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Interictal burden in migraine patients at the outset of CGRP monoclonal antibody prevention

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Abstract

Background The total burden of migraine includes not only the episodes with headache pain but extends throughout the interictal periods. Interictal symptoms and associated psychological responses may profoundly impact well-being and drive treatment-seeking behavior.

Methods A cross-sectional online survey was conducted with participants aged ≥ 18 years, 250 with episodic migraine (EM) and 250 with chronic migraine (CM), having ≥ 4 monthly migraine headache days. All were naïve to galcanezumab or began ≤ 6 months before survey completion. The study evaluated factors associated with the Migraine Interictal Burden Scale (MIBS-4), including social determinants of health and well-being. Multiple linear regression, logistic regression, and random forests (RF) were used to explore predictors of MIBS-4.

Results The majority of participants (90%) were female with a mean (standard deviation) age of 40.6 (± 12.0) years and 18.1 (± 12.7) years since the first migraine episode. Sociodemographically, the EM and CM groups were similar. Common comorbidities were anxiety disorder (45%) and depression (44%). Migraine family history was reported in 59% of participants. MIBS-4 was correlated with a number of diverse variables, including well-being, anxiety sensitivity, income, aura symptoms, and the worst migraine pain in the year before starting galcanezumab. Linear and logistic regression identified years since the first symptom, worst migraine attack pain, premonitory symptoms, and income as significant predictors. RF explained more of the variance than multiple linear regression and introduced additional concepts to the prediction of MIBS, identifying well-being (WHO-5 total score), the WHO-5 item "cheerful and in good spirits," worry about exercise, and fear of missing social obligations as significant predictors. Socioeconomic status and income were also critical explanatory variables for interictal burden (IIB) based on regression modeling and RF. Still, income was the only variable significantly associated with IIB across regression and RF methods.

Conclusions Interictal burden should be considered in the medical care of people with migraine. This additional burden is holistic, with psychosocial and socioeconomic elements in addition to residual symptoms. It is essential to consider this when assessing the impact of IIB.

Keywords CGRP antibody, Interictal burden of migraine, Migraine

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Introduction

Migraine is a common neurologic disease that is the second leading cause of years lived with disability overall and the leading cause among adult women less than age 50 years [1, 2]. It adversely impacts quality of life (QoL) and places a significant burden on an individual's ability to function at their best at work, at home, and socially. Nevertheless, reluctance to seek professional help is common and is associated with a lack of awareness or prior unhelpful experiences [3]. Migraine is a chronic disease characterized by episodic symptom manifestations, and assessing reductions in monthly migraine headache days is a standard primary outcome measure across clinical trials [4, 5]. However, as our understanding of the disease grows, it is becoming clear that people with migraine may also be significantly affected during headache-free phases between their headache episodes (attacks) [6].

The constellation of symptoms associated with migraine, including photophobia, phonophobia, osmophobia, nausea and/or vomiting, allodynia, fatigue, and cognitive shortcomings, can be disabling in and of itself and adversely affects QoL [7]. Notably, some of these symptoms can persist into the interictal period. People with migraine may feel anticipatory anxiety about their next migraine episode and engage in avoidance of routine activities (such as eating out, studying, or exercising) for fear of a migraine episode, or they may experience depressed mood when canceling or modifying activities in anticipation of a migraine episode [6–13]. Such interictal burden (IIB) is a key driver for people seeking medical care for migraine [7, 14–16]. In contrast, broader societal conceptualizations and stereotypes pertaining to migraine minimize the burden of the disease (e.g., migraine is "just a headache") and are mainly inconsistent with the experience of IIB. People with migraine may not even be aware that interictal symptoms can be a component of their migraine disease and can negatively impact QoL. Such social stigma may inhibit patients from seeking treatment and add to the emotional burden of migraine [16–18].

Guidelines recommend assessing health-related QoL and/or disability when evaluating the impact of migraine preventive treatments [19]. While most of these measures focus on the head pain phase of the migraine episode, there is a growing appreciation of the importance of IIB and the beneficial effect of preventive treatment on the patient's QoL [20]. We recently explored the patient's journey from their initial realization that they may have migraine through diagnosis and eventually receiving therapy with a calcitonin gene-related peptide monoclonal antibody (CGRP mAb) [3]. The aim of this exploratory study in the same sample was to assess the severity of IIB, associated contributing factors, and potential predictors of IIB many years after the diagnosis of migraine and while starting therapy with galcanezumab. The study contrasted findings in people with both episodic migraine (EM) and chronic migraine (CM).

Methods

Design

This cross-sectional survey study evaluated IIB using social determinants of health; validated measures, including the Migraine Interictal Burden Scale (MIBS-4), the Five-Item World Health Organization Well-being Index (WHO-5), and the Anxiety Sensitivity Index-3 (ASI-3); and bespoke questions in patients who enrolled in the Emgality® Patient Support Program (PSP) from March through December 2022. This program provides guidance, including an Emgality® pharmacy savings card, for eligible, commercially insured patients who were preauthorized by their healthcare provider to receive a prescription for galcanezumab. The PSP was used as a vehicle to identify and enroll participants for this survey. The therapeutic effects of galcanezumab in people with migraine were not a topic of this investigation.

Participants

The inclusion and exclusion criteria have been described in detail in a previous publication [3]. In brief, participants were ≥ 18 years of age and diagnosed with migraine. Enrollment in the Emgality® PSP required confirmation of diagnosis by a healthcare professional and the participant to be a candidate for a galcanezumab prescription. The study did not verify if the diagnosis of migraine strictly adhered to the International Classification of Headache Disorders-3 [21] criteria. The PSP site required participants to register with an email address and sign a Health Insurance Portability and Accountability Act of 1996 (HIPAA) agreement. Consequently, this provided a means to contact potential participants who either recently started on galcanezumab or were about to begin taking galcanezumab. Participants also had to be naïve to galcanezumab or to have initiated galcanezumab ≤ 6 months before survey completion, have a diagnosis of migraine from their physician, and self-report having at least 4 migraine days in the past month. Recruitment was limited to 500 participants. We used quota sampling to ensure equal numbers of patients to compare EM (4 to < 15 headache days per month) and CM (≥ 15 headache days per month) (i.e., 250 participants each).

