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ORIGINAL RESEARCH

Monthly Headaches and Severity in Patients on Galcanezumab or Traditional Preventive Migraine Medication: A 24-Month Claims and Electronic Health Records Study

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ABSTRACT

Introduction: Migraine, affecting millions globally, imposes a significant burden on patients and healthcare systems. Calcitonin gene-related peptide monoclonal antibodies are recommended as first-line preventive treatments by international guidelines, yet real-world prospective studies comparing their year-long effectiveness to standard of care (SOC) treatments are time-consuming, resource-intense and therefore limited. This study aimed to test the utility of claims data and electronic health records (EHR) by evaluating changes in monthly headache days (MHDs) and disease severity among US patients with migraine receiving galcanezumab versus traditional standard-of-care preventive migraine medications.

Methods: A real-world study was conducted using Optum data from US administrative claims and EHR of patients diagnosed with migraine and receiving galcanezumab or SOC. Changes in MHDs over a 24-month follow-up were converted from changes in acute medication using the Pharmacy Quality Alliance (PQA) measure for Migraine Preventive Therapy, and migraine severity was assessed using EHR free text. Data were analyzed using two-sample *t*-test, chi-square and Fisher exact tests.

Results: Of 63,939 patients with eligible claims, 28,264 (44.2%) had notes in EHR; of those, 227 and 65 patients had information for migraine severity and headache days, respectively. Patients receiving galcanezumab showed significant improvement in MHDs compared to the SOC cohort when assessed using PQA measures (mean [SD] change from baseline to follow-up, −0.18 [4.76] vs 0.15 [3.85]; $p<0.001$). A significantly greater proportion of patients treated with galcanezumab exhibited a 50% reduction (25.9% vs 16.7%; $p<0.001$) and 75% reduction (15.7% vs 11.6%; $p<0.001$) in MHDs than the standard-of-care cohort. Mean change in migraine severity and MHDs was not determined by EHR because of low sample sizes.

Conclusion: In this exploration of multiple data sources and methodologies, changes in MHDs over 24 months were small in patients treated with galcanezumab or SOC. While real-world data from administrative claims and EHR provided insights, limitations such as small sample sizes for migraine severity data

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and challenges in extracting clinical outcomes underscore the need for further research.

Keywords: Galcanezumab; Migraine; Real-word; Administrative claims; Electronic health records; Monthly headache days

Key Summary Points

Why carry out this study?

Robust real-world prospective clinical data comparing 12–24 months of long-term effectiveness of calcitonin gene-related peptide monoclonal antibodies (CGRP-mAbs) to traditional standard of care (SOC) preventive migraine treatments are time-consuming, resource intense and therefore limited

We hypothesized administrative claims data and electronic health records (EHR) could be an alternative approach to evaluate long-term changes in monthly headache days (MHDs) and disease severity among US patients with migraine treated with a CGRP-mAb, such as galcanezumab, and compared to traditional SOC preventive migraine medications

What was learned from the study?

Real-world data from administrative claims and EHR provided insights, but limitations such as small sample sizes for migraine severity data and challenges in extracting clinical outcomes underscore the need for further research. Despite these limitations, we found that:

Both the Pharmacy Quality Assurance measure algorithm and Natural Language Processing model showed significant, though small, improvements in MHDs for patients treated with galcanezumab compared to SOC, although results varied by method

Galcanezumab demonstrated significant benefit over SOC, with greater reductions in MHDs and a higher proportion of patients achieving a 75% reduction in headache days over 24 months

INTRODUCTION

Migraine is characterized by recurrent and debilitating episodes of throbbing headaches, often accompanied by nausea, vomiting and sensitivity to light and sound [1, 2]. Migraine impacts around 68.5 million people in the US and is the third leading cause of disability worldwide [3–5], imposing a significant burden on both patients and healthcare systems [6]. Despite the availability of various treatment options, many patients with migraine continue to experience inadequate relief, frequent attacks and significant impairment in daily functioning [1, 7]. While recent literature highlights that health equity and access to care remain major challenges in the management of migraine, with many patients unable to access the most effective treatments due to socioeconomic factors, there are ongoing efforts such as patient support and copay assistance programs to reach these underserved patient populations [8, 9]. Traditional commonly used preventive standard of care (SOC) treatments for migraine include β-blockers, tricyclic antidepressants, antiepileptics, angiotensin-converting enzyme inhibitors and onabotulinumtoxinA [10]. However, inconsistent efficacy and tolerability issues limit the utility of these agents [1, 7, 11].

