance Portability and Accountability (HIPAA) compliant, de-identified, and have been described in previous studies (Velentgas et al, 2006; Walker et al, 2004). The data undergo audits and quality control procedures by the insurer at regular intervals.

The Marketscan® databases contain fully adjudicated eligibility, pharmacy, procedure, and medical claims data for patients enrolled in a large US health plan (IBM Watson, formerly Truven Healthcare). The health plan provides coverage for physician, hospital, and prescription drug services and captures medical claims or encounter data from all available health care sites (inpatient hospital, outpatient hospital, emergency room, physician's office, surgery center, etc.) for virtually all types of provided services. Each facility inpatient admission record contains information on up to sixteen diagnoses (outpatient records contain up to four diagnoses), recorded with ICD-10-CM diagnosis codes and up to sixteen procedures (outpatient records allow for only one procedure) recorded with ICD-10-CM procedure codes, Current Procedural Terminology (CPT), or HCPCS codes. Data are linked at the patient level by a unique identifier that is consistent across services, health plans, and time, and, so, patients can be tracked over multiple years even if they switch health plans when working with a particular employer. Laboratory test results can be linked to the medical and pharmacy claims data for a limited subpopulation of enrollees within the Marketscan® databases. Undiagnosed conditions, and lifestyle and biometric factors (eg, smoking status) are not well captured in claims data. Data are captured when close to 100% of claims have been paid, which results in a lag time between date of service and date of payment of about 3-6 months.

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The following pharmacy claims data allow for longitudinal tracking of medication refill patterns and changes in medications used:

- NDC or HCPCS
- Medication brand name
- Generic product identifier
- Medication strength
- Quantity prescribed

- Days of supply
- Fill date

This analysis will also utilize data from the Marketscan® Medicaid Database, which contains the pooled healthcare experience of more than 44 million Medicaid enrollees, covered under fee-for-service and managed care plans, across multiple states. It includes information on inpatient admissions and services, outpatient services, and prescription drug claims, as well as information on enrollment, long-term care, and other medical care. In addition to standard demographic variables such as age and gender, the Marketscan® Medicaid Database also includes valuable information such as ethnicity, service and provider type, Medicare eligibility, and other federal aid.

8.5 Study Size

Based on recent analyses (Amgen Study 20200218) to evaluate the rate of hypertension in migraine patients, the following number of patients with a migraine preventive treatment were identified within the Marketscan® Early View claims database from May 2018 through January 2020:

- 15 212 erenumab-aooe users
- 17 239 galcanezumab-gnlm or fremanezumab-vfrm users
- 9242 onabotulinumtoxinA users

These migraine preventive treatment users were required to be 18-64 years of age, have a diagnosis for migraine based on ICD-10-CM diagnosis codes or one prescription order for a triptan/ergot in the prior 12 months, continuous enrollment in the claims database for at least 12 months prior to the index date, and no prior prescription for any medication targeting the CGRP pathway. These counts were generated before the February 2020 approval of eptinezumab-jjmr. Assuming a conservative 3-month growth rate of 15%, the expected number of new users during the study period (17 May 2018 – 31 May 2020) will be ~20 000 new users of erenumab-aooe, ~23 000 new users of other mAbs targeting the CGRP pathway, and ~13 000 new users of onabotulinumtoxinA. While new users of the SOC migraine preventive medications (anti-epileptics) were not evaluated, other analyses in the Optum electronic health record database suggest that this new user cohort will be at least as large as the erenumab-aooe new user cohort.

Table 2 provides the 95% confidence interval estimates for various potential risk estimates of the three cardiovascular outcomes (0.2%, 0.5%, 1%, 3%, 5%, 20%, and

30%) based on the projected sample size described above for erenumab-aooe, other mAbs targeting the CGRP pathway, and onabotulinumtoxinA. The risk of acute MI and stroke is expected to be relatively rare across all new user cohorts, while the risk of hypertension is expected to be common.

Table 2. 95% CI Estimates and Half-widths for a Range of Cardiovascular Outcome Values, Based on a Sample Size of 20 000 Erenumab-aooe Users, 23 000 Users of Other mAbs Targeting the CGRP Pathway and 13 000 Onabotulinumtoxin A Users

CV Outcome (%)	Erenumab-aooe N = 20 000		Other mAbs Targeting the CGRP Pathway N = 23 000		OnabotulinumtoxinsA N = 13 000	
	95% CI	Half-width of CI	95% CI	Half-width of CI	95% CI	Half-width of CI
0.20	0.14, 0.26	0.06	0.14, 0.26	0.06	0.12, 0.28	0.08
0.50	0.40, 0.60	0.10	0.41, 0.59	0.09	0.38, 0.62	0.12
1.00	0.86, 1.14	0.14	0.87, 1.13	0.13	0.83, 1.17	0.17
3.00	2.76, 3.24	0.24	2.78, 3.22	0.22	2.71, 3.29	0.29
5.00	4.70, 5.30	0.30	4.72, 5.28	0.28	4.63, 5.37	0.37
20.0	19.5, 20.6	0.55	19.5, 20.5	0.52	19.3, 20.7	0.69
30.0	29.4, 30.6	0.64	29.4, 30.6	0.59	29.2, 30.8	0.79

Abbreviations: CI: confidence interval; mAbs: monoclonal antibodies; CGRP: calcitonin gene-related peptide

Table 3 provides a range of detectable risk ratios for two outcomes of interest (acute MI and stroke), assuming 80% power, alpha-level of 0.05, and equal number of patients in each medication cohort, if a comparative analysis of the erenumab-aooe cohort to each comparator cohort (other mAbs targeting the CGRP pathway, selected SOC migraine preventive medications (anti-epileptics), or selected onabotulinumtoxinA) were conducted. This table assumes a background rate of acute MI of 0.15 per 100 PYs and a background rate of stroke of 0.60 per 100 PYs (Gill et al, 2020).

Table 3. Detectable Risk Ratios for Two Cardiovascular Outcomes

Outcome	Total Population in Each Medication Cohort			
	N = 13 000	N = 17 000	N = 20 000	N = 25 000
Acute MI	2.10	1.94	1.85	1.75
Stroke	1.58	1.51	1.46	1.41

The estimates provided above are for informational purposes only. The final sample size for the study will change due to the criteria applied during the conduct of the protocol.

8.6 Data Management

8.6.1 Obtaining Data Files

The MarketScan® Commercial and Medicare Supplemental medical claims database is part of Amgen's portfolio of licensed data assets.

8.6.2 Linking Data Files

Linking data files will not be necessary for the objectives of this study.

8.6.3 Review and Verification of Data Quality

The MarketScan® Commercial and Medicare Supplemental medical claims database is constructed through collection and standardization of raw data from the appropriate payers, and linking files across time and data type to create a comprehensive and efficient set of database tables. Variables specific to particular employers are added, as are details on clinical information such as therapeutic class, generic product identifier, therapeutic group, etc. Other enhancements are made to improve the data quality and efficiency, for example: updating diagnosis and procedure codes to reflect changes in codes over time if necessary; creating a common synthetic patient identifier that enables patients to be tracked over time and across data types; integrating benefit plan characteristics, enrollment, outpatient pharmaceutical claims, and medical/surgical data. A comprehensive series of edits on the reasonableness and validity of the data are conducted. For example, checking diagnosis against age and gender, charge against payment, and diagnosis and procedure codes against lists of valid values, etc. No data editing, beyond what is applied in the database production process, will be conducted for this study.

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Primary Analysis

For the primary analysis, we will describe baseline patient characteristics, and estimate the risk of three CV outcomes (hypertension, stroke, acute MI) in the following four new user cohorts: (1) erenumab-aooe, (2) other mAbs targeting the CGRP pathway, (3) select anti-epileptic medications, and (4) onabotulinumtoxinA. If appropriate based on comparability analyses, we will also separately compare the risk of acute MI and stroke in patients treated with erenumab-aooe to the risk in each of the other three medication cohorts.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

All descriptive and comparative analyses will be undertaken in the interactive Casual Studio application. Characterization of patient populations by baseline characteristics is easily accommodated by the software. In addition, the application allows for the estimation of the cumulative risk of a right censored outcome that may be subject to dependent (right) censoring. Overall estimates of risk at various time points, as well as estimates of risk stratified by medical history, demographic characteristics, and medication usage can be presented in both tabular and graphical formats.

A major challenge in observational comparative analyses is the lack of exchangeability, with baseline characteristics that may be unbalanced between study groups and potential differential drop-out across the two arms of the study. Causal Studio is a tool designed to address exchangeability in observational studies. More specifically, the application allows for the estimation of the cumulative risk of a right-censored counterfactual outcome that may be subject to dependent censoring and confounding. Causal Studio is structured as follows: (1) based on user-specified propensity score models and/or censoring models, generate inverse probability of treatment weights (IPTWs) and inverse probability of censoring weights (IPCWs); (2) provide diagnostics (eg, distribution of the propensity score, by treatment groups; and, standardized mean differences between treatment groups for categorical and continuous variables) that enable the user to assess whether the analyses should proceed to the comparative stage, and, if appropriate, (3) execute the structural (ie, weighted) model to estimate the effect of treatment on the outcome. For our purpose, we will use Causal Studio to separately compare the risk of acute MI and stroke in new users of erenumab-aooe versus new users of each of the other three new user comparator cohorts.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

This study is based on an analysis of automated medical and prescription claims data, and, because claims are collected for the purpose of payment, we assume that diagnoses and prescriptions reported in claims data are a true and accurate reflection of the health status, and medication and health service usage, for an individual. This will not always be true because individuals will sometimes not use medications as prescribed and will not report certain diagnoses. However, for the serious diagnoses, and related medication usage considered here, the presence of an associated claim will be interpreted as indicating that the procedure was conducted, the disease was present,

or the drug was consumed. The absence of a claim will indicate the opposite. As a result, when using claims data for research, missing data will be a concern mainly when lifestyle and biometrics are important for a given analyses because these items are not well captured in claims.

