Summary Table of Study Protocol

Title	Sentinel Template Protocol – Estimating Event Rates Using the Medication Cohort Module: Hypertension and Negative Control Outcomes in New Users of Onabotulinumtoxin A and Monoclonal Antibodies Targeting the Calcitonin-Gene-Related Pathway in the Marketscan EarlyView Claims Database
Protocol version identifier	Version 1.0
Date of last version of the protocol	*15 April 2020*
EU Post Authorisation Study (PAS) Register No	N/A
Active Substance	erenumab-aooe
Medicinal Product	erenumab-aooe (Aimovig®), 70 mg or 140 mg
Product Reference	AMG 334
Procedure Number	BLA 761077
Joint PASS	Yes
Research Question and Objectives	This study will estimate event rates in four medication cohorts based on available data in a claims database: new users of erenumab-aooe, new users of fremanezumab-vfrm, new users of galcanezumab-gnlm, and new users of onabotulinumtoxin A. The outcomes of interest include any hypertension, serious hypertension, hypertensive crisis, road traffic accidents, falls, and influenza vaccination. Event rates will be estimated with the Medication Cohort Module, using Amgen's deployment of the Food and Drug Administration Sentinel System.
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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Study Design Schema

Medication Cohort Module Schema

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2. List of Abbreviations

Abbreviation/Acronym	
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence Interval
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
NDC	National Drug Code
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
mAb	Monoclonal Anti-body
MCM	Medication Cohort Module
QC	Quality Control

3. Responsible Parties

Amgen Inc. is the study Sponsor, responsible for authoring the protocol and regulatory interactions.

4. Abstract

- Study Title

  Sentinel Template Protocol – Estimating Event Rates Using the Medication Cohort Module: Hypertension and Negative Control Outcomes in New Users of Onabotulinumtoxin A and Monoclonal Antibodies Targeting the Calcitonin-Gene-Related Pathway in the Marketscan EarlyView Claims Database

- Study Background and Rationale

  Erenumab-aooe (Aimovig®) became the first monoclonal antibody (mAb) targeting the calcitonin-gene-related pathway (CGRP) to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of migraine, followed by approval of fremanezumab-vfrm (Ajovy®) and galcanezumab-gnlm (Emgality®). During the fourth quarter of 2019, the FDA identified hypertension as a potential signal of serious risk / new safety information for erenumab-aooe based on review of data in the FDA Adverse Event Reporting System (FAERS). The primary aim of this study is to provide preliminary data related to hypertension in users of CGRP mAbs, using a data source that is based on medical encounters in a claims database.

- Research Question and Objective(s)

  Primary Objective(s)

  This study will estimate event rates in four medication cohorts based on available data in a claims database: new users of erenumab-aooe, new users of fremanezumab-vfrm, new users of galcanezumab-gnlm, and new users of onabotulinumtoxin A. The outcomes of interest include any hypertension, serious hypertension, hypertensive crisis, road traffic accidents, falls, and influenza vaccination.

- Study Design/Type

  Retrospective Cohort Study

- Data Resource

  Marketscan EarlyView

- Summary of Eligibility Criteria

  Patients must be 18+ years of age on the index date, have one year of continuous medical and pharmacy eligibility prior to the index date (ie, the baseline period), and have a diagnosis of migraine during the baseline period.

- Follow-up

  Exposure during follow-up will be evaluated in two ways:

  (1) In an 'intention-to-treat' analysis, patients are 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 on 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.

(2) With a 'per-protocol analysis' patients are followed for as long as they are actively taking the medication of interest during their first treatment episode. Follow-up begins on the index date and ends at first occurrence of : (1) the outcome of interest, (2) disenrollment from a health plan, or (3) end of study period. For new users of CGRP mAbs, patients will also be censored when they switch to an alternate CGRP mAb. For new users of onabotulinumtoxin A, patients will be censored if they initiate a CGRP mAb during the follow-up period.

- Variables
  - Outcome Variable(s)
    Any hypertension, serious hypertension, hypertensive crisis, road traffic accidents, falls, influenza vaccination
  - Exposure Variable(s)
    Erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, and onabotulinumtoxin A
- Study Sample Size

  This is a descriptive retrospective cohort study in which available patients who meet all eligibility criteria will be included in the study.
- Data Analysis

  This is a descriptive study. Event rates based on grouped data will be calculated as the number of events during the follow-up period divided by the total person-time at risk. All event rates will be presented per 1,000 person-years, and confidence intervals for the event rates will be based on the Poisson distribution or approximations of the Poisson distribution for small sample sizes.

5. Amendments and Updates

None.

6. Rationale and Background

In the fall of 2007, Congress passed the Food and Drug Administration Amendments Act (FDAAA), mandating the Food and Drug Administration (FDA) to establish an Active Postmarket Risk Identification and Analysis. FDAAA requires the FDA to develop, in collaboration with public, academic, and private entities, methods to obtain access to disparate data sources and validated methods for the establishment of a system to link and analyze safety data from multiple sources. In May 2008, the FDA launched the Sentinel Initiative to create a national electronic system, the Sentinel System, for medical product safety surveillance (Platt et al, 2012). The FDA has since provided the modular programs utilized by the Sentinel System to the public.

