Patient Preference and Adherence

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ORIGINAL RESEARCH

Patient Preferences for Episodic Migraine Medications: A Discrete Choice Experiment of Self-Injectable Versus Oral Treatments Targeting Calcitonin Gene-Related Peptide Pathway

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Purpose: To understand the trade-offs that patients with episodic migraine are willing to make between attributes of self-injectable calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) and oral small-molecule calcitonin gene-related peptide receptor antagonists (gepants).

Patients and Methods: This was an online discrete choice experiment survey among adults with episodic migraine (≥4 and <15 migraine headache days and <15 headache days per month over 3 months) in the United States. Hypothetical treatments were characterized by five attributes: chance of ≥50% migraine reduction, impact on daily activities, onset of treatment effect, reduction in number of acute medications, and treatment administration. The attributes were selected based on insights gained from a previously conducted literature review and focus group study and aligned with the primary and secondary outcome measures in the double-blind Phase IV head-to-head clinical trial of a CGRP mAb versus gepant.

Results: 601 patients (mean age: 44.8 years) completed the survey. Treatment preferences differed significantly between patients. However, for all patients, the most important driver of treatment preferences was the chance of a ≥50% reduction in monthly migraine headache days (relative attribute importance: 38.3%), followed by the impact on daily activities (23.5%), the onset of treatment effect (19.5%), the reduction in need for acute medication (15.4%), and finally the route of administration (3.4%). Patients were willing to consider a one-week delayed onset of treatment effect or one-day increased need for acute medication for a higher chance (by 2.06% and 2.65% respectively) of a ≥50% reduction in monthly migraine headache days. Patients would trade a reduction of migraine's impact on daily activities from "extreme" to "moderate" or "minimal" with a lower chance (17.09%, 12.06% respectively) of halving the number of monthly migraine headache days.

Conclusion: A ≥50% reduction in monthly migraine headache days was the most important treatment attribute for which participants were willing to trade against other attributes. The variation in treatment preferences between patients emphasizes the importance to align decision-making with individual patients' preferences.

Plain Language Summary: Patients seeking care for migraine have varying levels of migraine severity, disability, and different experience with prior treatment. In this study, we researched patients' preferences for different preventive treatments, by having 601 patients complete an online survey. The survey presented a 'discrete choice experiment' where hypothetical migraine treatments described by five treatment characteristics, including whether the treatment was an oral pill or an injection, and asked patients to choose between them. Our results suggested that the chance of reducing the number of migraine days each month by half was the most important therapeutic characteristic, for which patients were willing to exchange other treatment characteristics in order to have a greater chance of achieving this improvement. Patients also valued if treatments worked quickly or reduced the impact of migraine on everyday activities. Whether a treatment was given as an injection or oral pill did not affect preferences.

Keywords: gepants, self-injectable treatment, treatment preferences, preventive treatment, United States

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Introduction

Migraine is a chronic debilitating neurologic disease, and the migraine impact according to migraine frequency, duration, and intensity may vary greatly among patients throughout the course of their illness.[1] Moreover, preventive therapies for migraine differ not only in terms of treatment efficacy and side effects but also with regards to onset of treatment effect, need for additional acute medication, functional improvement, cost, or route and frequency of administration.[2] Consequently, to optimize therapy at the individual level, patients with migraine and their healthcare professionals (HCP) need to examine and choose from a broad variety of treatment characteristics.[2,3] In addition, previous studies have demonstrated heterogeneity in patients' treatment choices, suggesting that each patient places different values on distinct treatment features.[3–11] Understanding choices among diverse treatments requires an understanding of what trade-offs patients are willing to make between treatment characteristics.

Traditional preventive therapies for migraine were initially approved for other indications, and though commonly used, their suboptimal efficacy, tolerability issues, and drug-drug interactions make their use challenging. [2,5,12] Since 2018, six new medications targeting calcitonin gene-related peptide (CGRP), a neuropeptide involved in migraine pathophysiology,[13] or its receptor have been approved for migraine prevention by the United States (US) Food and Drug Administration (FDA). Moreover, consensus statements from the American Headache Society and the European Headache Foundation recommend considering CGRP-targeted medications as first-line therapy for the preventive treatment of migraine without a requirement for prior failure of other classes of migraine preventive treatment. [2,14,15] These comprise four monoclonal antibodies (mAbs) targeting CGRP (galcanezumab, fremanezumab, and eptinezumab) or its receptor (erenumab) and two small-molecule CGRP receptor antagonists (the "gepants" rimegepant and atogepant). Some contradicting evidence exists on the comparison between mAbs targeting CGRP and gepants. [16–18] A meta-analysis of 19 Phase III randomized-controlled clinical studies showed that all reduced mean monthly migraine days compared to placebo, with rimegepant reducing them by 0.8 days and galcanezumab by 2.3 days. [17] A single double-blind, double-dummy, head-to-head clinical trial of galcanezumab vs rimegepant in people with episodic migraine (EM) showed no statistical significant difference with >60% of patients experiencing ≥50% reduction in monthly migraine headache days. However, 84% of the patients were preventive treatment naive.[18]

CGRP-targeted medications differ substantially in their dosing, frequency, and route of administration. Some CGRP mAbs are self-injectable subcutaneous formulations that are administered monthly (erenumab, fremanezumab, and galcanezumab)[19–21] or once every three months (fremanezumab).[20] The CGRP mAb eptinezumab[22] requires a healthcare provider to administer it as an intravenous infusion once every three months. The gepants atogepant[23] and rimegepant[24] are orally administered. Previous preference studies comparing mode of administration have reported that it is relatively less important than other treatment attributes; however, the relative importance of different dosing frequencies and routes of administration compared in these studies varied widely.[3–5]

Some patient preference studies have been conducted following the advent of these newer treatments specifically developed for migraine.[3–5,7,8] However, these studies did not directly compare attributes of self-injectable CGRP mAbs and oral gepants. Such comparison is needed to ensure that patients and HCPs are able to make optimal decisions that align with individual patient preferences. For example, patients may prefer one mode of administration over an alternative, but this may be compensated by better performance in other attributes, such as efficacy. The degree to which compensation is possible depends on the trade-offs that patients are willing to make. To address this evidence gap, we conducted this preference study to evaluate which treatment attributes of a self-injectable CGRP mAb or an oral gepant are most valued by patients deciding among different preventive treatments for EM and aimed to understand the trade-offs the patients are willing to make between these attributes.

