1. ABSTRACT

- **Title**

Inpatient Constipation Among Migraine Patients Treated With Preventive Medications: A Retrospective Cohort Study in a United States Electronic Health Record Database

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- **Keywords**

Constipation, erenumab, monoclonal antibodies, migraine, risk factors

- **Rationale and Background**

Erenumab was approved by the United States (US) Food and Drug Administration (FDA) on 17 May 2018, followed by fremanezumab on 14 September 2018, galcanezumab on 27 September 2018, and eptinezumab on 21 February 2020, for the prevention of migraine in adults. The erenumab United States Prescribing Information (USPI) includes constipation as an adverse reaction and constipation with serious complications in the Warning and Precautions section. Serious complications were not identified during the erenumab clinical development program, but these events were observed in post-marketing surveillance data. Constipation is not currently listed in the prescribing information for fremanezumab, galcanezumab, or eptinezumab. This retrospective observational study estimated the incidence proportion of inpatient constipation and the incidence proportion of serious complications (evaluated within 30 days after the index event) of inpatient constipation among migraine patients treated with monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway and standard of care (SOC) antiepileptic preventive medications, to give context to events observed in real-world observations from post-marketing surveillance data.

- **Research Question and Objectives**

This study addressed the following objectives:

1. To describe baseline characteristics for the following three cohorts of migraine patients initiating a migraine preventive treatment: erenumab, other mAbs targeting the CGRP pathway, and SOC antiepileptic preventive medications.
2. To estimate the incidence proportion of inpatient constipation in migraine patients treated with erenumab, other mAbs targeting the CGRP pathway, or SOC antiepileptic preventive medications.
3. To estimate the incidence proportion of serious complications of inpatient constipation (defined by occurrence of a complication within 30 days following the inpatient constipation event) in migraine patients treated with erenumab, other mAbs targeting the CGRP pathway, or SOC antiepileptic preventive medications.
4. To assess the comparability of migraine patients treated with erenumab to migraine patients treated with other mAbs targeting the CGRP pathway, and, separately, to SOC antiepileptic preventive medications, with respect to baseline patient characteristics.
5. [GATED ANALYSES] If the cohorts are comparable, compare the incidence proportion of inpatient constipation among migraine patients treated with erenumab to migraine patients treated with other mAbs targeting the CGRP pathway and, separately, to migraine patients treated with SOC antiepileptic preventive medications.

- **Study Design**

Retrospective observational cohort study.

- **Setting**

US patients identified in the Optum Electronic Health Record (EHR) research database from 17 May 2018 through 31 March 2020.

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

The study population included patients with migraine who had a prescription order for selected migraine treatments during the study period, 17 May 2018 (the date of US FDA approval for erenumab) through 31 March 2020. The following exposure cohorts were identified:

1. Patients initiating erenumab,
2. Patients initiating other CGRP antagonists (fremanezumab, galcanezumab, or eptinezumab),
3. Patients initiating the following SOC antiepileptic preventive medications: carbamazepine, gabapentin, topiramate, valproate sodium/valproic acid/divalproex sodium, or zonisamide

For each exposure cohort, the first prescription order for medications that were identified during the study period were assessed for the following study criteria:

- At least 18 years of age on the prescription order date.
- At least two diagnosis codes for migraine (International Classification of Diseases, Tenth-Revision, Clinical Modification [ICD-10-CM] G43.-) on two different days in the 12 months prior to and including the prescription order date, or at least one prescription order for an acute migraine treatment (triptan or ergot) and at least one diagnosis code for migraine in the 12 months prior to and including the prescription order date.
- At least one outpatient clinical visit greater than one year prior to the prescription order date to establish a 12-month baseline period for assessment of prevalent medication use, patient characteristics, and comorbidities.
- No prescription order for any CGRP antagonist during the 12-month baseline period.
- Cohort members with missing or conflicting age or sex information were excluded.
- For the SOC antiepileptic preventive medication cohort only, no prescription order for any of the 5 antiepileptic medications during the 12-month baseline period.