The US Food and Drug Administration has approved calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) erenumab, fremanezumab, galcanezumab and eptinezumab for migraine prevention [10]. The American Headache Society (AHS) 2021 position statement recommended that CGRP mAbs be initiated in patients with moderate disability or those unable to tolerate or with inadequate response to 2 or more classes of traditional preventive migraine medications at a dose established to be potentially effective or to at least two

quarterly injections of onabotulinumtoxinA in an 8-week interventional trial [7]. However, the 2022 European Headache Federation consensus statement and the recent 2024 AHS position statement recommended that CGRP antagonists be used as first-line treatment for patients who require preventive migraine therapy without 2 prior SOC treatment attempts [10, 12]. The safety and efficacy of CGRP mAbs have been well documented in several double-blind randomized controlled trials (RCTs) for the prevention of both episodic and chronic migraine [13–21]. Specifically, galcanezumab significantly reduced monthly headache days (MHDs) and migraine severity compared with placebo in individuals with episodic migraine (EVOLVE-1 and EVOLVE-2) [13, 14], chronic migraine [21] and those who experienced prior treatment failure with two to four categories of migraine preventive medications (CONQUER) [22]. Placebo-controlled clinical trials evaluating clinical outcomes in patients with migraine treated with CGRP mAbs are typically limited to 3 to 6 months [13, 14, 22], and few clinical trials have evaluated the efficacy of CGRP mAbs versus SOC [23]. Limited real-world evidence (RWE) is available comparing long-term clinical outcomes in patients with migraine treated with CGRP mAbs, including galcanezumab, to those of SOC preventive migraine medications.

Earlier claims-based real-world studies assessed treatment patterns, health care resource utilization and cost of CGRP mAb and/or galcanezumab compared to SOC preventive migraine medications over 12 and 24 months of follow-up [24–26]. Despite these studies, RWE studies on the effectiveness and optimal use of galcanezumab versus SOC preventive migraine medications in clinical practice are scarce. Robust real-world prospective studies to evaluate long-term effectiveness of migraine preventive agents are costly and time-consuming, and they require significant resources, often limiting the feasibility of such studies [27]. Given this, novel approaches to assessing migraine clinical outcomes of interest including changes in disease severity and MHDs are warranted to understand the long-term impact of migraine preventive therapy [28]. Recently, the Pharmacy Quality Alliance (PQA) developed and endorsed the quality measure for Migraine Preventive Therapy (MPT), which can be considered as a means to evaluate changes in MHDs by exploring migraine medication utilization via administrative claims data [29]. Natural Language Processing (NLP) is a method that can be used to extract clinical information from electronic records to evaluate clinical outcomes of interest like migraine severity and MHDs [30]. This study aimed to test the utility of these two approaches using administrative claims data and electronic health records (EHR) in identifying differences in monthly migraine headache days and disease severity over 24 months in patients with migraine in the US who initiated treatment with galcanezumab or SOC preventive migraine medications. To our knowledge, this is the first reported study of these novel approaches to evaluating changes in migraine severity and MHDs. The observed results may offer insights into less costly and timely approaches to evaluating long-term effectiveness and clinical outcomes in patients treated with preventive migraine medications as well as ways to improve upon and further explore these approaches.

METHODS

Study Design and Patient Population

This was a retrospective observational cohort study that used administrative claims and EHR data from the deidentified Optum Market Clarity Dataset for the period of 1 September 2017 through 31 March 2022. Details on the study design, patient selection and medications included in SOC treatment have previously been published [24]. The study included adult patients aged ≥ 18 years who were diagnosed with migraine (based on the International Classification of Diseases, 9th and 10th Revisions, Clinical Modification code from baseline through the index date) and newly initiating galcanezumab or SOC preventive migraine therapy between 01 September 2018 and 31 March 2020 (identification period) with continuous enrollment in medical and pharmacy benefits for 12 months before (baseline) and 24 months after

(follow-up) the index date. The index date was defined as the date of a first claim for galcanezumab or SOC during the identification period [24]. The NLP model included eligible populations from a broader population in claims. The SOC treatments included medications described in the 2021 AHS consensus statement and additional medications for migraine prevention [7, 25] from the following drug categories of β-blockers: anticonvulsants, tricyclic antidepressants, calcium channel blockers, angiotensin type II receptor antagonists and onabotulinumtoxinA [25].

All data were accessed in compliance with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996 regulations (HIPAA). All databases used are de-identified and fall under the US Department of Health and Human Services Policy for the Protection of Human Subjects. Therefore, informed consent and Institutional Review Board approval were not required. The authors obtained permission to use the Optum Market Clarity Database.

Outcome Measures

Demographics, which were reported previously [24], and migraine-related clinical outcomes were evaluated during the 12-month baseline and 24-month follow-up periods.

Migraine-Related Clinical Outcomes

Assessment of Monthly Headache Days Using the Pharmacy Quality Alliance Measure

MHDs were assessed in patients diagnosed with migraine using a claims-based proxy for migraine headache frequency, derived from a conversion calculation of acute migraine medication doses to MHDs [29]. This calculation was based on the quality measure for MPT developed and endorsed by the PQA [31] (see the electronic Supplementary Material for more details). This quality measure for MPT compares headache frequency from acute migraine medications against a set threshold (12 headaches per a 120-day or less evaluation period) to determine eligibility for preventive treatment [29]. The measure's components were adapted to calculate the number of MHDs per 30 days at the patient level during a 12-month baseline period and a 24-month follow-up period. The classes of acute medications included in the PQA quality measure algorithm for MPT are provided in **Table S2** (see the electronic Supplementary Material). The calculation used prescription claims for acute migraine medications during the respective observation periods. For each acute migraine medication claim, the number of headaches was calculated by multiplying the quantity by a conversion factor. If there were multiple claims with the same date of service, all claims were considered.