Materials and Methods

Study Design

A web-based discrete choice experiment (DCE) was conducted among patients with migraine between April and October 2022 to quantify the relative importance they place on different treatment attributes of self-injectable CGRP mAbs and oral gepants and the trade-offs they are willing to make among those attributes. We also investigated preference

heterogeneity depending on patients' sociodemographic or clinical characteristics, as well as migraine diagnoses being self-reported or confirmed by a physician's diagnosis. The study design process began by defining treatment attributes and levels based on previous research evidence. The resulting DCE instrument was tested in qualitative interviews and quantitative pilot with patients before being completed by the study population.

Eligible for recruitment, were adults (≥18 years) living in the US with self-reported diagnosis of migraine by a physician or with a physician-provided confirmation of diagnosis (COD), if they had EM, as shown by their answers to a detailed clinical screener. EM was defined as ≥4 and <15 migraine headache days and <15 headache days per month over 3 months (Supplemental Methods). Patients could self-report physicians' diagnosis for migraine, however, to balance competing concerns of recruitment feasibility, patient and HCP burden, and confidence that patients report their disease status accurately, a target recruitment quota of 50% was set so that half of the enrolled patients would submit a physician-provided confirmation of diagnosis (COD) in addition to self-reporting. This was an online or paper form confirming the diagnosis of episodic migraines and the number of migraine headache days and headache days the patient experiences per month. Eligible patients had at least moderate migraine severity, as evaluated by the Migraine Symptom Severity Score (MSSS; moderate severity was defined as: "scoring '3-5' on any of the first four 'pain' items and scoring 3-5 on the 'nausea' item or both the 'photophobia' and 'phonophobia' item. (Supplemental Methods)". A healthcare research organization specializing in internet-based panels recruited the study patients via online databases and panels, social media, and patient associations.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was submitted to Ethical & Independent (E&I) Review Services, a fully accredited institutional review board (IRB), for central ethical approval. IRB approval for the initial submission was granted on 27 April 2021 (E&I study number: 21069–01), and IRB approval of translated documents (from English to Spanish and Puerto Rican Spanish) was granted on 14 May 2021 (E&I study number: 21069–01A). Following modifications to the survey (incorporating the qualitative pilot interview feedback), IRB approval was received for the amended protocol on 24 February 2022 (E&I study number: 21069–01B). Lastly, continuing review approval was granted on 8 June 2022 (E&I study number: 21069–02).

All patients reviewed and completed an online informed consent form before participating in the study. The DCE study was conducted according to best-practice guidelines concerning pharmacovigilance practices[25,26] and preference-based analyses, as recommended by the International Society for Pharmacoeconomics and Outcomes Research.[27–29]

DCE Survey

The first section of the survey introduced patients to the treatment attributes with examples and practice questions designed to engage patients with the DCE attributes and encourage attentive evaluation of the attributes. The second section of the survey contained 13 experimental and two non-experimental DCE choice tasks (Figure 1).

In the final survey section, patients were asked to complete sociodemographic and clinical questionnaires. Health literacy was also assessed with three questions from the Set of Brief Screening Questions (SBSQ),[30] and numeracy was assessed with five questions from the Numeracy Scale.[31,32] Patients completed several patient-reported outcome (PRO) assessments to evaluate migraine-associated symptoms. The Migraine-Specific Quality of Life Questionnaire (MSQ) measures the impact of migraines on daily activities.[33,34] The MSQ score assesses patient functioning on a scale from 0 to 100, with scores of <40 indicating extreme impairment and scores of 85–100 indicating no or minimal impairment.[35] The Patient Global Impression of Severity (PGI-S) measures severity of illness, with scores ranging from 1 (normal, not at all ill) to 7 (extremely ill).[36] The Migraine Disability Assessment questionnaire (MIDAS) measures headache-related disability on a scale ranging from little or no disability (0–5) to severe disability (> 20).[37] The MSSS score ranges from 8 to 40 with higher scores indicating more severe disability.[38]

DCE Choice Tasks

In each choice task, patients were asked to choose between hypothetical treatment alternatives that were characterized by a set of attributes with different levels (eg, 40%, 55%, or 70% chance of reduction in monthly migraine headache days) (Table 1). The order of experimental choice tasks was randomized across patients,[39] (Supplemental Statistics).