Patient demographics may be missing for a small subset of patients in claims data. Complete case analysis will be used when the overall missing observations (due to missing age and gender) is small. If a combination of these two covariates is missing for 5% or less of the study population, we will adopt a complete case analytic approach. An alternative solution that will be explored to account for the missing data is the use of inverse probability of missing weights, with one weight that would be estimated for missing age, and another weight that would be estimated for missing gender.

The MarketScan® claims database contains death information for a limited number of individuals who died in the inpatient setting. As a result, we assume that information on death is missing in MarketScan®. This missing data presents a challenge in observational studies with long follow-up, where competing risk by death might influence the study results. Our study, with a maximum possible follow-up of ~2.5 years, will be undertaken in a relatively young population, and we assume that the impact of competing risk by death will be minimal.

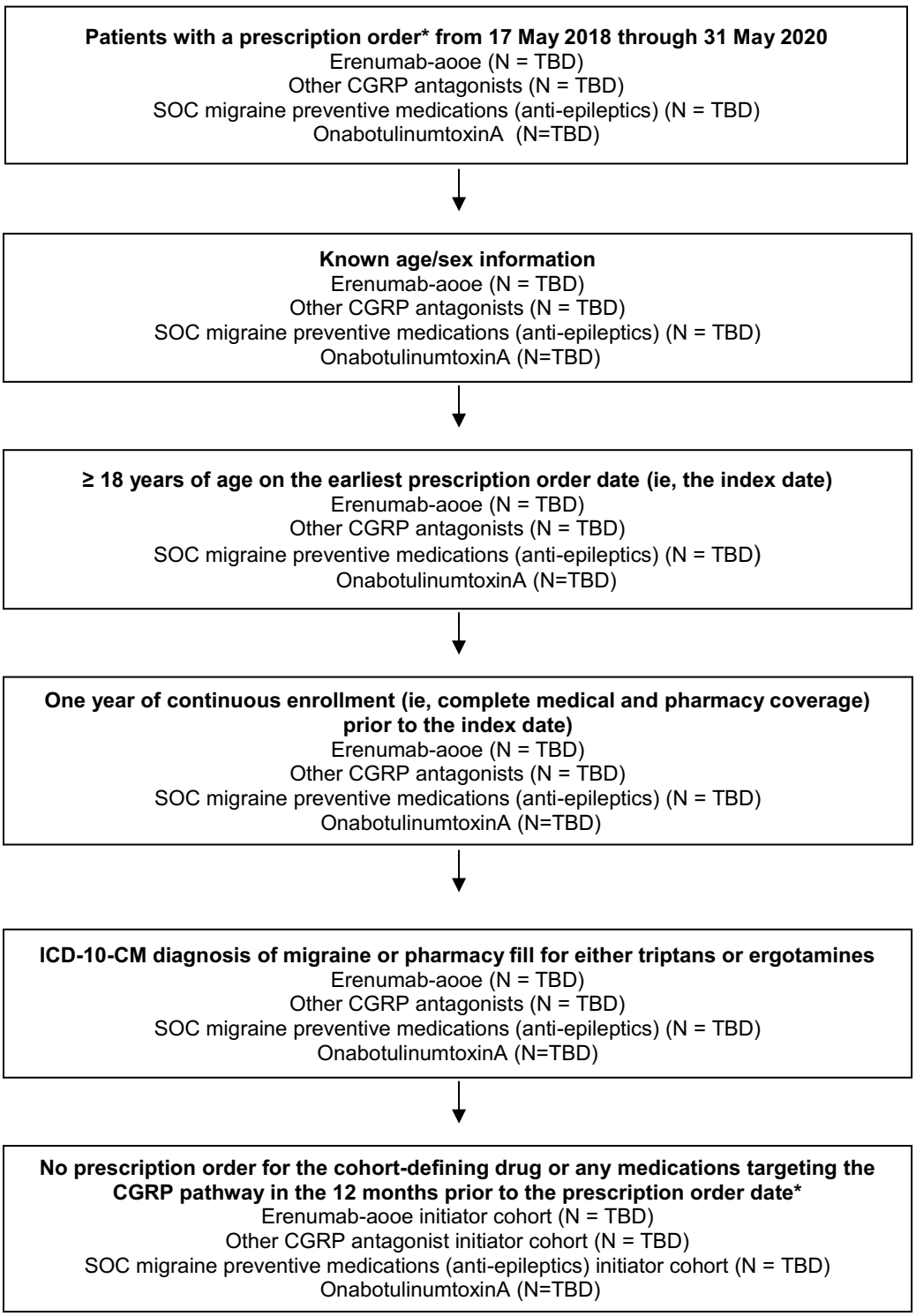
In claims data, loss to follow-up may occur as a result of plan disenrollment from the MarketScan® database. We will evaluate any loss to follow-up with descriptive statistics, and account for potential differential loss of follow-up with inverse probability of censoring weights.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

Selection of cohort members will begin by identifying all patients with at least one prescription order for erenumab-aooe, other mAbs targeting the CGRP pathway, selected anti-epileptic medications, and onabotulinumtoxinA , between 17 May 2018 through 31 May 2020 (or, the most recent data available in MarketScan®). Cohort members who meet the inclusion/exclusion criteria for the study will be included in the final analytic data files. Attrition for all four cohorts will be described in a flow chart (Figure 1).

Figure 1. Formation of Erenumab-aooe, Other mAb Targeting the CGRP Pathway, SOC Migraine Preventive Medications (anti-epileptics), and OnabotulinumtoxinA Cohorts



8.7.2.3.2 Description of Subject/Patient Characteristics

Baseline characteristics, including the most prevalent diagnoses, procedures, and medication class prescriptions will be summarized for the four study cohorts. Descriptive statistics using mean and standard deviation or median and $25^{th}/75^{th}$ percentile estimates for continuous variables and number and percentages (n, %) for categorical variables will be used to examine patient characteristics.

8.7.2.4 Analysis of the Primary Endpoints

For exposition of the descriptive and comparative analytic methods below, we will focus on comparing the effect of erenumab-aooe versus other mAbs targeting the CGRP pathway on the outcome of acute MI, accounting for both confounding and differential loss to follow-up / switching / discontinuation. Note, however, that the same methods will also be applied for the outcome of stroke, for the following comparisons:

(1) Erenumab-aooe vs other mAbs targeting the CGRP pathway (galcanezumab-gnlm, fremanezumab-vfrm, eptinezumab-jjmr)

(2) Erenumab-aooe vs selected SOC migraine preventive medications (anti-epileptics) (topiramate, valproic acid, divalproex sodium)

(3) Erenumab-aooe vs. onabotulinumtoxinA

The technical description of the study analyses below is ordered in the following manner. First, the naïve, unadjusted cumulative incidence (ie, risk) of acute MI is estimated in both new users of erenumab-aooe and new users of other mAbs targeting the CGRP pathway. This first step constitutes the descriptive analyses. Second, the overlap of the propensity score across treatment groups is evaluated, the mean standardized difference for all variables included in the propensity score model is assessed, and a determination is made on whether the negative control outcomes showed treatment associations within the acceptable bounds around the null. Finally, based on these comparability analyses, gated analyses in which the risk of acute MI in new users of erenumab-aooe is compared to the risk of acute MI in new users of other mAbs targeting the CGRP pathway, accounting for both confounding and differential loss to follow-up / switching / discontinuation, will be initiated.

Descriptive Analyses

Estimating the Cumulative Distribution of a Right-Censored Outcome

Following the notation by Cole et al (Cole et al, 2015) and Brookhart (Brookhart, 2019), let T_i be the continuous random variable for the time from treatment initiation to acute MI

for the i^{th} patient, and let t represent the realization (ie, a specific value) of T_i. The cumulative incidence (ie, risk) of the acute MI outcome at time t is the complement of the Kaplan-Meier survival function,

$$R(t)=1-S(t)=\Pr(T_i<t).$$

The entire function over time is of interest, but the cumulative incidence of acute MI at times *t=6 months, t=1 years, and t=2 years* after the start of treatment will also be estimated.

The naïve, unadjusted cumulative incidence of the outcome, $R(t)$, subject to right-censoring by C, can be conveniently estimated with the following estimating function:

$$\widehat{Pr}(T<t)=\frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i I\ (T_i<t)}{Pr\ (\Delta_i=1)},$$

where $\Delta=I(T<C)$ is an indicator that the patient was uncensored. In the denominator $Pr\ (\Delta_i=1)$ implies that censoring is non-informative (ie, $C \perp T$), and, so, the cumulative incidence curve that is initially estimated assumes that censoring occurs at random.

In addition to estimating the cumulative incidence, the incidence rate, overall, and by selected baseline characteristics, with 95% confidence intervals based on the Poisson distribution, will also be estimated.