The total number of headache days across prescription claims was divided by the number of months (12 for baseline and 24 for fixed follow-up) to determine the MHDs per patient. Patients with no acute migraine medication claims during the observation period were assigned a value of zero.

Assessment of Monthly Headache Days Using NLP

An advanced NLP model was developed to extract clinical information from EHR physician notes to identify headache days for patients. Data experts mined the provider notes and then normalized, validated and integrated them into the database. NLP techniques were used to extract migraine frequency and frequency unit concepts from the unstructured medical record notes, which were transformed and provided in a structured, standard format for the analysis (see the electronic Supplementary Material for more details on NLP). This process captured explicit frequencies of migraine or MHDs, including numeric frequency amounts and countable expressions such as "daily" (see Table S3 in the electronic Supplementary Material for details). Narrative expressions (increased or decreased frequency) or modifiers (greater or less than) were not included to capture migraine frequency. Change in MHDs was estimated using both best scenario and worst scenario. Best scenario is an estimation of

the change in MHDs by comparing the highest value from the latest date in the baseline period relative to the lowest value from the latest date in the follow-up period. Worst scenario is an estimation of the change in MHDs by comparing the lowest value from the latest date in the baseline period relative to the highest value from the latest date in the follow-up period.

Assessment of Migraine Severity Using NLP

A categorical variable describing migraine severity (mild, moderate or severe) was created for a subset of patients with linked EHR data using existing Optum NLP-derived variables based on evidence of migraine severity records in the structured NLP-produced EHR data tables. Claims data for patients with available migraine severity information for both baseline and follow-up periods underwent assessment for changes to the severity category. This involved identifying improvement (increased severity level), no change (same severity level) or worsening (decreased severity level) between baseline and follow-up. The severity recorded on the latest date within each period was considered. Patients with multiple unique severity mentions on the latest date within the period were excluded from the analysis for that specific period.

Statistical Analysis

Numbers and percentages were provided for dichotomous and polychotomous variables. Means, medians, standard deviations (SDs) and quartiles were provided for continuous variables. A two-sample *t*-test was used for continuous measures. The Fisher exact test or chi-square test was used for binary measures.

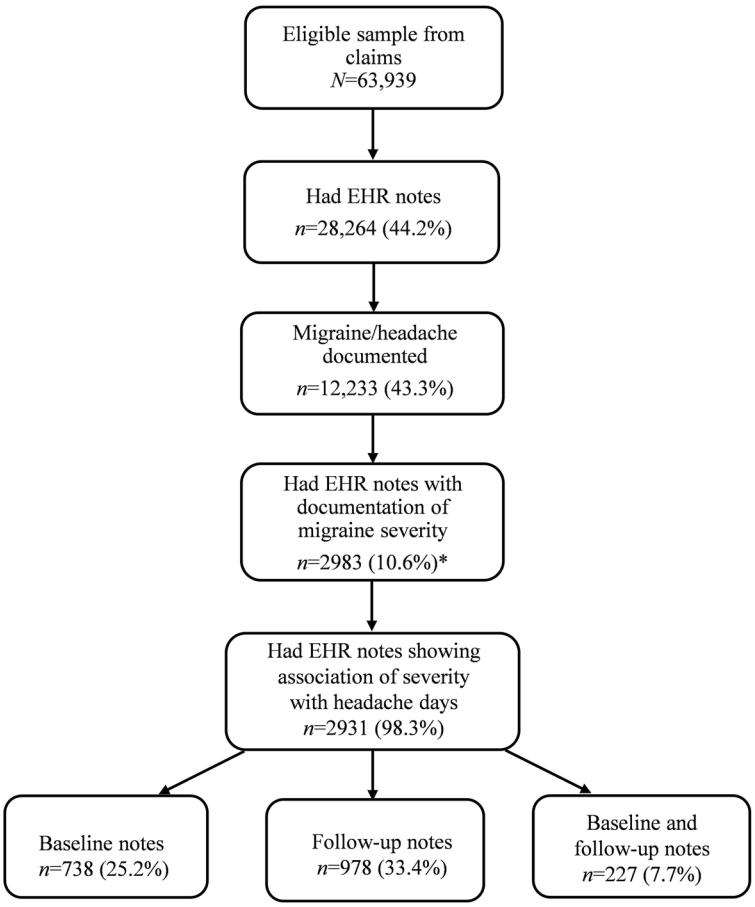
Pearson's correlation coefficient was used to summarize the association between migraine severity categories and the baseline and follow-up claims-based migraine days outcome. Migraine severity outcomes were stratified by the indicator of baseline preventive migraine therapy by cohort. The correlation was tested between NLP-derived and PQA quality measure algorithm-derived MHDs and for the baseline and follow-up severity categories (mild, moderate and severe) using a regression model. Statistical analyses were conducted using Statistical Analysis Software (SAS), V 9.4. All statistical tests were performed at a two-sided 5% significance level, and p-values < 0.05 were considered statistically significant.