The index date was defined as the date of the earliest prescription order that met all of the above criteria. Because it was expected that patients would have started erenumab or another CGRP antagonist after attempting treatment with an SOC preventive medication, the SOC antiepileptic preventive medication cohort was selected from the remaining population of migraine preventive treatment users after the erenumab and CGRP antagonist cohorts were formed.

The baseline period for assessing patient characteristics was the 12-month period before the index date (inclusive of the index date).

To address the 4th and 5th objectives of this study, the erenumab cohort was matched to the other CGRP antagonist cohort and, separately, to the SOC antiepileptic preventive medication cohort using propensity score (PS) matching. PSs were estimated by logistic regression models that incorporated risk factors for constipation and *a priori* identified potential confounders.

- **Variables and Data Sources**

This study utilized data from the Optum EHR database, a de-identified patient-level database that integrates multiple electronic medical record data systems with medical claims, prescription, and practice management data.

Outcome variable: Inpatient constipation was defined using ICD-10-CM diagnosis codes for constipation in an emergency department (ED) or inpatient (IP) hospital setting only. Among patients with inpatient constipation, the presence of serious complications was also captured and described as the presence of at least one ICD-10-CM diagnosis code for fecal impaction, intestinal obstructions, anal fissures and/or fistulas as well as other symptoms identified in an emergency department or inpatient hospital setting within 30 days following the date of the inpatient constipation event.

Exposure variable: Initiators of erenumab, other CGRP antagonists, and SOC antiepileptic preventive medications were identified during the study period using National Drug Codes (NDC) as recorded in the prescription order table within the EHR database.

Covariates: We evaluated the following types of variables during the baseline period: demographics and *a priori* defined covariates of interest, including comorbidities, concomitant medications, and risk factors for the outcome.

- **Statistical Analysis**

The incidence proportion and 95% confidence intervals (CIs) of the primary endpoint of inpatient constipation was estimated in the 3 cohorts by dividing the total number of patients with an event observed by the number of cohort members at risk at the start of follow-up. Multiple risk windows for outcome assessment (30-, 60-, 90-day risk windows and all available follow-up) were evaluated, with the 90-day risk window specified *a priori* as the primary risk window of interest. Incidence proportions were calculated before and after PS matching. The incidence proportion of serious complications of inpatient constipation was estimated in a similar manner.

For the comparative analysis, the incidence proportion of inpatient constipation was compared between the erenumab cohort versus the matched other CGRP antagonist cohort, and, separately, versus the matched SOC antiepileptic preventive medication cohort. Logistic regression models were used to estimate the odds ratios (ORs) and corresponding 95% CIs.

Because the date of drop-out could not easily be identified in the Optum EHR database and therefore patients could not be censored at drop-out, the incidence proportion of inpatient constipation was also estimated in post-hoc analysis among the subset of PS-matched erenumab and other CGRP antagonist initiators whose index date was on or after 01 January 2019. This date was selected to ensure that both cohorts would have the opportunity to evaluate events during similar follow-up periods, rather than differential follow-up periods defined by the launch date of the medications of interest.

- **Results**

A total of 18 012 initiators of erenumab, 13 450 initiators of other CGRP antagonists, and 49 617 initiators of SOC antiepileptic preventive medications met all eligibility criteria.

The mean (standard deviation) age of patients was 46 years (12.7) in the erenumab cohort, 45 years (12.7) in the other CGRP antagonist cohort, and 45 years (14.6) in the SOC cohort. The majority of patients in each cohort were female, including 87.5% of erenumab initiators, 88.2% of other CGRP antagonist initiators, and 86.4% of SOC antiepileptic preventive medication initiators.

Prior to PS matching, a small number of cohort members with missing geographic region (n=276) were excluded from the analysis. After PS matching initiators of erenumab to initiators of other CGRP antagonists, 13 200 study members in the erenumab cohort were successfully matched and 4702 were unmatched. Among initiators of erenumab and SOC antiepileptic preventive medications, 15 441 study members in the erenumab cohort were successfully matched and 2461 were unmatched. Following PS matching of the erenumab initiator cohort to the other CGRP antagonists and to the SOC antiepileptic preventive medication initiator cohorts, the matched cohorts were balanced with regard to the *a priori* selected confounders and risk factors for constipation.