MIBS-4

The MIBS-4 is a four-item, patient-reported outcome (PRO) questionnaire that measures the domains of impairment in school or work, family and social life,

and emotional, affective, and cognitive distress. The four items are (1) "My headaches affect my work or school at times when I do not have a headache"; (2) "I worry about planning social or leisure activities because I might have a headache"; (3) "My headaches impact my life at times when I do not have a headache"; and (4) "At times when I do not have a headache, I feel helpless because of my headaches." The recall period is the past 4 weeks. For each item, the respondent indicates "Don't know or N/A" (scored as 0), "Never" (scored as 0), "Rarely" (scored as 1), "Some of the time" (scored as 2), "Much of the time" (scored as 3), or "Most or all of the time" (scored as 3) [8]. The scores for each question are added together to compile a total MIBS-4 score, where higher scores indicate a more significant disease burden. This is a validated instrument that measures the burden of migraine between episodes [8, 22]. The Cronbach's alpha was 0.85 in this study.

Bespoke IIB questions

The bespoke IIB questions were a set of six questions developed to assess IIB, including its impact on hobbies and exercise. The bespoke IIB questions were developed after the MIBS to ask about additional issues. These questions are as follows: "I worried about missing upcoming social obligations because of migraine attacks"; "I canceled upcoming social obligations because of my fear of migraine attacks"; "I had less energy for my job or schoolwork"; "I was afraid of the impact of migraine on my job or schoolwork"; "I worried about being unable to do my usual hobbies because of migraine attacks"; and "I worried about being unable to exercise because of migraine attacks." The participants were instructed to think back to the year before they started using galcanezumab (or the past year if they had not yet started galcanezumab) and to answer questions based on the interictal period, referring to any potential upcoming migraine attacks. The response options to each question were "Never," "Rarely," "Sometimes," "Often," and "Always" and referred to the periods in between migraine episodes (on days when the participant did not have a migraine). The number of participants who chose each response was tallied. The questions were tested in a small pilot study that included 6 patients with migraine.

In addition to the bespoke IIB questions, participants also answered questions related to sociodemographic data and migraine disease, including symptoms, the path to diagnosis, experiences, and previous treatments. Responses to these questions were recently published [3]. Each participant's social vulnerability index (SVI) was based on their ZIP code, which was mapped to US census data SVI tables. The mean SVI was chosen when there was more than one SVI for a given ZIP code.

WHO-5

The WHO-5 is a PRO measure of psychological well-being [23]. The respondent is asked to rate five items: (1) "I have felt cheerful and in good spirits"; (2) "I have felt calm and relaxed"; (3) "I have felt active and vigorous"; (4) "I woke up feeling fresh and rested"; and (5) "My daily life has been filled with things that interest me." Respondents score how well each item applied to them over the previous 2-week recall period using a scale of 0 (at no time) to 5 (all the time). The sum of the raw scores, ranging from 0 to 25, is multiplied by 4 such that the index ranges from 0 (absence of well-being) to 100 (maximal well-being) [23, 24]. Whereas this instrument has been validated and is applicable across several study fields [24, 25], it has not been explicitly validated in patients with migraine. The Cronbach's alpha was 0.90 for this study.

ASI-3

The ASI-3 assesses the different concerns participants may have regarding their anxiety sensitivity based on responses to 18 questions, e.g., "It is important for me not to appear nervous" and "When I cannot keep my mind on a task, I worry that I might be going crazy" [26, 27]. This instrument does not specify a recall period and measures how the participant is feeling at the moment they are responding to the questionnaire. Respondents indicate on a 5-point scale (0 = very little, 1 = a little, 2 = some, 3 = much, 4 = very much) the number that best describes each of the 18 items' typical or characteristic for them. Scores for each item are added and can range from 0 to 72. Scores of 0 to 17 indicate almost no anxiety sensitivity, 18 to 35 indicate low anxiety sensitivity, 36 to 53 indicate moderate anxiety sensitivity, and 54 to 72 indicate high anxiety sensitivity [26, 27]. This instrument has been validated [26, 27]. The Cronbach's alpha was 0.93 for this study.

Statistical analyses

Descriptive statistics were calculated for sociodemographic and clinical characteristics; bespoke IIB questions, including item responses on IIB; the patient's previous understanding of migraine; migraine experience; and management. Mean, median, standard deviation (SD), and range were used for continuous variables. Frequency and percentages were used for categorical variables, and t-tests were used to compare mean MIBS-4 scores between groups (EM vs CM).

This study used three broad techniques to evaluate variables associated with IIB: multiple linear regression, logistic regression, and a form of machine learning known as random forests analysis (RF). These

variables were chosen empirically based on our clinical experience and past migraine research.

Multiple linear regression

We evaluated predictors using the MIBS-4 score in a series of regression analyses, using forward stepwise and backward elimination techniques. We then conducted a series of logistic regression analyses, where each of the six individual bespoke IIB questions was used as an outcome variable with multiple categories, and the results indicated the probability of moving from one category to the next. These analyses used a subset of study variables that could be related to IIB as predictors. Associations between IIB, participant demographic, migraine, or social characteristics were first evaluated with correlational analyses with the correlation coefficients estimating the degree of the linear (straight-line) relationship between the two variables. This is a standard step in regression analysis to evaluate whether there may be redundant variables in the dataset.

For the regression models, categorical variables were dummy-coded into dichotomous variables based on the distribution of responses (e.g., race: White vs non-White). The correlations were used to determine the strength of linear associations between IIB and the variables of interest for the overall study sample and by EM and CM diagnoses. Point-biserial correlations were used to examine the relationship between categorical variables and MIBS-4 scores. Pearson correlations were used to compare continuous variables and the MIBS-4 scores. All variables of interest were included in the regression analysis.

Some categorical variables were recoded for the regression models to make them more ordinal. For example, employment status categories, such as unemployed and retired, were combined to reflect not working. The forward stepwise models were constructed using adjusted R^2, such that the variable was added at each step, which maximized the adjusted R^2. The final model regarding goodness of fit was evaluated using R^2 and root mean square error. This process was repeated for the EM and CM subgroups.

As another exploratory step, a backward elimination regression model was run, where all variables of interest were entered on the first step. The variable with the highest p-value was removed from the model, and this process was repeated until all variables in the model had a p-value below a given threshold (e.g., $p < 0.1$). This was conducted to predict the MIBS-4 score using the entire study sample and separated by EM and CM subgroups.

Logistic regression

We then conducted a series of logistic regression analyses, where each of the six individual bespoke IIB questions was used as an outcome variable with multiple categories, and the results indicated the probability of moving from one category to the next. These analyses used the predictors from the final multiple regression forward stepwise model.