Leveraging the FDA's publicly available methodology and programs, Amgen developed an internal instance of the Sentinel capability hereinafter referred to as "Amgen's deployment of Sentinel." Amgen's deployment of Sentinel is comprised of semi-automated analytic programs that enable rapid standard queries across Amgen's

Real World Data assets. Modules are designed to run against the FDA's Sentinel Common Data Model, and are currently available for use in MarketScan, MarketScan EarlyView, Optum, and the Japanese Medical Data Center claims databases. Parameters defining study design, cohort creation, exposures, outcomes, date ranges, enrollment requirements, age ranges, and others are specified by the requestor in intake forms. Amgen's deployment of Sentinel has undergone system validation consistent with Amgen IS standards (SOP-429133) and quality control (QC) programming in which specific queries conducted by the FDA have been replicated.

This study will specifically use the Medication Cohort Module (MCM) in Amgen's deployment of the Sentinel System using the MarketScan EarlyView database to estimate event rates in medication cohorts.

6.1 Diseases and Therapeutic Area

Migraine is a neurological condition characterized by recurrent, unilateral, throbbing headaches and is often accompanied by nausea, phonophobia, and photophobia (Dodick, 2018). Migraine affects 39 million individuals in the United States and is the second largest cause of disability in the world affecting nearly 1.04 billion individuals or 15% of the world's population (Migraine Research Foundation, 2019; GBD Collaborators, 2017). In the United States, migraine is three times more common among women (18% prevalence) than men (6% prevalence) and is most common among people 25 to 55 years of age (Migraine Research Foundation, 2019; Bigal and Lipton, 2009). Preventive migraine medications are indicated in patients with frequent or disabling migraine attacks (D'Amico and Tepper, 2008; Silberstein et al., 2012). Traditional preventive migraine medications include some antiepileptic agents, some antihypertensive agents, some antidepressants, onabotulinumtoxin A, and other migraine preventive agents (eg, cyproheptadine) (American Migraine Foundation, 2019; Estemalik et al, 2013). On 17 May 2018, erenumab-aooe (Aimovig®) became the first monoclonal antibody (mAb) targeting the calcitonin-gene-related pathway (CGRP) to be approved by the FDA, with fremanezumab-vfrm (Ajovy®) and galcanezumab-gnlm (Emgality®) receiving FDA approval shortly thereafter in September 2018.

6.2 Rationale

CGRP is a neuropeptide that is expressed in the central and peripheral nervous systems and has long been assumed to play an important role in migraine pathophysiology. In addition, CGRP can mediate vasodilation (Russell et al, 2014), and therefore at least in theory inhibition of the CGRP pathway might result in vascular effects, such as

increased blood pressure, although the relative importance of the CGRP pathway compared with the other vasodilatory pathways (eg, nitric oxide) has not been established. Monoclonal antibodies (mAbs) targeting the CGRP pathway were developed for migraine prevention by either inhibiting the canonical CGRP receptor (erenumab-aooe) or by binding to the CGRP ligand (fremanezumab-vfrm and galcanezumab-gnlm). 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 not reported any cardiovascular side effects, including hypertension. Moreover, during the development of erenumab, a number of dedicated clinical and nonclinical studies were conducted to address a theoretical vascular/cardiovascular risk, and collectively these studies support the vascular safety of erenumab (Kudrow et al, 2020).

During the fourth quarter of 2019, the FDA identified hypertension as a potential signal of serious risk / new safety information for erenumab-aooe based on review of data in the FDA Adverse Event Reporting System (FAERS) (FDA, 2019). FAERS data has limitations, including the following: (1) presence of duplicate and incomplete reports, (2) information in reports has not been verified, (3) rates of outcomes cannot be established with reports alone, and (4) existence of a report does not establish causation (FDA, 2019). Also, FAERS does not account for the great variability in reporting volume by manufacturers. Through Quarter 1 2019, Amgen submitted many more reports for erenumab-aooe (n=9,938), when compared to reports from manufacturers of galcanezumab-gnlm (n=1,020) and fremanezumab-vfrm (n=457) (Quarterwatch™, 2019). The aim of this study is to provide preliminary data related to hypertension and also negative control outcomes using a data source that is based on medical encounters. As rates cannot be calculated using FAERS due to the potential for missing and duplicative reports, the results of this analysis will provide a better understanding of the rates of hypertension across the three anti-CGRP mAbs as well as other events that have shown discrepant reporting within FAERS. In addition, a negative control migraine preventive medication, onabotulinumtoxin A, will be assessed given its use in migraine prevention and the lack of a known causal relationship with hypertension.

6.3 Statistical Inference (Estimation or Hypothesis)

The MCM, within Amgen's deployment of the Sentinel System, will provide descriptive information only and no hypotheses will be tested.

7. Research Question and Objectives

7.1 Primary

This study will estimate event rates and 95% confidence intervals (CIs) in four medication cohorts based on available data in a claims database: new users of erenumab-aooe, new users of fremanezumab-vfrm, new users of galcanezumab-gnlm, and new users of onabotulinumtoxin A. The outcomes of interest include any hypertension, serious hypertension, hypertensive crisis, road traffic accidents, falls, and influenza vaccination. Each of the six outcomes of interest will be considered individually in six separate analyses. Use of CGRP mAbs based on free/discount/coupon programs is not captured in claims data, therefore in the current protocol the term “new users” 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.

