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RESEARCH SUBMISSIONS

A stated preference survey to explore patient preferences for novel preventive migraine treatments

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Abstract

Objective: The objective of this study was to explore patient preference for attributes of calcitonin gene-related peptide (CGRP) inhibitors for the preventive treatment of migraine and to describe differences in treatment preferences between patients.

Background: CGRP inhibitors are a novel class of migraine drugs specifically developed for the preventive treatment of migraine. Clinicians should understand patient preferences for CGRP inhibitors to inform and support prescribing choices.

Methods: Patients with migraine in the US and Germany were recruited to participate in an online discrete choice experiment (DCE) survey, which presented hypothetical treatment choices using five attributes: mode of administration, side effects, migraine frequency, migraine severity, and consistency of treatment effectiveness. Attribute selection was informed by a literature review and semi-structured patient interviews ($n = 35$), and evaluated using patient cognitive debriefing interviews ($n = 5$).

Results: Of 680 who consented to participate, 506 participants completed the survey and were included in the study (US = 257; Germany = 249). Overall, participants placed highest importance (preference weight, beta = 1.65, $p < 0.001$) on the treatment's ability to reduce the severity of migraine (mild vs. unchanged severity), followed by consistent treatment effectiveness (beta = 1.13, $p < 0.001$), and higher chance of reduced migraine frequency (beta = 1.00, $p < 0.001$). Participants preferred an oral tablet every other day (beta = 1.00, $p < 0.001$) over quarterly infusion, quarterly injections ($p = 0.019$), or monthly injection ($p < 0.001$). Preference for all treatment attributes were heterogeneous, and the subgroup analyses found that participants naïve to CGRP monoclonal antibody treatments had a stronger preference for oral therapy compared to those with such experience ($p = 0.006$).

Conclusion: In this DCE assessing CGRP inhibitors attributes, the main driver of patient choice was treatment effectiveness, specifically reduced migraine severity, and consistent treatment effectiveness. Further, patients exhibited an overall preference

Abbreviations: CGRP, calcitonin gene-related peptide; CI, confidence interval; DCE, discrete choice experiment; IMXL, interacted mixed logit; mAb, monoclonal antibody; MIBS-4, migraine interictal burden scale; MMD, monthly migraine day; MXL, mixed logit; RAI, relative attribute importance.

for an oral tablet every other day over injectables. Patients' experience with previous treatments informs the value they place on treatment characteristics.

KEYWORDS
calcitonin gene-related peptide inhibitors, discrete choice experiment, migraine, patient preference, preventive treatments

BACKGROUND

Migraine affects more than one billion people worldwide and is characterized by recurrent episodes of severe head pain, which often occur concurrently with several other symptoms, including dizziness, irritability, nausea, sensitivity to light and sound, and problems with vision.[1–3] Acute migraine medications, including triptans and nonsteroidal anti-inflammatory drugs, can offer short-term symptom relief, but patients still have migraine attacks[4] and, if acute medications are taken regularly, can develop medication-overuse-headache.[5] In addition to the acute medications that are used, antiseizure medications, antidepressants, and beta blockers are all used for the prevention of migraine. These treatments have been shown to reduce the frequency and severity of migraine, although side effects and limited efficacy are common.[6] Consequently, despite a broad range of available migraine treatments, preventive medications for migraine have high rates of discontinuation and low adherence.[6]

More recently, monoclonal antibody (mAb) treatments have been approved specifically for the prevention of chronic and episodic migraine.[7–10] MAb treatments inhibit the vascular calcitonin gene-related peptide (CGRP) receptors that are suspected to be the cause of migraine pain. The treatments are administered as a subcutaneous or intravenous injection once per month or every three months. In contrast with traditional migraine treatments, current evidence suggests that CGRP inhibitors have relatively mild side effects.[11] However, a complete reduction of monthly migraine days (MMDs) (i.e., no breakthrough) with mAbs is rare, and patients continue to need acute medications.[12] In addition, one study assessing the real-world effectiveness of the mAb erenumab observed that the treatment effect wears off among around one-third of patients, on average one week before the next injection.[13]

Understanding the importance to patients of different treatment characteristics can support the management of chronic disease such as migraine.[14,15] Previous research in patient preferences for migraine treatments has found that treatment effectiveness is more important to patients than issues such as safety or mode of administration.[14,16]

This study is designed to add to the existing literature by exploring patient preference for attributes of novel CGRP inhibitors for preventive migraine treatments and assessing heterogeneity within these preferences for different subgroups of patients with migraine. A discrete choice experiment (DCE) was developed to quantify patients' preferences for different treatment attributes and to assess the relative importance of these attributes on their treatment decisions. DCE is a stated preference method that has been used extensively to elicit patient preference in healthcare settings.[17] It involves asking participants to choose between hypothetical treatment alternatives that differ in key attributes such as efficacy, safety, and mode of administration. We hypothesized that participants would be willing to make trade-offs between the selected attributes, as previous studies have shown all the attributes to be relevant to patients. The results obtained from a DCE help to quantify the value that patients gain by changes in the treatment attributes and can be used to facilitate treatment decision-making by various stakeholders.