Non-significant variables were removed from the model.

RF analysis

Random forests [28–30] were used to identify IIB severity. This analysis was a nonparametric, hypothesis-free approach that used all available data to develop predictions about IIB across the entire dataset, using the MIBS-4 score as the outcome of interest. Analyses were run utilizing the R package randomForest (RF; Salford Systems, San Diego, CA) [31] in regression mode. The purpose was to reduce the set of potential predictor variables to a smaller one while retaining predictive accuracy. The variable importance measure used was the percent increase in mean square error (% Inc MSE) resulting from the random permutation of the values of the variable. Noise variables were defined as those with % Inc MSE less than the absolute value of the most negative % Inc MSE and equally distributed about the "zero importance" point. For some categorical variables (e.g., race) for which the instructions were "Check all responses that apply", response options were recoded as dichotomous (e.g., Black = 1, not Black = 0). Since the RF package requires complete data, missing values induced by skip patterns in the survey were assigned responses based on the logic of the skip. Accordingly, if a participant did not complete a set of questions because they answered "No" to a screening question, their responses to the subquestions were all assigned a score of "0". A small number of additional missing responses were singly imputed to the median response of the entire sample.

Three analytic paths were followed: first, a preliminary analysis was performed using all 549 variables as a starting point; a second analysis was performed with the 41 variables of interest previously identified in the SAP (Supplemental Table 1); and a third analysis was performed with 545 variables from the entire dataset excluding the four individual MIBS-4 items. Noise variables were removed, and runs were repeated as needed.

Results

Participant flow

A total of 19,088 prospective participants who enrolled in the PSP between March and December 2022 were

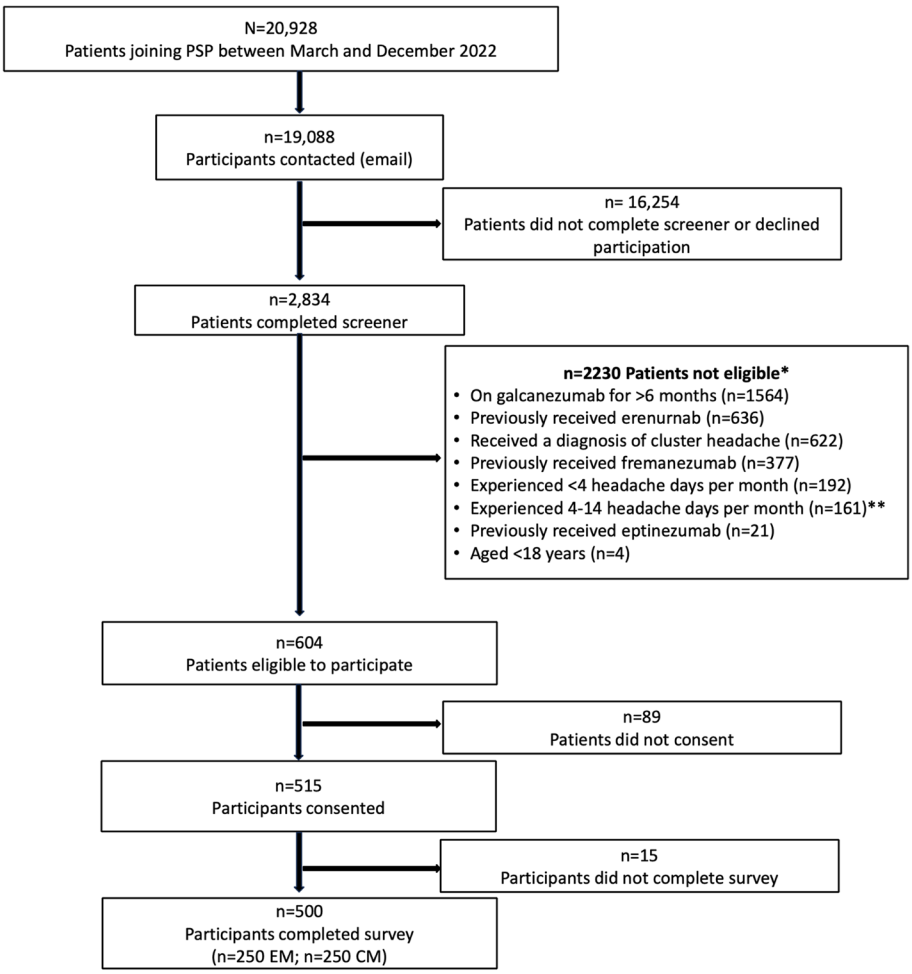

Fig. 1 The disposition of participants is presented. *Some respondents were disqualified on more than 1 criterion. **Respondents were only ineligible once the EM quota ($n = 250$) was reached. Abbreviations: CM = chronic migraine; EM = episodic migraine; PSP = Patient Support Program

contacted. Of these, 2834 completed screenings, 604 were deemed to be eligible to participate (Fig. 1), 515 provided informed consent, and 500 (250 who self-identified as having EM and 250 with CM) completed the survey.

These 500 participants comprised the analytic sample. These 500 participants included 6 participants who had not yet started galcanezumab, and 494 who did. Consequently, the results were combined because n = 6 was not a sufficient sample size to characterize.

Participant characteristics

Most of the participants were women (90%; n/N = 450/500) and White (90%; n/N = 448/500). Most (92%; n/N = 459/500) had at least some college education, and 73% (n/N = 366/500) were employed full-time (Table 1). The mean age of the participants at the time of the survey was 40.6 (± 12.0) years, and the mean time since the first migraine episode was 18.1 (± 12.7) years. Participants were, on average, 26.2 (range: 3 to 73 years) years of age when they were diagnosed with migraine. The sociodemographic characteristics of the participants who were characterized as having EM and CM at the time of the survey were similar (Table 1).

The most common comorbidities reported were anxiety disorder in 45% (n/N = 225/500) and depression in 44% (n/N = 218/500) (Table 1). A migraine family history (immediate family member with migraine) was present in 59% (n/N = 295/500) of the participants. At the time of the survey, 6 participants had not initiated galcanezumab, while 494 participants had been on galcanezumab for a mean of 4.6 ± 2.1 months (median of 4 months). A full description of the participant demographics and disease characteristics has been disclosed previously [3].

