Therapeutics and Clinical Risk Management

Dovepress
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ORIGINAL RESEARCH

Real-World Clinical Effectiveness and Migraine-Related Healthcare Resource Utilization in Patients Initiating Fremanezumab in Germany and the United Kingdom

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Purpose: Fremanezumab, a humanized monoclonal antibody targeting calcitonin gene-related peptide, is approved in Germany and the United Kingdom (UK) for patients experiencing migraine ≥4 days per month, and it is reimbursed for patients where ≥4–5 (Germany) or ≥3 (UK) prior migraine preventive treatments have failed. We evaluated real-world clinical effectiveness and healthcare resource utilization (HCRU) in patients initiating fremanezumab in Germany and the UK.

Methods: This non-interventional, retrospective, physician panel-based, online, multicenter chart review study included adult patients with chronic migraine (CM) or episodic migraine (EM) with first fremanezumab treatment initiation (index date) from June 2019 or later (Germany), and from June 2020 or later (UK). Changes in monthly migraine days (MMD), monthly headache days (MHD), and disability outcomes (Migraine Disability Assessment [MIDAS] and Headache Impact Test-6 [HIT-6]) were evaluated from baseline (pre-index) to 3 months post-index, and changes in HCRU were evaluated from 6 months pre-index to 6 months post-index.

Results: The study population included 207 German and 183 UK patients (CM, 48.3% and 95.1%; monthly dosing, 59.4% and 51.9%, respectively). Reductions in MMD and MHD were observed in the German cohort (percent reductions: 60.2% and 55.1%, respectively) and the UK cohort (51.9% and 47.3%, respectively; all $p < 0.001$ vs baseline). Reductions in mean MIDAS and HIT-6 scores (all $p < 0.01$ vs baseline), outpatient office visits, urgent care/emergency room visits, and inpatient admissions were also observed (all $p < 0.05$ vs baseline) for both countries.

Conclusion: Fremanezumab demonstrated real-world clinical effectiveness in German and UK cohorts and may decrease the burden of migraine for patients and providers.

Plain Language Summary:

Why was this study conducted?

- Fremanezumab is a migraine preventive treatment approved in Germany and the UK for patients experiencing ≥4 days with migraine symptoms per month, and is reimbursed for patients where ≥4–5 (Germany) or ≥3 (UK) prior preventive treatments have been ineffective or were not well-tolerated.
- There is a need for real-world data on the impact of fremanezumab treatment on migraine and the use of migraine-related healthcare services, and these data can inform healthcare decisions makers.

What did this study do?

- This study looked at the impact of fremanezumab treatment in adults with chronic or episodic migraine in Germany and the UK.

https://doi.org/10.2147/TCRM.S529550
Received: 20 March 2025
Accepted: 14 December 2025
Published: 14 January 2026

- Researchers recruited German and UK physicians who could provide patient records without patient names or personal details, to collect data on the number of days per month that a patient experienced migraine, migraine-related disability questionnaire scores, outpatient visits, inpatient admissions, and urgent care/ER visits from before and during treatment with fremanezumab.

What does this study find?

- After 3 months of fremanezumab treatment, patients reported that the number of days per month that they experienced migraine had been reduced by more than half compared with before they started treatment, and that the level of disability caused by their migraine had also decreased.
- After 6 months of fremanezumab treatment, outpatient visits, urgent care/ER visits, and inpatient admissions were all significantly reduced compared with before patients started treatment.

Interpretation

- Treatment with fremanezumab was effective in German and UK patients with migraine in real-world clinical practice.
- Fremanezumab treatment also reduced the need to seek additional healthcare, relieving the burden of migraine on patients and healthcare providers.

Keywords: burden of migraine, calcitonin gene-related peptide, migraine-related disability, cost effectiveness

Introduction

Migraine, a highly debilitating neurological disease, is the leading cause of years lived with disability among individuals <50 years of age.[1,2] The associated direct and indirect costs and social consequences contribute to the substantial burden of migraine worldwide.[3,4] Although many migraine preventive medications can help reduce the frequency and severity of migraine attacks and symptoms, they have limited efficacy and tolerability in patients with migraine with prior preventive treatment failures.[5–9]

Fremanezumab, a humanized monoclonal antibody (mAb) that selectively targets calcitonin gene-related peptide (CGRP), has proven efficacy and tolerability in a wide range of patients with migraine, including those with prior preventive treatment failures or patients with migraine complicated by medication overuse.[10,11] Fremanezumab is approved in Germany and the United Kingdom (UK) for patients experiencing migraine ≥4 days per month, and it is reimbursed in Germany for patients where ≥4 (episodic migraine [EM]) or ≥5 (chronic migraine [CM]) other preventive migraine treatments have failed and, in the UK, is approved for those where ≥3 other preventive treatments have failed.[12,13]

While the clinical effectiveness of fremanezumab in patients with prior preventive treatment failures has been evaluated in various real-world studies, few studies report both the clinical effectiveness of fremanezumab and its impact on healthcare resource utilization (HCRU).[14–20] There is therefore a need for real-world data on both the impact of fremanezumab treatment on migraine and migraine-related HCRU in the same cohort of patients with migraine.

This retrospective, online, physician panel-based chart review evaluated real-world effectiveness, treatment patterns, and migraine-related HCRU in patients with CM or EM initiating fremanezumab treatment in Germany and the UK.

Methods

Study Design

This non-interventional, retrospective, online, physician panel-based chart review was conducted in Germany and the UK. Physicians were recruited through a certified vendor using a well-established panel of physicians from a variety of settings within these countries. Participating physicians extracted data from eligible patient medical records using an electronic case report form (eCRF). The eCRF mandated completion of all data fields; however, in instances where specific information was unavailable in the patient's medical record, participating physicians were permitted to select "unknown". The proportion of patients for whom data were recorded as "unknown" is reported. Each physician was asked to submit up to ten patient records (each requiring approximately 25 minutes), with patient selection guided by a randomization algorithm to minimize selection bias.

Baseline measures were collected from the 12-month period prior to first fremanezumab initiation, and data on prior migraine treatments were collected for any amount of time prior to fremanezumab initiation. Study outcomes were

evaluated during the follow-up period after fremanezumab initiation based on data availability; effectiveness outcomes were reported at 3 months, and HCRU outcomes were reported at 6 months post-index. The date of first fremanezumab initiation was designated as the index date.

This study and its protocol were approved by a central Institutional Review Board (IRB) in July 2021 (Pearl IRB^{TM}, Indianapolis, USA). The IRB determined the study to be exempt from needing patient consent for inclusion according to the Electronic Code of Federal Regulations 46.104(b)(4).