METHODS

Study and survey design

The DCE was developed in line with best practice recommendations on preference-based methods from the International Society for Pharmacoeconomics and Outcomes Research.[17,18] Potential treatment attributes and levels describing CGRP inhibitors (fremanezumab, erenumab, galcanezumab, eptinezumab, rimegepant) approved as preventive migraine treatments at the time of the survey were identified from clinical trials, real-world evidence studies, and qualitative interviews with patients (n = 35) with migraine.[19] The qualitative interviews explored the relevance of different treatment attributes defined as different aspects of treatment efficacy, side effects, and mode of administration, to patients. Based on this evidence, attributes and levels were selected and developed to represent treatment attributes that were deemed important and most relevant to patients' treatment choices. Further details on the attribute development are provided in Supporting Information Appendix S1.

The survey included a bespoke questionnaire with items on participants' demographic and clinical background, and experience with acute and preventive migraine treatments. Participants also completed two standardized instruments, the Headache Impact Test[20] and migraine interictal burden scale (MIBS-4),[21] validated for their use in migraine.[22,23] Participants were presented with a brief description of each treatment attribute in lay language and a test choice task with a superior treatment alternative. Then, participants were asked to complete the DCE, where they chose between two hypothetical treatment alternatives, described by the treatment attributes, in a series of choice questions. An example choice task is shown in Figure 1. The survey used adaptive questioning (i.e., routing of survey questions) to ensure questions were relevant to participants.

The complete survey (background questionnaire and DCE survey) was tested in cognitive debriefing interviews with five patients to ensure that the selected attributes and levels were relevant and to confirm comprehension of the overall survey. Participants were also asked if there were any other treatment attributes relevant to

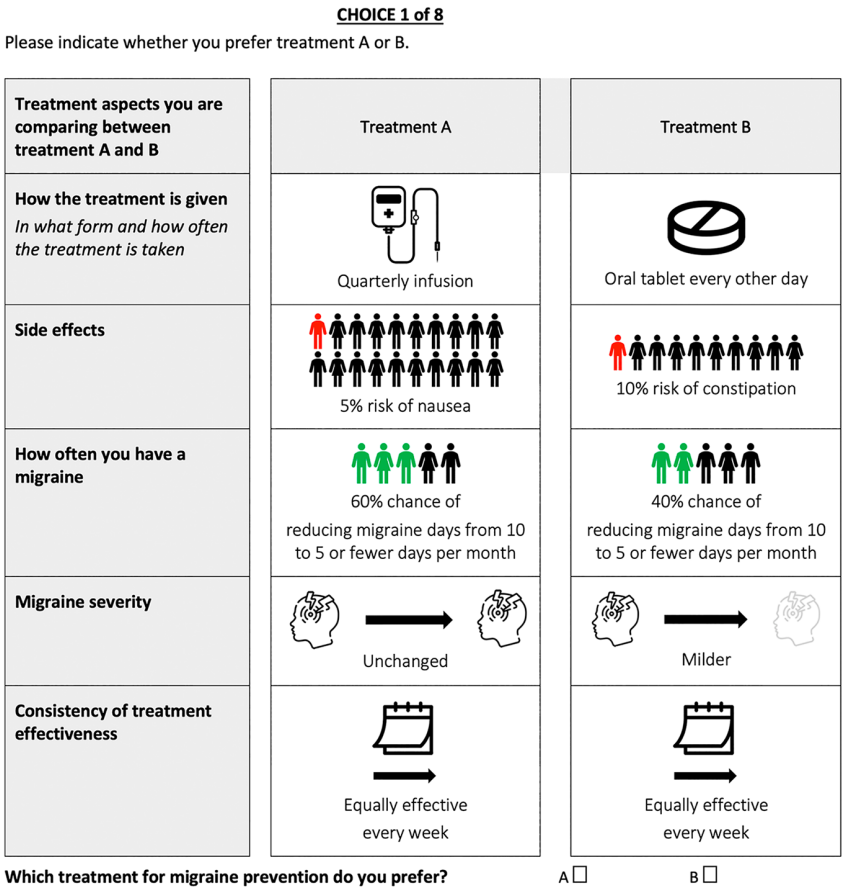

FIGURE 1 Example choice task tailored to a participant who reported 10 migraine days per month in the last 3 months. [Color figure can be viewed at wileyonlinelibrary.com]

their treatment choices. Most participants confirmed that the chosen attributes covered all attributes that are important to them. Only one participant mentioned that they may also consider how long the medication takes to be effective; this attribute was not included in the final DCE choice set due to lack of evidence on variation in response onset between available CGRP inhibitors indicated for migraine prevention. The clinical accuracy of the descriptions of the attributes and levels was assessed by a clinical expert in migraine treatment (T.S.). The final attributes and levels included in the DCE are summarized in Table 1. Supporting Information Appendix S2 includes the final attribute descriptions as presented in the DCE survey.

The experimental design of the DCE was generated using a D-efficient design in NGene 1.2.1[24] to ensure that the impact of attribute changes on participants' choices could be independently and precisely identified. The experimental design included 16 choice tasks, split into two blocks. Participants were randomized into either block, with each participant completing eight choice tasks. This paper reports the findings from the a priori, primary analysis of the DCE survey data.