Comparability Analyses

Estimating the Propensity Score

Next, a linear-logistic model for the conditional probability of treatment, $Pr\ (\mathrm{A}_i{=}a|L_i)$, where L_i is a vector of measured confounders of the exposure and the outcome, as well as risk factors for the outcome, will be fit (Brookhart et al, 2006). The conditional probability of treatment given a set of covariates is commonly referred to as the propensity score (PS).

For the first set of comparability analyses, overlap of the propensity score across treatment groups will be evaluated. Non-overlap in the PS will be addressed with trimming of subjects at the extremes of the PS distribution. In addition, the mean standardized difference for all variables included in the PS model will be estimated. An absolute mean standardized difference $>$ 0.1 for a given confounder or risk factor for the outcome will be used as a measure of potential imbalance (Austin, 2009; Austin et al, 2007). Covariates in the propensity score model with an absolute standardized difference $>$ 0.1 will be examined for potential inclusion in the outcome model or will be used as evidence of insufficient overlap in the distribution of baseline characteristics across treatment groups. Using PS overlap and cut points for the mean standardized difference to make decisions about cohort comparability are part of an iterative process that potentially involves trimming of subjects (because of poor overlap in the PS) and accounting for confounders in the outcome model rather than the exposure model. As such, this process provides guidance on whether cohorts are comparable and contributes additional information to the body of evidence used to determine whether comparative analyses should be initiated or not.

Negative Control Outcome Analyses

Negative control outcome studies are designed to detect and reduce residual bias between treatment groups (Lipsitch et al, 2007, Arnold and Ercumen, 2016). Negative control outcomes are chosen that have no plausible mechanism by which they can be caused by the treatment of interest but do share unmeasured confounders (eg, lifestyle [smoking history, alcohol use], and anthropometric [BMI] variables) with the primary treatment-outcome relation. After controlling for measured confounders, any observed association between the treatment and negative control outcome can be attributed to unmeasured confounding between the groups, rather than a true causal relationship. For example, if the outcome for a comparative safety study is acute MI, the ideal negative control outcomes would share a similar confounding structure as would be hypothesized

for treatment selection (eg, erenumab-aooe vs. other mAbs targeting the CGRP pathway) and the outcome of interest (acute MI). Common outcomes used as negative controls in prior epidemiologic studies of treatments include risks of accidents or hospitalizations for trauma or injury (Dormuth et al, 2009; Brookhart et al, 2007; Jackson et al, 2006).

Selection of migraine preventive treatment is likely affected by many factors associated with a patient's prognosis that can lead to bias when comparing treatment groups in non-interventional settings. Patients initiating newer medications, such as mAbs targeting the CGRP pathway, may have more severe disease and be at higher risk for poor outcomes in comparison to patients initiating other migraine preventive therapies, such as selected SOC migraine preventive medications (anti-epileptics) or onabotulinumtoxinA . It is of interest to understand whether the incidence of clinical outcomes among patients initiating erenumab-aooe can be validly compared with the incidence among patients initiating other migraine preventive medications after controlling for measured confounding factors. We will use a negative control study design to investigate this comparability of patients initiating different types of migraine preventive treatments. The results of this analysis will help inform the appropriateness of comparative safety analysis for the two CV outcomes of interest (acute MI and stroke). The negative control outcomes that may be included in the analysis are:

- Decubitus ulcer
- Dementia
- Transfusions
- Accidents
- Annual wellness visit
- Pelvic exams for cancer screening
- Influenza vaccine use
- Mohs surgery
- Herpes zoster vaccine
- Colon cancer screening
- Visual field tests
- Non-skin cancers
- Fractures

We will estimate the cumulative incidence (ie, risk) and risk ratios of negative control outcomes for each treatment group comparison, controlling for measured confounders and potential differential loss to follow-up with inverse probability weights. Null

associations between the migraine preventive treatments and the negative control outcome are hypothesized. For this component of the study, an expert panel will guide selection of the final set of negative control outcomes to be used for this study.

We will use Bayesian analyses to provide evidence of treatment group comparability. The negative control effect estimates will be included as inputs (priors) for each treatment comparison, to create a posterior distribution of the bias parameter. Based on the distribution of the bias parameter, we will then estimate the probability that the bias for treatment comparison X vs. Y is less than some threshold. We will subjectively set the threshold for the risk ratio as anything between 0.91 and 1.10 as acceptable, and the Bayesian analysis will provide the posterior probability that the level of bias (unmeasured confounding) is $<10\%$ of the null. If this probability is greater than 90% we will proceed with the comparative analysis.

Decision to Proceed to Comparative Analyses

The decision to move forward with the comparative analysis for either the acute MI or the stroke outcome will be made after assessment of covariate balance across treatment groups (eg, based on an absolute standardized mean difference of $>$ 0.10 for covariates included in the PS model, and adequate overlap in the PS across treatment arms), null findings for the final set of negative control outcomes (ie, posterior probability $>$ 90% that the level of bias is less than 10% of the null), and sufficient sample size to detect a risk ratio of 2.0 or greater. For the relatively rate outcome of acute MI, a total of 15,000 patients in each comparator arm will be needed in order to detect a risk ratio of 2.0 or greater, assuming 80% power and a background rate of acute MI of 0.15 per 100 person-years. In contrast, for the outcome of stroke, 3,750 patients will be required in each treatment arm to detect a risk of 2.0 or greater, assuming 80% power and a background rate of stroke of 0.60 per 100 peson-years..

Gated Analyses

Estimating the Cumulative Distribution of a Right-Censored Counterfactual Outcome

If appropriate based on comparability analyses, a comparison of the effect of erenumab-aooe versus other mAbs targeting the CGRP pathway on acute MI at t=6 months, t=1 year, and t=2 years will be undertaken, where the effect measure of interest is the RR, and the possible sources of bias are confounding and dependent censoring.

First, to address confounding, let A_i be a discrete random variable denoting exposure to erenumab-aooe (a=1) or other mAbs targeting the CGRP pathway (a=0) for patient i,

and let T_i^a be the counterfactual time from medication initiation to the acute MI outcome for patient i. The counterfactual cumulative incidence of the outcome is then $R^a(t)=\Pr(T_i^a<t)$, and the estimate of the RR is:

$$RR(t)=\frac{R^1(t)}{R^0(t)}$$

To account for confounding we will use IPTWs, which will be constructed as follows:

$$\widehat{W}_i^1=\frac{1}{\widehat{Pr}(A_i=a|L_i)}$$

For the analyses described here, $Pr\ (A_i=a|L_i)$ is the conditional probability of treatment (ie, the propensity score described previously). The set of covariates comprising L_i are listed in Appendix D. The cumulative incidence curves for acute MI, weighted by IPTWs, now account for confounding by measured covariates, but still assume that censoring occurs at random. As previously noted, the risk ratio estimates and 95% confidence intervals at six months, at one year, and at two years will be presented; however, we are also interested in the entire cumulative incidence curve over time. The cumulative incidence curve will be presented graphically.

Estimating the Cumulative Distribution of a Right-Censored Counterfactual Outcome, Accounting for Informative Censoring

To accommodate informative censoring due to drop-out from a health plan, switching to an alternate medication, or discontinuation of study medication, IPCWs will be estimated. Specifically, a linear-logistic model for the conditional probability of remaining uncensored $Pr\ (\Delta_i=1|D_i,A_i)$, where D_i is a vector of measured confounders of drop-out / switching / discontinuation and the outcome and A_i is a discrete random variable denoting exposure to erenumab-aooe ($a=1$) or other mAbs targeting the CGRP pathway ($a=0$) for patient i, will be fit. IP censoring weights will then be constructed as:

$$\widehat{W}_i^2=\frac{1}{\widehat{Pr}(\Delta_i=1|D_i,A_i)}$$

Variables to be included in the censoring model will include demographic characteristics, medication usage, disease history, and utilization of medical resources, all of which will be included in the censoring model (see Appendix D). For new users of erenumab-aooe and other mAbs targeting the CGRP pathway, the cumulative incidence curves weighted

by inverse probability of censoring weights provide a valid estimate of the risk for acute MI at various time points, now accounting for informative censoring.

The cumulative incidence curves for acute MI, weighted by the multiple of IPTWs (ie, $\widehat{W}_i^1$) and IPCWs (ie, $\widehat{W}_i^2$), account for both confounding by measured covariates and informative censoring. The full estimating function for the counterfactual cumulative incidence of acute MI is then defined as:

$$\widehat{Pr}(T^a<t)= \frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i I\ (T_i<t) I(A_i=a)}{Pr\ (\Delta_i=1|D_i, A_i)\ \Pr(A_i=a|L_i)}$$

Modeling Assumptions

Results from these analyses will be subject to limitations if certain assumptions of the methods are violated. The assumptions include the following:

i. Conditional exchangeability, given measured covariates
ii. No misclassification of the exposure, outcome, or other study variables
iii. Stable unit treatment value assumption (SUTVA), which requires that outcomes are not correlated
iv. Consistency, such that exposures can be mapped to well-defined interventions
v. Positivity, wherein there are at least some exposed and unexposed individuals at each level of the confounders
vi. No misspecification of the three models considered in these analyses: (a) the structural (ie, weighted) model, (b) the exposure model (ie, the PS model), and (c) the censoring model(s).

Discussion of the impact of violations of these assumptions are deferred to later sections.