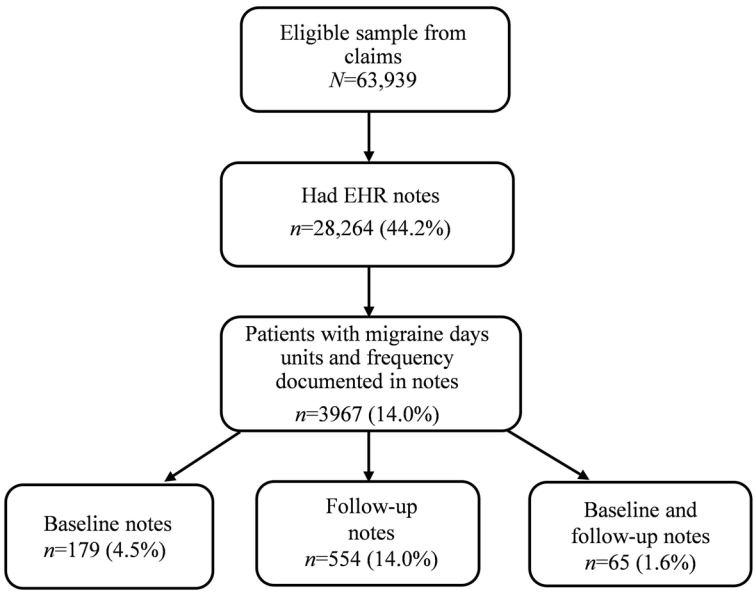
RESULTS

Patient Population and Baseline Characteristics

Baseline characteristics of the overall population have been previously described in detail elsewhere [24]. A total of 2363 and 61,576 patients were receiving galcanezumab and SOC preventive migraine medications, respectively. There was no significant difference in the mean (SD) age of patients between the galcanezumab and SOC cohorts (44.5 [12.0] vs. 43.3 [13.9] years; standardized difference, 9.1%), and 87.1% and 81.9% of the patients were female in the respective cohorts. About 17% of patients in both cohorts were receiving traditional preventive migraine medications.

Among the eligible sample from claims data ($N = 63{,}939$), 28,264 patients had EHR notes; of these, 2983 patients (10.6%) had EHR notes with documentation of migraine severity. Of 2983 patients, 2931 (98.3%) had EHR notes indicating a severity descriptor during the study period, and 227 (7.7%) had EHR notes with both baseline and follow-up severity data (Fig. 1A). Overall, 3967 of 28,264 patients (14.0%) had migraine day units and frequency documented in the EHR notes; of these, 65 patients (1.6%) had data for both baseline and follow-up migraine days (Fig. 1B).


Eligible sample from claims
N=63,939
Had EHR notes
n=28,264 (44.2%)
Migraine/headache documented
n=12,233 (43.3%)
Had EHR notes with documentation of migraine severity
n=2983 (10.6%)*
Had EHR notes showing association of severity with headache days
n=2931 (98.3%)
Baseline notes
n=738 (25.2%)
Follow-up notes
n=978 (33.4%)
Baseline and follow-up notes
n=227 (7.7%)


Eligible sample from claims
N=63,939
Had EHR notes
n=28,264 (44.2%)
Patients with migraine days units and frequency documented in notes
n=3967 (14.0%)
Baseline notes
n=179 (4.5%)
Follow-up notes
n=554 (14.0%)
Baseline and follow-up notes
n=65 (1.6%)

◂**Fig. 1** Study disposition for patients with EHR notes for (i) migraine severity and (ii) MHDs associated with migraine severity captured by the natural language processing model relative to their index date. *Only specific severity descriptors were included for analysis. Percentage of 2983 is based on the final number of 28,264. *EHR* electronic health record, *MHDs* monthly headache days

Migraine-Related Clinical Outcomes

Assessment of Monthly Headache Days Using the PQA Measure

A small difference in the mean (SD) of MHDs was observed between patients in the galcanezumab and SOC cohorts at both baseline (2.9 [6.6] vs 1.3 [5.2]) and the 24-month follow-up (2.8 [6.0] vs 1.4 [4.7]). Patients in the galcanezumab cohort had a significantly larger mean change from baseline to follow-up in MHDs compared with those in the SOC cohort (−0.18 [4.76] vs 0.15 [3.85]; $p<0.001$) (Fig. 2).

A significantly greater proportion of patients in the galcanezumab cohort than in the SOC cohort exhibited a 50% reduction (25.9% vs 16.7%; $p<0.001$) and 75% reduction (15.7% vs 11.6%; $p<0.001$) in MHDs during the 24-months of follow-up, as estimated by the PQA quality measure algorithm (Fig. 3).