Participant recruitment

The survey was conducted online between September and November 2021 in patients with migraine from the US and Germany. A minimum quota (n = 150) was set for patients who had taken a mAbs treatment for 3+ months (US: 100; Germany: 50), which is the time frame in which a treatment effect can be observed.[25] The traditional calculation of sample size based on standard statistical theory of hypothesis testing cannot be applied for sample size estimation for a DCE survey because a priori, patients' preference for a treatment and the strength of their preferences are unknown. The target sample size was 500 (US: 250; Germany: 250), based on sample sizes common in DCE studies.[26]

Participants were recruited by a specialist healthcare recruitment agency through commercial databases (patient panels) using convenience sampling. The web-based survey was open to each visitor of the survey site; visitors interested in participating were screened based on the following eligibility criteria: aged 18 years or above, self-reported medical diagnosis of migraine, at least one migraine day in the last three months, and resident in the US or Germany. Eligible participants were provided with additional information about the study and their rights and asked to complete an online consent form before proceeding to the survey. The main survey contained 20 to 41 questions, each item presented on a separate page, and presented in the same order for all participants. Participants were able to go back and review previous responses and had to complete the full survey for their responses to be recorded. All data were collected and stored in accordance with the EU

TABLE 1 Summary of treatment attributes and attribute levels

Attributes	Levels
Mode of administration (*How the treatment is given*)	Quarterly infusion
	Oral tablet every other day[a]
	Monthly injection
	Quarterly injection
Side effects	10% risk of injection site pain (*sore, painful, or itchy thigh or stomach*)
	10% risk of constipation
	5% risk of nasopharyngitis (*blocked or runny nose, sore throat, and coughing*)
	5% risk of nausea
Migraine frequency (*How often you have a migraine*)[b]	40% chance of at least halving MMDs
	60% chance of at least halving MMDs
Migraine severity	Unchanged (*migraine symptoms are the same*)
	Milder (*migraine symptoms are milder*)
Consistency of treatment effectiveness[a]	Varies week by week
	Equally effective every week

Abbreviation: MMD, monthly migraine day.

[a]To avoid implausible combinations, the attribute level "Oral tablet every other day" and "Effectiveness varies week by week" were not shown together.

[b]The level "migraine frequency" was presented as 50% of each patient's reported MMDs in the last 3 months.

General Data Protection Regulation (GDPR) and UK Data Protection Act 2018.

Participation in this study was voluntary and participants received remuneration for their participation in the study. To prevent multiple entries of the same participant, an IP address blocker was used, and responses were manually checked for duplicates.

The study received approval upon ethical review by WCG Institutional Review Board (Study Number: 1305360; IRB Tracking Number: 20211304) before recruitment.

Analysis

The analysis was conducted in R 4.1.0[27]; the R package apollo was used for choice modeling.[28] Results of two-tailed hypothesis tests were considered statistically significant if $p \leq 0.05$. Participants who completed the DCE survey questions in less than one minute were excluded. No missing data were recorded due to participants being required to complete all questions, with response completion verified by the survey platform software. Analysis was conducted on unweighted data.

Patient characteristics were summarized using descriptive statistics (categorical variables: count, percentage; continuous variables: mean, standard deviation [SD]), for the total sample, and stratified by country and experience with mAbs for 3+ months.

The DCE data were analyzed within the random utility maximization framework.[29–31] All attribute levels were categorical and dummy coded. To allow for preference heterogeneity across participants, a mixed logit (MXL) model was estimated using a simulated maximum likelihood procedure with 3000 Halton draws. The MXL model allows for preferences to vary between individuals and was estimated using the assumption that the distribution of preference weights for each attribute level can be described by a Gaussian (normal) distribution.[32] Patient preferences for each attribute level can then be described using the mean (with SD) to indicate the degree of variation in patient preferences. Model fit was assessed using statistical log-likelihood, Bayesian Information Criterion, and McFadden's pseudo-R^2. Allowing for preference heterogeneity improved model fit. Sensitivity analyses were conducted to assess model robustness adjusting for (potential) data quality issues (internal validity, non-trading, lexicographic behavior)[33] and differences in gender distribution, and to confirm feasibility of pooling choice data from the US and Germany. Further details on the MXL model specifications and sensitivity analyses are provided in Supporting Information Appendix S3.

In addition, subgroup analyses were also conducted to explore the influence of participants' sociodemographic and clinical characteristics on preference heterogeneity. The following subgroups were introduced as effects-coded interaction terms with each attribute level in the MXL model: chronic migraine (yes/no); mAbs treatment experience (yes/no); age (younger/older than average), sex (female/male), country (US/Germany), and interictal burden as measured by the MIBS-4 (severe/little to moderate). These interaction effects captured the effect of participants' characteristics on their preferences in the MXL model and thus allowed for both observed and unobserved preference heterogeneity in the model. The selection of subgroup analyses was based on an a priori expectation of participants' characteristics that were likely to impact their preferences for a preventive treatment. The change in statistical performance of each interaction model was assessed relative to the MXL model using the likelihood ratio test; a statistically significant improvement in model fit indicates participants' characteristics were significant drivers of preferences heterogeneity.

