1. ABSTRACT

- **Title**

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

- **Keywords**

Erenumab-aooe; Aimovig; hypertension; acute myocardial infarction; stroke

- **Rationale and Background**

Calcitonin gene-related peptide (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. During the fourth quarter of 2019, the Food and Drug Administration (FDA) identified hypertension as a potential adverse drug reaction 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 United States Prescribing Information (USPI) for erenumab-aooe based on spontaneous reports in the post-marketing setting. 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.

- **Research Question and Objectives**

This study addressed the following objectives:

(1) To describe baseline characteristics of four cohorts of migraine patients initiating a migraine preventive treatment: erenumab-aooe, other monoclonal antibodies (mAbs) targeting the CGRP pathway, selected standard of care (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 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 was evaluated with propensity score analyses, evaluation of the standardized mean difference (SMD) 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.

- **Study Design**

This study utilized an observational retrospective cohort study design, using secondary data from a medical claims database.

- **Setting**

The study evaluated administrative claims data for US patients in both inpatient and outpatient settings. The study period was from 17 May 2018, which is the date of US FDA approval for erenumab-aooe, to 30 June 2021. The index date for all medication cohorts was the earliest prescription claim date for a given medication occurring during the study period that satisfied the inclusion/exclusion criteria. The 365 days of continuous enrollment (ie, complete medical and pharmacy coverage) prior to and including the index date was the baseline period.

- **Subjects and Study Size, Including Dropouts**

The following four new user cohorts based on available data in a claims database were 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 was defined as the date of first claim for each of these group of medications.

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

After applying the eligibility criteria, there were 19 220 patients in the erenumab-aooe cohort, 23 244 patients in the other CGRP mAbs cohort, 53 842 patients in the SOC antiepileptic cohort, and 11 713 patients in the onabotulinumtoxinA cohort.

- **Data Source(s) and Methods**

This analysis utilized data from the MarketScan® Commercial and Medicare Supplemental medical claims database.

The cohorts of erenumab-aooe, other mAbs targeting the CGRP pathway (galcanezumab-gnlm, fremanezumab-vfrm, eptinezumab-jjmr), select SOC migraine preventive medications (antiepileptics: topiramate, valproic acid, divalproex sodium), and onabotulinumtoxinA initiators were identified. New use of medications was based on NDCs or HCPCS codes as captured in the pharmacy tables within the MarketScan® claims database.

The outcomes of interest (hypertension, acute MI, and stroke), were identified using ICD-10-CM diagnosis codes. The following algorithms were 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.

Baseline characteristics, including the most prevalent diagnoses, procedures, and medication class prescriptions were summarized for the four study cohorts. Descriptive

statistics using mean and standard deviation or median and 25th/75th percentile estimates for continuous variables and number and percentages (n, %) for categorical variables were used to examine patient characteristics.

The naïve, unadjusted cumulative incidence (ie, risk) of hypertension, acute MI, and stroke were estimated in the following new user cohorts: (1) erenumab-aooe , (2) other mAbs targeting the CGRP pathway, (3) select SOC migraine preventive medications (antiepileptics), and (4) onabotulinumtoxinA.

Next, the overlap of the propensity score across treatment groups was evaluated, the mean standardized differences for all variables included in the propensity score model were assessed, and a determination was made on whether null findings were or were not estimated for the negative control outcomes (NCOs) chosen for the study. NCOs were chosen that had no plausible mechanism by which they could be caused by the treatment of interest but share unmeasured confounders. Therefore, null associations between the migraine preventive treatments and the NCO were hypothesized and associations between erenumab-aooe and an NCO suggested the possibility of residual confounding. The final set of NCOs was selected with guidance from an expert panel, which included the following:

- Accidents
- Anemia
- Asthma
- Electrocardiogram utilization
- Echocardiogram utilization
- Fractures
- Herpes vaccination
- Influenza vaccination
- Mammography (among women)
- Osteoarthritis
- Pelvic exams for cancer screening (among women)

Comparability between erenumab-aooe and each of the other treatment cohorts was evaluated separately and each of the comparative analyses was gated. Specifically, the decision to move forward with the comparative analyses for either the acute MI or the stroke outcome was made after assessment of covariate balance across treatment groups; whether the NCOs showed treatment associations within the accepted bounds around the null; and sufficient sample size. Analyses proceeded only in the treatment pairs where comparability and sufficient sample size were achieved, and not in others. Given the challenges of evaluating drug-induced hypertension when using administrative claims data (eg, high levels of misclassification), a decision was made a priori not to conduct formal comparative analysis for this outcome.