Assessment of Monthly Headache Days Using NLP

The baseline and follow-up MHDs in the galcanezumab and SOC cohorts assessed using EHR best and worst scenarios are reported in Table 1. MHDs decreased from baseline to follow-up as per the best scenario estimate and increased from baseline to follow-up as per the worst scenario estimate in both the galcanezumab and SOC cohorts. In the overall population, 44.6% of patients had a 50% reduction in MHDs and 24.6% had a 75% reduction as per the best change estimate, while 16.9% of patients had a 50% reduction in MHDs and 6.2% had a 75% reduction as estimated by the worst change estimate (Fig. 4). Few patients had available data for both migraine severity and MHDs across baseline and follow-up in the galcanezumab cohort ($n<10$ for mild and moderate severity; $n=13$ for severe category); hence, mean change in MHDs and percentage reduction in MHDs for the galcanezumab and SOC cohorts are not reported for the NLP method.

Assessment of Severity Using NLP

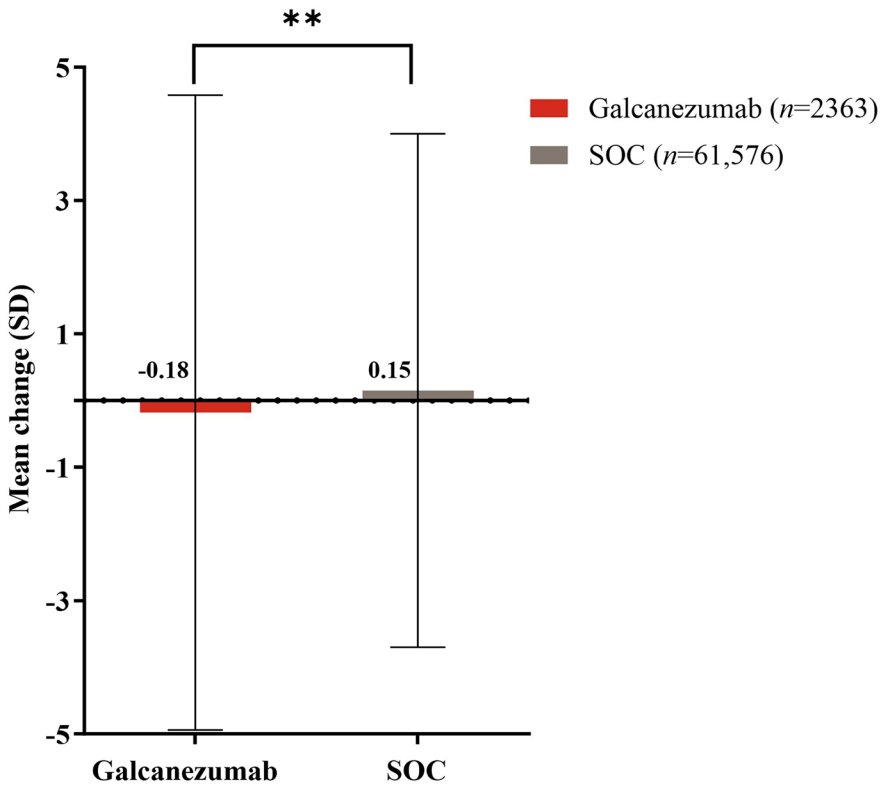
A total of 722 and 957 patients had baseline and follow-up severity data with 70.9% and 71.4% of the patients in the severe category at baseline and follow-up, respectively (Table 2). Severity data are not presented by cohort because of the low sample size in the galcanezumab cohort.

Correlation Between NLP-Based and PQA Quality Measure Algorithm-Based Monthly Headache Days and Migraine Severity

A weak, non-significant correlation ($r<0.1$) was observed between the NLP-based and PQA quality measure algorithm-based MHDs at baseline and follow-up and between baseline and follow-up migraine severity categories (mild, moderate and severe) (Table 3).

DISCUSSION

In this exploration of multiple data sources and methodologies, we attempted to measure changes in monthly headache based on a conversion calculation of acute migraine medication doses to MHDs using the PQA quality measure algorithm and modeled from EHR free-text based on NLP. While these approaches presented limitations and challenges from small sample sizes to difficulty in extracting clinical information from electronic records, insights were gained to understand directional trends that can be observed from these research methods. The mean changes in MHDs during 24 months of follow-up among patients treated with galcanezumab or SOC were small. However, a greater reduction in MHDs was



	Galcanezumab (*n*=2363)	SOC (*n*=61,576)	*P* value
Baseline MHDs, mean (SD)	2.9 (6.6)	1.3 (5.2)	<0.001
MHDs at 24-m follow-up, mean (SD)	2.8 (6.0)	1.4 (4.7)	<0.001