8. Research Methods

8.1 Study Design

The MCM in Amgen’s deployment of Sentinel programs utilizes a retrospective cohort study design for event rate estimation.

8.2 Setting and Study Population

8.2.1 Study Period

The study period will be from 17 May 2018 to 31 October 2019 or the latest date of database release with a baseline period extended back to 17 May 2017. Pending sample size evaluation for the onabotulinumtoxin A cohort only, the date for this one cohort may need to be adjusted to include additional years.

8.2.2 Subject/Patient/Healthcare Professional Eligibility

The following four new user cohorts based on available data in a claims database will be created: (1) erenumab-aooe, (2) fremanezumab-vfrm, (3) galcanezumab-gnlm, and (4) onabotulinumtoxin A. The index date is defined as the date of first claim for one of these four medications. Medication codes used to identify the four cohorts are detailed in Appendix B. As noted above, use of CGRP mAbs based on free/discount/coupon programs is not captured in claims data, therefore in the current protocol the term “new users” 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.

8.2.2.1 Inclusion Criteria

Patients must meet the following inclusion criteria:

1. 18 + years of age on the index date.
2. One year of continuous enrollment (ie, complete medical and pharmacy coverage) prior to the index date.
3. A diagnosis of migraine in the year prior to index, based on one of the following criteria:
    i. ≥ 1 inpatient claim with a diagnosis of migraine (International Classification of Diseases, Tenth Revision [ICD-10] diagnosis code of G43.xxx; see Appendix B).
    ii. ≥ 1 outpatient evaluation and management claim with a diagnosis of migraine and a specialty code of 260 (neurologist).
    iii. ≥ 1 claim for emergency room visit with a diagnosis of migraine.
    iv. ≥ 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
    v. ≥ 2 outpatient evaluation and management claims with a diagnosis of migraine between 7 and 365 days apart.
    vi. ≥ 2 pharmacy fills for migraine-specific triptans or ergotamine class medications between 7 and 365 days apart.

8.2.2.2 Exclusion Criteria

For the CGRP mAbs new user cohorts, no prior use of CGRP mAbs during the baseline period. For the onabotulinumtoxin A new user cohort, no prior use of onabotulinumtoxin A or CGRP mAbs during the baseline period.

8.2.3 Matching

No matching will be performed.

8.2.4 Baseline Period

The index date for all medication cohorts is the earliest prescription claim date for a given medication (erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm or onabotulinumtoxin A) occurring during the study period that satisfies the inclusion/exclusion criteria. The 365 days of continuous enrollment prior to the index date will be the baseline period.

8.2.5 Study Follow-up

Exposure during follow-up will be evaluated in two ways.

1. In an 'intention-to-treat' analysis, patients are 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 on 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.
2. With a 'per-protocol analysis' patients are followed for as long as they are actively taking the medication of interest during their first treatment episode. For the first treatment episode small gaps in treatment (eg, 30 days) are allowed, but follow-up ends at the end of the last prescription which includes the day supply (+30 day extension) where a gap greater than the allowable gap is encountered. Follow-up begins on 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. For new users of CGRP mAbs, patients will also be censored when they switch to an alternate CGRP mAb. For new users of onabotulinumtoxin A, patients will be censored if they initiate a CGRP mAb during the follow-up period.

8.3 Variables

8.3.1 Exposure Assessment

As previously described, exposure will be evaluated with an 'intention-to-treat' analysis and a 'per-protocol' analysis.

8.3.2 Outcome Assessment

Primary outcomes:

- Any hypertension
- Serious hypertension
- Hypertensive crisis

Negative control outcomes:

- Road traffic accidents
- Falls
- Influenza vaccination

Appendix B provides full code lists and algorithms for all outcomes. The 'serious hypertension' outcome will use the same ICD-10-CM diagnosis codes as are used to identify the 'any hypertension' outcome, but for 'serious hypertension' the diagnosis codes must be identified in an inpatient (IP) or emergency room (ER) setting and must occur in the primary diagnosis position. For the 'any hypertension' outcome, in contrast, the diagnosis codes can occur in the IP, ER, or outpatient setting, in any diagnosis position.

The negative control outcomes were chosen because it was hypothesized that there is no plausible mechanism by which they could be caused by the treatment(s) of interest. In addition, road traffic accidents and falls were both outcomes that showed discrepant reporting rates across the three CGRP mAbs in the FAERS database.

Note that although any hypertension, serious hypertension, and hypertensive crisis are treated separately in the data analysis, the definition of any hypertension includes both serious hypertension and hypertensive crisis and the definition of serious hypertension includes hypertensive crisis. So for the outcome of any hypertension, event counts will stop if any of the three hypertension outcomes occur. And for the outcome of serious hypertension, event counts will stop if serious hypertension or hypertensive crisis occur.

Although anti-hypertensive medication use was also considered as an outcome, prior internal analyses have shown that over 30% of CGRP mAb users have used a “migraine preventive anti-hypertensive” agent in the year prior to starting the mAb and approximately 50% have used “any anti-hypertensive” agent. Because this is a significant proportion of patients and there is no accurate way to link a prescription claim with a specific diagnosis (migraine or hypertension or both migraine/hypertension), this outcome was not included. This will avoid misclassification where we would count an event of new anti-hypertensive use as a signal that someone has new hypertension when they might actually be receiving the medication to treat migraine.