Among the PS-matched erenumab initiators and SOC antiepileptic preventive medication initiators, the incidence proportion of inpatient constipation within a 90-day risk window was 0.53% (95% CI 0.42 – 0.66) and 0.76% (95% CI 0.62 – 0.92), respectively (Table 1). The OR for inpatient constipation within a 90-day risk window was 0.69 (95% CI 0.51 – 0.94) when PS-matched erenumab initiators were compared to SOC antiepileptic preventive medication initiators. The ORs comparing the incidence proportion of inpatient constipation between erenumab initiators versus SOC antiepilepic preventive medication initiators for the 30-day, 60-day, and all available follow-up risk windows were 0.62 (95% CI 0.41 – 0.94), 0.67 (95% CI 0.48 – 0.93), and 0.82 (95% CI 0.69 – 0.97), respectively.

Table 1. Incidence Proportion of Inpatient Constipation Within Different Risk Windows Following the Index Date, Erenumab and SOC Antiepileptic Preventive Medication Initiators, Post-Propensity Score Matching

Risk Window	Cohort	Initiators	Inpatient Constipation Events	Incidence Proportion (95% CI)	Odds Ratio (95% CI)
30-day	Erenumab	14 973	36	0.24 (0.17 - 0.33)	0.62 (0.41 - 0.94)
	SOC antiepileptic	14 983	58	0.39 (0.30 - 0.50)	Reference
60-Day	Erenumab	14 360	58	0.40 (0.31 - 0.52)	0.67 (0.48 - 0.93)
	SOC antiepileptic	14 430	87	0.60 (0.49, 0.74)	Reference
90-Day	Erenumab	13 669	72	0.53 (0.42 - 0.66)	0.69 (0.51 - 0.94)
	SOC antiepileptic	13 752	104	0.76 (0.62 - 0.92)	Reference
All Available Follow-up	Erenumab	15 441	233	1.51 (1.33 - 1.71)	0.82 (0.69 - 0.97)
	SOC antiepileptic	15 441	284	1.84 (1.64 - 2.06)	Reference

SOC = standard of care

The incidence proportion of serious complications of inpatient constipation within a 90-day risk window was 0.05% (95% CI 0.02 – 0.11) in the PS-matched erenumab cohort and 0.09% (95% CI 0.05 – 0.15) in the PS-matched SOC cohort.

The incidence proportion of inpatient constipation within a 90-day risk window following the index date was 0.46% (95% CI 0.35 – 0.60) among matched erenumab initiators and 0.44% (95% CI 0.33 – 0.58) among matched other CGRP antagonist initiators (Table 2). The OR for inpatient constipation within a 90-day risk window was 1.06 (95% CI 0.72 – 1.55) when PS-matched erenumab initiators were compared to other CGRP antagonist initiators. The corresponding ORs for the 30-day, 60-day, and all available follow-up risk windows were 1.16 (95% CI 0.67 – 2.03), 1.20 (95% CI 0.78 – 1.85), and 1.40 (95% CI 1.13 – 1.74), respectively.

Table 2. Incidence Proportion of Inpatient Constipation Within Different Risk Windows Following the Index Date, Erenumab and Other CGRP Antagonist Initiators, Post-Propensity Score Matching

Risk Window	Cohort	Initiators	Inpatient Constipation Events	Incidence Proportion (95% CI)	Odds Ratio (95% CI)
30-day	Erenumab	12 795	27	0.21 (0.15 - 0.31)	1.16 (0.67 - 2.03)
	Other CGRP antagonists	12 651	23	0.18 (0.12 - 0.27)	Reference
60-Day	Erenumab	12 261	47	0.38 (0.29 - 0.51)	1.20 (0.78 - 1.85)
	Other CGRP antagonists	11 927	38	0.32 (0.23 - 0.44)	Reference
90-Day	Erenumab	11 670	54	0.46 (0.35 - 0.60)	1.06 (0.72 - 1.55)
	Other CGRP antagonists	11 172	49	0.44 (0.33 - 0.58)	Reference
All Available Follow-up	Erenumab	13 200	200	1.52 (1.32 - 1.74)	1.40 (1.13 - 1.74)
	Other CGRP antagonists	13 200	143	1.08 (0.92 - 1.27)	Reference

CGRP = calcitonin gene-related peptide

In the subset of PS-matched erenumab and other CGRP antagonist initiators whose index date was on or after 01 January 2019, the incidence proportion of inpatient constipation during all available follow-up was 1.15% (95% CI 0.95 – 1.40) among erenumab initiators and 1.01% (95% CI 0.85 – 1.21) among other CGRP antagonist initiators; the corresponding OR was 1.14 (95% CI 0.87 – 1.49) (Table 3).