Fig. 2 Mean change in MHDs for the galcanezumab and SOC cohorts derived from the PQA measure. A negative change indicates improvement in MHDs (follow-up-baseline). The chi-square test was used to compare cohorts. $^{**}p < 0.001$ vs SOC. *m* month, *MHDs* monthly headache days, *PQA* Pharmacy Quality Alliance, *SD* standard deviation, *SOC* standard of care

observed for patients with migraine receiving galcanezumab than for those receiving SOC over a 24-month follow-up as assessed by the PQA quality measure algorithm. Furthermore, greater proportions of patients receiving galcanezumab had a ≥ 50% and ≥ 75% reduction in MHDs compared with those receiving SOC preventive migraine medications when assessed using the PQA quality measure algorithm. The assessment of disease severity was compromised by a small sample size of EHR with sufficient baseline and endpoint text. Extracting information on the clinical improvement of patients from claims data and EHR is challenging. This study evaluated clinical outcomes including MHDs and disease severity using a novel approach with administrative claims and EHR data over a long-term follow-up. Given this, it is important to consider the methodology utilized in this study when interpreting the observed results. While directional trends primarily favorable to galcanezumab over SOC were observed,

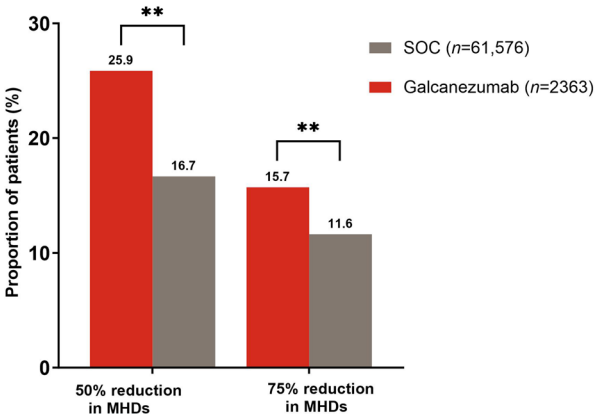


Fig. 3 Reduction in MHDs for the galcanezumab and SOC cohorts based on the PQA measure. The Fisher exact test was used for analysis. $^{**}p < 0.001$ vs SOC. *MHDs* monthly headache days, *PQA* Pharmacy Quality Alliance, *SOC* standard of care

there are inherent limitations of the evolving methodologic approaches utilized in this study.

Patients receiving galcanezumab showed significantly greater improvement in the mean change in MHDs compared with SOC as estimated by the PQA quality measure algorithm. Compared to baseline, reductions in MHDs were observed over a 24-month follow-up in the overall sample as estimated by a custom NLP model.

We explored the use of EHR data to assess migraine severity and MHDs from a custom NLP model that was not available in administrative claims data. In administrative claims studies, the claims are collected for payment rather than research, and all clinical characteristics of patients are not available in the administrative claims data [32]. Some clinical characteristics not measured in claims data are usually supplemented by clinical data or captured using proxies in claims data. Additionally, the EHR data are limited by sampling sizes and inconsistent reporting of headache days and migraine severity in captured notes [24]. Hence, in this study, we developed an advanced NLP model to extract clinical information and identify migraine days for patients that was dependent on available data using EHR physician notes.

Previous RWE studies [33–35] and RCTs [13, 14, 36] confirmed that initiating treatment with galcanezumab reduced the number of MHDs in patients with migraine. Previous real-world studies evaluating the effectiveness of galcanezumab reported a greater reduction in monthly headaches by 7.2 days [35], 5 to 10 days (after 3 and 6 doses of galcanezumab, respectively) [33] and 10 days [34] at 12 months, 3 months and 6 months of treatment, respectively. The overall mean change from baseline in the number of monthly migraine headache days was −4.3 to −4.7 days in patients treated with 120 mg galcanezumab and −4.2 to −4.6 days in patients treated with 240 mg galcanezumab in EVOLVE-1 [13] and EVOLVE-2 [14] RCTs at 6 months and −5.1 days in another active-controlled RCT [36] at 3 months. In an open-label RCT, patients

Table 1 Mean MHDs for galcanezumab and SOC cohorts derived by the natural language processing model

	Best scenario			Worst scenario		
	SOC	Galcanezumab	*P* value	SOC	Galcanezumab	*P* value
Baseline, *n*	153	26		153	26	
No. of MHDs, mean (SD)	12.5 (10.0)	14.1 (7.8)	0.43	9.6 (9.4)	9.6 (7.1)	0.99
Follow-up, *n*	519	35		519	35	
No. of MHDs, mean (SD)	9.6 (8.8)	8.4 (7.6)	0.40	12.5 (9.4)	10.9 (7.4)	0.34

Best scenario/least conservation is an estimation of the change outcome by comparing the highest value from the latest date in the baseline period relative to the lowest value from the latest date in the follow-up period. Worst scenario/most conservative is an estimation of the change outcome by comparing the lowest value from the latest date in the baseline period relative to the highest value from the latest date in the follow-up period

MHDs monthly headache days, *n* number of patients in the cohort, *SD* standard deviation, *SOC* standard of care