Based on the comparability analyses and sample size considerations, the risk of acute MI and the risk of stroke that were under consideration for comparison were the following three exposure contrasts: (1) erenumab-aooe vs other mAbs targeting the CGRP pathway, (2) erenumab-aooe vs select SOC migraine preventive medications (antiepileptics), and (3) erenumab-aooe vs onabotulinumtoxinA. For these gated analyses, we utilized inverse probability of treatment weights to account for confounding and inverse probability of censoring weights to account for informative censoring.

- **Results**

Most baseline demographics and clinical characteristics were similar (SMD<0.10) across the treatment groups, except for SOC antiepileptics. Chronic migraine without aura had a higher prevalence in erenumab-aooe (40.0%) vs other CGRP mAbs (33.6%, SMD: 0.13) and SOC antiepileptics (7.7%, SMD: 0.82), but had a similar prevalence to onabotulinumtoxinA users (37.3%, SMD: 0.05). Erenumab-aooe users were different from SOC antiepileptic users in many other important potential confounders, including age, chronic migraine with aura, various classes of acute and preventive migraine treatments, and weight loss prescriptions (SMDs>0.10).

The unadjusted cumulative incidences (95% CIs) for acute MI at 36 months were estimated to be 0.41% (0.22%, 0.59%), 0.39% (0.25%, 0.52%), 0.49% (0.24%, 0.74%), and 0.53% (0.38%, 0.67%) for for new users of erenumumab-aooe, other CGRP mAbs, SOC antiepileptics, and onabotulinumtoxinA, respectively.

The unadjusted cumulative incidences for stroke at 36 months were estimated to be 0.91% (0.61%, 1.22%), 0.93% (0.68%, 1.17%), 1.23% (0.78%, 1.68%), and 1.07% (0.93%, 1.22%) for new users of erenumumab-aooe, other CGRP mAbs, SOC antiepileptics, and onabotulinumtoxinA, respectively.

The unadjusted cumulative incidences for hypertension at 12 months were estimated to be 9.34% (8.79%, 9.89%), 9.42% (8.92%, 9.92%), 9.11% (8.40%, 9.83%), and 9.09% (8.77%, 9.41%) for for new users of erenumumab-aooe, other CGRP mAbs, SOC antiepileptics, and onabotulinumtoxinA, respectively.

After evaluation of NCO risk ratios (RRs), it was determined that comparative analyses between erenumab-aooe vs other CGRP mAbs and erenumab-aooe vs onabotulinumtoxinA could proceed. However, it was determined that comparative analyses between erenumab-aooe and SOC antiepileptics could not proceed due to multiple NCO RRs suggesting residual bias and convergence problems when conducting bootstrapped cumulative risk models.

For the comparison of erenumab-aooe with other CGRP mAbs, the adjusted cumulative incidence (95% CI) of acute MI after 36 months was 0.37% (0.24%, 0.59%) in the erenumab-aooe group and 0.37% (0.26%, 0.52%) in the other CGRP mAbs group; the RR (95% CI) of acute MI with erenumab-aooe compared to other CGRP mAbs was 1.02 (0.45, 1.59). The adjusted cumulative incidence (95% CI) of stroke after 36 months of treatment was 0.84% (0.64%, 1.10%) in the erenumab-aooe group and 0.94% (0.71%, 1.23%) in the other CGRP mAbs group; the RR (95% CI) of acute MI with erenumab-aooe compared to other CGRP mAbs was 0.90 (0.56, 1.25).

For the comparison of erenumab-aooe with onabotulinumtoxinA, the adjusted cumulative incidence (95% CI) of acute MI after 36 months was 0.41% (0.24%, 0.67%) in the erenumab-aooe group and 0.47% (0.28%, 0.70%) in the onabotulinumtoxinA group; the RR (95% CI) of acute MI with erenumab-aooe compared to onabotulinumtoxinA was 0.87 (0.19, 1.55). The adjusted cumulative incidence (95% CI) of stroke after 36 months of treatment was 1.01% (0.69%, 1.49%) in the erenumab-aooe group and 1.05% (0.73%, 1.50%) in the onabotulinumtoxinA group; the RR (95% CI) of acute MI with erenumab-aooe compared to onabotulinumtoxinA was 0.97 (0.42, 1.52).

- **Discussion**

The adjusted cumulative incidence of acute MI and stroke with erenumab-aooe treatment was not increased relative to treatment with other CGRP mAbs or with

onabotulinumtoxinA in a real-world setting. The unadjusted cumulative incidence of hypertension with erenumab-aooe treatment was not increased relative to treatment with other CGRP mAbs, onabotulinumtoxinA, or SOC antiepileptics. This study indicates that the risk of cardiovascular or cerebrovascular events is comparable between migraine patients treated with erenumab-aooe and other migraine preventive treatments, including other CGRP monoclonal antibodies, and thus there is no impact on the benefit-risk balance of erenumab.

- **Marketing Authorization Holder(s)**

Amgen, Inc.

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