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RESEARCH SUBMISSION

Psychometric validation and meaningful within-patient change of the Migraine-Specific Quality of Life questionnaire version 2.1 electronic patient-reported outcome in patients with episodic and chronic migraine

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Abstract

Objective: To evaluate the measurement properties of all three domains of the Migraine-Specific Quality of Life questionnaire version 2.1 (MSQ v2.1) electronic patient-reported outcome (ePRO) to assess the functional impact of migraine in patients with episodic or chronic migraine (CM); and identify meaningful within-patient change thresholds for the Role Function-Restrictive (RFR), Role Function-Preventive (RFP), and Emotional Function (EF) domains.

Methods: Data were drawn from three double-blind, placebo-controlled, and randomized Phase 3 clinical studies (episodic migraine [EM]: EVOLVE-1 and EVOLVE-2; CM: REGAIN). The psychometric properties of the MSQ v2.1 ePRO domains were demonstrated by evaluating reliability (internal consistency and test–retest), construct validity (convergent and known groups), and responsiveness. Meaningful within-patient change thresholds for domains were estimated using anchor-based approaches, supplemented by empirical cumulative distribution function curves and probability density function plots to enable interpretation of meaningful change over 3 months. The Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Improvement served as anchors.

Results: A total of 2,850 patients with either EM (EVOLVE-1: 851; EVOLVE-2: 909) or CM (REGAIN: 1,090) were included. The Cronbach's alpha estimates of internal consistency exceeded the recommended threshold of ≥0.70 for all domains from the three studies, indicating adequate internal consistency. Test–retest reliability intraclass correlation coefficients were ≥0.80 for all domains across all three studies, demonstrating

Abbreviations: ANOVA, analysis of variance; CM, chronic migraine; eCDF, electronic cumulative distribution function; EF, Emotional Function; EM, episodic migraine; ePRO, electronic patient-reported outcome; FDA, Food and Drug Administration; ICHD-3β, International Classification of Headache Disorders, 3rd edition beta version; IHS, International Headache Society; MIDAS, Migraine Disability Assessment Score; MSQ v2.1, Migraine-Specific Quality of Life questionnaire version 2.1; NCT, National Clinical Trial; PDF, probability density function; PGI-I, Patient Global Impression of Improvement; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome; RFP, Role Function-Preventive; RFR, Role Function-Restrictive.

almost perfect agreement. Convergent validity was supported by moderate-to-strong correlation ($r \geq 0.30$) between all domains of MSQ v2.1 ePRO and studied anchors (Migraine Disability Assessment Score and PGI-S scores) across all three studies. Known group validity was established between all domains and subgroups of patients stratified by baseline PGI-S scores and baseline number of monthly migraine headache days for all three studies. The 3-month meaningful within-patient change thresholds were the same for EM and CM for RFP: 20.00 and EF: 26.67; and for RFR: 25.71.

Conclusions: These findings demonstrate that all three domains of the MSQ v2.1 ePRO have sufficient reliability, validity, responsiveness, and appropriate interpretation standards. Our results suggest that MSQ v2.1 ePRO is a well-defined and reliable patient-reported outcome instrument that is suitable for use in clinical studies for evaluating the impact of migraine on patient functioning in episodic and CM.

KEYWORDS
chronic migraine, episodic migraine, Migraine-Specific Quality of Life questionnaire, patient-reported outcomes

INTRODUCTION

Globally, migraine is among the top five leading causes of years lived with disability, with higher years lived with disability rates reported in females than in males.[1] Migraine attacks are common among patients aged 15–49 years with peak prevalence reported among patients aged 35–39 years.[2]

Patients with migraine often experience impairment of functional aspects during attacks as well as impairment of emotional aspects, both during and between migraine attacks.[3,4] Patient-reported outcome (PRO) instruments that gather patients' perspectives often provide valuable insights into impact of the disease on health-related quality of life (HRQoL) and disease-related disability.[4] PROs are often preferred by health-care providers (HCPs) to make informed decisions based on patient's perspectives and to identify challenges with treatment compliance. This eliminates chances of skipped treatment opportunities for providing acute, preventive, and biobehavioral interventions.[4–7] Both general health and disease-specific instruments are used to evaluate HRQoL in patients with migraine.[4] However, the Migraine-Specific Quality of Life questionnaire version 2.1 (MSQ v2.1) PRO has gained recognition by HCPs over the decades owing to its increased precision and focus on aspects specific to migraine.[8] The 14-item MSQ v2.1 electronic patient-reported outcome (ePRO) comprises the domains of Role Function-Restrictive (RFR; 7-items), Role Function-Preventive (RFP; 4-items), and Emotional Function (EF; 4-items).[9] The original 16-item MSQ v1.0 PRO was developed by Glaxo Wellcome Inc.[3] in 1992 and over the years, has been subsequently revised following additional psychometric testing (versions 2.0[10] and 2.1[9]).

