1. ABSTRACT

- **Title**

Hypertension and Negative Control Outcomes in New Users of Onabotulinumtoxin A and Monoclonal Antibodies Targeting the Calcitonin-Gene-Related Peptide Pathway in the Marketscan Early View Claims Database

- **Keywords**

Erenumab-aooe; Aimovig; hypertension; traffic accidents; falls

- **Rationale and Background**

Erenumab-aooe (Aimovig®) was the first monoclonal antibody (mAb) targeting the calcitonin-gene-related peptide (CGRP) pathway 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®). On 03 October 2019 the FDA opened a new Tracked Safety Issue (TSI) for the potential safety risk of hypertension for Aimovig based on review of data in the FDA Adverse Event Reporting System (FAERS).

- **Research Question and Objectives**

Estimate unadjusted event rates in the following four medication cohorts based on data from 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 included three hypertension outcomes: (1) any hypertension, (2) serious hypertension, defined as a diagnosis of hypertension occurring in the primary diagnosis position in either the emergency room or inpatient setting, and (3) hypertensive crisis, as well as three negative control outcomes: (1) road traffic accidents, (2) falls, and (3) influenza vaccination.

- **Study Design**

We used a retrospective cohort study design to identify new users of erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, or onabotulinumtoxin A between 17 May 2018 and 31 January 2020.

- **Setting**

The study evaluated administrative claims data for US patients in both inpatient and outpatient settings.

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

All migraine patients who were 18+ years of age on the index date, had one year of continuous enrollment (ie, complete medical and pharmacy coverage) prior to the index date, had a diagnosis of migraine in the year prior to index, and were new users of erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, or onabotulinumtoxin A were eligible to be in the study. A total of 15212 new users of erenumab, 6383 new users of fremanezumab, 10856 new users of galcanezumab, and 9242 new users of onabotulinumtoxin A were identified. Patients were then followed from first use of one of these treatments through 31 January 2020 for the occurrence of any hypertension, serious hypertension, hypertensive crisis, road traffic accidents, falls, and influenza vaccination.

Follow-up was evaluated in two ways:

1. With the 'per-protocol' analysis, patients were followed for as long as they were actively taking the medication of interest during their first treatment episode. For the first treatment episode small gaps in treatment (eg, 30 days) were allowed, but follow-up ended at the end of the last prescription which included the days supplied (+30 day extension) where a gap greater than the allowable gap was encountered. Follow-up began on the index date and ended at first occurrence of: (a) the outcome of interest, (b) disenrollment from a health plan (c) treatment discontinuation, or (d) end of study period. For new users of CGRP mAbs, patients were also censored when they switched to an alternate CGRP mAb. For new users of onabotulinumtoxin A, patients were censored if they had initiated a CGRP mAb during the follow-up period.
2. In the 'intention-to-treat' analysis, patients were followed for all available time after they initiated a medication, irrespective of whether they discontinued the medication or not, or whether they switched to an alternate medication or not. Follow-up began on the index date and ended at first occurrence of: (a) the outcome of interest, (b) disenrollment from a health plan, or (c) end of study period.

- **Variables and Data Sources**

The data source for this study was the Marketscan Early View database. We used International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes to identify outcomes, and National Drug Codes (NDCs) or Healthcare Common Procedure Coding System (HCPCS) codes to identify exposures.

- Outcome Variables
  Any hypertension, serious hypertension, hypertensive crisis, road traffic accidents, falls, influenza vaccination
- Exposure Variables
  Erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, and onabotulinumtoxin A

- **Results**

The proportion of patients with the following demographic/disease characteristics were similar across all three CGRP mAbs: female ~86%, migraine with aura ~26%, baseline hypertension ~22%, baseline anxiety ~27%, baseline depression ~23%, and baseline use of any prior migraine preventive(s) ~89%. The mean (SD) age of new users of erenumab was 45.9 (12.1), slightly higher than the mean age for the other new user cohorts (fremanezumab: 44.9 [11.7]; galcanezumab: 44.4 [11.8]; onabotulinumtoxin A: 44.9 [12.2]). New users of erenumab had a higher proportion of patients with chronic migraine (58%), when compared to the other CGRP mAbs (~50%). The onabotulinumtoxin A cohort was similar to the CGRP mAb cohorts with respect to most baseline characteristics, but had a higher proportion (69% onabotulinumtoxin A, 58% erenumab, 50% fremanezumab, and 49% galcanezumab) of patients with chronic migraine and a lower proportion (84% onabotulinumtoxin A, ~89% for the CGRP mAb cohorts) of patients with baseline use of any migraine preventives.

For all negative control outcomes (road traffic accidents, falls, influenza vaccination) and hypertensive outcomes (any hypertension, serious hypertension, hypertensive crisis), unadjusted rates based on either the 'intention-to-treat' analyses or the 'per-protocol' analyses were similar across all four new user cohorts. Below we present only event rates based on the 'per-protocol' analytical approach.