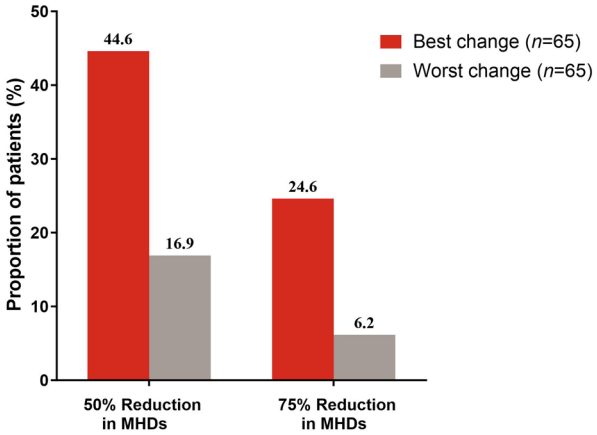


Fig. 4 Reduction in MHDs in the overall population based on natural language processing model. Best change is an estimation of the change outcome by comparing the highest value from the latest date in the baseline period relative to the lowest value from the latest date in the follow-up period. Worst change is an estimation of the change outcome by comparing the lowest value from the latest date in the baseline period relative to the highest value from the latest date in the follow-up period. *MHDs* monthly headache days

treated with galcanezumab 120 mg and 240 mg had a mean change of −9.0 and −8.0, respectively, at 12 months [37]. Our study showed a much smaller improvement in the mean change in MHDs of −0.18 versus+0.15 days, as derived by the PQA quality measure algorithm, among patients receiving galcanezumab versus SOC. Since the baseline MHD in our study was significantly lower than that reported in RCTs, the mean change in MHD was correspondingly smaller. In the EVOLVE-1 [13] and EVOLVE-2 [14] studies, a 50% reduction in MHDs at month 6 was observed in 59.3% to 62.3% of patients treated with 120 mg galcanezumab and 56.5% to 60.9% of those treated with 240 mg. A 75% reduction was reported in 33.5% to 38.8% of patients on either dose. In contrast, our study reported a lower percentage of patients achieving these reductions, with 44.6% showing a 50% reduction and 24.6% experiencing a 75% reduction in MHDs. These results are likely due to the small sample sizes, challenges in extracting clinical data from electronic records and gaps in MHDs reporting within the EHR.

Table 2 Mean MHDs at baseline and follow-up by migraine severity for the galcanezumab and standard of care cohorts derived from the Pharmacy Quality Alliance measure

	Total (*N* = 63,939)
Baseline	*N* = 722
Mild, *n* (%)	160 (22.2)
No. of MHDs, mean (SD)	1.6 (6.4)
Moderate, *n* (%)	50 (6.9)
No. of MHDs, mean (SD)	1.0 (1.9)
Severe, *n* (%)	512 (70.9)
No. of MHDs, mean (SD)	1.8 (4.5)
Follow-up	*N* = 957
Mild, *n* (%)	196 (20.5)
No. of MHDs, mean (SD)	1.3 (2.4)
Moderate, *n* (%)	78 (8.2)
No. of MHDs, mean (SD)	1.4 (2.2)
Severe, *n* (%)	683 (71.4)
No. of MHDs, mean (SD)	2.0 (5.8)

MHDs monthly headache days, *N* number of patients in the cohort, *n* number of patients in each category, *SD* standard deviation

Previous RWE studies based on claims data evaluated treatment patterns of galcanezumab compared to SOC preventive migraine medications over 12 and 24 months of follow-up in patients with migraine [24, 25]. Although these studies did not assess the reduction in MHDs or migraine severity, they found that patients in the galcanezumab cohort had significantly higher treatment adherence and persistence than those in the SOC cohort. Our study demonstrated a smaller yet significant improvement in mean change in MHDs over a 24-month period. The smaller improvement may be due to inadequacies in our model, and the significant difference may be attributed to the large sample size in the PQA quality measure algorithm. We did not compare early vs late initiation of preventive medications, but recent studies have

Table 3 Correlation matrix for MHDs and migraine severity derived from natural language processing and Pharmacy Quality Alliance methods

Measure	Baseline		Follow-up	
	Claims headache days	Severity	Claims headache days	Severity
Minimum EHR headache days	0.06	− 0.13	− 0.02	0.21
Maximum EHR headache days	0.03	− 0.22	0.03	0.22
Claims headache days	1.0	0.02	1.0	0.06
Severity	0.02	1.0	0.06	1.0

EHR electronic health records, *MHD* monthly headache day

reported improved outcomes with early CGRP mAb treatment in real-world settings, highlighting the need to redefine patient management by initiating an established preventive therapy earlier before the disease becomes severely disabling [38].