Based on the MXL model estimates, relative attribute importance (RAI) scores were calculated for each attribute. RAI scores capture the importance of an attribute relative to all other attributes conditional on the range of levels for that attribute. It is calculated using the following formula:

$$\mathrm{RAI}_k = 100 \times \frac{\hat{\beta}_k^{\max} - \hat{\beta}_k^{\min}}{\sum_{k\in[1;K]}\left(\hat{\beta}_k^{\max} - \hat{\beta}_k^{\min}\right)},$$

where $(\hat{\beta}_k^{\max} - \hat{\beta}_k^{\min})$ corresponds to the utility range obtained when moving from the worst (least desirable) to best (most desirable) level of the kth attribute. The RAI score can be expressed as a percentage and represents the proportion of change in utility

attributed to changes in a particular attribute. The 95% confidence intervals (CIs) around the RAI scores were computed using the Delta method.[34]

RESULTS

Overall, 10,075 people accessed the survey, of which 592 (6%) left the survey after the first page and 8250 (82%) were not eligible to participate. Of the 680 (7%) participants who consented to participate, 147 (22%) participants were excluded due to completing the DCE survey in under one minute. The full survey was completed by 506 participants from the US (n = 257, 51%) and Germany (n = 249, 49%). A subsample of 195 (39%) participants who had taken mAbs treatment for at least 3 months were recruited.

Sample characteristics

Patients' demographic and clinical background characteristics are shown in Table 2. Most participants (64%) described their sex as female, and the remaining participants stated they were male (36%). The mean age of the sample was 45 (SD = 13.8) years. On average, patients reported 8.5 (SD = 6.4) MMDs and 10.4 (SD = 7.1) monthly headache days in the last three months. Around half (47%) stated that they were diagnosed with chronic migraine, and a quarter (26%) reported that they were diagnosed with episodic migraine (26%) by their doctor. Most participants (57%) did not take a preventive treatment in the three months prior to survey completion, and only a third of non-mAbs patients (32%) had taken a preventive treatment recently.

Patient preferences

On average, participants completed the DCE choice tasks in 3.1 (SD = 4.1) minutes.

Results of the MXL model are presented in Table 3 and Figure 2 and show the relative strength of preference for each attribute level in relation to the reference level. A McFadden adjusted pseudo-R^2 of 0.20 to 0.40 can be considered a good model fit,[35] and our model fit of 0.12 is not uncommon and may be considered as moderately good. All estimated preference weights were statistically significant ($p < 0.05$), which suggests that participants considered all attributes relevant when choosing between the two hypothetical treatments presented in the DCE. Positive preference weights indicate a preference for this attribute level over the reference level. Participants preferred attribute levels with greater treatment benefit in attributes describing treatment efficacy (i.e., migraine frequency, migraine severity, consistency of treatment effectiveness), which confirms the internal validity of the DCE results.

Results from the MXL model suggest that, overall, attributes relating to treatment effectiveness were the most important to patients. On average, patients placed most value on improvement in migraine severity: They preferred a treatment with milder migraine severity than one that did not change migraine severity (1.65, SE = 0.13). Patients also preferred a treatment that is equally effective every week over one that varies week by week (1.13, SE = 0.10). Patients also preferred a treatment with a higher chance of fewer migraine days (1.00, SE = 0.10).

For mode of administration, patients preferred an oral tablet every other day (1.00, SE = 0.14), quarterly injections (0.45, SE = 0.09), or monthly injection (0.62, SE = 0.09) over quarterly infusion. Patients also preferred an oral administration over monthly

TABLE 2 Patient demographic and clinical background overall and stratified by country and CGRP mAb treatment (3+ months)

Characteristic	Overall $N = 506$	US $n = 257$	Germany $n = 249$	No CGRP mAb $n = 311$	CGRP mAb $n = 195$
Age, mean (SD)	45.0 (13.8)	44.8 (14.7)	45.2 (12.9)	47.6 (14.6)	40.9 (11.3)
Education					
No formal qualification[a]	2 (0%)	2 (1%)	0 (0%)	1 (0%)	1 (1%)
Secondary school[a]	233 (46%)	61 (24%)	172 (69%)	175 (56%)	58 (30%)
College/university degree or higher[a]	262 (52%)	185 (72%)	77 (31%)	129 (41%)	133 (68%)
Other	8 (2%)	8 (3%)	0 (0%)	5 (2%)	3 (2%)
MMDs (last 3 months), mean (SD)	8.5 (6.4)	10.4 (6.8)	6.6 (5.2)	7.3 (6.1)	10.5 (6.2)
MHDs (last 3 months), mean (SD)	10.4 (7.1)	12.1 (7.7)	8.7 (6.0)	9.9 (7.3)	11.1 (6.8)
Type of migraine (ever diagnosed)					
Episodic migraine	131 (26%)	62 (24%)	69 (28%)	63 (20%)	68 (35%)
Chronic migraine	239 (47%)	148 (58%)	91 (37%)	120 (39%)	119 (61%)
Taken any preventive treatment (last 3 months)	217 (43%)	125 (49%)	92 (37%)	98 (32%)	119 (61%)

Abbreviations: CGRP mAb, calcitonin gene-related peptide monoclonal antibody; MHD, monthly headache day; MMD, monthly migraine day; SD, standard deviation.

[a]No formal qualification includes primary school education. Response options for secondary school levels were adapted for differences in US and Germany; "College/university degree" was translated in the German version of the survey as university degree.