Table 3. Incidence Proportion of Inpatient Constipation Within Different Risk Windows Following the Index Date, Erenumab and Other CGRP Antagonist Initiators, Post-Propensity Score Matching: Post-Hoc Analysis Among Initiators Whose Index Date is on or after 01 January 2019

Risk Window	Cohort	Initiators	Inpatient Constipation Events	Incidence Proportion (95% CI)	Odds Ratio (95% CI)
30-day	Erenumab	8375	18	0.21 (0.14 - 0.34)	1.10 (0.59 - 2.04)
	Other CGRP antagonists	11218	22	0.20 (0.13 - 0.30)	Reference
60-Day	Erenumab	7841	30	0.38 (0.27 - 0.55)	1.09 (0.67 - 1.76)
	Other CGRP antagonists	10494	37	0.35 (0.26 - 0.49)	Reference
90-Day	Erenumab	7250	32	0.44 (0.31 - 0.62)	0.90 (0.57 - 1.40)
	Other CGRP antagonists	9739	48	0.49 (0.37 - 0.65)	Reference
All Available Follow-up	Erenumab	8780	101	1.15 (0.95 - 1.40)	1.14 (0.87 - 1.49)
	Other CGRP antagonists	11767	119	1.01 (0.85 - 1.21)	Reference

CGRP = calcitonin gene-related peptide

The incidence proportion of serious complications of inpatient constipation within a 90-day risk window was 0.02% (95% CI 0.00 – 0.06) in the erenumab cohort and 0.04% (95% CI 0.02 – 0.10) in the PS-matched other CGRP antagonist cohort.

- **Discussion**

In this study, the incidence proportion of inpatient constipation within a 90-day risk window (*a priori* primary risk window of interest) among patients who initiated erenumab was similar to the incidence proportion among patients who initiated other CGRP antagonists and lower than the incidence proportion among patients who initiated SOC antiepileptic preventive medications. Similar patterns were observed for the 30-day risk window and 60-day risk windows when comparing the incidence proportion of inpatient constipation in the matched erenumab cohort to that of the other CGRP antagonist cohort, and separately, to the SOC antiepileptic preventive medications cohorts.

The risk of inpatient constipation was higher among the erenumab cohort compared to the other CGRP antagonist cohort when evaluating events during all available follow-up (OR = 1.40 [95% CI 1.13 – 1.74]). Comparing these results to those obtained from the post-hoc analysis, in which the PS-matched erenumab and other CGRP antagonist initiators were restricted to the subset whose index date was on or after 01 January 2019, the OR was attenuated (OR = 1.14 [95% CI 0.87 – 1.49]). This finding suggests that a longer period of available follow-up among the erenumab initiators in the primary analysis (due to the earlier launch of erenumab versus the other CGRP mAbs) may have contributed to a higher incidence proportion of inpatient constipation observed in this cohort compared to the other CGRP antagonist initiators during all available follow-up. Also, reassuringly, when comparing the incidence proportion of inpatient constipation across all available follow-up in the primary analysis between erenumab initiators and the initiators of SOC antiepileptics (which were available at the launch of erenumab), the odds ratio was 0.82 (95% CI 0.69 – 0.97).

The incidence proportion of serious complications of inpatient constipation was low across all 3 cohorts and comparable in the erenumab and other CGRP antagonist cohorts, but slightly higher in the SOC antiepileptic preventive medication cohort.

The results of this study do not impact the benefit-risk profile of erenumab.

- **Marketing Authorization Holder(s)**

Amgen, Inc.

- **Names and Affiliations of Principal Investigator**

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