In recently published pivotal studies on galcanezumab, significant reductions in monthly migraine headache days (monthly migraine headache days, $p < 0.001$) were observed in galcanezumab-treated patients compared to placebo. In EVOLVE-1 and EVOLVE-2 studies, reduction in migraine headache days/month was 4.3, 4.2, 2.3, and 4.7, 4.6, and 2.8 days, respectively, in patients receiving galcanezumab 120 mg, 240 mg, and placebo.[11,12] In the REGAIN study, reduction in migraine headache days per month was 4.8, 4.6, and 2.7 days in patients receiving galcanezumab 120 mg, 240 mg, and placebo, respectively.[13] A key secondary end point in the galcanezumab studies was the RFR domain of the MSQ v2.1 at Months 4–6 for patients with chronic migraine (CM) and Month 3 for patients with episodic migraine (EM) and patient data from the three Phase 3 studies were retrospectively analyzed to evaluate the psychometric performance of that domain.[14] In this post hoc analysis, we aim to assess the reliability, validity, ability to detect change, and meaningful within-patient change at Month 3 for all three domains of the MSQv2.1 ePRO using data from the same Phase 3 clinical studies.

METHODS

Study design

The EVOLVE-1 (n = 858; NCT02614183), EVOLVE-2 (n = 915; NCT02614196), and REGAIN (n = 1,113; NCT02614261) studies were Phase 3, multicentered, randomized, double-blind, placebo-controlled studies. The study designs have been described previously.[11–13] Briefly, male and female patients aged 17–65 years and with a diagnosis of EM (EVOLVE-1 and EVOLVE-2 studies) or CM (REGAIN study), per the International Headache Society (IHS) International Classification of Headache Disorders, 3rd edition, (ICHD-3) beta version,[15] were enrolled. Patients were required to have a migraine onset at or before 50 years of age and a diagnosis of migraine for at least 1 year before enrollment. Patients with a history of failure to respond to three or more classes of migraine preventive treatments, as defined by the American Academy of Neurology/American Headache Society treatment guidelines level A and level

B evidence,[14] were excluded. Eligible patients were randomized in a ratio of 2:1:1 to one of the three treatment groups, placebo, galcanezumab 120 mg or galcanezumab 240 mg, respectively.

The primary end point in all three studies assessed the superiority of at least one dose of galcanezumab (120 or 240 mg/month) to placebo in preventing migraine headache. Secondary outcomes included proportions of patients with a reduction in monthly migraine headache days (≥50%, ≥75%, or ≥100% response rates), migraine headache days with acute medication use, and scores from the MSQ v2.1 ePRO, Patient Global Impression of Severity (PGI-S), and Migraine Disability Assessment Score (MIDAS) were also assessed.[11–13]

The study protocols were reviewed and approved by the Institutional Review Board, Medical Ethics Committee, or Medical Research & Ethics Committee of the participating study sites for all three studies. The studies were conducted in concordance with the ethical principles that have their origin in the Declaration of Helsinki guidelines. All patients provided written informed consent before study participation.

Migraine-Specific Quality of Life questionnaire, version 2.1

The MSQ v2.1 ePRO is a self-administered questionnaire comprised of three domains. Items in the RFR domain assess how migraines limit one's daily social and work-related activities, RFP items assess how migraines prevent these activities, and EF items assess the emotions associated with migraines.[9] During clinical site visits, patients provided their inputs directly into a "tablet" device at baseline. Post-baseline, patients entered their inputs at Months 1–6 in EVOLVE studies and at Months 1, 2, and 3 in REGAIN study. The responses for each item range from 0 ("none of the time") to 6 ("all of the time"). The MSQv2.1 ePRO domain scores for each of the three domains are determined separately by adding the score of each item under that domain. Domain scores are transformed linearly on a scale of 0–100, with higher scores indicating improved health status. The MSQ has been found to be a reliable and valid questionnaire in several different populations, including EM and CM, initiators of preventive treatment, global clinical trial, and clinical practice research. It is recommended as a core instrument for headache studies by the National Institute of Health and has been translated and culturally adapted into multiple languages.[8,16,17]