8.3.3 Covariate Assessment

The following covariates will be assigned on the index date:

- Age (18-24, 25-34, 35-44, 45-54, 55-64, 65+)
- Gender

The following covariates will be evaluated during the baseline period:

- Any hypertension
- Diabetes
- Hyperlipidemia
- Acute Myocardial Infarction
- Ischemic stroke
- Transient Ischemic Attack

- Migraine with Aura
- Chronic Migraine
- Anxiety
- Depression
- Epilepsy/Seizure/Convulsion
- Preventive Migraine Medications (Appendix C): Anti-Epileptic Agents, Anti-Hypertensives Agents, Anti-Depressants, Botulinum toxin, Other migraine preventive agents
- Acute Migraine Medications (Appendix C): Ergotamines, Triptans, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Opioids, Non-NSAID Non-Opioid Analgesics.

8.3.4 Validity and Reliability

Amgen's deployment of Sentinel modular programs has undergone two levels of QC and validation 1) system validation conducted through a formal Amgen validation process, and 2) results compared to previously conducted studies. The MCM was tested by running example analyses of prevalent outcomes in incident cohorts (eg, estimating the rate of prevalent acute pancreatitis in new users of statin medications). The results, cohort entry date (index date), outcome date (first date of event during follow up), were independently generated and compared against module output. Differences of less than 5% were considered valid. Results from all analyses conducted in Amgen's deployment of Sentinel should be compared to the existing literature and *a priori* knowledge regarding outcomes of interest in the specified cohorts to determine the external validity of the results.

8.4 Data Source

MarketScan (Early View):

The Truven MarketScan Commercial and Medicare Supplemental databases capture person-specific health insurance enrollment, clinical utilization, and expenditures across inpatient, outpatient, prescription drug services from approximately 100 payers, including large employers, health plans, and government and public organizations. Data are collected 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. More than 500 million claim records are available in the MarketScan Databases with currently 190 million unique patients. The MarketScan databases include:

- Commercial Claims and Encounters - Healthcare coverage eligibility and service use of individuals in plans or product lines with fee-for-service plans and fully capitated or partially capitated plans. Contains data on active employees and dependents, early (non-Medicare) retirees and dependents, and individuals who continue with Consolidated Omnibus Budget Reconciliation Act.
- Medicare Supplemental and Consolidated Omnibus Budget - Healthcare coverage eligibility and service use of individuals in plans or product lines with fee-for-service plans and fully capitated or partially capitated plans. Contains data on Medicare-eligible active and retired employees and their Medicare-eligible dependents from employer-sponsored supplemental plans.

For the current analyses, we will use data from the MarketScan EarlyView database, which contains information similar to the MarketScan database described above. The advantage of the EarlyView database is that data are made available much faster (within 45 days of the end of the service month) and are provided in monthly updates. One limitation of the EarlyView database, however, is that more recent claims may not have been adjudicated and so are missing from the database. Inpatient claims take the longest to adjudicate and pay because they are the most expensive and undergo the most scrutiny during the claims review process.

8.5 Study Size

This is a descriptive retrospective cohort study in which available patients who meet all eligibility criteria will be included in the study. Based on the most recent data available in Marketscan EarlyView through 31 October 2019 there were 12,771 migraine patients who had at least one claim for erenumab-aooe, 5,407 who had at least one claim for fremanezumab-vfrm, and 8,250 who had at least one claim for galcanezumab-gnlm.

8.6 Data Management

8.6.1 Obtaining Data Files

The MarketScan EarlyView 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

This is secondary data. The MarketScan EarlyView 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

This study will estimate event rates in four medication cohorts based on available data in in a claims database: new users of erenumab-aooe, new users of fremanezumab-vfrm, new users of galcanezumab-gnlm, and new users of onabotulinumtoxin A. The outcomes of interest include any hypertension, serious hypertension, hypertensive crisis, road traffic accidents, falls, and influenza vaccination. Event rates will be estimated with the MCM, using Amgen's deployment of the FDA Sentinel System.

8.7.2 Planned Method of Analysis

Event rates based on grouped data will be calculated as the number of events during the follow-up period divided by the total person-time at risk. All event rates will be presented per 1,000 person-years, and CIs for the event rates will be based on the Poisson distribution or approximations of the Poisson distribution for small sample sizes.

8.7.2.1 General Considerations

The MCM will present overall event rates and event rates by gender and age categories for the following outcomes: any hypertension, serious hypertension, hypertensive crisis, road traffic accidents, falls, and influenza vaccination.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Missing data will not be imputed in these analyses.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

Study enrollment will be summarized in a standard attrition table similar to that provide in Table 1.