Physician and Patient Eligibility Criteria

Eligible physicians were Germany-based neurologists or pain management specialists, including headache specialists, and UK-based neurologists who routinely treated patients with EM or CM; had personally treated at least five adult patients diagnosed with EM or CM with fremanezumab in the past 12 months; and had treated at least one patient meeting the patient inclusion criteria in the past 12 months.

Eligible patients included adults (≥18 years) who were diagnosed with EM or CM (in Germany or Scotland), or CM only (England, Wales, or Northern Ireland); had experienced ≥4 migraine days per month at fremanezumab initiation; were treated with fremanezumab following migraine diagnosis; first initiated fremanezumab in June 2019 or later (Germany) and in June 2020 or later (UK); and received ≥3 months of continuous fremanezumab treatment; had information on dosage of fremanezumab used; had at least one follow-up visit since fremanezumab initiation; had recorded monthly migraine days (MMD) measurements at fremanezumab initiation or within 1 month prior to and at 3 months (± 15 days) after fremanezumab initiation; had recorded information about migraine treatments received ≥3 months before first fremanezumab initiation; were not pregnant in the period 12 months prior to fremanezumab initiation or during treatment; and did not receive fremanezumab as part of a clinical trial or other interventional or non-interventional study. Migraine subtype determination was based on physician diagnosis of EM or CM. At the time of data collection completion (Germany: October 2021; UK: January 2022), fremanezumab treatment for EM was not approved for reimbursement in England, Wales, and Northern Ireland, but has since been approved by the National Institute for Health and Care Excellence.[21]

Outcomes

All outcomes were evaluated based on information reported in patient medical records. Baseline demographics, comorbidities, and treatment history were evaluated in the overall patient population. Changes in treatment patterns from 12 months pre-index to post-index (follow-up was variable) were also evaluated, including reductions in acute and preventive migraine medication use, adherence and persistence (time to treatment discontinuation), discontinuation rates, and patients switching from the monthly to quarterly dosage of fremanezumab.

Effectiveness outcomes were evaluated in the overall population in both the German and UK cohorts, as well as in subgroups divided by migraine type (CM or EM, including low-frequency EM [LFEM, 0–7 headache days per month] or high-frequency EM [HFEM, 8–14 headache days per month]) and dosing regimen (monthly or quarterly fremanezumab). Effectiveness outcomes included changes from baseline (index date) to Month 3 in MMD and average monthly headache days (MHD) of at least moderate severity. Effectiveness was also assessed based on the proportion of patients achieving ≥30% and ≥50% reductions in MMD and MHD at Month 3 post-index. Change from baseline to Month 3 in disability were assessed using Migraine Disability Assessment (MIDAS)[22] and Headache Impact Test-6 (HIT-6) scores.[23] Clinically meaningful improvements in HIT-6 scores were defined as a ≥5-point reduction per previous guidelines.[6] Measures of migraine-related HCRU, specifically the number of outpatient visits, inpatient admissions, urgent care or emergency room visits, and telehealth consultations, were evaluated at 6 months pre-index and 6 months post-index.

Statistical Analyses

Based on the results of a feasibility assessment, a maximum sample size of 160–200 patients from each of the UK and Germany, was anticipated. These anticipated sample sizes would ensure sufficient power (≥80%) for the Wilcoxon signed-rank test to detect changes in MMD from baseline, assuming a type I error rate (α) equal to 0.05, and similar

effect sizes (ranging between 4–8) and standard deviations (ranging between 3–6) as observed in a similar study in the United States.[24]

Physician and patient characteristics, effectiveness outcomes, treatment patterns, and HCRU outcomes were summarized using mean, standard deviation, median, and interquartile range for continuous variables and frequency counts and percentages for categorical variables. For endpoints with missing data, the number of patients with available data are reported and analyses were conducted among the subset of patients with available data. Missing or spurious data were assumed to occur completely at random.

Pre- versus post-index comparisons were performed using clustered Wilcoxon signed-rank tests (continuous variables) and clustered McNemar's test (categorical variables) that accounted for the correlation structure of the data (ie, patient- and physician-level correlation from repeated observations and multiple patients per physician).

Statistical comparisons between subgroups were performed, when sample size allowed, using Wilcoxon rank-sum tests for continuous variables and Chi-squared tests for categorical variables. For categorial variables with expected counts <5, Fisher's exact tests were used instead of Chi-squared tests. All statistical tests were performed at the 0.05 α-level. All analyses were conducted separately for the UK and Germany, and results were not compared between countries.

Results

Physicians

A total of 105 physicians were recruited from various settings across Germany (n = 63) and the UK (n = 42). Within the UK, data were collected from physicians across England (n = 37), Scotland (n = 4), and Wales (n = 1). Physicians were primarily neurologists (Germany, 79.4%; UK, 100.0%; Table 1). Germany-based physicians practiced in publicly owned (54.0%) and private settings (46.0%), while those in the UK were exclusively in National Health Service (NHS)-funded clinics. Quarterly fremanezumab dosing was preferred by approximately half of the physicians (Germany, 49.2%; UK, 45.2%). The most frequently reported reasons for the physician preference for quarterly versus monthly dosing were: better adherence, reduction of monthly injection burden, and increased convenience for the patient due to less frequent doctor visits (Figure 1).

Table 1 Physician Baseline Characteristics

Physician Characteristic	German Cohort (n = 63)	UK Cohort (n = 42)
Specialist type, n (%)		
Neurologist	50 (79.4)	42 (100)
Pain management specialist	13 (20.6)	0
Practice setting, n (%)		
Privately owned	29 (46.0)	0
Publicly owned	34 (54.0)	0
NHS center/clinic	0	42 (100)
Time in practice treating patients with migraine (years), mean (SD)	16.2 (6.4)	15.1 (6.9)
Number of migraine patients treated in the last 12 months, mean (SD)	191.3 (143.5)	348.7 (396.4)
Number of adult patients with EM or CM treated with fremanezumab, mean (SD)	48.1 (84.0)	48.3 (68.1)
Number of patient records per physician, mean (SD)	3.3 (2.9)	4.4 (4.1)
Preferred fremanezumab dosing schedule, n (%)		
Monthly	32 (50.8)	23 (54.8)
Quarterly	31 (49.2)	19 (45.2)

Abbreviations: CM, chronic migraine; EM, episodic migraine; NHS, National Health Service; SD, standard deviation; UK, United Kingdom.