Headache-related disability, level of illness for migraine, and impression of migraine improvement were evaluated using the patient self-administered questionnaires, namely, MIDAS, PGI-S, and Patient Global Impression of Improvement (PGI-I). The MIDAS is a 5-item patient-rated instrument that reflects the number of days reported as either missing completely or experiencing reduced productivity in school or work, household work, and/or social or leisure activities within the past 3 months. A higher MIDAS score is indicative of increased disability in terms of lost days due to migraine.[18,19] The PGI-S and PGI-I scales assess the patient's global impression of severity of their current condition and improvement in disease (migraine) since randomization to treatment, respectively, on a scale ranging from 1 to 7. The PGI-S includes a range of possible responses, from 1 ("normal, not at all ill") to 7 ("extremely ill"). The PGI-I has a 7-point scale in which a rating of 1 indicates the patient is "Very much better," 2 = "Much better," 3 = "A little better," 4 = "No change," 5 = "A little worse," 6="Much worse," and 7 indicates the patient is "Very much worse."

Patients used a handheld electronic daily diary device to record their headache information, including duration, severity, symptoms, and utilization of acute headache medication. A migraine headache day was defined as a calendar day on which a migraine or probable migraine headache occurred; for the clinical studies, headache duration needed to last at least 30 minutes. Migraine headache criteria were based on the IHS International Classification of Headache Disorders —3rd edition beta (ICHD-3β); probable migraine headache was defined the same as migraine headache but failing to meet the criteria for either feature A or B.[15]

Statistical analysis

For this post hoc analysis, responsiveness and meaningful within-patient change estimates for EM and CM were calculated from baseline to Month 3. The distribution of scores for the three domains was determined using descriptive statistics, including mean, standard deviation, median, range, and floor and ceiling effects. The sample size for all analyses was motivated by the available data from the EVOLVE-1, EVOLVE-2, and REGAIN studies. Details on patient enrollment, sample size calculation, randomization, and blinding have been published previously.[11–13] All tests of significance were two-sided with alpha set at a p-value of 0.05. Assumption of normality was applied and supported by histograms of the baseline MSQ v2.1 data. All statistical analyses were completed using SAS version 9.4.

Reliability

Internal consistency was assessed using Cronbach's alpha (α) coefficient at baseline; $\alpha \geq 0.70$ was considered an adequate magnitude for demonstrating internal consistency.[20,21] Stability of domain scores over time within a stable population was demonstrated using test–retest reliability. Stable patients were defined as those who had either no change or a change of only 1 day in their number of migraine headache days per month during the last two time points for the treatment phase (Months 5 and 6 for EVOLVE-1 and EVOLVE-2, and Months 2 and 3 for REGAIN) and had been randomized to placebo. Test–retest reliability was estimated using intraclass correlation coefficients (ICCs). The ICC was calculated using the analysis of variance (ANOVA) approach.[22] The F-statistic is based on the ratio of between group mean square error versus within group mean square error. The ICC values were classified in the following manner: 0.01 to 0.20 = "slightly fair," 0.21 to 0.40 = "fair," 0.41 to 0.60 = "moderate," 0.61 to 0.80 = "substantial," and 0.81 to 1.00 indicates "almost perfect agreement."[23]

Validity

Convergent validity of the MSQ domains with MIDAS, PGI-S, and monthly migraine headache days was assessed using Spearman rank correlation coefficient at baseline. A moderate-to-strong relationship was hypothesized for the domain scores with MIDAS and PGI-S. A correlation coefficient of ≥0.30 was considered moderate convergent validity, whereas a correlation coefficient ≥0.5 was considered as strong convergent validity.[24] It was hypothesized that the RFR domain would have a moderate-to-strong relationship with the MIDAS and the PGI-S and be moderately correlated with the number of monthly migraine headache days. Correlations between the RFP and EF domains and the MIDAS, PGI-S, and monthly migraine headache days were expected to be slightly lower, though still in the moderate range.