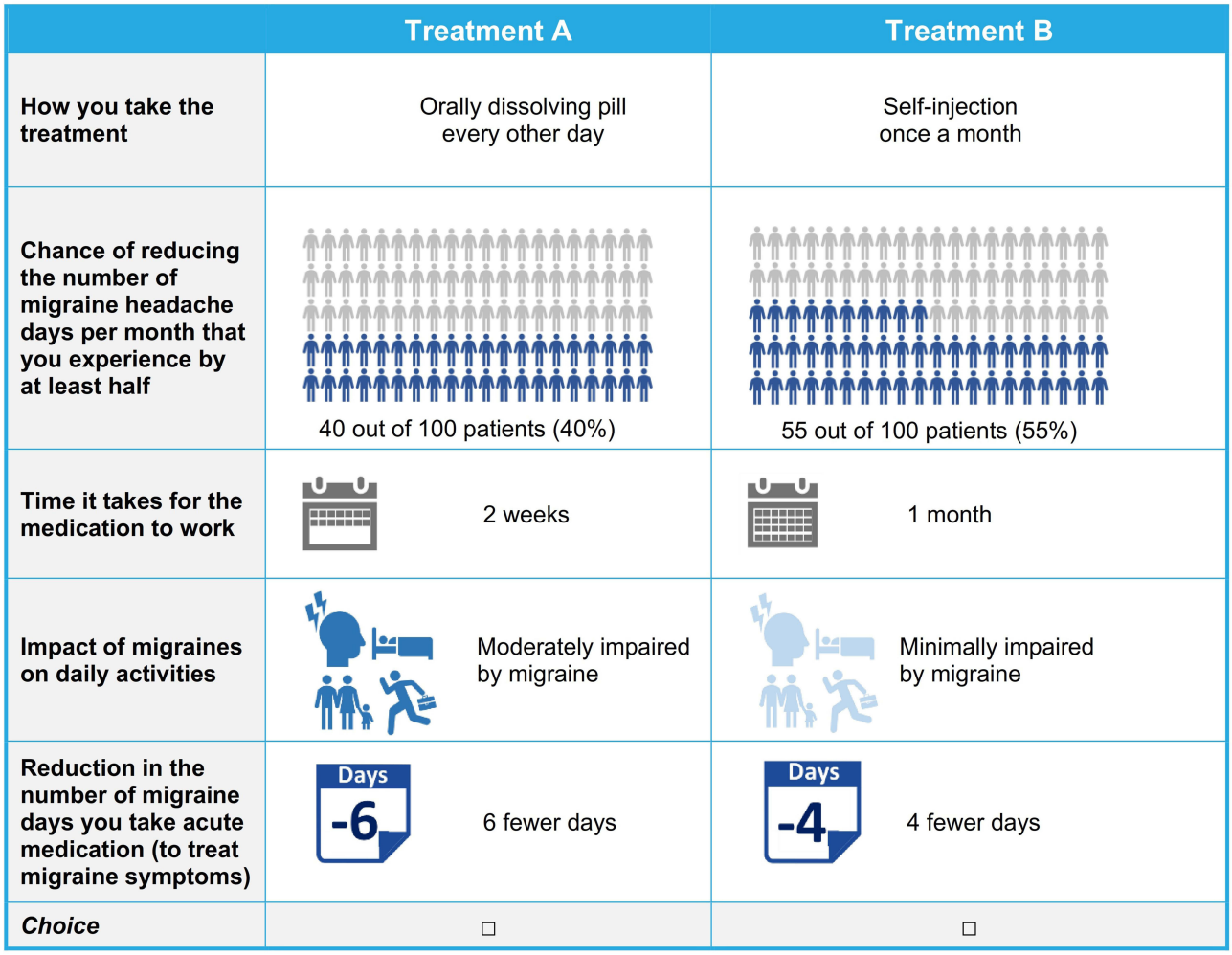

Figure 1 Example of a DCE choice task[a].
Note: [a]Patients were presented with 13 pairs of such hypothetical scenarios and were asked to choose which one they would prefer.
Abbreviation: DCE, discrete choice experiment.

DCE attributes were selected based on insights gained from a previously conducted literature review and focus group study,[8] which explored patients' preferences for attributes of preventive migraine treatments. Additionally, attributes were aligned with the primary and secondary outcome measures in the double-blind phase IV head-to-head clinical trial of galcanezumab versus rimegepant (Table 1). Attributes did not include safety or tolerability as CGRP mAbs and oral gepants are generally well tolerated and no available study data have suggested a major difference in safety between CGRP mAbs and oral gepants.[16] Attribute levels were selected to cover the likely ranges of outcome measures reported in clinical trials of galcanezumab[42–44] and rimegepant.[40] A D-efficient experimental design was used (Ngene® software version 1.2.1, ChoiceMetrics, Australia) to select the subset of choice tasks that could be used to estimate each attribute's effect on preferences.[46–48]

An initial version of the DCE instrument was developed and tested in qualitative and quantitative pilot tests (Supplemental Methods/Results). Qualitative pilot interviews were conducted with 13 patients in web-based teleconferences and aimed to assess whether patients considered the selected DCE attributes and levels relevant, tradeable, and understandable. The complexity, clarity, length, wording, and completeness of the questions were also assessed. The attribute presentation and wording were then refined accordingly. Quantitative pilot testing followed in 101 patients and aimed to evaluate whether attribute levels covered the preference-relevant range, identify other meaningful parameter estimates, and update attribute levels where necessary.[29] Because no changes were made to the attributes, levels or experimental design at this stage, quantitative pilot testing data were added to the main DCE sample as recruitment proceeded.

Table 1 Treatment Attributes and Levels Used in the DCE

Attributes	Levels	Rationale for selection of levels
How you take the treatment	Self-injection once per month Orally dissolving pill every other day Oral pill every day	Levels reflect the different modes of administration for galcanezumab (monthly self-injection) and the oral gepants rimegepant (orally dissolving tablet every other day) and atogepant (oral pill every day)[21,40,41]
Chance of reducing the number of migraine headache days per month that you experience by at least half	40% 55% 70%	Levels reflect results from previous clinical trials measuring a ≥50% reduction in monthly migraine headache days in EVOLVE-1 (galcanezumab 120 mg: 62.3%, 240 mg: 60.9%; placebo: 38.6%), EVOLVE-2 (galcanezumab 120 mg: 59.3%, 240 mg: 56.5%; placebo: 36.0%),[42,43] and CONQUER ITT EM (rimegepant 120 mg: 41.8%; placebo 17.1%).[44]
Time it takes for the medication to work	2 weeks 1 month 2 months	Levels were informed by reduction in migraine headache days within the first month of treatment and over time in a combined analysis of EVOLVE-1 and EVOLVE 2 trials.[44] Both tested doses of galcanezumab (120 and 240 mg) achieved a statistically significant reduction in the number of monthly migraine headache days beginning at month 1 and continuing through month 6. A 240 mg loading dose of galcanezumab had a significant effect at week 1 that continued throughout the remaining weeks of month 1
Impact of migraines on daily activities	Minimally impaired by migraine Moderately impaired by migraine Extremely impaired by migraine	Levels correspond to changes from baseline in the role function-restrictive subdomain of the MSQ. The role function-restrictive domain measures the impact of migraines on daily activities[33,34] and has previously been used in clinical trials of galcanezumab.[45] The lower-, middle-, and higher-level categories (minimally, moderately, and extremely impaired) were chosen as attribute levels to ensure sufficient differentiation of levels across the spectrum of functioning and disability
Reduction in the number of days you take acute medication (to treat migraine symptoms)	2 fewer days 4 fewer days 6 fewer days	Levels reflect the reduction in monthly migraine headache days requiring acute medication use in EVOLVE-1 (galcanezumab 120 mg: −4.0 days; 240 mg: −3.8 days; placebo: −2.2 days)[43] and EVOLVE-2 (galcanezumab 120 mg: −3.7 days; 240 mg: −3.6 days; placebo: −1.9 days).Levels reflect the reduction in monthly migraine headache days requiring acute medication use in EVOLVE-1 (120 mg: −4.0 days; 240 mg: −3.8 days; placebo: −2.2 days)[43] and EVOLVE-2 (120 mg: −3.7 days; 240 mg: −3.6 days; placebo: −1.9 days).[42,43]

Abbreviations: DCE, discrete choice experiment; MSQ, Migraine-Specific Quality of Life Questionnaire.