Table 1. Attrition in a Cohort of New Users of MEDICATION[1], in the Marketscan EarlyView Database, by Inclusion/Exclusion Criterion (5/17/2018 – 10/31/2019)

Criterion Description	Patients Excluded	Patients Remaining[2]
Database Restrictions		
Birth date and gender data available		
Drug coverage during enrollment		
Medical coverage during enrollment		
Medical-only and drug-only coverage during enrollment		
Meets age criterion during study period		
Medication Cohort Restrictions		
Meets medication definition (prior to inclusion/exclusion criteria)		
Meets continuous enrollment criterion		
Meets continuous enrollment to evaluate exclusions		
Meets exclusion criteria		
Meets inclusion criteria		

[1] *Describe the medication cohort of interest (eg, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, onabotulinumtoxin A).*
[2] *The number of patients remaining should never be missing, even if the criterion description is informational only.*

8.7.2.3.2 Description of Subject/Patient Characteristics

The MCM provides counts of patients in each medication cohort, overall, by demographic characteristics (ie, by age and gender categories), and also by categories of the Charlson/Elixhauser combined comorbidity score (Gagne et al, 2011; Sun et al, 2017), by extent of medical encounters (eg, number of hospitalizations during the baseline period), and by drug utilization metrics (eg, number of prescriptions during the baseline period).

8.7.2.4 Analysis of the Primary, Secondary and Exploratory Endpoint(s)

Event rates will be presented as incidence rates (per 1,000 person-years) for the outcomes of interest, overall, and stratified by age, gender, and year of cohort entry.

Optionally, stratification by the Charlson/Elixhauser combined comorbidity score, and medical and drug utilization metrics are also available.

8.7.2.5 Sensitivity Analysis

N/A

8.7.2.5.1 Subgroup Analysis

We will estimate event rates overall, and by history of hypertension during the baseline period.

8.7.2.5.2 Stratified Analysis

N/A

8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

The modules described in this protocol are descriptive in nature.

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

This study will assess the rate of hypertension among individuals who are exposed to erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, and onabotulinumtoxin A. Hypertension outcomes will be identified with ICD-10-CM codes.

8.8 Quality Control

Amgen's deployment of Sentinel is a set of automated program modules that do not require additional QC under the assumption that custom coding is not needed for the analyses. QC of the system is described in Section 8.3.4. Intake forms and output tables are reviewed by an epidemiologist and programmer prior to submission and after results are available. When customized cohorts are built for analyses, the level of QC will be determined as specified in Amgen MAN-002344.

8.9 Limitations of the Research Methods

8.9.1 Internal Validity of Study Design

8.9.1.1 Measurement Error(s)/Misclassification(s)

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 occur due to the free drug and coupon programs that have been available after launch of CGRP mAbs. 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 both galcanezumab-gnlm and fremanezumab-vfrm. 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 rates in people who have *newly* started CGRP mAbs, but rather as rates in people *who have a first claim* in the database.

8.9.1.2 Information Bias

We do not anticipate any potential information bias.

8.9.1.3 Selection Bias

We do not anticipate selection bias as patients are not selected based on factors that are related to both exposure and outcome.

8.9.1.4 Confounding

N/A. This is a descriptive study only.

8.9.2 External Validity of Study Design

This study is limited to individuals with employer-sponsored health coverage included in the MarketScan EarlyView database. Thus, results of this analysis may not be generalizable to individuals with other type of insurance coverage or those without health insurance.

8.9.3 Analysis Limitations

N/A.

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 CGRP mAbs, 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

N/A.

9. Protection of Human Subjects

9.1 Institutional Review Board

This is a retrospective cohort study using the MarketScan EarlyView Database and is considered secondary data collection. No primary data collection will occur, consent is not needed, and Institutional Review Board approval is not needed. 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 EarlyView Database, which is an administrative claims database. The safety outcomes that are listed in Section 8.3.2 will be documented in the administrative claims and analyzed in this study. These will be reported in aggregate in the final study report as rates. See Section 8.3.2 for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Safety 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 study at any time.

12. Plans for Disseminating and Communicating Study Results

12.1 Publication Policy

The results of this study will not be submitted for publication.

13. References

American Migraine Foundation. Understanding Migraine Medications. https://americanmigrainefoundation.org/resource-library/understanding-migraine-medications/. Published 2019. Accessed April 08, 2019.

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14. Appendices

Appendix A. ENCePP Checklist for Study Protocols

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

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: Sentinel Template Protocol – Estimating Event Rates Using the Medication Cohort Module: Hypertension and Negative Control Outcomes in New Users of Onabotulinumtoxin A and Monoclonal Antibodies Targeting the Calcitonin-Gene-Related Pathway in the Marketscan EarlyView Claims Database

EU PAS Register® number: to be provided
Study reference number (if applicable): 20200218

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]	☐	☒	☐	
1.1.2 End of data collection[2]	☐	☒	☐	
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	

[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 1: Milestones	Yes	No	N/A	Section Number
1.1.6 Final report of study results.	☐	☒	☐	

Comments:

This is a retrospective administrative claims database analysis

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Descriptive study only, no hypotheses

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. 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?	☒	☐	☐	8.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.7.1.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	8
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	8
4.2.2 Age and sex	☒	☐	☐	8

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin	☒	☐	☐	8
4.2.4 Disease/indication	☒	☐	☐	8
4.2.5 Duration of follow-up	☒	☐	☐	8
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8

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? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	8
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

This is a retrospective administrative claims database analysis

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
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8 Appendix
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. 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? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	8.9.1.3
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9.1.2 8.9.4