Table 1 Sociodemographic and clinical characteristics

	Overall (*N* = 500)	EM (*N* = 250)	CM (*N* = 250)
Female, n (%)	450 (90.0)	228 (91.2)	222 (88.8)
Age in years, mean (SD)	40.6 (12.0)	41.1 (11.7)	40.1 (12.4)
White, n (%)	448 (89.6)	221 (88.4)	227 (90.8)
Not Hispanic or Latino, n (%)	459 (91.8)	228 (91.2)	231 (92.4)
Employed, full-time, n (%)	366 (73.2)	191 (76.4)	175 (70.0)
Time since first symptom in years, mean (SD)	18.1 (12.7)	18.7 (12.9)	17.4 (12.5)
Most common highest education level (Top 3), n (%)			
Some college, no degree	83 (16.6)	41 (16.4)	42 (16.8)
Bachelor's degree	154 (30.8)	81 (32.4)	73 (29.2)
Master's degree	97 (19.4)	47 (18.8)	50 (20.0)
Most common comorbidities (top 3), n (%) [a]			
Anxiety disorder	225 (45.0)	108 (43.2)	117 (46.8)
Depression	218 (43.6)	98 (39.2)	120 (48.0)
Hay fever/Seasonal or year-round allergies	133 (26.6)	64 (25.6)	69 (27.6)
Number of migraine headache days per month before galcanezumab, n (%)			
4 to 7	93 (18.6)	93 (37.2)	0 (0.0)
8 to 14	157 (31.4)	157 (62.8)	0 (0.0)
15 or more	250 (50.0)	0 (0.0)	250 (100.0)
Migraine in immediate family, n (%)	295 (59.0)	158 (63.2)	137 (54.8)

Abbreviations: *CM* chronic migraine, *EM* episodic migraine, *SD* standard deviation

[a] Responses are not mutually exclusive

Table 2 Interictal burden, well-being and anxiety sensitivity scale scores (*N* = 500)

	Total (*N* = 500)	EM (*N* = 250)	CM (*N* = 250)
MIBS-4 score			
Mean (SD)	4.3 (3.2)	3.8 (3.0)	4.8 (3.4)
Median (range [min, max])	4.0 (0.0–12.0)	4.0 (0.0–12.0)	5.0 (0.0–12.0)
T-test (p-value)[a]		0.0005	
Well-being index (WHO-5) scores			
Mean (SD)	57.3 (19.2)	58.0 (18.4)	56.6 (19.9)
Median (range [min, max])	60.0 (0.0–100.0)	60.0 (0.0–100.0)	60.0 (0.0–100.0)
T-test (*p*-value)[a]		0.4022	
Anxiety Sensitivity Index 3 (ASI-3)			
Mean (SD)	18.5 (14.4)	17.8 (13.9)	19.1 (14.9)
Median (range [min, max])	15.0 (0.0–72.0)	15.0 (0.0–72.0)	16.0 (0.0–67.0)
T-test (*p*-value)[a]		0.2885	

Abbreviations: *CM* chronic migraine, *EM* episodic migraine, *MIBS-4* Migraine Interictal Burden Scale, *SD* standard deviation, *WHO-5* World Health Organization Well-Being Index

[a] T-test compared scores for EM vs CM

MIBS-4 scores

The overall mean (SD) MIBS-4 total score was 4.3 (3.2), indicating moderate to severe IIB on average. The total MIBS-4 for patients with CM was significantly greater ($p = 0.0005$) than for those with EM (Table 2).

More than 60% of participants overall, as well as within the EM or CM groups, reported moderate to severe IIB (Fig. 2). A higher proportion of patients with CM (53.2%) than with EM (39.6%) reported severe IIB. A slightly greater proportion of patients with EM (18%) than those with CM (14%) reported no IIB.

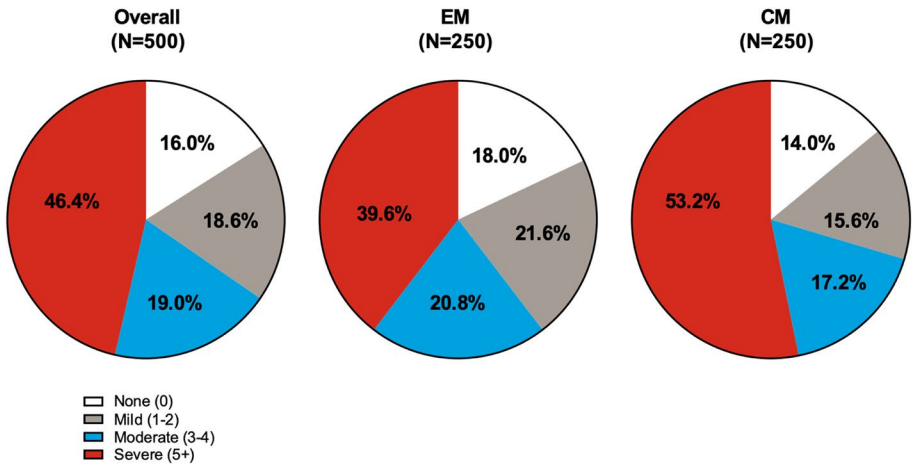

Fig. 2 The proportion of participants with no (MIBS-4 score 0), mild (MIBS-4 score 1–2), moderate (MIBS-4 score 3–4), and severe (MIBS-4 score ≥ 5) IIB are presented for the overall population and for participants with EM or CM. Abbreviations: CM = chronic migraine; EM = episodic migraine; IIB = interictal burden; MIBS-4 = Migraine Interictal Burden Scale

At the item level, almost five times as many participants with CM (n = 14/250; 5.6%) than participants with EM (n = 3/250; 1.2%) indicated that headaches affect their work or school at times when they do not have a headache "Most or all of the time." Just over three times as many participants with CM (n = 28/250; 11.2%) than participants with EM (n = 9/250; 3.6%) noted that at times when they do not have a headache, they feel helpless because of their headaches "Much of the time."