TABLE 3 Mixed logit (MXL) model estimates ($N = 506$) of mean preference weights for attribute levels and standard deviations (SD) of the sample's preference distribution

Attribute	Level	Preference weight (SE)	*p*-value	SD (SE)	*p*-value
Mode of administration	Quarterly infusion	*Reference category*			
	Oral tablet every other day	1.00 (0.14)	<0.001	1.84 (0.19)	<0.001
	Monthly injection	0.45 (0.09)	<0.001	0.65 (0.17)	<0.001
	Quarterly injections	0.62 (0.09)	<0.001	0.68 (0.15)	<0.001
Side effects	10% risk of injection site pain	*Reference category*		–	
	10% risk of constipation	0.26 (0.08)	0.001	0.11 (0.21)	0.609
	5% risk of nasopharyngitis	0.41 (0.08)	<0.001	0.29 (0.14)	0.035
	5% risk of nausea	0.36 (0.08)	<0.001	0.73 (0.18)	<0.001
Migraine frequency	40% chance of halving MMDs	*Reference category*			
	60% chance of halving MMDs	1.00 (0.10)	<0.001	0.92 (0.12)	<0.001
Migraine severity	Unchanged	*Reference category*			
	Milder	1.65 (0.13)	<0.001	1.19 (0.14)	<0.001
Consistency of treatment effectiveness	Varies week by week	*Reference category*			
	Equally effective every week	1.13 (0.10)	<0.001	0.94 (0.13)	<0.001

Note: A significant positive preference weight suggests a preference of the attribute level over the reference category. Significant SDs suggest preference heterogeneity. AIC: 4918; BIC: 5037; Adjusted Rho^2: 0.124.

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; MMD, monthly migraine days; SD, standard deviation; SE, standard error.

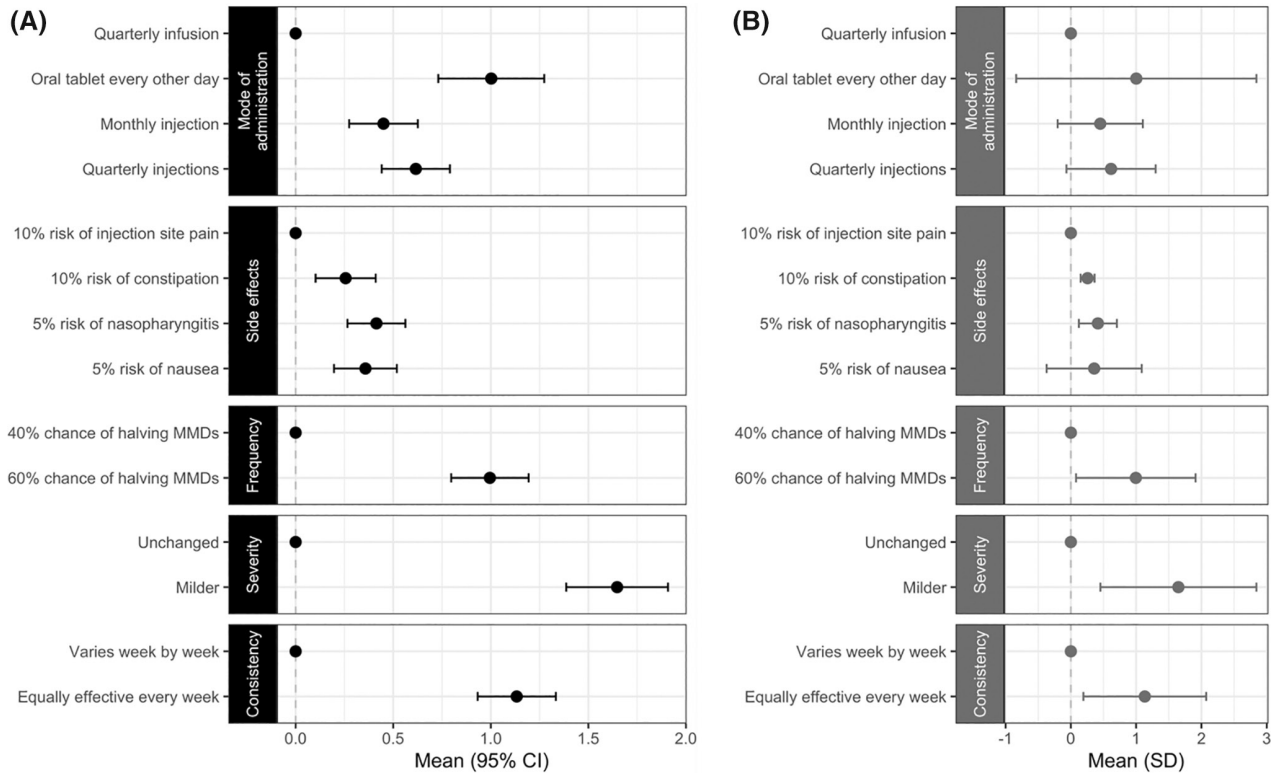

FIGURE 2 Results of mixed logit (MXL) model ($N = 506$). (A) Mean preference weights and 95% confidence interval (CI, error bar); positive mean estimates with 95% CI spanning a range of >0 suggest overall preference for attribute level over reference level (0). (B) Mean preference weights and standard deviation (SD, error bar) of the preference distribution. The SD shows the distribution of patient preferences. Except for the attribute level "10% risk of constipation," the SDs of all levels were statistically significant, which suggests that patient preferences were heterogeneous. MMD, monthly migraine day.

or quarterly injections ($p < 0.001$; $p = 0.019$). Overall, patients placed the least importance on avoiding side effects. Comparing side effects, patients were most concerned about a 10% risk of injection site pain compared with a 10% risk of constipation (0.26, SE = 0.08), 5% risk of nausea (0.36, SE = 0.08), and 5% risk of nasopharyngitis (0.41, SE = 0.08).