8.7.2.5 Sensitivity Analysis

8.7.2.5.1 Subgroup Analysis

Not applicable.

8.7.2.5.2 Stratified Analysis

The cumulative incidence for all three CV outcomes (hypertension, acute MI, stroke) will be stratified by prior history of cardiovascular disease (defined as the occurrence of any of the following events during the baseline period: ischemic stroke, hemorrhagic stroke, unspecified stroke, transient ischemic attack, subarachnoid hemorrhage, intracerebral hemorrhage, other acute cerebrovascular events, other ischemic cerebrovascular events, acute myocardial infarction, myocardial ischemia, congestive heart failure, acute

ventricular tachycardia, acute atrial fibrillation, paroxysmal atrial fibrillation, acute ventricular fibrillation, premature atrial contractions, Prinzmetal angina, unstable angina pectoris, other and unspecified angina pectoris, coronary revascularization, peripheral artery disease, or venous thromboembolism), by prior history of risk factors for cardiovascular disease, including hyperlipidemia, diabetes, and hypertension, and by migraine aura. In addition, the cumulative incidence of acute MI, and, separately, the cumulative incidence of stroke will be stratified by prior history of hypertension only.

8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

For the comparative analyses, in addition to identifying confounders for the PS models based on literature review, we will also empirically identify covariates for inclusion with a high-dimensional PS approach. Covariates will be identified from each of five data dimensions in claims data (drug class, ICD-10-CM diagnosis codes, ICD-10-CM procedure codes, HCPCS codes, and CPT codes), and ranked on association with the exposure, association with the outcome, and association with the exposure and the outcome (ie, confounders). In the final high-dimensional PS model, we will include the top 25 variables associated with the exposure and the outcome (because these variables help to reduce bias) and the top 25 variables associated with the outcome only (because these variables help to improve precision, without also increasing bias) (Brookhart 2006). Use of high-dimensional PS can help to identify potential residual confounding bias when compared to PS models based on variables selected via subject-matter knowledge.

8.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

This study will estimate the risk of hypertension, stroke, and acute MI among individuals who are exposed to erenumab-aooe, other mAbs targeting the CGRP pathway (galcanezumab-gnlm, fremanezumab-vfrm, eptinezumab-jjmr), select SOC migraine preventive medications (anti-epileptics) (topiramate, valproic acid, divalproex sodium), and onabotulinumtoxinA. Hypertension, stroke and acute MI outcomes will be identified with ICD-10-CM codes.

8.8 Quality Control

The following list details the items that were considered or the actions that will be undertaken, as part of the specific quality assurance and data handling processes for this study:

- When customized cohorts are built for analyses, the level of QC will be determined as specified in Amgen MAN-002344.

- The Causal Studio SOP-431037 will be followed to ensure reproducible results.
- The study protocol, including analytic specifications, will be reviewed by the entire study team for overall clarity and validity of the study approach.
- The epidemiologist will check the distributions of enrollment data and sample data to ensure basic eligibility requirements are met. The epidemiologist will confirm that the distributions of age and index dates for the study cohorts are consistent with expectations. Cross-tabulation of variables included in final tables are reviewed for plausibility of results.
- The study team will review the preliminary and final output for consistency with expectations based on prior knowledge of the disease states.
- The epidemiologist will confirm that tables and content match the study protocol, that column percentages are computed accurately, and that tables are free of errors.
- Statistical programs and analytical data files produced to generate results will be archived for future reference.

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

8.9.1.1 Measurement Error/Misclassification

Measurement error may occur when identifying medication cohorts in claims databases because the presence of a claim for a prescription does not necessarily mean that the medication was taken as prescribed. Also, medication given as free samples by a physician will not be observed in claims data. For the current analyses, measurement error may also occur due to the free drug and coupon programs that have been available after launch of CGRP mAbs. Patient assistance programs are often sponsored by pharmaceutical companies to provide drugs at low or no cost to patients who lack prescription drug coverage for a particular medication. Using a different data source (not claims-based), it has been reported that 76% of the first 64 439 new users of erenumab-aooe were covered through “discount/coupon” programs (Hines et al, 2019). Analyses using more recent data show that the majority of erenumab-aooe patients (~60%) continue to have coverage using this program. Similar programs have been in place for the other mAbs targeting the CGRP pathway. Although this will result in missing claims, it is not expected that this would introduce bias when assessing claims in relation to the outcomes under study. Care should be taken, however, to ensure that results are not interpreted as risk for the outcome in people who have *newly* started CGRP mAbs, but rather as risks in people *who have a first claim* in the database.

Patients who receive medical insurance from federal programs, such as Medicaid, are not eligible to receive additional financial assistance (through the Aimovig™ Ally Card) for erenumab-aooe (with the exception of the Safety Net program for Medicare

recipients), as this is stipulated by the federal government. This restriction of not allowing patients on government-funded health care programs to receive any financial assistance applies to all pharmaceutical companies, and, thus, patients on other mAbs targeting the CGRP pathway through government-funded health programs would also not be eligible to receive any financial assistance. As a consequence, the Marketscan® Medicaid Database provides an opportunity to indirectly evaluate the impact of the free drug and coupon programs on estimating risk amongst commercially insured patients, albeit in a study population that is potentially sicker and with higher levels of comorbidities. Through December 2019, there were 3181 new users of erenumab-aooe and 1692 new users of other mAbs targeting the CGRP pathway in the Marketscan® Medicaid Database. The expected number of new users through the administrative end of the study (31 May 2020) is: erenuamb ~ 4000; other mAbs targeting the CGRP pathway ~2500. We will estimate the cumulative incidence (ie, risk) of hypertension in both of these cohorts. Given the relatively small cohort sizes, estimation of the risk of rare outcomes such as acute MI and stroke will not be feasible. Comparative analyses will not be undertaken in the Marketscan® Medicaid Database.

8.9.1.2 Information Bias

There is the potential for the selected SOC migraine preventive medications (anti-epileptics) cohort and the onabotulinumtoxinA cohort to take their index medication for an indication other than migraine. To ensure these cohort members are migraine patients, a combination of two migraine diagnosis codes and/or prescription orders for migraine treatments will be required in the 12-month baseline period.

8.9.1.3 Selection Bias

Differential loss to follow-up is a type of selection bias that poses a potential threat to the internal validity of any study, including randomized studies. Loss to follow-up can be broadly conceptualized as any termination of treatment prior to the administrative end of the study, including, but not limited to, discontinuation of assigned treatment, switching to the alternate study arm, drop-out as a result of change in health plan, drop-out due to illness/frailty, etc. If all disenrollment occurred at random (eg, because of the loss of a health plan at the end of the calendar year), there would be loss in precision, but no increase in bias of the effect estimate. In most studies using claims data, however, we assume that health plan disenrollment, particularly mid-year disenrollment, does not occur at random. Under these circumstances, we must use methods such as IP weights to account for differential health plan disenrollment. These methods have been

described earlier and assume that we are able to identify strong confounders of disenrollment / switching / discontinuation and the outcome. Such covariates can be difficult to identify in claims data, but recent research has elucidated several baseline predictors of health plan disenrollment (Butler et al, 2019). More relevant predictors may be time-varying covariates (such as medical history indicators) that occur proximate to health plan disenrollment. We will explore inclusion of time-varying covariates in our censoring models, to address differential health plan disenrollment / switching to an alternate CGRP mAb / discontinuation of study medication.

8.9.1.4 Confounding

A few studies suggest that there is a positive correlation between cigarette smoking and migraine (Sacco and Kurth, 2015; Le et al, 2011; Winsvold et al, 2011), and other studies describe a three- to nine-fold increased risk of ischemic stroke in migraineur women who smoke (Chang et al, 2019; Tzouiro et al, 1993). Smoking is a confounder in our study but is unmeasured in claims data. Estimates of the relative risk for our two cardiovascular outcomes (acute MI and stroke) may be biased upward or downward in a comparative study when an important confounder is not accounted for in the analysis. We propose the use of simple quantitative bias methods to provide a corrected effect estimate for the case of a dichotomous exposure, a dichotomous outcome, and an unmeasured but known dichotomous confounder (Lash et al, 2009).

When exposure, confounder, and outcome are dichotomous, accounting for confounder bias is possible if three parameters are known:

1. The hypothesized association between the known but unmeasured confounder (C) and the outcome (or disease, D), ie, the risk ratio (RR_{CD}). The relevant effect estimate chosen to describe the association between the unmeasured confounder and the outcome should be the same as the effect estimate used to describe the association between the exposure and the outcome in the comparative analysis. For our study the effect estimate of interest is the risk ratio.
2. The hypothesized proportion of subjects with the confounder in the exposed group, p_1
3. The hypothesized proportion of subjects with the confounder in the unexposed group, p_0

These bias parameters can be estimated from literature values, or they can be based on the experience of the investigator. A range of values can also be substituted to form a sensitivity analysis, to investigate the degree to which the bias must be present before the study conclusions are affected. We will use bias parameters identified from the

literature as our starting point, and then undertake additional sensitivity analyses by specifying a range of values for the bias parameters around the initial starting values. The goal of the quantitative bias tool in this case is to provide an adjusted effect estimate, accounting for the bias introduced by the unmeasured confounder.