Data Quality

Patients completed two non-experimental choice tasks, stability and the dominance tests, which were not included in the final DCE analysis but were used as data quality indicators.[49,50] The stability test repeated the third choice task at the end of the DCE survey to check whether the respondent provided the same answer twice. This was followed by the dominance test, evaluating the rationality in the choice behavior of patients ie, whether they would choose the superior option among two choices: one with favorable levels for all attributes and an alternative with less favorable levels for chance of migraine reduction, impact on daily activities and reduction in acute medication.[49,50] Finally, response time was measured to quantify the time patients took to complete all 13 experimental tasks.

Data Analysis

Descriptive statistics were used to summarize patient characteristics and data on health literacy, numeracy, dominance and stability tests, dominated decision-making, serial non-participation, and response time. DCE choice data were analyzed in a random utility maximization framework.[51–53] Mixed multinomial logit (MXL) models were chosen to summarize the main analyses due to model fit and flexibility in assumptions.[54,55] MXL models were estimated with fully correlated covariance matrices; this was done in a Bayesian framework to make computation feasible. Marginal utilities were calculated as a measure of attribute desirability, where a higher marginal utility for a specific attribute level indicates a greater likelihood that a treatment scenario including that attribute level will be chosen, everything else being equal. Relative attribute importance (RAI) scores quantify the maximum percentage contribution of each attribute to a preference relative to all other attributes. RAI scores were calculated by estimating the difference between the attribute level with the highest preference weight and the level with the lowest preference weight, relative to the preference weight of the other DCE attributes. RAI values for all attributes total 100%. Marginal rates of substitution were estimated to determine the willingness of a patient to exchange a proportion of one attribute for a proportion of another attribute that is equally satisfying (Supplemental Statistics).[55] Subgroup analyses, by physician's COD availability, demographics, and clinical characteristics, were conducted to examine whether patient characteristics rather than treatment attributes influenced preference heterogeneity.

Results

Out of the 5000 invited potentially eligible individuals, approximately 3000 agreed to participate in the study (Figure 2). Of these, 784 were eligible, and 601 completed the survey. The mean age of the patients was 44.8 years (standard deviation [SD]=13.0, range 19–85) (Table 2). Patients were mainly male (67.6%) and about 82.7% had obtained at least some college education. Three-hundred patients provided physician's COD, and 301 provided a self-reported diagnosis only. To account for potential scale heterogeneity across the COD and no-COD samples and allow pooling, MXL models were estimated with fully correlated covariance matrices.

About half of patients (51.0%) had experienced more than eight migraine headache days per month (Table 2). A greater number of (12 to 14) migraine headache days per month were more frequent among patients with physician's COD than among those without physician's COD (43.3% vs 27.6%; Supplemental Table 1). Some patients (30.0%) had never previously used a preventive medication for migraine (Table 2). About half the patients (53.2%) had experience using a self-injectable medication for a health condition. Over half of the patients (57.8%) were "not at all" or "a little" afraid of injecting themselves with a medicine; however, 25.5% were "moderately" afraid, and 16.8% were "very" or "extremely" afraid (Table 2). Lack of fear of self-injecting a medicine was more frequently reported by patients with physician's COD than by those without physician's COD (48.3% vs 24.3%; Supplemental Table 1).

Results from the four PRO instruments indicated that the patients experienced moderate to severe migraine-related symptoms and disability (Table 2); patients with a physician's COD scored significantly higher on average than patients without physician's COD on every PRO instrument (Supplemental Table 1). Most patients had high health literacy (overall: 84%; physician's COD: 90% vs no physician's COD: 79%) and health numeracy (overall: 97%; physician's COD: 95% vs no physician's COD: 100%) scores (Supplemental Tables 2 and 3).

Most patients made consistent choices in the stability test (80.9%) and passed the dominance test (88.4%) (Supplemental Table 4). Moreover, nearly all patients (91.3%) did not show dominant preferences toward any single attribute, indicating that they made trade-offs among different attributes. About half of the patients (50.7%) took ≥3 minutes to complete the DCE survey.

Preference Elicitation

As shown in Figure 3, at least one marginal utility was significant for all attributes except treatment administration, which did not significantly affect respondent choices. In Figure 4 we see that the chance of a ≥50% reduction in monthly migraine days was the most important driver of patients' preferences for a migraine treatment (RAI: 38.3%; 95% confidence interval [CI]: 34.0–42.4), and treatment administration was the least important (RAI: 3.4%; 95% CI: 0.7–7.2)