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.7.2.5.1

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? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8
9.1.3 Covariates and other characteristics?	☒	☐	☐	8
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8 Appendix
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8 Appendix
9.3.3 Covariates and other characteristics?	☐	☒	☐	8
9.4 Is a linkage method between data sources described? (e.g. 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
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8
10.3 Are descriptive analyses included?	☒	☐	☐	8
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Descriptive study only

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8
11.2 Are methods of quality assurance described?	☒	☐	☐	8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8

Comments:

Administrative claims database

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
12.1.2 Information bias?	☒	☐	☐	8
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8

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?	☒	☐	☐	9
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9

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?	☒	☐	☐	Summary table

Comments:

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

Comments:

Name of the main author of the protocol: PPD

Date: 20/April/2020

Signature: _____

Appendix B. Code Lists and Algorithms to Identify Study Variables

Erenumab, fremanezumab, galcanezumab, and onabotulinumtoxin A codes

Code	Code type	Code description
55513084101	NDC	Erenumab
55513084102	NDC	Erenumab
55513084001	NDC	Erenumab
55513084002	NDC	Erenumab
55513084301	NDC	Erenumab
55513084201	NDC	Erenumab
51759020410	NDC	Fremanezumab
51759020210	NDC	Fremanezumab
51759020222	NDC	Fremanezumab
J3031	HCPCS	Fremanezumab
00002143611	NDC	Galcanezumab
00002143627	NDC	Galcanezumab
00002237711	NDC	Galcanezumab
00002237727	NDC	Galcanezumab
00002311509	NDC	Galcanezumab
J0585	HCPCS	Onabotulinumtoxin A
00023114501	NDC	Onabotulinumtoxin A
54868412300	NDC	Onabotulinumtoxin A
00023392102	NDC	Onabotulinumtoxin A
00023391950	NDC	Onabotulinumtoxin A
00023923201	NDC	Onabotulinumtoxin A
00023923250	NDC	Onabotulinumtoxin A
54868412300	NDC	Onabotulinumtoxin A

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
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

Code	Code type	Code description	Setting (Any diagnosis position)
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
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

Code	Code type	Code description	Setting (Any diagnosis position)
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
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
G43.A	ICD-10-CM Diagnosis	Cyclical vomiting	1 IP / 1 ER / 2OP
G43.A0	ICD-10-CM Diagnosis	Cyclical vomiting, not intractable	1 IP / 1 ER / 2OP
G43.A1	ICD-10-CM Diagnosis	Cyclical vomiting, intractable	1 IP / 1 ER / 2OP

Code	Code type	Code description	Setting (Any diagnosis position)
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.C	ICD-10-CM Diagnosis	Periodic headache syndromes in child or adult	1 IP / 1 ER / 2OP
G43.C0	ICD-10-CM Diagnosis	Periodic headache syndromes in child or adult, not intractable	1 IP / 1 ER / 2OP
G43.C1	ICD-10-CM Diagnosis	Periodic headache syndromes in child or adult, 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

Any hypertension codes

Code	Code type	Code description	**Setting (**Any diagnosis position**)**
I10	ICD-10-CM Diagnosis	Essential (primary) hypertension	1 IP / 1 ER / 2 OP
I11	ICD-10-CM Diagnosis	Hypertensive heart disease	1 IP / 1 ER / 2 OP
I11.0	ICD-10-CM Diagnosis	Hypertensive heart disease with heart failure	1 IP / 1 ER / 2 OP
I11.9	ICD-10-CM Diagnosis	Hypertensive heart disease without heart failure	1 IP / 1 ER / 2 OP
I12	ICD-10-CM Diagnosis	Hypertensive chronic kidney disease	1 IP / 1 ER / 2 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 / 2 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 / 2 OP
I13	ICD-10-CM Diagnosis	Hypertensive heart and chronic kidney disease	1 IP / 1 ER / 2 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 / 2 OP
I13.1	ICD-10-CM Diagnosis	Hypertensive heart and chronic kidney disease without heart failure	1 IP / 1 ER / 2 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 / 2 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 / 2 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 / 2 OP
I15	ICD-10-CM Diagnosis	Secondary hypertension	1 IP / 1 ER / 2 OP
I15.0	ICD-10-CM Diagnosis	Renovascular hypertension	1 IP / 1 ER / 2 OP
I15.1	ICD-10-CM Diagnosis	Hypertension secondary to other renal disorders	1 IP / 1 ER / 2 OP
I15.2	ICD-10-CM Diagnosis	Hypertension secondary to endocrine disorders	1 IP / 1 ER / 2 OP
I15.8	ICD-10-CM Diagnosis	Other secondary hypertension	1 IP / 1 ER / 2 OP
I15.9	ICD-10-CM Diagnosis	Secondary hypertension, unspecified	1 IP / 1 ER / 2 OP
I16	ICD-10-CM Diagnosis	Hypertensive crisis	1 IP / 1 ER / 1 OP

Code	Code type	Code description	**Setting (**Any diagnosis position**)**
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