Bespoke IIB questions

The dimensions of IIB were explored in patients with EM and CM using the bespoke IIB questions (Table 3). For the item that asked how regularly they worried about missing upcoming social obligations because of migraine attacks, the most frequently reported response was "Sometimes" for participants with EM (41.2%; n/N = 103/250) and "Often" for participants with CM (42.8%; n/N = 107/250). For the item about canceling upcoming social obligations because of the fear of migraine attacks, the most common response was "Rarely" for the EM group (29.2%; n/N = 73/250) and "Sometimes" for the CM group (29.6%; n/N = 74/250). One item asked participants how frequently they had less energy for their jobs or school work, and 43.2% of the EM cohort (n/N = 108/250) noted that this happened "often", while 39.6% of the CM cohort (n/N = 99/250) indicated that this was "always" the case. Almost one-third of the CM cohort (n/N = 67/250; 26.8%) reported that they "always" worried about being unable to do usual hobbies because of migraine attacks, whereas only 11.2% (n = 28/250) of EM reported this. For the final item, 22.4% of the CM population (n/N = 56/250) indicated that they "always" worried about being unable to exercise because of migraine attacks, compared to only 10.0% of the EM population (n/N = 25/250).

WHO-5

The mean WHO-5 score for the overall sample was 57.3 ± 19.2 (Table 2). The median score was 60.0, and scores ranged from 0.0 to 100.0. The most popular response was feeling cheerful, "Some of the time" (n = 210/500, 42.0%). The most frequently reported response for item two was feeling calm and relaxed "Less than half of the time" (186/500; 37.2%). Thirty percent of the total sample reported that they felt active and vigorous "Less than half of the time" (n = 150/500; 30.0%), and 27% percent of the total sample (n = 135/500) indicated that they woke up feeling fresh and rested "More than half of the time." For the final item regarding how often the participants' lives were filled with things that interest them, the most common response was "Less than half of the time" (n = 169/500; 33.8%), followed by "Some of the time" (n = 165; 33.0%). There were no significant differences in WHO-5 score between participants with EM and those with CM (Table 2).

ASI-3

The mean ASI-3 score for the total population was 18.5 ± 14.4 (Table 2). The scores ranged from 0.0 to the maximum possible score of 72.0, with a median score of 15.0. This indicates a low amount of anxiety sensitivity. For the first item, 28.6% (n = 143/500) of the total sample indicated that they placed "much" importance on not appearing nervous, making this the most frequently reported response. For the third item, participants indicated most frequently that they felt "a little" scared when

Table 3 Bespoke interictal burden questions

I worried about missing upcoming social obligations because of migraine attacks, n (%)	
Never	29 (5.8%)
Rarely	55 (11.0%)
Sometimes	159 (31.8%)
Often	182 (36.4%)
Always	75 (15.0%)
I canceled upcoming social obligations because of my fear of migraine attacks, n (%)	
Never	102 (20.4%)
Rarely	126 (25.2%)
Sometimes	134 (26.8%)
Often	112 (22.4%)
Always	26 (5.2%)
I was afraid of the impact of migraine on my job or schoolwork, n (%)	
Never	12 (2.4%)
Rarely	27 (5.4%)
Sometimes	112 (22.4%)
Often	187 (37.4%)
Always	162 (32.4%)
I had less energy for my job or schoolwork, n (%)	
Never	10 (2.0%)
Rarely	21 (4.2%)
Sometimes	115 (23.0%)
Often	206 (41.2%)
Always	147 (29.4%)
Missing	1 (0.2%)
I worry about being unable to do my usual hobbies because of migraine attacks, n (%)	
Never	25 (5.0%)
Rarely	43 (8.6%)
Sometimes	142 (28.4%)
Often	195 (39.0%)
Always	95 (19.0%)
I worry about being unable to exercise because of migraine attacks, n (%)	
Never	40 (8.0%)
Rarely	75 (15.0%)
Sometimes	154 (30.8%)
Often	150 (30.0%)
Always	81 (16.2%)

their heart beat rapidly (n = 139/500; 27.8%). The most frequently reported response for the rest of the items that make up the ASI-3 was "Very little," which is the lowest level of anxiety sensitivity that can be reported on this scale. There was no significant difference ($p = 0.2885$) in ASI-3 score between participants with EM and those with CM (Table 2).

Association between items that evaluate IIB and variables of interest

For the full sample, higher MIBS-4 scores were associated with lower WHO-5 scores ($r = -0.36$; $p < 0.0001$). Conversely, higher MIBS-4 scores were associated with higher ASI-3 scores ($r = 0.31$; $p < 0.0001$). Weaker but significant correlations were observed between the MIBS-4 and lower income, lower incidence of aura symptoms, and higher rates of worse migraine pain in the year before starting galcanezumab (Table 4). For the EM cohort, the MIBS-4 also correlated moderately with the WHO-5 and the ASI-3. The MIBS-4 correlated significantly, although weakly, with education, age, and years since disease onset. In the subgroup of participants with CM, MIBS-4 correlated with the WHO-5 and the ASI-3 and with the presence of aura symptoms, income, and

Table 4 Correlations between MIBS-4 scores and variables of interest

	r[a]	*p*-Value[b]
Path to diagnosis		
Years since first symptom	−0.14586	0.0011
Reluctance to seek professional help (yes/no)	−0.03123	0.5564
Believed migraines were due to factors within their control (yes/no)	−0.03989	0.3735
Previous migraine experience and management prior to starting galcanezumab		
Attack duration	0.13037	0.0035
Average migraine attack pain	0.16174	0.0003
Worst migraine attack pain	0.16996	0.0001
Premonitory symptoms (yes/no)	−0.10557	0.0183
Aura symptoms (yes/no)	−0.18127	< 0.0001
Use of OTC pain medication (yes/no)	−0.06582	0.1417
Use of prescription pain medication (yes/no)	−0.00132	0.9765
Use of prescription preventive medication (yes/no)	−0.06781	0.1300
Well-being (WHO-5) and sensitivity to anxiety (ASI-3) scores		
WHO-5 score	−0.35681	< 0.0001
ASI-3 score	0.31032	< 0.0001
Selected social determinants of health		
Income	−0.18440	< 0.0001
Employment status[c]	0.02149	0.6324
Education[c]	−0.11716	0.0087
Sex	−0.00867	0.8468
Ethnicity	−0.11023	0.0142
Age	−0.12153	0.0065
SVI percentile ranking for socioeconomic status (by location ZIP)	−0.00676	0.8808
SVI percentile ranking for household characteristics (by location ZIP)	−0.02316	0.6072
SVI percentile ranking for racial and ethnic minority status (by location ZIP)	0.00432	0.9236
SVI percentile ranking for housing type/transportation (by location ZIP)	0.01186	0.7923
SVI overall percentile ranking (by location ZIP)	−0.00171	0.9698

Abbreviations: *ASI-3* Anxiety Sensitivity Index, *CM* chronic migraine, *EM* episodic migraine, *OTC* over the counter, *SVI* social vulnerability index, *WHO-5* World Health Organization Well-Being Index

[a] Spearman's rank sum correlations

[b] Significance levels for correlation p-values

[c] Encoding adjusted for employment and education to make them meaningful as ordinals

average migraine attack pain in the year before starting galcanezumab.