Known groups validity was analyzed using PGI-S and the number of monthly migraine headache days per month at baseline. Patients who indicated a higher degree of illness on the PGI-S were hypothesized to have lower domain scores than those who indicated a low severity of illness; similarly patients with a greater number of migraine headache days per month were hypothesized to have lower domain scores than those who had fewer migraine headache days per month. Analysis of covariance (ANCOVA) models were adjusted for age and sex. Multiple comparisons for known groups validity were adjusted using Bonferroni correction and Cohen's *d* effect sizes (δ) were calculated. Adjustments for multiple comparisons were done with each study and each known group analysis. Cohen's *d* effect size was interpreted as a percentage of the standard deviation, meaning a Cohen's *d* of 0.5 means the difference equals half a standard deviation.[25]

Responsiveness

The ability to detect change was evaluated with one-way ANOVA methods to assess the mean change from baseline to Month 3 for RFR, RFP, and EF domains by change from baseline to Month 3 in MIDAS, PGI-S, and percent change in monthly migraine headache days and Month 3 PGI-I values. It was hypothesized that the domain score changes would be statistically significantly different between anchor groups. The anchor groups were defined as follows: MIDAS – no grade improvement versus ≥1 grade improvement (e.g., MIDAS grade 3 to MIDAS grade 2); PGI-S – no category improvement versus ≥1 category improvement (e.g., "moderately ill" to "mildly ill"); percent change in monthly migraine headache days – <50% improvement versus ≥50% improvement; PGI-I – no change or worsening versus ≥ improvement (e.g., "a little better," "much better," and "very much better"). The Spearman rank correlation coefficients for change in the MSQ domains from baseline to Month 3 and the percent change in monthly migraine headache days were also calculated.

Meaningful change thresholds

Meaningful within-patient change thresholds (i.e., the individual patient PRO score change over a predetermined period indicating a meaningful change in her or his condition) were estimated for the MSQ v2.1 ePRO domains using an anchor-based approach with the PGI-S and PGI-I serving as anchors; specifically 1-level and 2-level improvement. The optimal meaningful within-patient change estimate for baseline to Month 3 was obtained by calculating the median and mean of the baseline to Month 3 MSQ v2.1 ePRO domain change scores by PGI-S change group from baseline to Month 3 and PGI-I group at Month 3. Empirical cumulative distribution function (eCDF) and probability density function (PDF) plots were generated to display the change scores from baseline to Month 3 by anchor change groups. To interpret the results and derive a recommended estimate for each domain, the following were key considerations. (1) The range of estimates from the 1-level and 2-level improvement groups were examined, with the 2-level estimates being more conservative. (2) The state change for each domain is the value on the 0 to 100 scale that is equivalent to a 1-point shift on the raw scale. The state change is calculated by dividing the total possible score (100) by the number of items (different for each domain), then, dividing by the number of level changes in response (5). The state changes were 2.857, 5.0, and $6.\overline{66}$ for the RFR, RFP, and EF, respectively. The meaningful within-patient change threshold should be a value that is attainable and interpretable on both the transformed and raw scale.[26]

RESULTS

A total of 2,850 patients with EM (EVOLVE-1: 851; EVOLVE-2: 909) or CM (REGAIN: 1,090) were included in this post hoc analysis. Table 1 presents sociodemographic, clinical, and psychometric characteristics. Most (>84%) of patients across the three studies were female. No significant floor or ceiling effects were observed for any of the three domains (data not shown). No missing item level data were observed for each of the three domains in the three studies. The mean RFR, RFP, and EF domain scores were similar for patients with EM in the EVOLVE studies and were relatively lower in patients with CM in the REGAIN study.[27,28]

Reliability

At baseline, Cronbach's α estimates of internal consistency for the RFR, RFP, and EF domains in all the three studies exceeded the recommended threshold of ≥0.70 (range 0.83 to 0.93) (Table S1). Test–retest reliability results were strong with the ICC values for the RFR, RFP, and EF domains ranging from 0.77 to 0.92, demonstrating substantial to almost perfect agreement (Table S2).[23]