The rate (per 1000 person-years [PYs]) of road-traffic accidents was 10.80 (95% CI: 7.97, 13.63) for the erenumab cohort; 5.29 (95% CI: 2.30, 8.28) for the fremanezumab cohort; 8.21 (95% CI: 4.99, 11.42) for the galcanezumab cohort; and 9.56 (95% CI: 6.83, 12.29) for the onabotulinumtoxin A cohort, while the rate (per 100 PYs) of falls was 2.74 (95% CI: 2.28, 3.19) for the erenumab cohort; 2.75 (95% CI: 2.06, 3.43) for the fremanezumab cohort; 2.57 (95% CI: 2.00, 3.14) for the galcanezumab cohort; and 3.08 (95% CI: 2.58, 3.57) for the onabotulinumtoxin A cohort. The rate (per 10 PYs) of influenza vaccination was 2.84 (95% CI: 2.69, 2.99) for the erenumab cohort; 2.25 (95% CI: 2.05, 2.45) for the fremanezumab cohort; 2.69 (95% CI: 2.50, 2.88) for the galcanezumab cohort; and 2.82 (95% CI: 2.67, 2.98) for the onabotulinumtoxin A cohort.

We found the rate (per 10 PYs) of any hypertension to be 3.56 (95% CI: 3.39, 3.73) for the erenumab cohort; 3.35 (95% CI: 3.10, 3.60) for the fremanezumab cohort; 3.54 (95% CI: 3.32, 3.76) for the galcanezumab cohort; and 3.16 (95% CI: 2.99, 3.32) for the onabotulinumtoxin A cohort.

We also evaluated the rate of any hypertension based on the presence or absence of baseline hypertension. For patients without baseline hypertension, the rate (per 10 PYs) of a new onset diagnosis of any hypertension during the follow-up period was similar across the four new user cohorts: erenumab: 0.57 (95% CI: 0.50, 0.65); fremanezumab: 0.53 (95% CI: 0.42, 0.63); galcanezumab: 0.54 (95% CI: 0.44, 0.63); onabotulinumtoxin A: 0.58 (95% CI: 0.50, 0.66). The rates of any hypertension for patients with baseline hypertension were also similar across the four new user cohorts.

The number of serious hypertension events and hypertensive crisis events identified during the follow-up period across all four medication cohorts was small, resulting in rate estimates with relatively wide confidence intervals. The rate of serious hypertension (per 1000 PYs) was 8.28 (95% CI: 5.81, 10.76) for the erenumab cohort; 12.36 (95% CI: 7.78, 16.93) for the fremanezumab cohort; 9.53 (95% CI: 6.06, 12.99) for the galcanezumab cohort; and 11.59 (95% CI: 8.58, 14.60) for the onabotulinumtoxin A cohort. The rate of hypertensive crisis (per 1000 PYs) was 2.50 (95% CI: 1.14, 3.86) for the erenumab cohort; 3.52 (95% CI: 1.66, 6.65) for the fremanezumab cohort; 3.94 (95% CI: 1.71, 6.17) for the galcanezumab cohort; and 4.06 (95% CI: 2.28, 5.83) for the onabotulinumtoxin A cohort.

- **Discussion**

In this study, new users of four medications (erenumab, fremanezumab, galcanezumab, and onabotulinumtoxin A) were separately followed for the occurrence of three negative control outcomes and three hypertensive outcomes. Overall, the four new user cohorts were similar with respect to baseline demographic characteristics, comorbidities, migraine features, and medication usage for the acute treatment of migraines, as well as medication usage for the prevention of migraines. The unadjusted rates for all six outcomes were also similar across the four new medication cohorts. Of particular note, the rate of hypertensive outcomes in the CGRP mAb cohorts was similar to the rate of these events in a cohort of new users of a medication (onabotulinumtoxin A) with no known safety issues related to hypertension. In patients without baseline hypertension, the rates for all three hypertensive outcomes were also similar across the three CGRP mAb new user cohorts.

There was no difference in the rate of hypertension outcomes or negative control outcomes for new users of erenumab, fremanezumab, and galcanezumab. This study provides evidence that erenumab is not associated with an increased risk of diagnosed

hypertension. However, we note that the results presented in this report are descriptive only, and are not intended for causal interpretation.

- **Marketing Authorization Holder(s)**

Amgen, Inc.

- **Names and Affiliations of Principal Investigators**

Gill, Karminder, PhD, Center for Observational Research, Amgen, Inc.

Paiva da Silva Lima, Gabriel, MD, Global Development, Amgen, Inc.

Park, Andrew, PhD, Center for Observational Research, Amgen, Inc.

Urman, Robert, PhD, Center for Observational Research, Amgen, Inc.

Loop, Brett, MPH, Safety, Amgen, Inc.