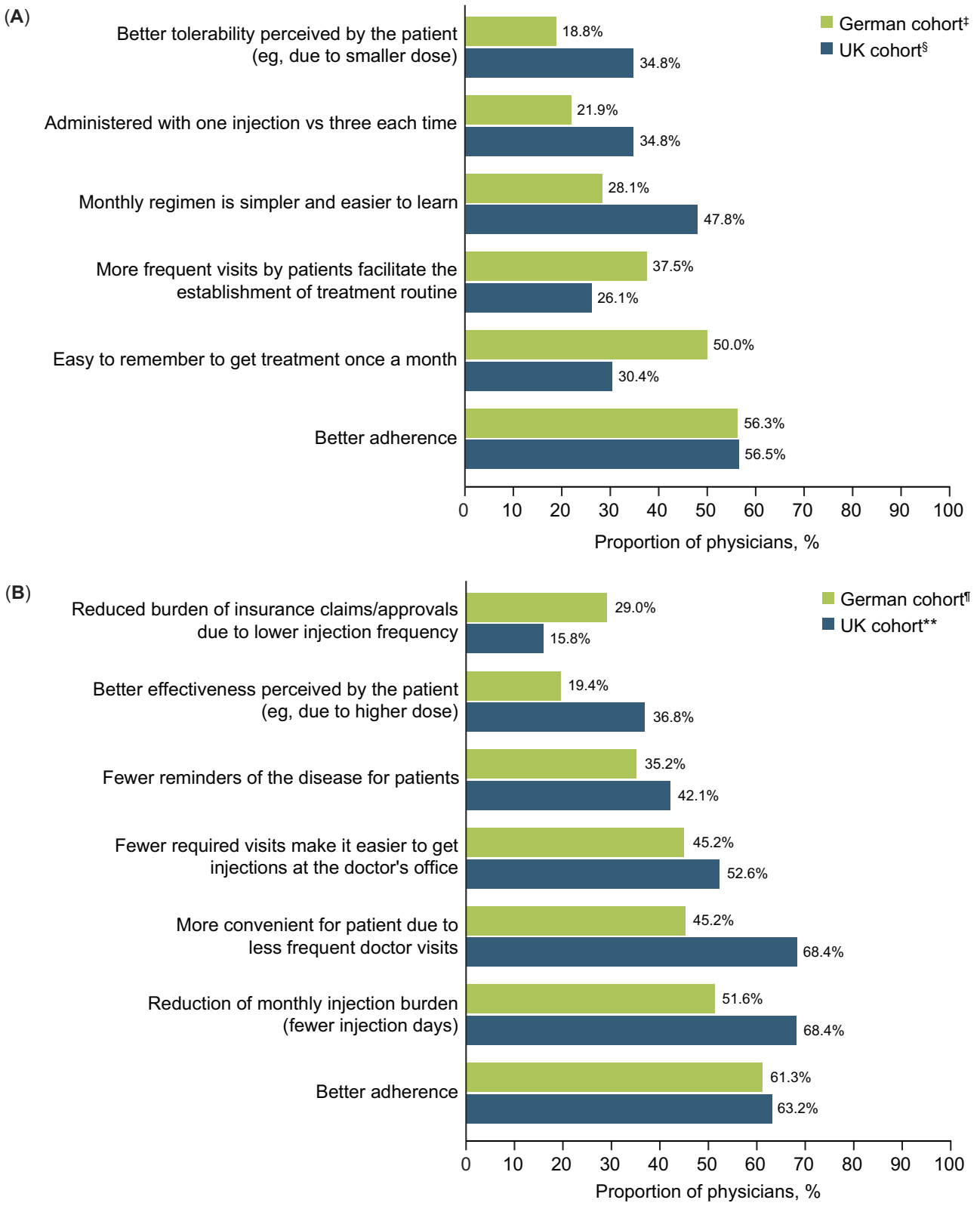


Figure 1 Reasons for preferred (**A**) monthly* and (**B**) quarterly† dosing schedule.
Notes: *Percentages are out of the number of physicians who preferred monthly dosing; †Percentages are out of the number of physicians who preferred quarterly dosing; ‡n = 32 physicians who preferred monthly dosing; §n = 23 physicians who preferred monthly dosing; ¶n = 31 physicians who preferred quarterly dosing; **n = 13 physicians who preferred quarterly dosing.
Abbreviation: UK, United Kingdom.

https://doi.org/10.2147/TCRM.S529550

Patients

Commonalities were found in patient characteristics between the German (n = 207) and UK (n = 183) cohorts (Table 2). The majority of patients in both cohorts were female, and mean age was approximately 40 years. Nearly equal percentages of patients had CM and EM diagnoses in Germany (CM, 48.3%; EM, 51.7%); 57.0% of those with EM had HFEM, and 41.1% had LFEM. Nearly all the UK cohort were diagnosed with CM (95.1%). Due to the predominance of CM in the UK cohort, the baseline MMD value was higher on average in that cohort (13.1) than in the German cohort (10.3). In Germany and the UK, 70.5% and 98.9% of patients had ≥4 and ≥3 prior treatment failures, respectively.

Table 2 Patient Baseline Characteristics

Patient Characteristic	German Cohort, All Patients (n = 207)	UK Cohort, All Patients (n = 183)
Age at index date (years), mean (SD)	40.3 (9.6)	40.5 (11.3)
Female, n (%)	153 (73.9)	129 (70.5)
Weight at index date (kg), mean (SD)	74.6 (16.0)	74.4 (12.4)
BMI at index date (kg/m^2), mean (SD)	27.2 (28.6)	26.2 (3.6)
Migraine diagnosis		
EM	107 (51.7)	9 (4.9)
CM	100 (48.3)	174 (95.1)
Subtype of EM[a,b]		
HFEM	61 (57.0)	9 (100.0)
LFEM	44 (41.1)	–
Time from date of diagnosis to index date (years), mean (SD)	4.5 (5.3)	4.8 (5.7)
Baseline MMD, mean (SD)	10.3 (4.4)	13.1 (6.9)
Baseline MHD, mean (SD)	12.1 (5.4)[c]	17.4 (7.3)[c]
Prior preventive treatment failures, n (%)		
≤3	61 (29.5)	96 (52.5)[d]
4	105 (50.7)	37 (20.2)
5	29 (14.0)	23 (12.6)
≥6	12 (5.8)	27 (14.8)
Medication overuse, n (%)	16 (7.7)	29 (15.8)
Initial fremanezumab dosing, n (%)		
Monthly	123 (59.4)	95 (51.9)
Quarterly	84 (40.6)	88 (48.1)
Baseline HIT-6 score, mean (SD)	58.1 (8.1)[e]	63.1 (9.6)[e]
Baseline MIDAS score, mean (SD)	13.7 (12.6)[f]	36.2 (48.0)[f]