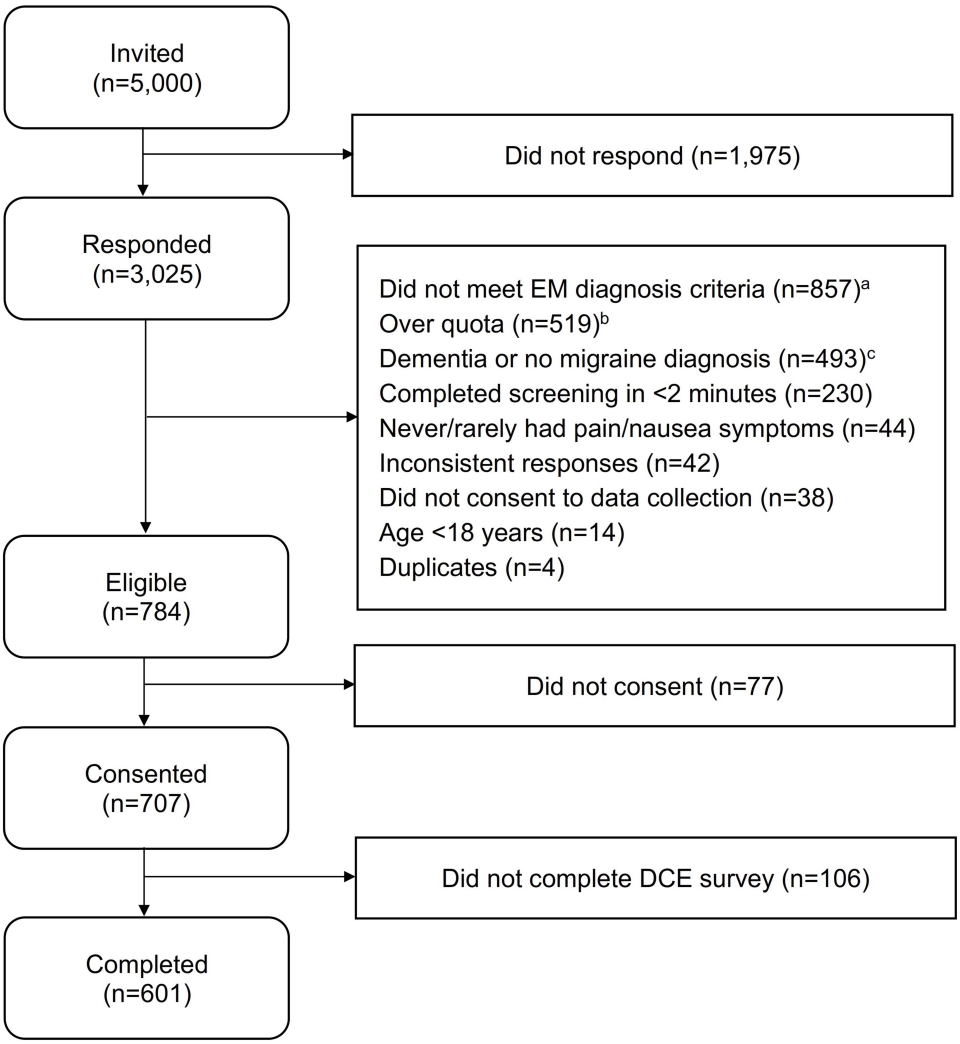

Figure 2 Patient disposition flow chart.
Note: [a]Patients were required to have a diagnosis of EM, defined as ≥4 and <15 migraine headache days and <15 headache days per month over 3 months; [b]A target recruitment quota of 50% was set for patients with a physician-provided confirmation of an EM diagnosis;[c] Patients with Alzheimer's disease/dementia, Parkinson's disease, or schizophrenia were excluded from the study.
Abbreviations: DCE, discrete choice experiment; EM, episodic migraine.

(Figure 4). In other words, having the chance to reduce the number of monthly migraine days by ≥50% was 11.2 times more important to patients than the way the treatment was administered. Impact on daily activities was also highly valued by patients (RAI: 23.5%; 95% CI: 19.0–27.8). Onset of treatment effect (RAI: 19.5; 95% CI: 16.4–22.9) and reduction in acute medication (RAI: 15.4%; 95% CI: 12.1–18.7) were comparable in their importance to patients.

Treatment Attribute Trade-Offs

The average trade-offs that patients were willing to make between different aspects of migraine treatments are presented in Figure 5. Based on these, patients would trade a reduction of migraine's impact on daily activities from "extreme" to "minimal" for a 17.09% (95% CI: 12.93–21.25) decrease in the chance of halving the number of migraine headache days per month. Similarly, patients would trade a treatment that reduced the impact of migraines on daily activities from "extreme" to "moderate" for a 12.06% (95% CI: 9.37–14.75) decrease in the chance that the treatment would reduce the number of migraine headache days per month. Patients would trade a one-week delay in onset of treatment effect for a 2.06% (95% CI: 1.60–2.53) higher chance of reducing the number of migraine headache days by ≥50%. Finally,

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Table 2 Patient Demographic and Clinical Characteristics

Characteristic	N=601
Age (years)	
Mean (SD)	44.8 (13.0)
Range (min, max)	19, 85
Sex (male), n (%)	406 (67.6)
Educational background, n (%[a])	
High school or less	104 (17.3)
Some college / university	194 (32.3)
College / university	185 (30.8)
Post graduate degree	118 (19.6)
Mean migraine headache days/month in past 3 months, n (%[a])	
4–7	294 (48.9)
8–11	207 (34.4)
12–14	100 (16.6)
Mean headache days/month in the past 3 months, n (%[a])	
4–7	171 (28.5)
8–11	217 (36.1)
12–14	213 (35.4)
Age at first diagnosis of migraine (years), mean (SD)	28.4 (11.8)
Prior use of a self-injectable for any health condition, n (%)	
No	281 (46.8)
Yes	320 (53.2)
Fear of self-injection, n (%[a])	
Not at all	218 (36.3)
A little	129 (21.5)
Moderately	153 (25.5)
Very	67 (11.1)
Extremely	34 (5.7)
Prior use of preventive treatments for your migraine, n (%[a])	
No, never used	180 (30.0)
Yes, currently using[b]	272 (45.3)
Yes, have used in the past[b]	173 (28.8)
MSSS score, mean (SD)	32.4 (4.4)
PGI-S score, mean (SD)	4.2 (1.1)
MSQ score, mean (SD)	47.2 (19.6)
MIDAS score, mean (SD)	41.6 (38.8)

Notes: [a]Percentages calculated over 470 (the denominator) received responses; [b]the two "Yes" categories were not mutually exclusive as both could be true for one patient.

Abbreviations: MIDAS, Migraine Disability Assessment; MSQ, Migraine-Specific Quality of Life Questionnaire; MSSS, Migraine Symptom Severity Score; PGI-S, Patient Global Impression of Severity; SD, standard deviation.

patients would trade a one-day increase in acute medication use for a 2.65% (95% CI: 1.96–3.35) increase in the chance of reducing the number of migraine headache days by ≥50%.