RAI scores were used to compare the relative contribution of treatment attributes to patient treatment choices and to identify the most important treatment attribute to patients relative to all other attributes. The RAI of "migraine severity" was 31.7% (95% CI: 29.1, 34.4), which indicates the attribute's contribution to participants' treatment choices. The second most important attribute was "consistent treatment effectiveness" with an RAI of 21.8% (95% CI: 19.1, 24.6). "Migraine frequency" (RAI = 19.2% [95% CI: 16.6, 21.7]) and "mode of administration" (RAI = 19.3% [95% CI: 15.5, 23.5]) were equally important to patients. "Side effects" were least relevant to patients (RAI = 8.0% [95% CI: 5.2, 10.7]). The RAI scores of attributes can be compared as follows: compared with "consistent treatment effectiveness," for example, "migraine severity" was 1.5 times (31.7%/21.3%) more important in driving patient choice.

All estimated preference weights (except 10% risk of constipation over 10% risk of pain) were associated with significant SD estimates ($p < 0.05$), which suggested the presence of preference heterogeneity (i.e., significant variation in preferences between patients). Preference heterogeneity was most prominent for the attribute "mode of administration." The large SD estimates relative to the mean preference weights suggest that while overall, patients least preferred a quarterly infusion, there were some patients who did prefer the infusion over an oral tablet (SD = 1.84, SE = 0.19), monthly injection (SD = 0.65, SE = 0.17), or quarterly injections (SD = 0.68, SE = 15). Preferences were also heterogeneous for the attribute "side effects," and while most participants were most concerned about a 10% risk of injection site pain, a minority of participants were more concerned about avoiding a 5% risk of nausea (SD = 0.73, SE = 0.18). For migraine frequency, migraine severity, and consistency of treatment effectiveness, all valued a treatment benefit, but participants differed in the extent to which they valued a benefit.

Describing drivers of preference heterogeneity

To further understand preference heterogeneity, subgroup analyses were conducted by extending the MXL model to include interaction effects with patients' characteristics (IMXL). Significant drivers of preference heterogeneity were identified as patient age, country, and mAbs treatment experience, as the IMXL significantly improved the model fit compared to the MXL. RAI scores for the overall sample and each subgroup and are presented in Figure 3; IMXL model results are provided in Supporting Information Appendix S4.

Reduced migraine severity was the most important treatment attribute to the overall sample (RAI = 31.7%) and all subgroups (RAI = 29.8–33.7%). The attribute "migraine frequency" was significantly more important to patients with severe interictal burden than to patients with little to moderate interictal burden (RAI = 21.5% [95% CI: 18.5, 24.8] vs. RAI = 15.6% [95% CI: 11.6, 19.7], $p = 0.016$). Patients with mAbs treatment experience placed more value on consistent treatment effectiveness than patients naïve to mAbs (RAI = 26.1% [95% CI: 20.5, 31.8] vs. RAI = 19.9% [95% CI: 16.9, 22.9], $p = 0.054$). In contrast,