Serious hypertension codes

Code	Code type	Code description	**Setting (**Primary diagnosis position**)**
I10	ICD-10-CM Diagnosis	Essential (primary) hypertension	1 IP / 1 ER
I11	ICD-10-CM Diagnosis	Hypertensive heart disease	1 IP / 1 ER
I11.0	ICD-10-CM Diagnosis	Hypertensive heart disease with heart failure	1 IP / 1 ER
I11.9	ICD-10-CM Diagnosis	Hypertensive heart disease without heart failure	1 IP / 1 ER
I12	ICD-10-CM Diagnosis	Hypertensive chronic kidney disease	1 IP / 1 ER
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
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
I13	ICD-10-CM Diagnosis	Hypertensive heart and chronic kidney disease	1 IP / 1 ER
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
I13.1	ICD-10-CM Diagnosis	Hypertensive heart and chronic kidney disease without heart failure	1 IP / 1 ER
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
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
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
I15	ICD-10-CM Diagnosis	Secondary hypertension	1 IP / 1 ER
I15.0	ICD-10-CM Diagnosis	Renovascular hypertension	1 IP / 1 ER
I15.1	ICD-10-CM Diagnosis	Hypertension secondary to other renal disorders	1 IP / 1 ER

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

Hypertensive crisis codes

Code	Code type	Code description	**Setting** (Any diagnosis position)
I16	ICD-10-CM Diagnosis	Hypertensive crisis	1 IP / 1 ER / 1OP
I16.0	ICD-10-CM Diagnosis	Hypertensive urgency	1 IP / 1 ER / 1OP
I16.1	ICD-10-CM Diagnosis	Hypertensive emergency	1 IP / 1 ER / 1OP
I16.9	ICD-10-CM Diagnosis	Hypertensive crisis, unspecified	1 IP / 1 ER / 1OP

Fall codes

Code[a]	Code type	Code description	**Setting (**Any diagnosis position**)**
W00	ICD-10-CM Diagnosis	Fall due to ice and snow	1 IP / 1 ER / 1OP
W01	ICD-10-CM Diagnosis	Fall on same level from slipping, tripping and stumbling	1 IP / 1 ER / 1OP
W03	ICD-10-CM Diagnosis	Other fall on same level due to collision with another person	1 IP / 1 ER / 1OP
W04	ICD-10-CM Diagnosis	Fall while being carried or supported by other persons	1 IP / 1 ER / 1OP
W05	ICD-10-CM Diagnosis	Fall from non-moving wheelchair, nonmotorized scooter and motorized mobility scooter	1 IP / 1 ER / 1OP
W06	ICD-10-CM Diagnosis	Fall from bed	1 IP / 1 ER / 1OP
W07	ICD-10-CM Diagnosis	Fall from chair	1 IP / 1 ER / 1OP
W08	ICD-10-CM Diagnosis	Fall from other furniture	1 IP / 1 ER / 1OP
W09	ICD-10-CM Diagnosis	Fall on and from playground equipment	1 IP / 1 ER / 1OP
W10	ICD-10-CM Diagnosis	Fall on and from stairs and steps	1 IP / 1 ER / 1OP
W11	ICD-10-CM Diagnosis	Fall on and from ladder	1 IP / 1 ER / 1OP
W12	ICD-10-CM Diagnosis	Fall on and from scaffolding	1 IP / 1 ER / 1OP
W13	ICD-10-CM Diagnosis	Fall from, out of or through building or structure	1 IP / 1 ER / 1OP
W14	ICD-10-CM Diagnosis	Fall from tree	1 IP / 1 ER / 1OP
W15	ICD-10-CM Diagnosis	Fall from cliff	1 IP / 1 ER / 1OP
W16	ICD-10-CM Diagnosis	Fall, jump or diving into water	1 IP / 1 ER / 1OP
W17	ICD-10-CM Diagnosis	Other fall from one level to another	1 IP / 1 ER / 1OP
W18	ICD-10-CM Diagnosis	Other slipping, tripping and stumbling and falls	1 IP / 1 ER / 1OP
W19	ICD-10-CM Diagnosis	Unspecified fall	1 IP / 1 ER / 1OP

[a] Only including codes ending in XA which indicate an initial encounter.

Road traffic accident codes

Code[a]	Code type	Code description	**Setting (**Any diagnosis position**)**
V20-V29	ICD-10-CM Diagnosis	Motorcycle rider injured in transport accident	1 IP / 1 ER / 1OP
V30-V39	ICD-10-CM Diagnosis	Occupant of three-wheeled motor vehicle injured in transport accident	1 IP / 1 ER / 1OP
V40-V49	ICD-10-CM Diagnosis	Car occupant injured in transport accident	1 IP / 1 ER / 1OP
V50-V59	ICD-10-CM Diagnosis	Occupant of pick-up truck or van injured in transport accident	1 IP / 1 ER / 1OP
V60-V69	ICD-10-CM Diagnosis	Occupant of heavy transport vehicle injured in transport accident	1 IP / 1 ER / 1OP
V70-V79	ICD-10-CM Diagnosis	Bus occupant injured in transport accident	1 IP / 1 ER / 1OP
V87[b]	ICD-10-CM Diagnosis	Traffic accident of specified type but victim's mode of transport unknown	1 IP / 1 ER / 1OP
V88[c]	ICD-10-CM Diagnosis	Nontraffic accident of specified type but victim's mode of transport unknown	1 IP / 1 ER / 1OP
V89[d]	ICD-10-CM Diagnosis	Motor- or nonmotor-vehicle accident, type of vehicle unspecified	1 IP / 1 ER / 1OP

[a] Only including codes ending in XA which indicate an initial encounter.
[b] Excludes code V87.9XXA [Person injured in other specified (collision)(noncollision) transport accidents involving nonmotor vehicle (traffic), initial encounter].
[c] Excludes code V88.9XXA [Person injured in other specified (collision)(noncollision) transport accidents involving nonmotor vehicle, nontraffic, initial encounter].
[d] Only includes codes V89.0XXA [Person injured in unspecified motor-vehicle accident, nontraffic, initial encounter] and V89.2XXA [Person injured in unspecified motor-vehicle accident, traffic, initial encounter].