The mean change in MHDs as derived by the NLP method is not reported as only a few patients had available data for both migraine severity and MHDs across the baseline and follow-up periods in the galcanezumab cohort. The reduction in mean MHD values was comparably low in our study, and the probable reason may be the small sample size. It is important to highlight that migraine severity and MHD data were available only for a small number of patients in the galcanezumab cohort across the baseline and follow-up periods. In clinical studies, patients treated with galcanezumab showed significant improvement in their disease severity in EVOLVE-1 (least-squares mean change, − 1.6 for both galcanezumab 120 mg and 240 mg) and EVOLVE-2 (least-squares mean change, − 1.2 for galcanezumab 120 mg and − 1.2 for galcanezumab 240 mg) [13, 14]. These clinical trials employed more rigorous assessments using repeated scales like the Patient Global Impression of Severity, a 7-point scale ranging from normal (1) to severely ill (7), for evaluating migraine severity. We explored the use of EHR data to identify migraine severity and MHDs using the PQA quality measure algorithm and NLP model. These data points were not available in administrative claims data. Findings were limited by the small sample size, as migraine severity data were not readily available within the study population. When severity was documented, the majority of qualifiers (~ 70%) indicated "severe" disease. There were over 400 patients in the SOC cohort with severity data, and about 77% of patients who newly started on SOC had moderate-to-severe migraine at baseline. Moreover, the three-level categorization of severity makes it hard to detect changes. Hence, we supplemented this with the headache days. Furthermore, we observed a weak correlation between the NLP- and claims-based measures across different follow-up time points, suggesting there was no strong relationship between the results obtained from the two methodologies. It is important to acknowledge the low sample size for migraine severity and MHD data in the galcanezumab cohort across the baseline and follow-up periods.

PQA-derived measures rely on the use of prescription treatments, while NLP-derived measures are based on provider documentation of patient-reported symptoms. This difference can lead to discrepancies or a low correlation between the two methods. Ultimately, all these approaches aim to understand migraine frequency. Future studies are suggested to further examine these outcomes using a prospective data collection study.

RWE studies comparing MHDs and migraine severity among patients receiving galcanezumab versus SOC are not available, except for the TRIUMPH study [39, 40]. TRIUMPH, an ongoing observational study with 24-month follow-up, was initiated to assess longitudinal effectiveness outcomes in

patients who initiated or switched to a new pharmacologic migraine preventive treatment [39–41]. Studies with larger population sizes using these methods are warranted to reevaluate the long-term effectiveness of galcanezumab compared to SOC. The ongoing real-world TRIUMPH study with 3-month data revealed that patients with migraine who switched to galcanezumab had significantly greater improvements in migraine severity, daily functioning and work productivity at 3 months compared with SOC [39, 40]. Unlike earlier clinical trials with a shorter follow-up of 6 months [13, 14], our study provided real-world evidence of the impact of galcanezumab on the number of headache days and overall preventive therapy on migraine severity over a more extended follow-up period of 24 months.

Strengths and Limitations

This experimental administrative claims data model study was an attempt to test an innovative method by evaluating the impact of galcanezumab on migraine-related outcomes over long-term follow-up. The study explored the use of the NLP model to assess MHDs and migraine severity for the first time in a claims-based real-world claims-linked EHR study. The study had the following limitations. The 24-month follow-up requirement inadvertently excluded patients with insufficient observation time because of study discontinuation [36]. Our analyses were restricted to members with available enrollment information; hence, we supplemented missing data with a claims-based proxy for migraine headaches. EHR data may report historical or current values, and our analysis assumed all data to be current. The PQA quality measure algorithm used to assess MHDs may not capture all acute medications or over-the-counter medications without a corresponding claim. Hence, patients may be using other medications not included in the PQA quality measure algorithm, which can affect the assessment of MHDs. This may explain the lower average MHDs derived from the PQA quality measure algorithm compared to the NLP model-derived outcome. The findings were constrained by the small sample size available for assessing migraine severity; thus, results were reported overall and not by cohort. These limitations underscore the need for further research to extract clinical outcomes from prospective data collection, thusenhancing the understanding of the impact of galcanezumab on migraine management.

CONCLUSION

In this exploration of multiple data sources and methodologies assessing changes in mean headache days over a 24-month follow-up period, patients with migraine treated with galcanezumab experienced a small but significantly greater improvement compared to SOC. Our research used innovative methodologies, including the PQA quality measure algorithm for MPT and an advanced NLP model, to evaluate MHDs in a real-world setting. We compared and reported the differences in findings from both methods. While the integration of claims data and EHR provides insights into directional changes in clinical outcomes over a long treatment duration, it is important to acknowledge the inherent limitations of these evolving approaches. Because these concepts are still in the early stages of adoption, further long-term studies such as controlled clinical trials or real-world studies are essential to fully understand the long-term effectiveness of galcanezumab and SOC preventive migraine medications.

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Data Availability. The data that support the study findings were provided by Optum. Restrictions apply to the availability of these data, which were used under license for this study and therefore are not publicly available. Requests may be sent to Optum for more information on data availability and licensing.

Declarations

Conflict of Interest. Oralee J. Varnado, Gilwan Kim, Margaret Hoyt, and Lars Viktrup are employees and minor shareholders of Eli Lilly and Company. Michelle Vu, Erin Buysman, Abhinav Nayyar, and Shikha Anand are employees and shareholders of United Health Group. The authors report no other conflicts of interest for this work.

Ethical Approval. All data were accessed in compliance with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996 regulations (HIPAA). All databases used are de-identified and fall under the US Department of Health and Human Services Policy for the Protection of Human Subjects, and therefore informed consent and Institutional Review Board approval were not required. The authors obtained permission to use the Optum Market Clarity Database.

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