The estimate of the observed effect estimate in the weighted cohort, not accounting for bias as a result of a missing confounder, will be calculated in the usual way:

$$\widehat{RR} = \frac{a\ (b+d)}{b\ (a+c)}$$

where a, b, c, and d are the counts in the 2x2 table for the four combinations of outcome and exposure, and m and n are the column totals:

	Exposure +	Exposure -
Outcome +	a	b
Outcome -	c	d
Total	m	n

If any of the counts are zero, then a continuity correction of +1/2 will be added to all the cells in the table, before any further calculations. The 95% confidence interval (CI) for the RR is calculated using the large sample formula:

$$\exp\{\ln(\widehat{RR}_{Obs}) \pm 1.96 \times \mathrm{SE}(\ln \widehat{RR}_{Obs})\}$$

where,

$$\mathrm{SE}(\ln \widehat{RR}_{Obs}) = \sqrt{1/a - 1/m + 1/c - 1/n}$$

The adjusted RR, accounting for the unmeasured confounder, are estimated as follows:

$$\widehat{RR}_{Adjusted} = \widehat{RR}_{Obs} \times \frac{RR_{CD}p_0 + (1-p_0)}{RR_{CD}p_1 + (1-p_1)},$$

In addition to undertaking bias analyses for a missing confounder, we will also estimate the relative risk of the cardiovascular outcomes in a subset of 'apparent smokers,' who will be identified by prescription medications approved for smoking cessation.

8.9.2 External Validity of Study Design

The primary analyses for this study are limited to individuals with employer-sponsored health coverage included in the MarketScan® Commercial and Medicare Supplemental

medical claims database. Thus, results of this analysis may not be generalizable to individuals with other types of insurance coverage or those without health insurance. Also, for individuals with employer-sponsored health insurance, the results of these analyses are likely also not generalizable to those who first obtained their medication through the free drug programs.

8.9.3 Analysis Limitations

This study is based on an analysis of automated medical and prescription claims. While claims data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, and health care resource utilization, all claims databases have certain inherent limitations because the claims are collected for the purpose of payment and not research. Presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. Medications obtained over-the-counter or provided as samples by the physician will not be observed in claims data. Presence of a diagnosis code on a medical claim is not positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Duration of follow-up can be limited in claims data due to individuals changing health insurance plans.

There are challenges to evaluating drug-induced hypertension when using administrative claims data. For example, it can be difficult in claims data to distinguish between transient and true hypertension given issues of 'rule-out' diagnoses, 'white coat' hypertension, and hypertension caused by other medical conditions (eg, migraine pain) and not the medication. Also, the blood pressure measurements on which the hypertension diagnosis is based can be inaccurate regardless of the healthcare setting.

Changes in blood pressure are difficult to assess, even in the context of randomized studies with active data collection. In real world settings, changes in blood pressure may be asymptomatic and under-ascertained versus the more acute outcomes of stroke and acute MI which require more immediate medical attention. Finally, hypertension has been conceptualized more as a risk factor and not strictly a cardiovascular outcome in validation studies using claims data. Modification of these validated algorithms is necessary when hypertension is evaluated not as a baseline characteristic but as a drug-induced outcome.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

As described in Section 8.9.1.1, because of available free drug coupon programs for mAbs targeting the CGRP pathway, prescriptions for initial use of the medications will be

missing for some patients. Consequently, when using claims data, the CGRP mAb medication cohorts will include incident users of CGRP mAbs, as well as prevalent users of CGRP mAbs.

8.10 Other Aspects

Not applicable.

9. Protection of Human Subjects

9.1 Institutional Review Board

This is a retrospective cohort study using the MarketScan® Commercial and Medicare Supplemental medical claims database and is considered secondary data collection. No primary data collection will occur, consent is not needed, and Institutional Review Board approval is not required. The data does not include any individually identifiable data. All database records are de-identified and fully compliant with the United States patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996.

10. Collection, Recording, and Reporting of Safety Information and Product Complaints

10.1 Safety Collection, Recording and Submission to Amgen Requirements

This study is analyzing secondary data from the MarketScan® Commercial and Medicare Supplemental medical claims database. The safety outcomes that are listed in Section 8.3.2 will be documented and analyzed in this study. These will be reported in aggregate in the final study report as incidence rates or cumulative incidence (ie risk). See Section 8.3.2 for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Reportable events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend or terminate the protocol at any time.

12. Plans for Disseminating and Communicating Study Results

12.1 Publication Policy

The results of the study will be submitted for publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

1. Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

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14. Appendices

Appendix A. List of Stand-alone Documents

None.

Appendix B. ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	8.2.1
1.1.2 End of data collection[2]	☒	☐	☐	8.2.1
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

This study will be registered in the EU PAS Register, after approval by our internal governance body (Observational Research Review Group)

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6.2
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2
2.1.2 The objective(s) of the study?	☒	☐	☐	7.1
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	6.4
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1
3.3 Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	8.7.2.4
3.4 Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.7.2.4
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10.1

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	8.2.1
4.2.2 Age and sex	☒	☐	☐	8.2.2
4.2.3 Country of origin	☒	☐	☐	8.4
4.2.4 Disease/indication	☒	☐	☐	8.2.2
4.2.5 Duration of follow-up	☒	☐	☐	8.2.5
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	8.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1
5.2 Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	8.4
5.3 Is exposure categorised according to time windows?	☐	☒	☐	
5.4 Is intensity of exposure addressed? (eg, dose, duration)	☐	☒	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	8.2.5
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.1

Comments:

Although the PK of erenumab are not specifically described, we note that the allowable gap between administrations of 30 + 60 days = 90 days is the time window allowed before are considered to have discontinued. The 90 day window approximates the half-life of the medication.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.2
6.3 Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8.3.4
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (eg, confounding by indication)	☒	☐	☐	8.9.1.4
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	8.9.1.3
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9.1.2

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.7.2.5.2

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.4
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3.2

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
	9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.4
	9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.4
	9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4	Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7.2
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	8.5
10.3	Are descriptive analyses included?	☒	☐	☐	8.7.2.3.2
10.4	Are stratified analyses included?	☒	☐	☐	8.7.2.5.2
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.7.2.4
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.2.2
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	8.7.2.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9.1
12.1.2 Information bias?	☒	☐	☐	8.9.1
12.1.3 Residual/unmeasured confounding?	☒	☐	☐	
(eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				8.9.1
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.5

Comments:

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

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	11

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol:
PPD

Date: 23/March/2021

Signature: _____

Appendix C. Code Lists and Algorithms to Identify Study Variables

Erenumab-aooe, galcanezumab-gnlm, fremanezumab-vfrm, eptinezumab-jjmr, topiramate, valproic acid, divalproex sodium, and onabotulinumtoxinA codes (Note: codes are subject to change upon further review at the time of analysis)

Code description	Code type	Code
Erenumab	NDC	55513084101, 55513084102, 55513084001, 55513084002, 55513084201, 55513084300, 55513084301
Fremanezumab	HCPCS	J3031
Fremanezumab	NDC	51759020410, 51759020210, 51759020222, 51759020411, 51759020211
Galcanezumab	NDC	00002143611, 00002143627, 00002237711, 00002237727, 00002311509, 00002143601, 00002237701, 00002311501, 00002143661, 00002143601
Eptinezumab	NDC	67386013051
OnabotulinumtoxinA	HCPCS	J0585
OnabotulinumtoxinA	NDC	00023114501, 54868412300, 00023392102, 00023391950, 00023923201, 00023923250, 54868412300
Topiramate	NDC	00245107115, 00245107130, 00245107215, 00245107230, 00245107415, 00245107430, 00245107515, 00245107530, 00245107315, 00245107330, 00045064265, 18837015498, 18837015598, 18837015690, 18837015698, 55887051720, 00045063965, 16590022630, 16590022656, 16590022660, 16590022672, 16590022690, 18837015530, 18837015560, 18837015596, 21695012815, 21695012860, 33358034156, 49999069801, 49999069815, 49999069830, 49999069860, 49999069890, 50458063965, 52959078060, 54569483100, 54868467200, 54868467201, 54868467202, 54868467203, 55045307601, 55045307606, 55289090130, 55887051730, 55887051760, 55887051782, 55887051790, 57866019001, 58016047800, 58016047810, 58016047830, 58016047840, 58016047860, 58016047890, 60760063930, 60760063960, 60760063990, 63629332101, 63629332102, 63629332103, 63874112806, 67544047782, 67544047787, 68115045615, 68115045630, 68115091860, 68258904301, 68387055512, 68387055560, 00045064065, 12280029815, 12280029830, 12280029860, 16590022730, 16590022760, 16590022772, 16590022790, 18837015660, 21695012915, 49999095560, 50458064065, 54868534300, 54868534301, 55289043330, 55887018630, 55887018660, 55887018690, 57866556102, 63629336501, 63629336502, 63629336503, 63629336504, 63629336505, 00045064165, 12280002215, 12280002290, 16590022830, 16590022845,