Preference Variation by Patient Characteristics

Treatment administration had greater importance among subgroups defined by reluctance to self-inject, MIDAS migraine disability ranged from no disability to moderate disability, MSQ score 67–100, age ≥65 years and 18–34 years, patient functioning, and than in the overall sample (Supplemental Figure 1). Therefore, patients with less headache-related disability or functional impairment placed greater relative importance on treatment administration than did patients in the overall sample (RAI for MIDAS little or no/mild/moderate scores: 20% vs 3.4%, $p<0.01$; RAI for MSQ score 67–100:

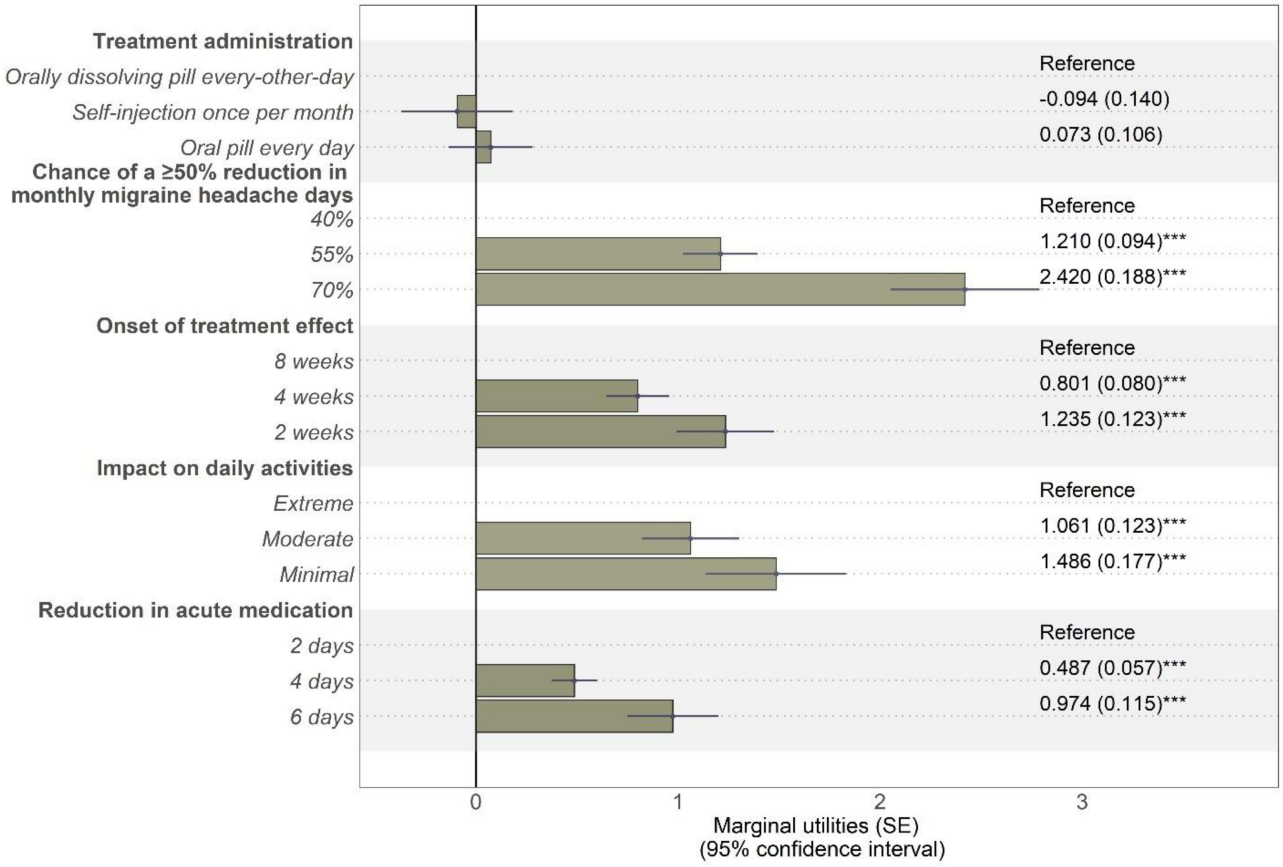

Figure 3 Marginal utilities derived from the mixed multinomial logit model (n=601).
Notes: The mean marginal utility and 95% CI of each attribute level, relative to the other levels included in the DCE, are shown. Estimates are marginal utilities that denote the effect of deviating from a reference level of on preferences. Positive mean estimates with a 95% CI >0 suggest an overall preference for the attribute level over the reference level. *** indicates p<0.001.
Abbreviations: CI, confidence interval; DCE, discrete choice experiment; SE, standard error.

18% vs 3.4%; p<0.01). Additionally, patients aged 18 to 34 years and >65 years attributed more importance to treatment administration than did patients in the overall sample (RAI: 14% vs 3.4%, p<0.05; RAI: 17% vs 3.4%; p<0.05, respectively).

The importance of other treatment attributes varied among subgroups. Patients with "little or no", "mild", or "moderate" disability according to MIDAS scores attributed less importance to a treatment's impact on daily activities than did patients in the overall sample (RAI: 13% vs 23.5%; p<0.05). Furthermore, patients with physician's COD attributed more importance to a treatment's impact on daily activities compared to the overall sample (RAI: 30% vs 23.5%; p<0.01), whereas patients without physician's COD attributed less importance (RAI: 14% vs 23.5%; p<0.01). In addition, patients with "moderate", "very", or "extreme" reluctance to self-inject placed lower relative importance on a treatment's ability to reduce acute medication usage than did patients in the overall sample (RAI: 10% vs 15.4%; p<0.05).