Predicting IIB as per MIBS-4 with multiple linear regression analyses

In the forward stepwise linear regression, the significant variables in the regression that predicted MIBS-4, in order of importance (based on unstandardized estimates), were socioeconomic status (b = −4.56; 95% confidence interval [CI]:−8.2, −0.9), total WHO-5 score (b = −0.06; 95% CI:−0.08, −0.04), aura symptoms (b = 0.86; 95% CI:0.21, 1.51), worse migraine attack pain (b = 0.5; 95% CI:0.19, 0.81)), and income (b = −0.16; 95% CI:−0.30, −0.01) (Table 5). The R^2 value was 0.33, the adjusted R^2 (total variance explained) was 0.30, and the mean square error was 2.71.

The backward elimination regression analysis produced similar results (table not shown). In this case, the R^2 value was 0.30, the adjusted R^2 was 0.28, and variables remaining in the model were socioeconomic status, WHO-5, years since diagnosis, worse migraine attack pain, aura symptoms, and premonitory symptoms. Income showed a trend towards significance ($p = 0.067$).

Predicting IIB as per bespoke IIB questions with logistic regression analyses

Logistic regressions were performed using individual bespoke IIB questions instead of the MIBS-4 as the outcome variables and the significant variables from

Table 5 Regression model predicting MIBS-4 score—final model from forward selection by adjusted R^2

Parameter	Estimate	SE	Lower 95% CI	Upper 95% CI	Standardized Estimate	*p*-Value
Years since first symptom	−0.02	0.01	−0.05	0.00	−0.09	0.0613
Attack duration	0.14	0.10	−0.06	0.34	0.07	0.1595
Worse migraine attack pain	0.50	0.16	0.19	0.81	0.16	0.0016
Premonitory symptoms (yes/no)	0.59	0.32	−0.04	1.22	0.09	0.0662
Aura symptoms (yes/no)	0.86	0.33	0.21	1.51	0.13	0.0098
Use of prescription preventive medication (yes/no)	0.68	0.53	−0.36	1.71	0.06	0.2009
ASI-3 score	0.02	0.01	−0.01	0.04	0.08	0.1312
WHO-5 score	−0.06	0.01	−0.08	−0.04	−0.36	< .0001
Income	−0.16	0.07	−0.30	−0.01	−0.11	0.0341
Employment status[a]	0.12	0.08	−0.05	0.28	0.07	0.1604
Education[a]	0.13	0.09	−0.05	0.30	0.07	0.1561
Ethnicity (yes/no – Hispanic)	0.97	0.64	−0.29	2.23	0.07	0.1342
SVI percentile ranking for socioeconomic status (by location ZIP)	−4.56	1.87	−8.22	−0.90	−0.37	0.0153
SVI overall percentile ranking (by location ZIP)	3.35	1.99	−0.55	7.25	0.25	0.0935

Abbreviations: *ASI-3* Anxiety Sensitivity Index, *CI* confidence interval, *SE* standard error, *SVI* social vulnerability index, *WHO-5* World Health Organization Well-Being Index

[a] Encoding adjusted for employment and education to make them meaningful as ordinal

the multiple regressions as the predictors. The results across the six questions were similar. For example, the logistic regression model for predicting worry about missing upcoming social obligations showed that a significant odds ratio (OR) of 0.98 (95% CI: 0.97, 0.99; $p = 0.006$) was found for "Years since first symptom." The model also predicted that increasing "Worse migraine attack pain" significantly increases the likelihood of increased worry about missing social obligations (OR:1.62; 95% CI: 1.37, 1.92; $p < 0.001$). A significant OR of 2.21 (95% CI; 1.56, 3.13; $p < 0.001$) was observed for "Premonitory symptoms," suggesting that the presence of these symptoms also increases the likelihood of worry about social events. Finally, an OR of 0.9 was found for income (95% CI: 0.83, 0.97; $p = 0.004$), suggesting that increasing income decreases the chance of worrying about upcoming social obligations. Significant ORs suggesting associations in the same directions as those seen in the model described above were observed in the models for predicting worry about canceling social obligations, fear about the impact on job/schoolwork, and having less energy for job/schoolwork.

Predicting IIB with RF analyses

As a test of the method, the preliminary RF analysis in the RF all-variables pathway (549) easily found the four questions comprising the MIBS score, explaining virtually all the variance (97.56%). When those four individual MIBS items were excluded, the variance explained decreased to 35.25%, with the WHO-5 raw score dominating the list of 37 variables important to the prediction (Table 6). Income was 12th in importance, the SVI based on household characteristics based on ZIP code was 30th in importance, and the SVI socioeconomic status theme was ranked 35th in importance in the RF analysis. Smaller subsets of variables also had good predictions, but the overall accuracy dropped as variables were dropped, indicating that even the less-important variables in this predictor set were still contributing to the overall prediction (a phenomenon called entanglement). The analysis pathway based on the preidentified variables of interest (Supplemental Table 1) could only explain 21.2% after removing noise variables, which was not high enough to warrant further investigation.

In summarizing the results of the modeling, four variables were consistently found to predict the MIBS across linear and logistic regression: "Years since first symptom," "Worse migraine attack pain," "Premonitory symptoms," and "Income." The RF analysis and linear regression analyses suggested that well-being (WHO-5 total score and items) was among the most important predictors of MIBS. The RF analysis also identified the importance of anxiety sensitivity. RF also provided granularity into premonitory symptoms by suggesting the importance of yawning and sensory aura symptoms before