TABLE 1 Patient demographics and disease characteristics: PRO population

Characteristics	EVOLVE-1 PRO population (*n* = 851)	EVOLVE-2 PRO population (*n* = 909)	REGAIN PRO population (*n* = 1,090)
Age (years), mean (SD) [range]	40.6 (11.6) [17.0–65.0]	41.8 (11.1) [18.0–65.0]	41.0 (12.1) [17.0–65.0]
Gender (female), *n* (%)	712 (83.7)	776 (85.4)	929 (85.2)
Years since migraine diagnosis, mean (SD) [range]	20.0 (12.4) [0.2–58.1]	20.6 (12.4) [0.1–57.7]	21.2 (12.8) [0.1–56.4]
Number of migraine headache days, mean (SD) [range]	9.1 (3.0) [4.0–16.7]	9.1 (2.9) [4.0–18.0]	19.4 (4.5) [8.0–29.0]
Race, *n* (%)			
White	683 (80.3)	638 (70.2)	863 (79.2)
Black or African American	94 (11.0)	63 (6.9)	69 (6.3)
Asian	24 (2.8)	102 (11.2)	53 (4.9)
American Indian or Alaska Native	3 (0.4)	41 (4.5)	6 (0.6)
Native Hawaiian or Other Pacific Islander	3 (0.4)	2 (0.2)	1 (0.1)
Multiple	44 (5.2)	63 (6.9)	97 (8.9)
Number of comorbid conditions, mean (SD), *n*	4.7 (3.6), 772	3.6 (3.1), 718	4.3 (3.5), 937
MIDAS total score			
Mean (SD)	33.15 (27.7)	33.0 (29.7)	67.2 (57.3)
Median (range)	26.0 (0–216.0)	25.0 (0.0–230.0)	50.0 (0.0–355.0)
RFR			
Mean (SD)	51.5 (16.0)	51.7 (15.6)	38.7 (17.2)
Median	51.4	51.4	37.1
Range (min–max)	0.0–94.3	(0.0, 100.0)	(0.0, 94.3)
Missing *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Floor *n* (%)	4 (0.5)	2 (0.2)	11 (1.0)
Ceiling *n* (%)	0 (0.0)	2 (0.2)	0 (0.0)
RFP			
Mean (SD)	67.0 (18.9)	67.6 (19.3)	55.7 (21.1)
Median (Q1–Q3)	70.0	70.0	55.0
Range (min–max)	0.0–100.0	0.0–100.00	0.0–100.0
Missing *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Floor *n* (%)	1 (0.1)	4 (0.4)	8 (0.7)
Ceiling *n* (%)	14 (1.6)	39 (4.3)	14 (1.3)
EF			
Mean (SD)	59.4 (24.6)	61.9 (24.0)	44.9 (26.3)
Median (Q1–Q3)	60.0	66.7	46.7
Range (min–max)	0.0–100.0	0.0–100.0	0.0–100.0
Missing *n* (%)	0 (0.0)	0 (0.0%)	0 (0.0)
Floor *n* (%)	25 (2.9)	18 (2.0%)	77 (7.1)
Ceiling *n* (%)	24 (2.8)	46 (5.1%)	13 (1.2)

Abbreviations: EF, Emotional Function; max, maximum; min, minimum; PRO, patient-reported outcomes; RFP, Role Function-Preventive; RFR, Role Function-Restrictive; SD, standard deviation.

Validity

At baseline, moderate-to-strong correlations were noted between RFR domain and MIDAS (0.51 to 0.57), and between RFR domain and PGI-S (0.46 to 0.54) in all three studies. Moderate-to-strong correlations between the RFP domain and MIDAS (0.52 to 0.57), and PGI-S (0.35 to 0.46), and between the EF domain and MIDAS (0.45 to 0.51) and PGI-S (0.38 to 0.44) were also observed. The baseline correlations between RFR, RFP, and EF domains, and the number of monthly migraine headache days were small for all three studies (RFR, 0.22 to 0.27; RFP, 0.13 to 0.22; EF, 0.17 to 0.22).

TABLE 2 Known groups validity: MSQ v2.1 ePRO domain scores at baseline (PGI-S, 5-level, and monthly migraine headache days)