Notes: Baseline measures were collected over the 12-month period prior to first fremanezumab initiation (index date), and data on prior migraine treatments were collected for any amount of time prior to initiation of fremanezumab. [a]LFEM was defined as 0 to 7 headache days per month, and HFEM was defined as 8 to 14 headache days per month; [b]n = 105. EM frequency was not known for two patients from the German cohort; [c]German cohort: available/N (%) = 116/207 (56.0); UK cohort: available/N (%) = 114/183 (62.3); [d]≥2 prior treatment failures: n = 2 (1.1%); three prior treatment failures: n = 94 (51.4%); [e]German cohort: available/N (%) = 48/207 (23.2); UK cohort: available/N (%) = 78/183 (42.6); [f]German cohort: available/N (%) = 66/207 (31.9); UK cohort: available/N (%) = 48/183 (26.2).

Abbreviations: BMI, body mass index; CM, chronic migraine; EM, episodic migraine; HFEM, high-frequency episodic migraine; HIT-6, Headache Impact Test-6; LFEM, low-frequency episodic migraine; MHD, monthly headache days; MIDAS, Migraine Disability Assessment; MMD, monthly migraine days; SD, standard deviation; UK, United Kingdom.

Effectiveness Outcomes

Overall

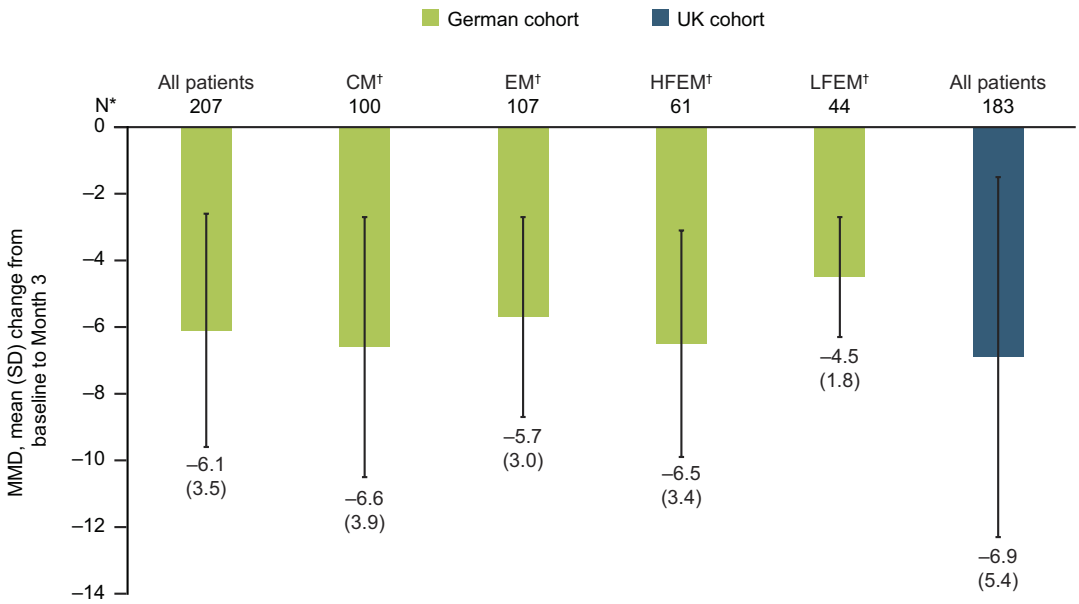
At Month 3, reductions from baseline were observed in MMD (mean percent reduction: Germany, 60.2%; UK, 51.9%; both $p < 0.001$ vs baseline; Figure 2). In addition, ≥30% and ≥50% MMD response rates at Month 3 were 86.5% and 73.9%, respectively, in Germany, and 83.6% and 61.7%, respectively, in the UK.

Among approximately 60% of patients in both cohorts with data on MHD, reductions in MHD at Month 3 were observed (both $p < 0.001$ vs baseline; Figure 3). The ≥30% and ≥50% MHD response rates at Month 3 were 81.0% and 62.1% in Germany, and 71.1% and 51.8% in the UK, respectively.

Mean (standard deviation [SD]) changes from baseline to Month 3 in MIDAS outcomes were –3.7 (4.8) in Germany (n = 66) and –14.7 (36.4) in the UK (n = 48) (both $p < 0.01$ vs baseline). Reductions in mean (SD) HIT-6 scores from baseline (Table 2) to Month 3 were –10.1 (12.6) in Germany (n = 48) and –11.8 (14.1) in the UK (n = 74) (both $p < 0.01$ vs baseline). A reduction of ≥5 points in HIT-6 scores was observed in 64.6% and 60.8% of the German and UK cohorts, respectively.

By Migraine Subtype

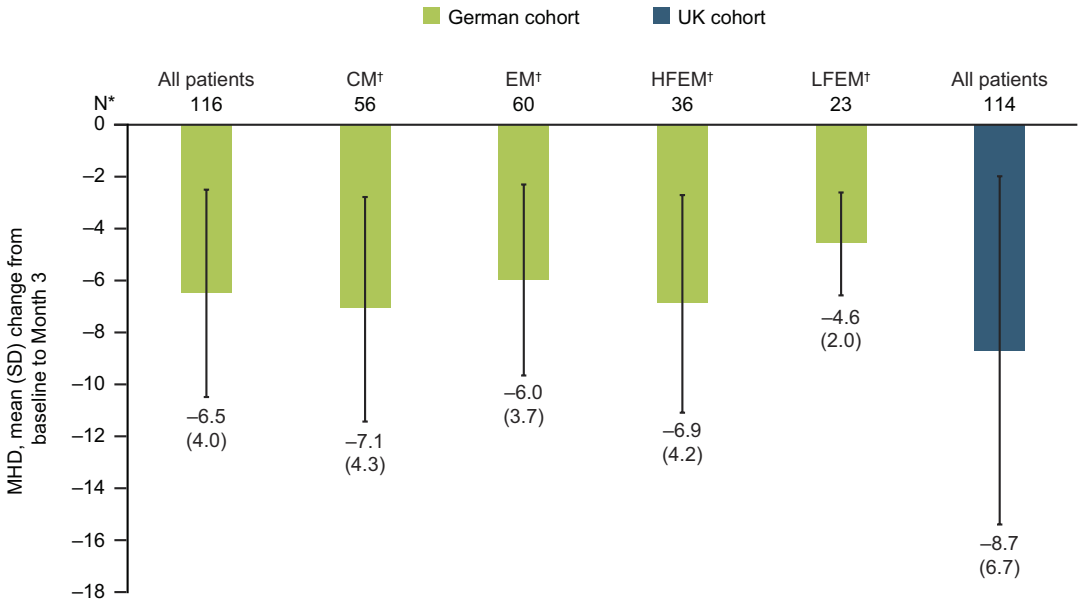
Analyses by migraine subtype are shown only for the German cohort due to the low number of patients with EM (n = 9) in the UK cohort. Mean percent reductions in MMD and MHD from baseline to Month 3 were observed in the German cohort for all migraine subtype groups analyzed (CM, EM, HFEM, and LFEM; all $p < 0.005$ vs baseline; Figures 2 and 3). The ≥30% and ≥50% MMD response rates at Month 3 were 82.0% and 72.0% for