Discussion

In this DCE study in patients with EM, the most important driver of patient treatment preferences was a ≥50% reduction in monthly migraine headache days, followed by the impact on daily activities, the onset of treatment effect, the reduction in need for acute medication, and finally the route of administration. Patients were willing to trade off any other treatment attribute for a chance of reducing migraine headache days by ≥50%, such as one-week delayed onset of treatment effect or a one-day increased need for acute medication. Patients would also consider a treatment with a lower chance of a ≥50% reduction in monthly migraine days in exchange for a reduced impact of migraines on daily activities. A recent three-month, double-blind, phase IV head-to-head clinical trial (NCT05127486) compared galcanezumab and

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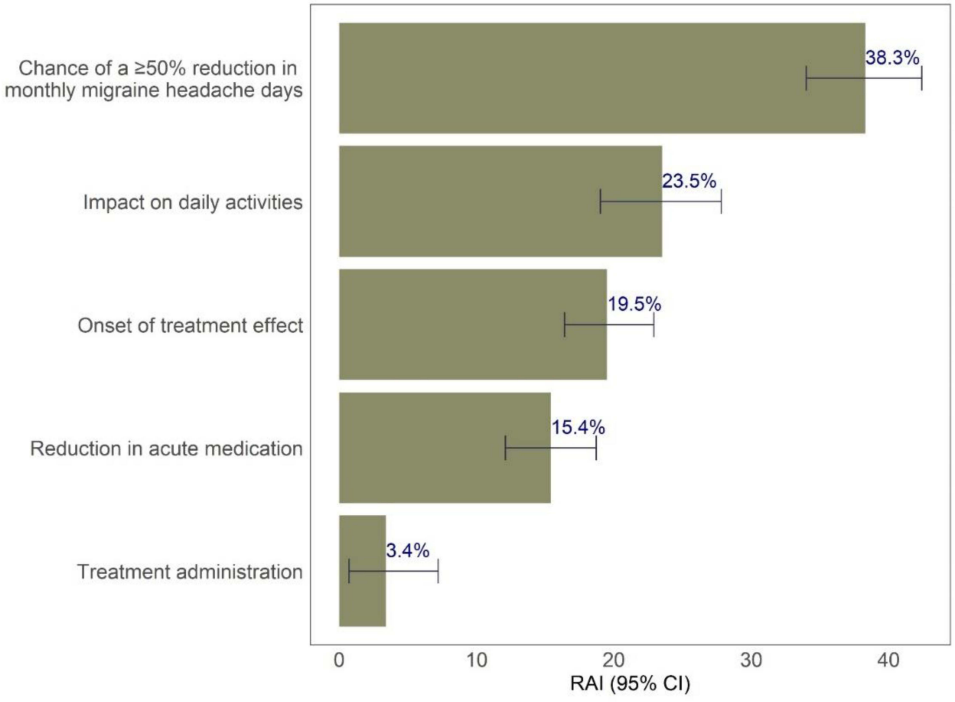

Figure 4 Mean RAI scores.
Note: RAI scores were calculated to facilitate the interpretation of the marginal utility estimates. RAI scores are reported on a scale of 0 to 100%, where 100% reflects choices driven entirely by that attribute, and 0% reflects choices completely ignored for that attribute. The RAI score and 95% CI for each attribute are shown.

rimegepant for EM prevention.[18] That trial used a ≥50% reduction from baseline in monthly migraine headache days as the primary outcome, which the present study supports as a patient-relevant primary endpoint in clinical trials.

Mode of treatment administration (self-injectable or oral medication) was the least important attribute, of all others considered, to this DCE survey patients, who were unwilling to accept any loss of treatment efficacy in exchange for a different mode of treatment administration. This is consistent with a previous DCE survey of adults with a self-reported physician diagnosis of migraine in the US, which found that the mode and frequency of administration (ie, daily oral pill, monthly injections, or twice-monthly injections) had minimal effects on patient preferences for migraine treatments.[5]

Only 16.8% of respondents were "very" or "extremely" afraid of injecting themselves with a medicine, and respondents were broadly familiar with self-injectables as nearly half of patients (53.2%) said they were either currently using a self-injectable medication or had done so in the past, although this may not have necessarily been specific for migraine treatments. One possible explanation for this high prevalence of self-injectable use might be previous migraine treatment with CGRP mAb, given that most patients were treated with migraine preventive treatment before entering the study. Only 23.5% reported using erenumab, fremanezumab, galcanezumab, or eptinezumab currently or in the past. Therefore, previous migraine injectable experiences could have influenced the present responses. A marked variability in patient preferences for self-injectable or oral medication was reported in a previous survey of 601 adults with migraine, with approximately 50% of patients favoring self-injectable medication, 30% preferring oral medication, and 20% tending to choose either depending on other treatment attributes, such as dosing schedule or mechanism of needle removal.[3] Another study found that patients exhibited an overall preference for an oral tablet every other day over a quarterly infusion, quarterly injection, or monthly injection; however, patient preferences were heterogeneous, in part because patients with previous CGRP mAb experience placed less importance on the mode of administration than other patients did.[4] Adding to such previous findings, the present DCE study findings indicate that subgroups of patients who are inexperienced with self-injectable medications or fear self-injection may place a greater value on treatment administration than other patient subgroups do.