Appendix C. Preventive and Acute Migraine Medications

Preventive migraine medications – Drug categories and generic names

Drug category	Drug sub-category	Generic name
Anti-epileptic agents	n/a	Carbamazepine *(note – diagnostic test kits excluded)*
		Gabapentin
		Levetiracetam
		Pregabalin
		Topiramate
		Valproate sodium / valproic acid / divalproex sodium
		Zonisamide
Anti-hypertensive agents	Beta blocker	Atenolol
		Bisoprolol
		Metoprolol
		Nadolol
		Nebivolol
		Pindolol
		Propranolol
		Timolol *(note – ophthalmic formulation excluded)*
	Calcium channel blocker	Flunarizine *(note – not available in USA or Japan)*
		Verapamil
	Anti-hypertensives, other	Candesartan
		Clonidine
		Lisinopril
Anti-depressants	Serotonin norepinephrine reuptake inhibitors	Duloxetine
		Desvenlafaxine
		Venlafaxine
	Tri-cyclics	Amitriptyline
		Desipramine
		Doxepin *(note – dermatologic formulation excluded)*
		Imipramine
		Nortriptyline
		Protriptyline
	Selective serotonin reuptake inhibitors	Escitalopram
		Citalopram
		Sertraline

Drug category	Drug sub-category	Generic name
Botulinum toxin	n/a	AbobotulinumtoxinA
		IncobotulinumtoxinA
		OnabotulinumtoxinA
		RimabotulinumtoxinB
Other migraine preventive agents	n/a	Carisoprodol
		Cyproheptadine
		Guanfacine
		Memantine
		Methysergide
		Milnacipran *(note – this is an SNRI but is not approved for depression in the USA, it is approved for fibromyalgia)*
		Tizanidine

Acute migraine medications – Drug categories and generic names

Drug category	Generic name
Ergotamines	Dihydroergotamine mesylate
	Ergotamine tartrate
	Ergotamine tartrate + caffeine
	Ergotamine tartrate + caffeine + belladonna + pentobarbital
Triptans	Almotriptan
	Eletriptan
	Frovatriptan
	Naratriptan
	Rizatriptan
	Sumatriptan (with and without naproxen)
	Zolmitriptan
NSAIDs*	Aspirin
	Celecoxib
	Diclofenac
	Diflunisal
	Etodolac
	Fenoprofen
	Flurbiprofen
	Ibuprofen
	Indomethacin
	Ketoprofen
	Ketorolac
	Magnesium salicylate
	Meclofenamic acid
	Mefanamic acid
	Meloxicam
	Nabumetone
	Naproxen
	Oxaprozin
	Piroxicam
	Rofecoxib
	Salicylamide
	Salsalate
	Sulindac
	Tolmetin
	Valdecoxib

Drug category	Generic name
Opioids**	Codeine
	Fentanyl
	Hydrocodone
	Hydromorphone
	Morphine sulfate
	Oxycodone
	Oxymorphone
	Tramadol
	Opioid other - Alfentanil, Buprenorphine, Butorphanol tartrate, Dezocine, Dihydrocodeine, Levomethadyl, Levorphanol, Meperidine, Methadone, Nalbuphine, Opium / belladonna alkaloids / opium alkaloids, Pentazocine, Propoxyphene, Remifentanil, Sufentanil, Tapentadol
Non-NSAID Non-Opioid Analgesics***	Acetaminophen
	Baclofen
	Butalbital
	Ziconotide

* main NSAID generic names are listed for brevity, the analysis will include drugs that contain the generic drug plus other ingredients
** List of opioid generic names based on Johnston et al., 2016; main opioid generic names are listed for brevity, the analysis will include drugs that contain the generic drug plus other ingredients as well as various formulations (ie, NaCl and HCl)
*** the analysis will include drugs that contain the acetaminophen plus other ingredients

Opioid, NSAID, and Analgesic categories have been created to be mutually exclusive even though many combination drugs exist that contain 2 or more of these ingredients. The following "hierarchy" was used to determine the ONE list each combination would be placed on:

Opioid >> NSAID >> acetaminophen

For example:

Butalbital-Aspirin-Caffeine --- added to NSAID list only

Acetaminophen-Aspirin Buffered --- added to NSAID list only

Acetaminophen-Salicylamide-Phenyltoloxamine --- added to NSAID list only

Tramadol-Acetaminophen --- added to Opioid list only

Carisoprodol w/ Aspirin & Codeine --- added to Opioid list only