Baseline MMD, mean (SD)	10.3 (4.4)	11.3 (5.0)	9.3 (3.5)	10.9 (3.3)	7.3 (2.7)	13.1 (6.9)
% reduction in MMD from baseline to Month 3, mean (SD)	60.2 (22.6)	59.0 (24.5)	61.3 (20.6)	59.4 (21.0)	64.2 (20.4)	51.9 (25.7)
Baseline vs Month 3, *p* values	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
≥30% responders,‡ %	86.5	82.0	90.7	86.9	95.5	83.6
≥50% responders,§ %	73.9	72.0	75.7	77.0	75.0	61.7

Figure 2 Mean change from baseline and percent response outcomes in MMD at 3 months post-index overall and by migraine diagnosis.
Notes: *Patients available for analysis; †Migraine subtype based on physician diagnosis of EM or CM; ‡Proportion of patients achieving a ≥30% reduction in MMD from baseline to Month 3; §Proportion of patients achieving a ≥50% reduction in MMD from baseline to Month 3.
Abbreviations: CM, chronic migraine; EM, episodic migraine; HFEM, high-frequency episodic migraine; LFEM, low-frequency episodic migraine; MMD, monthly migraine days; SD, standard deviation; UK, United Kingdom.

https://doi.org/10.2147/TCRM.S529550



	All patients	CM†	EM†	HFEM†	LFEM†	All patients
Baseline MHD, mean (SD)	12.1 (5.4)	13.8 (5.9)	10.4 (4.4)	12.4 (4.4)	7.5 (2.1)	17.4 (7.3)
% reduction in MHD from baseline to Month 3, mean (SD)	55.1 (23.3)	52.6 (24.2)	57.4 (22.5)	55.4 (23.6)	61.0 (21.1)	47.3 (27.0)
Baseline vs Month 3, *p* value	<0.001	<0.001	<0.001	0.004	<0.001	<0.001
≥30% responders,‡ %	81.0	78.6	83.3	80.6	87.0	71.1
≥50% responders,§ %	62.1	53.6	70.0	69.4	69.6	51.8

Figure 3 Mean change from baseline and percent response outcomes in MHD at 3 months post-index overall and by migraine diagnosis.
Notes: *Patients available for analysis; †Migraine subtype based on physician diagnosis of EM or CM; ‡Proportion of patients achieving a ≥30% reduction in MHD from baseline to Month 3; §Proportion of patients achieving a ≥50% reduction in MHD from baseline to Month 3.
Abbreviations: CM, chronic migraine; EM, episodic migraine; HFEM, high-frequency episodic migraine; LFEM, low-frequency episodic migraine; MHD, monthly headache days; SD, standard deviation; UK, United Kingdom.

patients with CM, and 90.7% and 75.7% for those with EM, respectively. The respective ≥30% and ≥50% MHD response rates were 78.6% and 53.6% for patients with CM, and 83.3% and 70.0% for patients with EM. Comparable response rates were found for the HFEM and LFEM subgroups.

By Dosing Regimen

Given the low number of patients with data on disability outcomes, results for dosing regimen subgroups are only described for MMD and MHD. Mean percent reductions in MMD and MHD from baseline to Month 3 were observed with both monthly and quarterly dosing in the German and UK cohorts (all $p < 0.001$ vs baseline; Supplementary Figures 1 and 2, respectively). MMD and MHD ≥30% and ≥50% response rates were similar among patients with monthly and quarterly dosing in both cohorts (Supplementary Figures 1 and 2, respectively).

Treatment Patterns

Patients in both cohorts had used fremanezumab for approximately 1 year (Table 3). Rates of discontinuation of fremanezumab therapy were low after the first 3-month dosing period (Germany, 4.3%; UK, 10.9%). The most common reasons for discontinuation were poor response to treatment and patient preference.

Nearly all patients in both cohorts were adherent to fremanezumab treatment using an 80% threshold (Germany, 89.9%; UK, 92.3%; Table 3). Among the patients that switched fremanezumab dosing regimens (Germany, n = 28; UK, n = 10), most changed from monthly to quarterly dosing (Germany, 96.4%; UK, 80.0%). Reasons for switching from monthly to quarterly dosing are shown in Table 3.

Table 3 Adherence and Dosing Schedule Preferences

Adherence and Dosing Schedule Preference and Changes	Germany n = 207	UK n = 183
Physician-estimated adherence, mean (SD)	92.4 (17.3)	92.6 (11.6)
Physician-reported patient adherence and discontinuation		
Patients with ≥80% adherence, n (%)	186 (89.9)	169 (92.3)
Fremanezumab treatment duration (months), mean (SD)	12.4 (6.2)	13.6 (5.9)
Discontinued fremanezumab after first dosing period, n (%)	9 (4.3)	20 (10.9)
Reasons for discontinuation, n (%)		
Patient preference	5 (55.6)	4 (20.0)
Poor response to treatment	4 (44.4)	9 (45.0)
Treatment stopped working	1 (11.1)	1 (5.0)
Cost of medication	1 (11.1)	1 (5.0)
Copay/coinsurance	1 (11.1)	–
Other medical reasons	1 (11.1)	0
No longer needs preventive medication	0	8 (40.0)
Inconvenient method of administration	0	2 (10.0)
Treatment side effects	0	2 (10.0)
Unknown	1 (11.1)	0
Patient dosing schedule changes[a]		
Switched from monthly to quarterly dosing, n (%)	27 (13.0)	8 (4.4)
Switched from quarterly to monthly dosing, n (%)	1 (0.5)	2 (1.1)
Reasons for switching from monthly to quarterly dosing, n (%)		
Reduction of monthly injection burden	18 (66.7)	4 (50.0)
Fewer required doctor's visits	17 (63.0)	2 (25.0)
More convenient	15 (55.6)	2 (25.0)
Other preference indicated by patient	12 (44.4)	0
Fewer reminders of the disease	11 (40.7)	1 (12.5)
Better adherence	7 (25.9)	3 (37.5)
Better perceived effectiveness	7 (25.9)	3 (37.5)

Note: [a]Given the small proportion of patients who switched from quarterly to monthly fremanezumab dosing, these data are not reported here.
Abbreviations: SD, standard deviation; UK, United Kingdom.