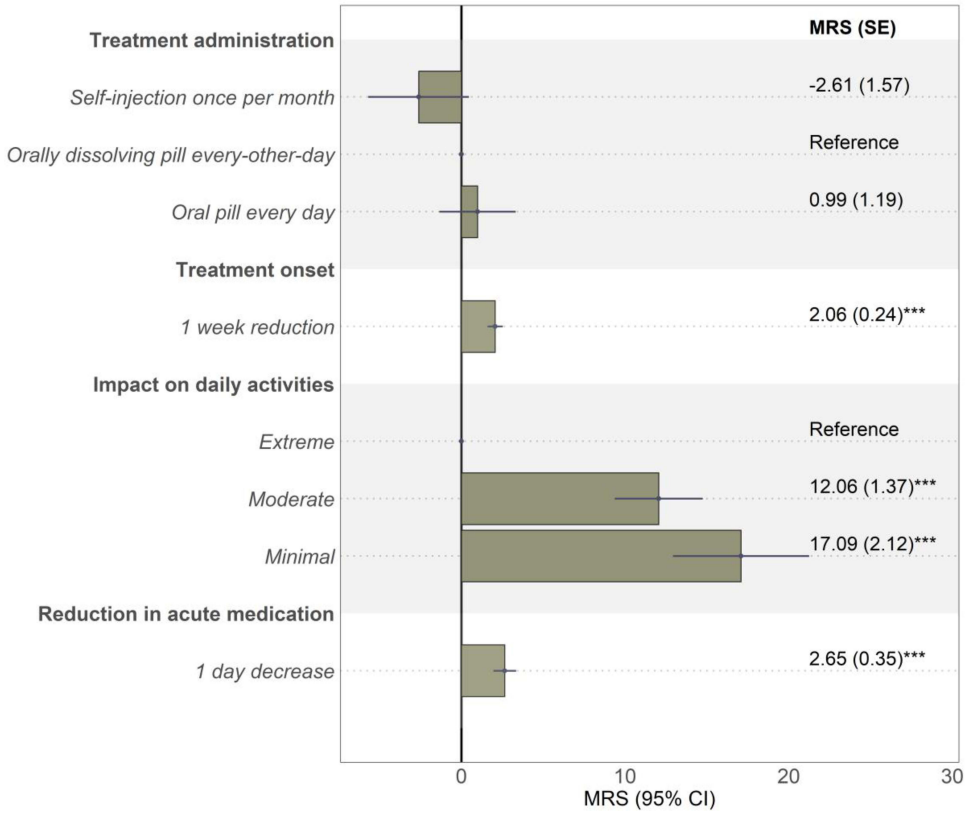

Figure 5 Willingness to trade attributes to reduce the number of headache days by half.
Note: Estimates of patients' willingness to exchange a proportion of one attribute for another equally satisfying were calculated using a mixed multinomial logit model that assumed log-normal distributions relative to the chance of reducing migraine headache days by half. Error bars represent 95% confidence intervals. *** indicates p-value <0.01%.
Abbreviation: SE, standard error.

In this study, preferences differed significantly between patients, emphasizing the importance of decision-making that aligns with patients' individual treatment priorities. These findings are consistent with previous preference research in this field, highlighting the importance of HCPs considering patient preferences when recommending migraine treatments.[7] Although the attributes were informed by previous literature and clinical endpoints, only five treatment characteristics were included. Therefore, the results and observations of this study are limited to these five attributes. This DCE study did not include safety and tolerability as treatment attributes; however, existing evidence does not suggest significant differences between self-injectable CGRP mAbs and oral gepants in these treatment characteristics. However, we included injection-related reactions in treatment attributes to ascertain the assessment of this unique side effect.

Selection bias is a potential limitation of this study, as the experiences and preferences of the sample may be systematically different from the general population of patients with migraine. For example, the male predominance among survey patients was surprising given the common epidemiological profile of patients with migraine, who are more often female.[56,57] Patients were identified through a convenience sample drawn from an opt-in panel of individuals. To minimize selection bias, several recruitment methods were used, including recruitment through online panels, clinical organizations, or social media. Enrolling patients with self-reported physician diagnosis of migraine is a common practice in patients preference research.[3–5,7,8] In this study, the overall sample was composed of patients who passed a detailed clinical screener, including the disease-specific MIDAS questionnaire, and were also asked to provide COD, and those who passed the screener but were not able to provide COD. Such diagnostic criteria are adequate for a web-based survey study assessing patient preferences. Furthermore, comprising the overall sample of these two groups of patients balanced competing concerns of recruitment feasibility, patient and physician burden, and confidence that patients report their disease status accurately. All CODs were checked twice by the study team, which was feasible for 300 CODs, but would have caused significant delays between participant recruitment and data collection if 600

needed to be collected and checked. By comparing the two samples, the hypothesis is tested that patient groups and preferences are similar, whether they self-report or not.

To account for potential scale heterogeneity across the physician's COD and no physician's COD samples and allow pooling, MXL models were estimated with fully correlated covariance matrices; this was done in a Bayesian framework for ease of computation. These two cohorts provided a comparison of preferences between self-reported and physician-confirmed patients, demonstrating that preferences were very similar, except for when it came to daily activities. This may be due to the fact that the physician's COD sample scored significantly higher migraine severity than the no physician's COD sample on every PRO instrument (MSSS, MSQ, MIDAS, PGI-S). Additionally, the physician's COD sample had more migraine headache days per month than the no physician's COD sample.

Additionally, hypothetical bias can occur in DCEs when patients respond to hypothetical scenarios in ways that do not reflect their actual responses in a clinical setting. However, the external validity of DCE methods has been shown to elicit trade-offs relevant to clinical decision-making[58] and aligned with real-world health choices.[59] To mitigate hypothetical bias by making the DCE credible and relevant to patients, the DCE design, question framing, and question wording were developed based on patient input from qualitative pilot interviews. Further, a tutorial was included in the warm-up to ensure that patients understood the attribute descriptions.

Conclusion

Patients with EM valued treatments that have a higher likelihood of reducing their migraine attacks. Other treatment attributes related to clinical efficacy were also important to patients, who highly valued a treatment's impact on daily activities and the time required for it to reach full effectiveness. While patients did not value a reduction in the need for acute medication as highly as other efficacy-related attributes, they still placed moderate value on this attribute. Patients were not concerned with the treatment's mode of administration. These results can be used to inform a patient-centered treatment strategy that considers the relative importance of treatment attributes in clinical decision-making. HCPs can use preference data to understand patient preferences for different attributes and ensure that treatment decisions align with their patients' individual preferences.

Abbreviations

CGRP, calcitonin gene-related peptide; CI, confidence interval; COD, confirmation of diagnosis; DCE, discrete choice experiment; EM, episodic migraine; FDA, US Food and Drug Administration; mAbs, monoclonal antibodies; MSQ, Migraine-Specific Quality of Life Questionnaire; MSSS, Migraine Symptom Severity Score; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome; SBSQ, Set of Brief Screening Questions; MIDAS, Migraine Disability Assessment questionnaire; RAI, relative attribute importance; SD, standard deviation.

Data Sharing Statement

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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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.

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LV, OJV, and ATH are employees and/or stockholders of Eli Lilly and Company. CW, MQ, and MT are employees of Evidera Inc. which received payment from Eli Lilly for work relating to this study. The authors report no other conflicts of interest in this work.

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