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Migraine codes

Code	Code type	Code description	**Setting** (Any diagnosis position)
G43	ICD-10-CM Diagnosis	Migraine	1 IP / 1 ER / 2OP
G43.0	ICD-10-CM Diagnosis	Migraine without aura	1 IP / 1 ER / 2OP
G43.00	ICD-10-CM Diagnosis	Migraine without aura, not intractable	1 IP / 1 ER / 2OP
G43.001	ICD-10-CM Diagnosis	Migraine without aura, not intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.009	ICD-10-CM Diagnosis	Migraine without aura, not intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.01	ICD-10-CM Diagnosis	Migraine without aura, intractable	1 IP / 1 ER / 2OP
G43.011	ICD-10-CM Diagnosis	Migraine without aura, intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.019	ICD-10-CM Diagnosis	Migraine without aura, intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.1	ICD-10-CM Diagnosis	Migraine with aura	1 IP / 1 ER / 2OP
G43.10	ICD-10-CM Diagnosis	Migraine with aura, not intractable	1 IP / 1 ER / 2OP
G43.101	ICD-10-CM Diagnosis	Migraine with aura, not intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.109	ICD-10-CM Diagnosis	Migraine with aura, not intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.11	ICD-10-CM Diagnosis	Migraine with aura, intractable	1 IP / 1 ER / 2OP
G43.111	ICD-10-CM Diagnosis	Migraine with aura, intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.119	ICD-10-CM Diagnosis	Migraine with aura, intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.4	ICD-10-CM Diagnosis	Hemiplegic migraine	1 IP / 1 ER / 2OP
G43.40	ICD-10-CM Diagnosis	Hemiplegic migraine, not intractable	1 IP / 1 ER / 2OP
G43.401	ICD-10-CM Diagnosis	Hemiplegic migraine, not intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.409	ICD-10-CM Diagnosis	Hemiplegic migraine, not intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.41	ICD-10-CM Diagnosis	Hemiplegic migraine, intractable	1 IP / 1 ER / 2OP

Code	Code type	Code description	**Setting** (Any diagnosis position)
G43.411	ICD-10-CM Diagnosis	Hemiplegic migraine, intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.419	ICD-10-CM Diagnosis	Hemiplegic migraine, intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.5	ICD-10-CM Diagnosis	Persistent migraine aura without cerebral infarction	1 IP / 1 ER / 2OP
G43.50	ICD-10-CM Diagnosis	Persistent migraine aura without cerebral infarction, not intractable	1 IP / 1 ER / 2OP
G43.501	ICD-10-CM Diagnosis	Persistent migraine aura without cerebral infarction, not intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.509	ICD-10-CM Diagnosis	Persistent migraine aura without cerebral infarction, not intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.51	ICD-10-CM Diagnosis	Persistent migraine aura without cerebral infarction, intractable	1 IP / 1 ER / 2OP
G43.511	ICD-10-CM Diagnosis	Persistent migraine aura without cerebral infarction, intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.519	ICD-10-CM Diagnosis	Persistent migraine aura without cerebral infarction, intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.6	ICD-10-CM Diagnosis	Persistent migraine aura with cerebral infarction	1 IP / 1 ER / 2OP
G43.60	ICD-10-CM Diagnosis	Persistent migraine aura with cerebral infarction, not intractable	1 IP / 1 ER / 2OP
G43.601	ICD-10-CM Diagnosis	Persistent migraine aura with cerebral infarction, not intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.609	ICD-10-CM Diagnosis	Persistent migraine aura with cerebral infarction, not intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.61	ICD-10-CM Diagnosis	Persistent migraine aura with cerebral infarction, intractable	1 IP / 1 ER / 2OP
G43.611	ICD-10-CM Diagnosis	Persistent migraine aura with cerebral infarction, intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.619	ICD-10-CM Diagnosis	Persistent migraine aura with cerebral infarction, intractable, without status migrainosus	1 IP / 1 ER / 2OP

Code	Code type	Code description	**Setting** (Any diagnosis position)
G43.7	ICD-10-CM Diagnosis	Chronic migraine without aura	1 IP / 1 ER / 2OP
G43.70	ICD-10-CM Diagnosis	Chronic migraine without aura, not intractable	1 IP / 1 ER / 2OP
G43.701	ICD-10-CM Diagnosis	Chronic migraine without aura, not intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.709	ICD-10-CM Diagnosis	Chronic migraine without aura, not intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.71	ICD-10-CM Diagnosis	Chronic migraine without aura, intractable	1 IP / 1 ER / 2OP
G43.711	ICD-10-CM Diagnosis	Chronic migraine without aura, intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.719	ICD-10-CM Diagnosis	Chronic migraine without aura, intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.8	ICD-10-CM Diagnosis	Other migraine	1 IP / 1 ER / 2OP
G43.80	ICD-10-CM Diagnosis	Other migraine, not intractable	1 IP / 1 ER / 2OP
G43.801	ICD-10-CM Diagnosis	Other migraine, not intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.809	ICD-10-CM Diagnosis	Other migraine, not intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.81	ICD-10-CM Diagnosis	Other migraine, intractable	1 IP / 1 ER / 2OP
G43.811	ICD-10-CM Diagnosis	Other migraine, intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.819	ICD-10-CM Diagnosis	Other migraine, intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.82	ICD-10-CM Diagnosis	Menstrual migraine, not intractable	1 IP / 1 ER / 2OP
G43.821	ICD-10-CM Diagnosis	Menstrual migraine, not intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.829	ICD-10-CM Diagnosis	Menstrual migraine, not intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.83	ICD-10-CM Diagnosis	Menstrual migraine, intractable	1 IP / 1 ER / 2OP
G43.831	ICD-10-CM Diagnosis	Menstrual migraine, intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.839	ICD-10-CM Diagnosis	Menstrual migraine, intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.9	ICD-10-CM Diagnosis	Migraine, unspecified	1 IP / 1 ER / 2OP

Code	Code type	Code description	**Setting** (Any diagnosis position)
G43.90	ICD-10-CM Diagnosis	Migraine, unspecified, not intractable	1 IP / 1 ER / 2OP
G43.901	ICD-10-CM Diagnosis	Migraine, unspecified, not intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.909	ICD-10-CM Diagnosis	Migraine, unspecified, not intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43.91	ICD-10-CM Diagnosis	Migraine, unspecified, intractable	1 IP / 1 ER / 2OP
G43.911	ICD-10-CM Diagnosis	Migraine, unspecified, intractable, with status migrainosus	1 IP / 1 ER / 2OP
G43.919	ICD-10-CM Diagnosis	Migraine, unspecified, intractable, without status migrainosus	1 IP / 1 ER / 2OP
G43A	ICD-10-CM Diagnosis	Cyclical vomiting	1 IP / 1 ER / 2OP
G43A0	ICD-10-CM Diagnosis	Cyclical vomiting, not intractable	1 IP / 1 ER / 2OP
G43A1	ICD-10-CM Diagnosis	Cyclical vomiting, intractable	1 IP / 1 ER / 2OP
G43C	ICD-10-CM Diagnosis	Periodic headache syndromes in child or adult	1 IP / 1 ER / 2OP
G43C0	ICD-10-CM Diagnosis	Periodic headache syndromes in child or adult, not intractable	1 IP / 1 ER / 2OP
G43C1	ICD-10-CM Diagnosis	Periodic headache syndromes in child or adult, intractable	1 IP / 1 ER / 2OP
G43.B	ICD-10-CM Diagnosis	Ophthalmoplegic migraine	1 IP / 1 ER / 2OP
G43.B0	ICD-10-CM Diagnosis	Ophthalmoplegic migraine, not intractable	1 IP / 1 ER / 2OP
G43.B1	ICD-10-CM Diagnosis	Ophthalmoplegic migraine, intractable	1 IP / 1 ER / 2OP
G43.D	ICD-10-CM Diagnosis	Abdominal migraine	1 IP / 1 ER / 2OP
G43.D0	ICD-10-CM Diagnosis	Abdominal migraine, not intractable	1 IP / 1 ER / 2OP
G43.D1	ICD-10-CM Diagnosis	Abdominal migraine, intractable	1 IP / 1 ER / 2OP

Acute migraine drug codes

Code description	Code type	Code
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Hypertension codes[a]

Code	Code type	Code description	**Setting** (Any diagnosis position)
I10	ICD-10-CM Diagnosis	Essential (primary) hypertension	1 IP / 1 ER / 1 OP
I11	ICD-10-CM Diagnosis	Hypertensive heart disease	1 IP / 1 ER / 1 OP
I11.0	ICD-10-CM Diagnosis	Hypertensive heart disease with heart failure	1 IP / 1 ER / 1 OP
I11.9	ICD-10-CM Diagnosis	Hypertensive heart disease without heart failure	1 IP / 1 ER / 1 OP
I12	ICD-10-CM Diagnosis	Hypertensive chronic kidney disease	1 IP / 1 ER / 1 OP
I12.0	ICD-10-CM Diagnosis	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease	1 IP / 1 ER / 1 OP
I12.9	ICD-10-CM Diagnosis	Hypertensive chronic kidney disease with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	1 IP / 1 ER / 1 OP
I13	ICD-10-CM Diagnosis	Hypertensive heart and chronic kidney disease	1 IP / 1 ER / 1 OP
I13.0	ICD-10-CM Diagnosis	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	1 IP / 1 ER / 1 OP
I13.1	ICD-10-CM Diagnosis	Hypertensive heart and chronic kidney disease without heart failure	1 IP / 1 ER / 1 OP
I13.10	ICD-10-CM Diagnosis	Hypertensive heart and chronic kidney disease without heart failure, with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	1 IP / 1 ER / 1 OP
I13.11	ICD-10-CM Diagnosis	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease	1 IP / 1 ER / 1 OP
I13.2	ICD-10-CM Diagnosis	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease	1 IP / 1 ER / 1 OP
I15	ICD-10-CM Diagnosis	Secondary hypertension	1 IP / 1 ER / 1 OP
I15.0	ICD-10-CM Diagnosis	Renovascular hypertension	1 IP / 1 ER / 1 OP
I15.1	ICD-10-CM Diagnosis	Hypertension secondary to other renal disorders	1 IP / 1 ER / 1 OP