Acute and preventive migraine medication use was reduced from 12 months pre-index to post-index in both cohorts (Table 4). The proportion of patients with medication overuse at baseline in the German (7.7%) and UK (15.8%) cohorts was drastically reduced with fremanezumab treatment, with no medication overuse in Germany and one patient with medication overuse in the UK post-index.

Table 4 Change in Acute and Preventive Migraine Medication Use Post-Fremanezumab Initiation

Medications Used for Migraine	Germany		UK	
	Pre-Index[a]	Post-Index (During Fremanezumab Treatment)[b]	Pre-Index[a]	Post-Index (During Fremanezumab Treatment)[c]
	n = 207	n = 207	n = 183	n = 183
Acute medication use, n (%)				
Anti-migraine drugs	140 (67.6)	64 (30.9)	108 (59.0)	71 (38.8)
NSAIDs	134 (64.7)	104 (50.2)	97 (53.0)	84 (45.9)
Opioids	21 (10.1)	11 (5.3)	35 (19.1)	24 (13.1)
Other analgesics	19 (9.2)	11 (5.3)	14 (7.7)	10 (5.5)
Preventive medication use, n (%)				
Other CGRP pathway mAbs[b]	12 (5.8)	4 (1.9)	6 (3.3)	3 (1.6)
Anticonvulsants	84 (40.6)	4 (1.9)	53 (29.0)	12 (6.6)
Beta blockers	90 (43.5)	23 (11.1)	64 (35.0)	29 (15.8)
Angiotensin II receptor antagonists	11 (5.3)	4 (1.9)	35 (19.1)	15 (8.2)
Antidepressants	26 (12.6)	7 (3.4)	22 (12.0)	16 (8.7)
Calcium channel blockers	45 (21.7)	2 (1.0)	33 (18.0)	11 (6.0)
Tricyclics	62 (30.0)	13 (6.3)	59 (32.2)	23 (12.6)
OnabotulinumtoxinA	26 (12.6)	2 (1.0)	54 (29.5)	6 (3.3)
Other preventive medications	5 (2.4)	1 (0.5)	2 (1.1)	2 (1.1)

Notes: [a]12 months; [b]The reported concomitant use of other CGRP pathway-targeted mAbs may have been related to a brief overlap of use of different types of CGRP pathway-targeted mAb treatment during switching or reporting errors in patient charts due to the retrospective data analysis used in the current study; [c]Variable follow-up (≥3 months required). Mean (SD) duration of fremanezumab treatment: Germany, 12.4 (6.2) months; UK, 13.6 (5.9) months.

Abbreviations: CGRP, calcitonin gene-related peptide; mAbs, monoclonal antibodies; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; UK, United Kingdom.

Migraine-Related HCRU

Migraine-related HCRU data were only available for analysis for a subset of the German and UK cohorts for each outcome assessed: outpatient office visits: n = 91 and n = 81, respectively; urgent care or ER visits: n = 70 and n = 79, respectively; inpatient admissions: n = 71 and n = 79, respectively; telehealth consultations: n = 61 and n = 79, respectively. Significant reductions in migraine-related HCRU were found 6 months post-index versus 6 months pre-index in both cohorts for outpatient office visits ($p \leq 0.005$), urgent care or ER visits ($p \leq 0.001$), inpatient admissions ($p < 0.05$), and numerical reductions were found in both cohorts for telehealth consultations (Figure 4). Of note, there were differences pre-index versus post-index in outpatient office-based visits in both Germany and the UK. In both cohorts, outpatient office-based visits were the most commonly used healthcare resource before and after fremanezumab initiation. The proportion of patients who had at least one outpatient visit in the 6-month pre-index period (Germany, 98.9%; UK, 92.6%) was significantly reduced in the 6-month post-index period (Germany, 93.4%; UK, 79.0%; both $p \leq 0.005$). Numbers of ER visits and inpatient admissions were also found to decrease following fremanezumab initiation in both cohorts (all $p \leq 0.05$).