Table 6 RF—final model reduced from all-variables set

Variables	Variance Explained: 35.25%	% Inc MSE[a]
1	WHO-5 total score	1.114
2	Worried about exercise (bespoke IIB question)	0.450
3	WHO-5 item 1: cheerful and in good spirits	0.448
4	Canceled social obligations due to fear of migraine attacks (bespoke IIB question)	0.399
5	Worried about missing social obligations (bespoke IIB question)	0.398
6	Personal relationships changed	0.207
7	ASI-3 Cognitive Concern Scale	0.189
8	Could not progress in career	0.181
9	WHO-5 item 2: calm and relaxed [b]	0.174
10	WHO-5 item 4: Woke up feeling fresh [b]	0.173
11	WHO-5 item 3: active and vigorous [b]	0.166
12	Income [b]	0.162
13	ASI-3 Physical Concern Scale	0.158
14	ASI-3 total score	0.142
15	Relaxation techniques used to manage migraine attacks	0.140
16	Worried about hobbies (bespoke IIB question)	0.112
17	Anxiety/Sensitivity Index Q2 [c]	0.108
18	Balance impairment on non-migraine days	0.102
19	Anxiety/Sensitivity Index Q3 [d]	0.099
20	Number of HCPs visited before diagnosis	0.097
21	Light sensitivity on non-migraine days	0.094
22	Experience visual disturbances with attack	0.091
23	Anxiety/Sensitivity Index Q5 [f]	0.083
24	Anxiety/Sensitivity Index Q4 [e]	0.083
25	Average pain before galcanezumab	0.076
26	Had less energy for my job or schoolwork	0.074
27	Afraid of impact on job/school (bespoke IIB question)	0.069
28	Sensory aura symptoms before galcanezumab	0.066
29	Aura before a migraine attack	0.065
30	Percentile ranking for SVI "household characteristics" (by ZIP code)	0.056
31	Adjust fluid intake to manage migraine attacks	0.047
32	Premonitory symptom: Drowsiness	0.043
33	Premonitory symptom: Dizziness	0.041
34	Anxiety/Sensitivity Index Q16 [g]	0.038
35	Percentile ranking for SVI "socioeconomic status" theme summary	0.032
36	No symptoms on non-migraine days	0.031
37	Pain sensitivity on non-migraine days	0.017

All variables set included 545 variables (the entire survey) except for the individual MIBS-4 items

Abbreviations: *ASI-3* Anxiety Sensitivity Index, *HCP* healthcare professional, *IIB* interictal burden, *MIBS-4* Migraine Interictal Burden Scale, *Q* question, *RF* random forest, *SVI* social vulnerability index, *WHO-5* World Health Organization Well-Being Index

[a] % Inc MSE: a measure of relative variable importance, equal to the percentage increase in mean square error after the variable's values were randomly permuted

[b] Variable imputed for some respondents

[c] Anxiety/Sensitivity Index Q2: "When I cannot keep my mind on a task, I worry that I might be going crazy"

[d] Anxiety/Sensitivity Index Q3: "It scares me when my heart beats rapidly"

[e] Anxiety/Sensitivity Index Q4: "When my stomach is upset, I worry that I might be seriously ill"

[f] Anxiety/Sensitivity Index Q5: "It scares me when I am unable to keep my mind on a task"

[g] Anxiety/Sensitivity Index Q16: "When I have trouble thinking clearly, I worry that there is something wrong with me"

starting galcanezumab. Worse migraine attack pain was expressed as average pain before galcanezumab. Income was the only variable in the dataset that was significantly associated with IIB across regression ($p < 0.10$) and RF methods.

Discussion

The most important set of findings in this study shows that 65% of participants experienced a moderate or severe level of IIB and that there is a broad set of variables associated with IIB. IIB is not merely a consequence of residual migraine symptoms, although they are relevant, but is also affected by socioeconomic status, income, and anxious avoidance of desirable activities. Therefore, a clinical approach that considers the patient's symptoms as well as psychosocial context is likely to be the most successful for treatment optimization.

This study showed that migraine is often associated with substantial IIB in people with longstanding migraine; 65% of participants reported moderate or severe IIB. At the time people with migraine enrolled in this survey were treated with a CGRP-mAb (18 years after their first symptoms), the majority was still worried about their migraine episodes impacting personal and social activities. These worries were more common in those with CM. Socioeconomic status and income were among the explanatory variables for IIB based on both regression modeling and RF. Well-being, as assessed by the WHO-5, and the bespoke IIB questions regarding worry about exercise and fear of missing social obligations were important explanatory variables for IIB when considered in the context of all 37 variables based on RF techniques.

There were positive, significant correlations between the MIBS-4 and some of the variables of interest, particularly for "Worse migraine pain," "Average migraine pain," "Duration of an episode," and "Presence of premonitory symptoms." These observations are to be expected, as greater intensity of migraine episodes would reflect an increase in the burden of each episode. This fact could justify an increase in the MIBS-4 score, since MIBS-4 questions are much related to anticipation of upcoming attacks.

However, our analysis clearly showed that other variables besides migraine symptoms were associated with IIB. For example, there was a highly significant inverse correlation between the WHO-5 and MIBS-4 scores, indicating that patients who are most affected interictally by migraine have worse well-being scores.

Additionally, higher ASI-3 scores correlated significantly with higher MIBS-4 scores. The ASI-3 is not a measure of anxiety itself; rather, it is intended to capture sensitivity to anxiety in general. Anxiety sensitivity can be defined as the fear of anxiety-related arousal sensations, harmful physical, cognitive, and socially observable consequences that may be interpreted by the subject as having potential consequences such as death, insanity, or social rejection [27]. Thus, anxiety sensitivity can be an amplifier of anxiety: when subjects with high anxiety sensitivity become anxious, they fear their arousal sensations and become even more anxious [27]. In a study of 2350 individuals (644 without headache, 903 with migraine, and 803 with tension-type headache), the ASI-3 index was shown to be distinct between primary headache diagnostic groups and to predict symptomatology and disability and was associated with greater perceived susceptibility to headache triggers [32]. Higher scores from all three ASI-3 subscales were significant univariate predictors of higher headache-related disability, which showed a strong positive relationship with headache frequency and severity. Moreover, the variance in disability that was accounted for by anxiety sensitivity far exceeded that attributable to depression and anxiety combined [32]. Taken together, these data suggest that anxiety sensitivity is a key indicator of migraine burden as well as IIB.

Some variables related to the social determinants of health were shown to be associated with IIB. To the best of our knowledge, this study is the first to find a correlation between IIB, income, and education. Although some reports suggest that there is an increased risk of migraine among people with less education and lower income in the US [33–35], these findings have not been confirmed [36, 37]. Knowledge about the impact of socioeconomic factors on migraine prevalence is limited by the fact that most studies come from the wealthiest countries [38]. The social causation hypothesis, incorporating poorer diets and worse lifestyles, could explain these income-related migraine prevalence discrepancies [39]. In terms of migraine impact severity, the 2005 American Migraine Prevalence and Prevention survey showed that people with CM had significantly lower income levels, were less likely to be employed full-time, and were more likely to be occupationally disabled than those with EM [40]. Different epidemiological studies show that disability is greater with CM than with EM [41, 42].