Code	Code type	Code description	**Setting** (Any diagnosis position)
I15.2	ICD-10-CM Diagnosis	Hypertension secondary to endocrine disorders	1 IP / 1 ER / 1 OP
I15.8	ICD-10-CM Diagnosis	Other secondary hypertension	1 IP / 1 ER / 1 OP
I15.9	ICD-10-CM Diagnosis	Secondary hypertension, unspecified	1 IP / 1 ER / 1 OP
I16	ICD-10-CM Diagnosis	Hypertensive crisis	1 IP / 1 ER / 1 OP
I16.0	ICD-10-CM Diagnosis	Hypertensive urgency	1 IP / 1 ER / 1 OP
I16.1	ICD-10-CM Diagnosis	Hypertensive emergency	1 IP / 1 ER / 1 OP
I16.9	ICD-10-CM Diagnosis	Hypertensive crisis, unspecified	1 IP / 1 ER / 1 OP

[a] The outcome of hypertension will also be evaluated by restricting to the following five diagnosis codes: I10, I16, I16.0, I16.1, I16.9.

Acute myocardial infarction

Code	Code type	Code description	**Setting** (Primary diagnosis position)
I21	ICD-10-CM Diagnosis	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	1 IP
I21.0	ICD-10-CM Diagnosis	ST elevation (STEMI) myocardial infarction of anterior wall	1 IP
I21.01	ICD-10-CM Diagnosis	ST elevation (STEMI) myocardial infarction involving left main coronary artery	1 IP
I21.02	ICD-10-CM Diagnosis	ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery	1 IP
I21.09	ICD-10-CM Diagnosis	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall	1 IP
I21.1	ICD-10-CM Diagnosis	ST elevation (STEMI) myocardial infarction of inferior wall	1 IP
I21.11	ICD-10-CM Diagnosis	ST elevation (STEMI) myocardial infarction involving right coronary artery	1 IP
I21.19	ICD-10-CM Diagnosis	ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall	1 IP
I21.2	ICD-10-CM Diagnosis	ST elevation (STEMI) myocardial infarction of other sites	1 IP

Code	Code type	Code description	**Setting** (Primary diagnosis position)
I21.21	ICD-10-CM Diagnosis	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery	1 IP
I21.29	ICD-10-CM Diagnosis	ST elevation (STEMI) myocardial infarction involving other sites	1 IP
I21.3	ICD-10-CM Diagnosis	ST elevation (STEMI) myocardial infarction of unspecified site	1 IP
I21.4	ICD-10-CM Diagnosis	Non-ST elevation (NSTEMI) myocardial infarction	1 IP
I21.9	ICD-10-CM Diagnosis	Acute Myocardial Infarction, Unspecified	1 IP
I21.A	ICD-10-CM Diagnosis	Other type of myocardial infarction	1 IP
I21.A1	ICD-10-CM Diagnosis	Myocardial infarction type 2	1 IP
I21.A9	ICD-10-CM Diagnosis	Other myocardial infarction type	1 IP
I22	ICD-10-CM Diagnosis	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	1 IP
I22.0	ICD-10-CM Diagnosis	Subsequent ST elevation (STEMI) myocardial infarction of anterior wall	1 IP
I22.1	ICD-10-CM Diagnosis	Subsequent ST elevation (STEMI) myocardial infarction of inferior wall	1 IP
I22.2	ICD-10-CM Diagnosis	Subsequent non-ST elevation (NSTEMI) myocardial infarction	1 IP
I22.8	ICD-10-CM Diagnosis	Subsequent ST elevation (STEMI) myocardial infarction of other sites	1 IP
I22.9	ICD-10-CM Diagnosis	Subsequent ST elevation (STEMI) myocardial infarction of unspecified site	1 IP

Ischemic Stroke Codes

Code	Code type	Code description	**Setting** (Primary diagnosis position)
I63	ICD-10-CM Diagnosis	Cerebral infarction	1 IP
I63.0	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of precerebral arteries	1 IP
I63.00	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of unspecified precerebral artery	1 IP
I63.01	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of vertebral artery	1 IP
I63.011	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of right vertebral artery	1 IP
I63.012	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of left vertebral artery	1 IP
I63.013	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of bilateral vertebral arteries	1 IP
I63.019	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of unspecified vertebral artery	1 IP
I63.02	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of basilar artery	1 IP
I63.03	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of carotid artery	1 IP
I63.031	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of right carotid artery	1 IP
I63.032	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of left carotid artery	1 IP
I63.033	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of bilateral carotid arteries	1 IP
I63.039	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of unspecified carotid artery	1 IP
I63.09	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of other precerebral artery	1 IP
I63.1	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of precerebral arteries	1 IP
I63.10	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of unspecified precerebral artery	1 IP
I63.11	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of vertebral artery	1 IP
I63.111	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of right vertebral artery	1 IP
I63.112	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of left vertebral artery	1 IP

Code	Code type	Code description	**Setting** (Primary diagnosis position)
I63.113	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of bilateral vertebral arteries	1 IP
I63.119	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of unspecified vertebral artery	1 IP
I63.12	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of basilar artery	1 IP
I63.13	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of carotid artery	1 IP
I63.131	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of right carotid artery	1 IP
I63.132	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of left carotid artery	1 IP
I63.133	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of bilateral carotid arteries	1 IP
I63.139	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of unspecified carotid artery	1 IP
I63.19	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of other precerebral artery	1 IP
I63.2	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries	1 IP
I63.20	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries	1 IP
I63.21	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of vertebral arteries	1 IP
I63.211	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of right vertebral arteries	1 IP
I63.212	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of left vertebral arteries	1 IP
I63.213	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries	1 IP
I63.219	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral arteries	1 IP
I63.22	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of basilar arteries	1 IP

Code	Code type	Code description	**Setting** (Primary diagnosis position)
I63.23	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of carotid arteries	1 IP
I63.231	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries	1 IP
I63.232	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries	1 IP
I63.233	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries	1 IP
I63.239	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid arteries	1 IP
I63.29	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries	1 IP
I63.3	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of cerebral arteries	1 IP
I63.30	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of unspecified cerebral artery	1 IP
I63.31	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of middle cerebral artery	1 IP
I63.311	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of right middle cerebral artery	1 IP
I63.312	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of left middle cerebral artery	1 IP
I63.313	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries	1 IP
I63.319	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of unspecified middle cerebral artery	1 IP
I63.32	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of anterior cerebral artery	1 IP
I63.321	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of right anterior cerebral artery	1 IP
I63.322	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of left anterior cerebral artery	1 IP
I63.323	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries	1 IP
I63.329	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of unspecified anterior cerebral artery	1 IP
I63.33	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of posterior cerebral artery	1 IP

Code	Code type	Code description	**Setting** (Primary diagnosis position)
I63.331	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of right posterior cerebral artery	1 IP
I63.332	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of left posterior cerebral artery	1 IP
I63.333	ICD-10-CM Diagnosis	Cerebral infarction to thrombosis of bilateral posterior cerebral arteries	1 IP
I63.339	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of unspecified posterior cerebral artery	1 IP
I63.34	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of cerebellar artery	1 IP
I63.341	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of right cerebellar artery	1 IP
I63.342	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of left cerebellar artery	1 IP
I63.343	ICD-10-CM Diagnosis	Cerebral infarction to thrombosis of bilateral cerebellar arteries	1 IP
I63.349	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of unspecified cerebellar artery	1 IP
I63.39	ICD-10-CM Diagnosis	Cerebral infarction due to thrombosis of other cerebral artery	1 IP
I63.4	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of cerebral arteries	1 IP
I63.40	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of unspecified cerebral artery	1 IP
I63.41	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of middle cerebral artery	1 IP
I63.411	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of right middle cerebral artery	1 IP
I63.412	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of left middle cerebral artery	1 IP
I63.413	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of bilateral middle cerebral arteries	1 IP
I63.419	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of unspecified middle cerebral artery	1 IP
I63.42	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of anterior cerebral artery	1 IP
I63.421	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of right anterior cerebral artery	1 IP
I63.422	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of left anterior cerebral artery	1 IP
I63.423	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of bilateral anterior cerebral arteries	1 IP

Code	Code type	Code description	**Setting** (Primary diagnosis position)
I63.429	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of unspecified anterior cerebral artery	1 IP
I63.43	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of posterior cerebral artery	1 IP
I63.431	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of right posterior cerebral artery	1 IP
I63.432	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of left posterior cerebral artery	1 IP
I63.433	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of bilateral posterior cerebral arteries	1 IP
I63.439	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of unspecified posterior cerebral artery	1 IP
I63.44	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of cerebellar artery	1 IP
I63.441	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of right cerebellar artery	1 IP
I63.442	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of left cerebellar artery	1 IP
I63.443	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of bilateral cerebellar arteries	1 IP
I63.449	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of unspecified cerebellar artery	1 IP
I63.49	ICD-10-CM Diagnosis	Cerebral infarction due to embolism of other cerebral artery	1 IP
I63.5	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries	1 IP
I63.50	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery	1 IP
I63.51	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of middle cerebral artery	1 IP
I63.511	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery	1 IP
I63.512	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery	1 IP
I63.513	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries	1 IP