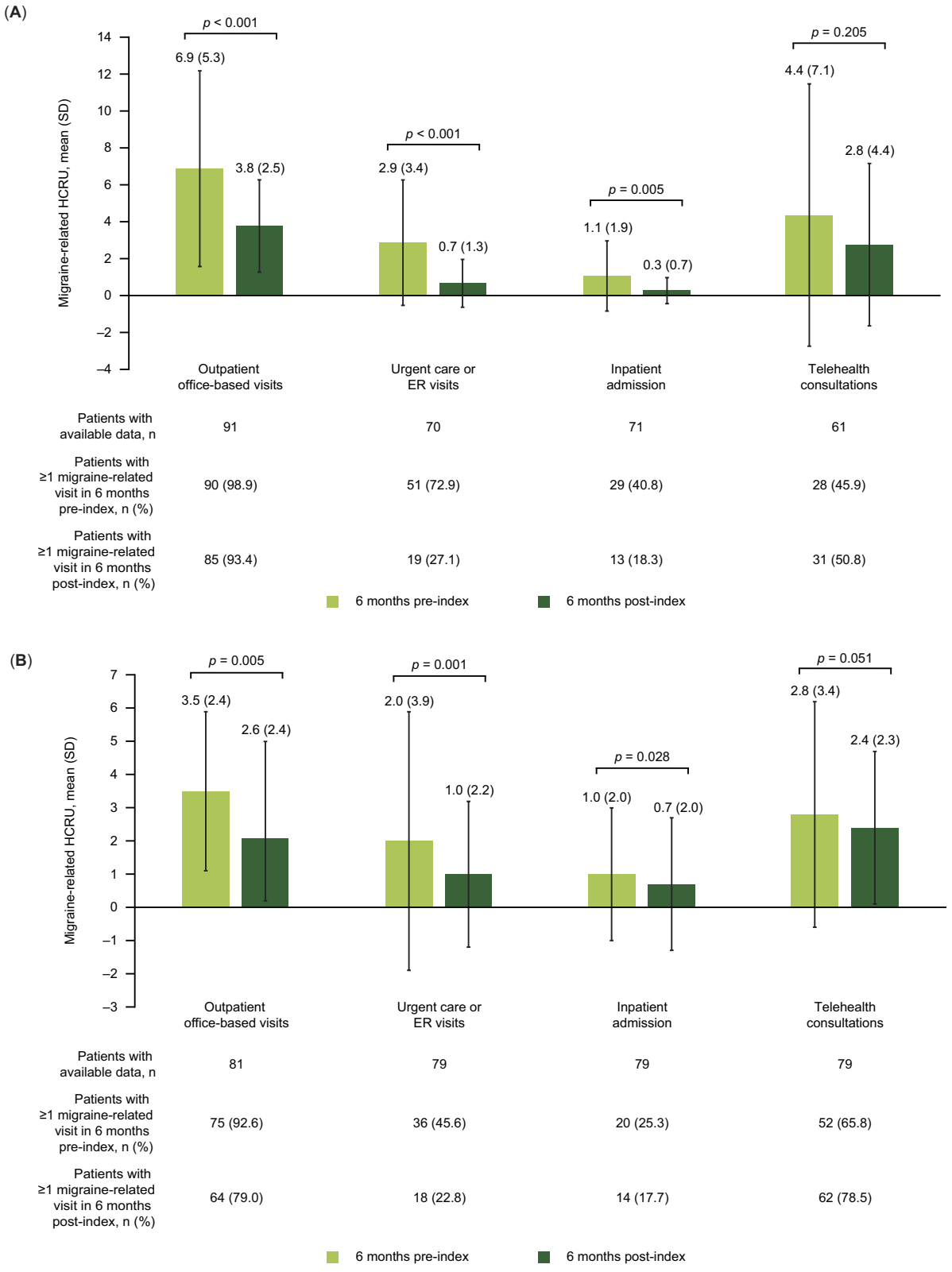


Figure 4 Mean changes in migraine-related HCRU pre-index versus post-index in (**A**) Germany and (**B**) the UK.
Abbreviations: ER, emergency room; HCRU, healthcare resource utilization; SD, standard deviation; UK, United Kingdom.

https://doi.org/10.2147/TCRM.S529550

Discussion

This retrospective physician panel-based chart review of patient data from real-world clinical settings demonstrates that treatment with fremanezumab is associated with reductions in migraine and headache frequency and in disability in patients with CM (both Germany and the UK) or EM (Germany only) experiencing ≥4 MMD and relatively treatment-resistant migraine. Subsequently, reductions in acute and preventive medication use and migraine-related HCRU were reported following fremanezumab treatment, which were comparable across both countries.

Interpretation of Findings

In the current study, ≥3 prior treatments had failed in 98% of the UK cohort, and ≥4 had failed in 70% of the German cohort. Around 95% of the UK cohort were diagnosed with CM, in line with reimbursement criteria at the time of the study, and similar percentages of the German cohort had EM and CM. Consistent with the higher proportion of patients with CM, baseline MMD, MHD, and medication overuse were higher in the UK than Germany.

Patients more severely impacted by their migraine symptoms are typically treated in the NHS in the UK or the public setting in Germany. For patients receiving treatment under statutory (public) health insurance, there are strict regulations and limitations for the prescription of medication such as CGRP pathway mAbs. However, for patients with private insurance, the limitations are set by the product label. As approximately half of the German cohort were treated in the private setting, the German cohort contained a range of severely and less severely affected patients with migraine.

Good adherence to treatment may be associated with improved clinical outcomes and reduced HCRU.[25] In our study, over an average of 12 to 13 months of fremanezumab treatment, 90% to 92% of patients in the German and UK cohorts were adherent to treatment based on a ≥80% adherence rate, with low rates of discontinuation demonstrated with quarterly and monthly fremanezumab. In both countries, statistically significant reductions in MMD, MHD, and MIDAS and HIT-6 scores were observed from baseline to Month 3 of fremanezumab treatment. In the German cohort, similar results to those in the overall population were observed for subgroups of patients with CM and with EM, regardless of migraine frequency. Further, improvements in study outcomes were comparable with monthly or quarterly dosing in both the German and UK cohorts. The two dosing schedules were used in a similar proportion of patients across both cohorts.

As a consequence of improvements in migraine-relevant clinical outcomes, concomitant acute and preventive migraine medication use was reduced when assessed during an average of 12 to 13 months following fremanezumab initiation. Medication overuse and the development of medication overuse headache (MOH) are common among patients with CM and result in further disability and reduced quality of life.[26,27] The reductions in acute and preventive medication use over an average of approximately 1 year of fremanezumab treatment observed in the current study could result in a reduced incidence of medication overuse and MOH, although additional analyses are required to support these findings.

Finally, evidence shows that higher numbers of MMD are associated with higher HCRU among patients with migraine.[28] The current study showed a reduction in MMD at 3 months in both Germany and the UK, which may have led to the statistically significant reductions observed in migraine-related outpatient office visits, urgent care or ER visits, and inpatient admissions during the 6 months after fremanezumab initiation, compared with the 6 months prior.

Comparisons with Other Studies

Results from this study support those of previous real-world studies evaluating the clinical effectiveness of fremanezumab in patients with prior migraine preventive treatment failures. In a retrospective chart review study in the United States, 59% of patients with 3–4 treatment failures and 44% of patients with ≥4 treatment failures experienced a ≥50% reduction in MMD 3 months after fremanezumab initiation.[14] In a prospective UK study from the Hull Migraine Clinic, 68% of patients with resistant and refractory CM reported a >50% reduction in migraine 4 months after initiation of fremanezumab treatment, and this response was maintained over 3 years.[15,16] In the multicenter, prospective FRIEND3 study in Italy, 70.8% of patients with HFEM or CM and ≥3 treatment failures reported a ≥50% reduction in MMD 12 weeks after initiating fremanezumab treatment.[17] In an interim analysis of the multicenter, FINESSE study in Germany and Austria, 53.8% of patients (EM: 58.4%, CM: 47.4%) achieved a MMD reduction of ≥50% in the 6 months post-initial fremanezumab dose,[18] with 38.6% of patients who had prior ineffective CGRP pathway mAb treatments achieving a ≥50% reduction.[19] In an interim analysis of the prospective PEARL study in patients with EM or CM across

11 European countries, in which the majority of patients had prior preventive treatment experience, 57.4% of patients experienced a ≥50% reduction in MMD during 6 months of fremanezumab treatment.[20]

The current study also demonstrated comparable effectiveness to real-world studies evaluating other CGRP pathway mAbs in Europe, including the multicenter GARLIT and EARLY studies in Italy. The GARLIT study demonstrated ≥50% MMD response rates of 69.8% and 64.9% in patients with EM and CM, respectively, after 3 months of treatment with galcanezumab.[29] While the EARLY study reported ≥50% MMD response rates of 59% and 56% in patients with HFEM and CM, respectively, after 3 months of erenumab treatment.[30]

Results from this study are also consistent with previous studies evaluating the impact of fremanezumab on migraine-related HCRU.[31,32] However, real-world evidence on the effect of fremanezumab on HCRU is lacking and largely consists of data from claims analyses conducted in the United States.