A recent analysis of data from the OVERCOME (US) study found that the severity of migraine per migraine headache days is correlated to the severity of IIB, as measured by MIBS-4 [16]. Similarly, in our study the severity of IIB was significantly greater in participants with CM when compared to those with EM, even though the occurrence of IIB in both groups was nearly the same. Only 18% of participants with EM and 14% of those with CM reported no IIB. However, the machine-learning

model suggested that the episodic vs chronic distinction was a noise variable that did not contribute to the variance in predicting IIB in patients. Thus, we suggest that migraine frequency alone should not be a consideration in determining IIB risk in patients with migraine.

The RF analyses identified predictive variables that required the support of less-important variables for an acceptable level of accuracy and revealed a complex, interrelated picture of predictors of IIB. We view the RF predictor set as perhaps more reliable than regression because RF makes no assumptions about the data and handles large numbers of potential predictors with ease, allowing an unlimited number of interactions. RF analyses are harder to interpret but may provide a more accurate picture of the complexity of IIB. Still, the regression results provided a consistent picture of IIB in this sample, and the variables identified across these techniques could be a fruitful source of hypotheses in future research.

Across all models, well-being was consistently the variable most strongly associated with IIB. Clearly, the presence of IIB contributes to worse well-being in patients with migraine. In other studies, semi-structured qualitative interviews [43] and online surveys [44] showed that migraine largely affects personal relations. For example, in the survey, 55% of people with migraine reported a fear of the next attack, and more than 80% felt compromised in their private, social, and professional lives [44]. People with migraine frequently experience poor understanding and consideration of the disease in their relationships [45]. Furthermore, studies have shown that the stigma associated with migraine is substantial [16, 45], which is consistent with our findings; many participants reported not seeking care because of fear of not being considered seriously by the healthcare provider. We suggest that at least part of the negative experiences imposed by migraine are associated with IIB, which is not well recognized, earning migraine the label of "the invisible disease" [45].

The linear regression analyses identified socioeconomic factors, level of well-being, selected migraine symptoms, and income as relevant predictors of IIB. The logistic regressions confirmed that disease characteristics (symptoms and duration) and income were important predictors of aspects of IIB. The RF analysis also confirmed the relevance of select disease symptoms as well as income to IIB and identified several other variables important to predicting IIB in people with migraine, especially socioeconomic status, and well-being. RF also revealed some additional nuances, such as anxiety sensitivity and the impact of migraine on work and relationships. We suggest that the ASI-3 be included in evaluating migraine patients and their treatment outcomes. We believe that the present study provides insights into how clinicians can appreciate that IIB is an important determinant of poor QoL in their patients. They can discuss treatment possibilities and outcomes more effectively with a greater understanding of IIB dimensions and predictors.

The study had some limitations that should be mentioned. Patients were required to answer the bespoke IIB questions based on experiences that took place during the year before galcanezumab initiation, and thus, their answers could have been affected by recall bias. Patients were required to answer the MIBS-4 questionnaire based on experiences that took place in the last 4 weeks and thus, their answers could have been affected by a reduction in symptoms due to treatment. However, this study was not designed to assess the effects of galcanezumab on IIB, no comparisons to placebo or pre-galcanezumab were conducted, and thus, no systematic effects of the mAb on IIB should be inferred here. Importantly, the participants had significant IIB, based on MIBS-4 scores, at the time of treatment with CGRP mAb. Men, ethnic minorities, people who have less education, and people with low socioeconomic status were underrepresented in our study. In the present study, females account for approximately 90% of respondents, compared with many observational studies reporting female to male ratios ranging from 2:1 to 3:1 [46–48]. This may limit the generalizability of the results, as there are sex differences in migraine symptoms and associated features. Women, compared with men, tend to have longer durations of migraine attacks and recovery time, more frequent accompanying symptoms, such as nausea, vomiting, photophobia, phonophobia, and allodynia, and they tend to have a greater burden of migraine [46, 47, 49, 50]. These differences might be partly attributed to the complex role that estrogens and progesterone play in regulating biological functions, including neuronal hyperexcitability and increasing responsiveness of brain structures that are important to migraine pathophysiology, such as the trigeminal nucleus caudalis [46, 51]. These factors may affect the IIB of migraine and can influence treatment outcomes, and merit further investigations.

To conclude, the results illustrate the importance of IIB as a concept to be considered in the medical care of people with migraine. If migraine can be called "the invisible disease," the IIB must be considered "the invisible burden." IIB in people with migraine is associated with worse well-being, higher sensitivity to anxiety, worse disease severity, lower income, and negative personal and social experiences. Ideally, the burden of the disease between attacks should also be considered in a holistic treatment approach, which does not ignore the significant IIB imposed by the disease, and merely highlight headache frequency, duration, and intensity.

Abbreviations

% Inc MSE	Percent increase in mean square error
ASI-3	Anxiety Sensitivity Index-3
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CM	Chronic migraine
EM	Episodic migraine
HIPAA	Health Insurance Portability and Accountability Act of 1996
IIB	Interictal burden
mAb	Monoclonal antibody
MIBS-4	Migraine Interictal Burden Scale
OR	Odds ratio
PRO	Patient-reported outcome
PSP	Patient Support Program
QoL	Quality of life
RF	Random forests
SD	Standard deviation
SVI	Social vulnerability index
WHO-5	Five-Item World Health Organization Well-being Index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-024-01927-8.

Supplementary Material 1.

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Authors' contributions
Study conception/design: WRL, MKL, MH, LV, MV. Acquisition of data: WRL, MKL, KM. Interpretation of data: WRL, MKL, KM, LV, MV. Drafting and/or critical revision of paper for important intellectual content: All authors. Approval of final version of the paper: all authors.

Data availability
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.

Declarations

Ethics approval and consent to participate
This study was approved by an institutional review board and conformed with International Conference on Harmonization guidelines and was conducted in accordance with the World Medical Association Declaration of Helsinki and applicable local data protection laws.

Consent for publication
Not applicable.

Competing interests
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William R. Lenderking, Mary Kate Ladd, and Karen Malley are employees of Evidera.

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