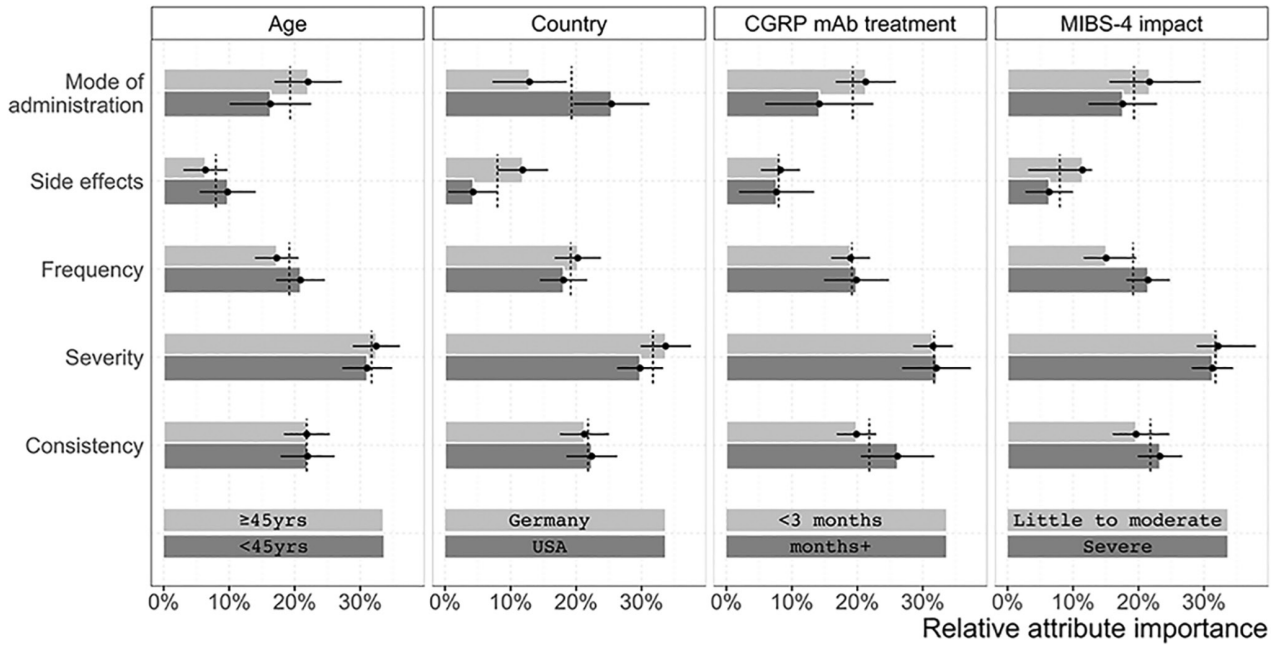

FIGURE 3 Relative attribute importance (RAI) by subgroup. The horizonal black lines indicate the 95% confidence intervals of the estimated RAI subgroup scores (point); the dashed vertical black lines show the overall mean RAI scores. CGRP mAb, calcitonin gene-related peptide monoclonal antibody; MIBS-4, migraine interictal burden scale.

those who were naïve to mAbs placed more value on the mode of administration than patients with mAbs experience (RAI = 21.3% [95% CI: 16.7, 25.9] vs. RAI = 14.2% [95% CI: 5.9, 22.5], $p = 0.142$).

Patient preferences for mode of administration differed significantly between patients of different ages, country, and mAbs treatment experience. Patients who were naïve to mAbs treatments had a stronger preference for an oral tablet over a quarterly infusion ($p = 0.006$) than patients with mAbs experience. In contrast, younger patients placed less value on a treatment that is an oral tablet ($p = 0.023$), monthly injection ($p = 0.002$), or quarterly injections ($p = 0.004$) compared to an infusion and did not prefer monthly injection significantly more ($p = 0.052$) than quarterly infusion. US patients had a stronger preference for oral tablet ($p = 0.013$) and monthly injection ($p = 0.033$) over infusion than German patients, who placed slightly higher utility on quarterly injections than on a monthly injection.

US patients cared significantly more about mode of administration (RAI = 25.4%) and significantly less about side effects (RAI = 4.3%) than patients from Germany (RAI = 12.9%, $p = 0.002$; RAI = 11.9%, $p = 0.006$). Comparing the relative importance of different side effects, US patients placed similar value on avoiding constipation, nausea, and injection site pain (differences were not statistically significant). In contrast, German patients placed more value on avoiding risk of nasopharyngitis ($p < 0.001$), nausea ($p < 0.001$), or constipation ($p < 0.001$) than avoiding risk of injection site pain.

DISCUSSION

The DCE study quantifies patient preferences for treatment attributes of CGRP inhibitors for the preventive treatment of migraine. Milder migraine severity was the most important treatment attribute, irrespective of patient demographic or clinical background, and was more important than reducing migraine frequency. The subgroup analysis suggested that an increased chance of reducing migraine frequency was especially important to patients with severe interictal burden, who placed significantly greater importance on this attribute than other patients.

A consistent treatment effect across weeks was the second most important attribute overall, potentially because it affects overall treatment effectiveness and diminishes the treatment's ability to reduce migraine severity and frequency. Especially patients who had mAbs treatment experience placed great importance on this attribute.

Mode of administration was ranked third, alongside migraine frequency. Overall, patients preferred an oral tablet every other day over injections and infusions. Previous studies in migraine[14] and other disease areas[36,37] have shown a preference of patients for oral treatment administration over injections. However, the MXL model suggested that patients' preferences are heterogeneous, and some patients may prefer an infusion over an oral administration. The subgroup analyses found that patients with previous mAbs experience placed less importance on mode of administration than other patients.

Side effects, which were described as mild and relatively unlikely to occur (5%–10% risk), were least important to participants' preferences, overall and in all subgroup analyses. It can therefore be concluded that the severity and risk of side effects was considered tolerable by participants.

Clinical implications

For clinical practice, a few key results of this study are important to highlight. Overall, attributes relating to effectiveness are the most important to patients' treatment choices. For existing CGRP drugs, current evidence suggests that treatments are similarly effective in reducing MMDs.[38–41] Milder migraine severity and consistent treatment effectiveness also make a treatment more attractive to patients; however, little trial and real-world evidence exists to support differences between treatments in terms of migraine severity and consistency of treatment benefit.

The most apparent difference between treatments is the mode of administration which may be particularly important to patients who have not previously used injectable therapy. The different formulations also have clinical considerations, as injectable treatments have a longer half-life than oral ones, complicating treatment cessation and use of concomitant medications.[42] Longer treatment cycles may lead to a waning of effectiveness. This varying treatment effectiveness within a treatment cycle was not shown in clinical trials,[43] but there is some real-world evidence that the treatment effectiveness of CGRP injectables can start to wane before the next administration.[13,19] The current study has produced evidence that suggests consistent treatment effectiveness is important to patients, this must be studied further and considered in a treatment decision.