Strengths and Limitations

This study has several notable strengths. This was a panel-based, not center-based, study; thus, physicians were from many different regions and settings. Along with the multiple geographic areas studied and varied practice settings (private and public), the wide range of clinical and HCRU outcomes assessed provides a robust representation of the real-world experience of migraine. The study also has a substantial number of patients with good coverage of MMD data, which has been shown to directly correlate with disability outcomes in migraine.[33] Furthermore, the study provides data on physician's reasoning for fremanezumab initiation.

The study was conducted shortly after the reimbursed launch of fremanezumab, and targeted Germany and the UK due to patient availability and sufficient treatment follow-up, which enabled the analysis of these two separate cohorts with satisfactory sample sizes and data quality. The cohorts consisted mainly of patients with treatment-resistant migraine,[34] reflecting real-world practice in headache centers. While most studies focus on CM and/or EM, this study also includes data on patients in Germany with different EM frequencies, HFEM and LFEM.

Limitations of this study include its reliance on patient medical records, which can be incomplete or inconsistent due to variability in documentation by physicians. Although all patients had MMD data at baseline and Month 3 as per the inclusion criteria, data for outcomes such as MIDAS and HIT-6 may be missing if physicians do not document these in the medical record. This limited data availability prohibited the ability to draw firm conclusions for MIDAS and HIT-6 in the overall population and precluded subgroup analyses by migraine type and dose regimen. In addition, as most patients in the UK had CM, analyses of subgroups by migraine diagnosis or frequency could not be performed in this cohort.

Although physicians reported an average fremanezumab treatment period of >12 months, effectiveness outcomes were assessed at Month 3 due to data availability and clinical relevance, as this is a typical clinical timeframe for evaluating treatment response after initiating a new CGRP pathway mAb treatment.[35] In contrast, healthcare resource utilization is less time-sensitive and could be extracted from medical records over 6 months. Restricting the study population to patients with MMD at 3 months may have introduced selection bias, as it excluded patients who discontinued treatment early due to lack of efficacy or poor tolerability, potentially leading to an overestimation of effectiveness. At the time of study conduct, treatment with fremanezumab was relatively new and it was likely administered first to patients most severely impacted by migraine or with suboptimal disease management. This may have also influenced the study sample, as such patients were more likely to be included. Additionally, data quality may have been higher for more severe cases due to more thorough physician documentation compared with milder presentations.

Overall, the data suggest that a very small number of patients were concomitantly using other CGRP pathway mAbs; however, reimbursement restrictions in both countries do not permit concomitant use of more than one mAb. Thus, it is likely that these patients were switched to fremanezumab and would not confound the results. Concomitant use of other CGRP pathway mAbs may be explained by brief overlaps when switching between therapies or, alternatively, by reporting errors in patient medical records.

Lastly, the overlap between the observational period and the COVID-19 pandemic may have introduced confounding factors in the HCRU data, as patients may have experienced restricted access to healthcare services or avoided seeking care due to pandemic-related concerns. However, both the pre- and post-treatment assessment periods for all UK patients

and all but nine German patients occurred during the pandemic, and so relative changes observed in HCRU therefore likely reflect true treatment-related effects.

Conclusion

In this study, fremanezumab demonstrated real-world effectiveness in German and UK cohorts by improving clinical outcomes and reducing migraine-related medication use. These results contribute to the growing body of real-world literature supporting fremanezumab as an effective migraine-preventive therapy for patients with CM and EM.

Abbreviations

CGRP, Calcitonin gene-related peptide; CM, Chronic migraine; EM, Episodic migraine; ER, Emergency room; HCRU, Healthcare resource utilization; HFEM, High-frequency episodic migraine; HIT-6, Headache Impact Test-6; IRB, Insitutional Review Board; LFEM, Low-frequency episodic migraine; mAb, Monoclonal antibody; MHD, Monthly headache days; MIDAS, Migraine Disability Assessment; MMD, Monthly migraine days; MOH, Medication overuse headache; NHS, National Health Service; SD, Standard deviation; UK, United Kingdom.

Data Sharing Statement

Qualified researchers may request access to patient level data and related study documents including the study protocol and the statistical analysis plan. Requests will be assessed for scientific merit, product approval status, and conflicts of interest. If the request is approved, patient level data will be de-identified and study documents will be redacted to protect the privacy of trial participants and to protect commercially confidential information. Please email USMedInfo@tevapharm.com to make your request.

Ethics Approval and Informed Consent

This study and its protocol were approved by a central Institutional Review Board (IRB) in July 2021. The IRB determined the study to be exempt from needing patient consent for inclusion according to the Electronic Code of Federal Regulations 46.104(b)(4).

Acknowledgments

We thank the online physician panel that participated in this study. Medical writing and editorial support was provided by Laura Weber, PhD, of Lumanity Communications Inc., and Olivia Morris, MA (Cantab), and Laura Colbran, BSc, of Ashfield MedComms, which was in accordance with Good Publication Practice (GPP3) guidelines and funded by Teva Pharmaceutical Industries.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by Teva Pharmaceuticals.

Disclosure

AH has received honoraria for lectures, and consulting fees for membership on advisory boards and steering committees from AbbVie, Lilly, Lundbeck, Novartis, and Teva Pharmaceuticals. SKA has received honoraria for participation in an advisory capacity and as a speaker in educational meetings for Eli Lilly, Novartis, Pfizer, and Teva Pharmaceuticals. TIT is an employee of Analysis Group which has received funding from Teva for this and other research. ET, RS, EY, and BY are former employees of Analysis Group, which received funding for these analyses from Teva Pharmaceuticals. LJK,

HA, DD, and MTD are employees of Teva Pharmaceuticals. JH is a former employee of Teva Pharmaceuticals. The authors report no other conflicts of interest in this work.

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