Code	Code type	Code description	**Setting** (Primary diagnosis position)
I63.519	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery	1 IP
I63.52	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of anterior cerebral artery	1 IP
I63.521	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery	1 IP
I63.522	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery	1 IP
I63.523	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries	1 IP
I63.529	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery	1 IP
I63.53	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of posterior cerebral artery	1 IP
I63.531	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery	1 IP
I63.532	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery	1 IP
I63.533	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries	1 IP
I63.539	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery	1 IP
I63.54	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of cerebellar artery	1 IP
I63.541	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery	1 IP

Code	Code type	Code description	**Setting** (Primary diagnosis position)
I63.542	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery	1 IP
I63.543	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries	1 IP
I63.549	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery	1 IP
I63.59	ICD-10-CM Diagnosis	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery	1 IP
I63.6	ICD-10-CM Diagnosis	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic	1 IP
I63.8	ICD-10-CM Diagnosis	Other cerebral infarction	1 IP
I63.81	ICD-10-CM Diagnosis	Other cerebral infarction due to occlusion or stenosis of small artery	1 IP
I63.89	ICD-10-CM Diagnosis	Other cerebral infarction	1 IP
I63.9	ICD-10-CM Diagnosis	Cerebral infarction, unspecified	1 IP

Hemorrhagic Stroke Codes

Code	Code type	Code description	**Setting** (Any diagnosis position)
I60	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage	1 IP
I60.0	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from carotid siphon and bifurcation	1 IP
I60.00	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from unspecified carotid siphon and bifurcation	1 IP
I60.01	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from right carotid siphon and bifurcation	1 IP
I60.02	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from left carotid siphon and bifurcation	1 IP
I60.1	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from middle cerebral artery	1 IP

Code	Code type	Code description	**Setting** (Any diagnosis position)
I60.10	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from unspecified middle cerebral artery	1 IP
I60.11	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from right middle cerebral artery	1 IP
I60.12	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from left middle cerebral artery	1 IP
I60.2	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from anterior communicating artery	1 IP
I60.20	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from unspecified anterior communicating artery	1 IP
I60.21	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from right anterior communicating artery	1 IP
I60.22	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from left anterior communicating artery	1 IP
I60.3	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from posterior communicating artery	1 IP
I60.30	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from unspecified posterior communicating artery	1 IP
I60.31	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from right posterior communicating artery	1 IP
I60.32	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from left posterior communicating artery	1 IP
I60.4	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from basilar artery	1 IP
I60.5	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from vertebral artery	1 IP
I60.50	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from unspecified vertebral artery	1 IP
I60.51	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from right vertebral artery	1 IP
I60.52	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from left vertebral artery	1 IP
I60.6	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from other intracranial arteries	1 IP
I60.7	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage from unspecified intracranial artery	1 IP
I60.8	ICD-10-CM Diagnosis	Other nontraumatic subarachnoid hemorrhage	1 IP

Code	Code type	Code description	**Setting** (Any diagnosis position)
I60.9	ICD-10-CM Diagnosis	Nontraumatic subarachnoid hemorrhage, unspecified	1 IP
I61	ICD-10-CM Diagnosis	Nontraumatic intracerebral hemorrhage	1 IP
I61.0	ICD-10-CM Diagnosis	Nontraumatic intracerebral hemorrhage in hemisphere, subcortical	1 IP
I61.1	ICD-10-CM Diagnosis	Nontraumatic intracerebral hemorrhage in hemisphere, cortical	1 IP
I61.2	ICD-10-CM Diagnosis	Nontraumatic intracerebral hemorrhage in hemisphere, unspecified	1 IP
I61.3	ICD-10-CM Diagnosis	Nontraumatic intracerebral hemorrhage in brain stem	1 IP
I61.4	ICD-10-CM Diagnosis	Nontraumatic intracerebral hemorrhage in cerebellum	1 IP
I61.5	ICD-10-CM Diagnosis	Nontraumatic intracerebral hemorrhage, intraventricular	1 IP
I61.6	ICD-10-CM Diagnosis	Nontraumatic intracerebral hemorrhage, multiple localized	1 IP
I61.8	ICD-10-CM Diagnosis	Other nontraumatic intracerebral hemorrhage	1 IP
I61.9	ICD-10-CM Diagnosis	Nontraumatic intracerebral hemorrhage, unspecified	1 IP

Appendix D: *A Priori* List of Covariates to be Included in the Treatment and Censoring Models[a]

Characteristic	Treatment Model	Censoring Model	Numerical (N) or categorical (C)	Covariate assessment period*
Demographics				Index Date
Age (years), 18-24, 25-34, 35-44, 45-54, 55-64	X	X	C	
Gender (male, female)				
Geographical region (eg, Midwest, Northeast, South, West)	X	X	C	
Select Migraine Diagnoses				Baseline period
Chronic migraine (without aura)	X	X	C	
Migraine with aura	X	X	C	
Acute Migraine Medications				Baseline period
Triptans	X	X	C	
Ergotamines	X	X	C	
Nonsteroidal anti-inflammatory drugs (NSAIDs)	X	X	C	
Opioids	X	X	C	
Non-opioid, non-NSAID analgesics	X	X	C	
Gepants	X	X	C	
Other acute migraine-specific treatments	X	X	C	
Non-CGRP Mediated Migraine Preventives				Baseline period
Any MPT	X	X	C	
Select anti-depressants	X	X	C	
Select anti-epileptics	X	X	C	
Botulinum toxins	X	X	C	
Other migraine preventive agents	X	X	C	

Footnotes defined on last page of table

Characteristic	Treatment Model	Censoring Model	Numerical (N) or categorical (C)	Covariate assessment period*
Healthcare Utilization				Baseline period, Follow-up
Ambulatory visits	X	X	N	
Emergency room visits	X	X	N	
Inpatient hospital visits	X	X	N	
Pneumococcal vaccination		X	C	
Influenza vaccination		X	C	
Herpes zoster vaccination		X	C	
Eye exam		X	C	
Screening colonoscopy		X	C	
Screening PSA test		X	C	
Screening fecal occult blood test		X	C	
Screening mammogram		X	C	
Oxygen equipment use		X	C	
Home hospital bed		X	C	
Mobility aids		X	C	
Mechanical ventilation		X	C	
Ambulance / life support		X	C	
Rehabilitation services		X	C	
Overall Medication Utilization				Baseline period, Follow-up
Generic medications dispensed	X	X	N	
Unique drug classes dispensed	X	X	N	

Footnotes defined on last page of table

Characteristic	Treatment Model	Censoring Model	Numerical (N) or categorical (C)	Covariate assessment period*
Other Medications				Baseline Period
Contraceptives	X	X	C	
Anti-hypertensives	X	X	C	
Anti-coagulants	X	X	C	
Anti-platelets	X	X	C	
Lipid-lowering agents	X	X	C	
Anti-diabetics	X	X	C	
Cardiac glycosides	X	X	C	
Calcium gluconate	X	X	C	
Fludrocortisone/ Midodrine	X	X	C	
Weight loss prescriptions	X	X	C	
Fludrocortisone/ Midodrine	X	X	C	
Hyperpolarization-activated cyclic nucleotide-gated channel blocker	X	X	C	
Comorbidities				Baseline Period
Diabetes mellitus	X	X	C	
Hypercholesterolemia	X	X	C	
Hypertension	X	X	C	
Liver disease / Cirrhosis	X	X	C	
Depression	X	X	C	
Chronic Obstructive Pulmonary Disease (COPD)	X	X	C	
Renal Disease	X	X	C	
Cardiac arrhythmia	X	X	C	
Asthma	X	X	C	
Human immunodeficiency virus (HIV)	X	X	C	
Lupus	X	X	C	
Epilepsy/Seizure/Convulsions	X	X	C	
Anxiety	X	X	C	

Footnotes defined on last page of table

Characteristic	Treatment Model	Censoring Model	Numerical (N) or categorical (C)	Covariate assessment period*
Comorbidities (continued)				Baseline Period
Depression	X	X	C	
Peripheral Artery Disease	X	X	C	
Venous thromboembolism	X	X	C	
Critical limb ischemia	X	X	C	
Myocardial Ischemia	X	X	C	
Congestive heart failure	X	X	C	
Acute myocardial infarction	X	X	C	
Unstable angina	X	X	C	
Prinzmetal angina	X	X	C	
Other and unspecified angina pectoris	X	X	C	
Acute atrial fibrillation	X	X	C	
Paroxysmal atrial fibrillation	X	X	C	
Acute ventricular fibrillation	X	X	C	
Premature atrial contractions	X	X	C	
Acute ventricular tachycardia	X	X	C	
Coronary revascularization	X	X	C	
Ischemic/hemorrhagic stroke	X	X	C	
Sub-arachnoid stroke	X	X	C	
Unspecified stroke	X	X	C	
Transient ischemic attack	X	X	C	
Other acute cerebrovascular events	X	X	C	
Other ischemic cerebrovascular events	X	X	C	

[a] Additional variables predictive of treatment assignment or censoring may be added to the respective models, based on identification of the most common diagnoses, procedures, and medications identified in the study population.

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