While the side effect profile of CGRP drugs may slightly differ, i.e., only injectables can have injection site reactions and constipation is mostly reported for erenumab,[13] the side effects are usually reported as mild and infrequent.[11,44,45] However, there is concern that inhibiting CGRP may affect the cardiovascular system,[46] but so far, no evidence has been found that CGRP inhibitors are associated with serious side effects.[47] As of now, the mild side effects reported are not of concern to patients and no major driver of treatment choice.

Limitations

DCEs are a popular method for eliciting patient preferences in healthcare research, but one which relies on patients making treatment choices in a hypothetical context. When patients make real treatment decisions, their preferences may be influenced by additional clinical and emotional factors.[48,49] In a DCE, treatments are described by a selection of key attributes and a limited number of attribute levels, so choice tasks may not reflect the full range of possible treatments. Results may therefore not be generalizable for different treatment scenarios or treatments. To represent treatment

decisions as close to real-world decision-making as possible, treatment attributes were modeled after CGRP drugs available at the time of study development. The survey was developed based on evidence from qualitative interviews exploring patients' treatment experiences and tested in cognitive debriefing interviews, which confirmed that the attributes were important to patients.

Patients' experience with migraine severity varies, and in order to reflect that the attribute "migraine severity" was described as reduced migraine symptoms, which could have been interpreted differently by patients, for example as reduced pain intensity, pain duration, improved functioning, or a combination of these. It was presented as deterministic (milder versus unchanged), and the attribute "migraine frequency" as probabilistic (40% vs. 60% chance to halve migraine days). This 20%-point difference in probability to reduce migraine frequency may not have been perceived as important as a certain reduction in migraine severity. In addition, migraine frequency was presented in relation to each participant's reported MMDs. Thus, the attribute may have been more relevant to patients with more severe disease, given the greater absolute reduction in migraine days. The operationalization of these treatment attributes has likely influenced the study results.

The study sample included a higher proportion of male participants (36%), especially in the US sample (43%), than is reported in this disease area. Population-based studies suggest that around 80% of patients with migraine are female,[50] and the 1-year prevalence of migraine is three times higher in women than in men.[51,52] Women are also more likely to experience chronic migraine than men and have more severe migraine attacks.[51,53,54] A sensitivity analysis was conducted to assess the impact of sex distribution in the sample on the study results by estimating a weighted MXL model. Sampling weights were generated for each participant to achieve the population-based sex distribution of migraine. Results from the sensitivity analysis showed that patient preference results were similar even after weighting the data to account for the higher proportion of males in the study sample. Almost half of the sample was diagnosed with chronic migraine, which is higher than chronic migraine rates reported in the general migraine population in the US (7%–9%).[55] Similarly, the current study over-sampled patients with experience with mAbs treatments, which are mainly accessible to patients with more severe and frequent migraine attacks. Overall, use of preventive non-CGRP mAb migraine treatments was high; a recent US study reported that overall, 17% of patients were using preventive treatments.[56] Further, the study was conducted in the United States and Germany, and the results may not be generalizable to other countries. For these reasons, the sample may not be fully representative of the wider, global population with migraine.

CONCLUSIONS

The patient preference survey showed the value that patients place on treatment effectiveness, in particular milder migraine severity, within the context of choosing a hypothetical treatment based on different treatment characteristics of existing novel CGRP preventive migraine treatments.

AUTHOR CONTRIBUTIONS

Study concept and design: Lena T. Hubig, Tim Smith, Andrew J. Lloyd, Lauren Powell, Karissa Johnston, Linda Harris, Gilbert L'Italien, Vladimir Coric, Siu Hing Lo. *Acquisition of data*: Lena T. Hubig, Siu Hing Lo. *Analysis and interpretation of data*: Lena T. Hubig, Gin Nie Chua, Andrew J. Lloyd, Siu Hing Lo. *Drafting of the manuscript*: Lena T. Hubig, Gin Nie Chua, Siu Hing Lo. *Revising it for intellectual content*: Lena T. Hubig, Tim Smith, Gin Nie Chua, Andrew J. Lloyd, Lauren Powell, Karissa Johnston, Linda Harris, Gilbert L'Italien, Vladimir Coric, Siu Hing Lo. *Final approval of the completed manuscript*: Lena T. Hubig, Tim Smith, Gin Nie Chua, Andrew J. Lloyd, Lauren Powell, Karissa Johnston, Linda Harris, Gilbert L'Italien, Vladimir Coric, Siu Hing Lo.

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CONFLICT OF INTEREST

GL, LH, and VC are employed by and own stock/stock options in Biohaven Pharmaceuticals Inc. SHL, LTH, and GNC are employees of Acaster Lloyd Consulting Ltd. AJL is an employee and shareholder of Acaster Lloyd Consulting Ltd. Acaster Lloyd Consulting Ltd were commissioned by Biohaven Pharmaceuticals Inc to conduct the study. TS is an employee of StudyMetrix Research LLC and has received consulting fees from Biohaven Pharmaceuticals Inc in the conduct of this study. LP and KJ are employees of Broadstreet HEOR, which received payment by Biohaven Pharmaceuticals Inc in the conduct of this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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