PGI-S at baseline (five groups) LS mean at baseline (SE), *n*						
Domain/study name	**Normal/borderline ill**	**Mildly ill**	**Moderately ill**	**Markedly ill**	**Severely/Extremely ill**	**Effect size[a,b]**
RFP						
EVOLVE-1	81.6 (2.6), 44	78.8 (1.7), 104	71.4 (1.0), 346	63.7 (1.2), 237	49.7 (1.6), 120	1 vs. 2 = 0.23; 1 vs. 3 = 0.65; 1 vs. 4 = 1.14; 1 vs. 5 = 1.67; 2 vs. 3 = 0.45; 2 vs. 4 = 0.96; vs. 5 = 1.59; 3 vs. 4 = 0.48; 3 vs. 5 = 1.23; 4 vs. 5 = 0.77
EVOLVE-2	78.1 (2.2), 75	78.3 (1.8), 118	71.7 (1.2), 320	66.0 (1.2), 295	53.9 (1.9), 101	1 vs. 2 = 0.02; 1 vs. 3 = 0.35; 1 vs. 4 = 0.63; 1 vs. 5 = 1.16; 2 vs. 3 = 0.41; 2 vs. 4 = 0.72; 2 vs. 5 = 1.42; 3 vs. 4 = 0.32; 3 vs. 5 = 0.99; 4 vs. 5 = 0.64
REGAIN	71.1 (2.5), 59	73.4 (2.9), 44	68.4 (1.3), 249	57.6 (1.1), 405	46.0 (1.2), 335	1 vs. 2 = 0.18; 1 vs. 3 = 0.12; 1 vs. 4 = 0.69; 1 vs. 5 = 1.23; 2 vs. 3 = 0.33; 2 vs. 4 = 0.89; 2 vs. 5 = 1.44; 3 vs. 4 = 0.59; 3 vs. 5 = 1.19; 4 vs. 5 = 0.61
EF						
EVOLVE-1	76.8 (3.4), 44	77.2 (2.3), 104	65.2 (1.4), 346	56.2 (1.6), 237	38.8 (2.1), 120	1 vs. 2 = 0.03; 1 vs. 3 = 0.56; 1 vs. 4 = 0.99; 1 vs. 5 = 1.53; 2 vs. 3 = 0.55; 2 vs. 4 = 1.01; 2 vs. 5 = 1.65; 3 vs. 4 = 0.43; 3 vs. 5 = 1.14; 4 vs. 5 = 0.72
EVOLVE-2	79.5 (2.7), 75	76.09 (2.2), 118	67.0 (1.5), 320	57.9 (1.5), 295	46.6 (2.3), 101	1 vs. 2 = 0.20; 1 vs. 3 = 0.60; 1 vs. 4 = 0.96; 1 vs. 5 = 1.41; 2 vs. 3 = 0.43; 2 vs. 4 = 0.81; 2 vs. 5 = 1.34; 3 vs. 4 = 0.40; 3 vs. 5 = 0.88; 4 vs. 5 = 0.46
REGAIN	60.1 (3.3), 59	64.8 (3.7), 44	57.6 (1.7), 249	46.1 (1.4), 405	34.3 (1.5), 335	1 vs. 2 = 0.20; 1 vs. 3 = 0.10; 1 vs. 4 = 0.55; 1 vs. 5 = 1.02; 2 vs. 3 = 0.33; 2 vs. 4 = 0.78; 2 vs. 5 = 1.29; 3 vs. 4 = 0.48; 3 vs. 5 = 0.98; 4 vs. 5 = 0.48

Monthly migraine headache days at baseline LS mean at baseline (SE), *n*				
	<8	**≥8**	**Effect size**	**Overall *F* value (*p*-value)**
RFP				
EVOLVE-1	71.3 (1.2), 291	65.4 (1.0), 560	−0.32	7.04 (0.0001)
EVOLVE-2	72.0 (1.2), 303	67.5 (1.0), 606	−0.24	6.12 (0.0004)
REGAIN	61.6 (1.0), 601	54.0 (1.1), 491	−0.36	17.61 (<0.0001)
EF				
EVOLVE-1	65.7 (1.6), 291	58.1 (1.3), 560	−0.33	9.97 (<0.0001)
EVOLVE-2	68.6 (1.5), 303	61.1 (1.3), 606	−0.33	10.10 (<0.001)
REGAIN	51.7 (1.3), 601	41.2 (1.4), 491	−0.41	18.13 (<0.0001)

Abbreviations: EF, emotional function; LS, least square; MSQv2.1 ePRO, Migraine-Specific Quality of Life questionnaire version 2.1 electronic patient-reported outcome; PGI-S, Patient Global Impression of Severity; RFP, Role Function-Preventive; RFR, Role Function-Restrictive; SE, standard error; vs., versus.

[a]Effect sizes calculated using Cohen's *d*.

[b]A one-way analysis of covariance (ANCOVA) model adjusting for age and sex, all *p*-values for overall *F* value <0.0001. Pairwise comparisons between LS means were performed using Bonferroni test adjusting for multiple comparisons. Results for RFR known groups validity was previously reported.[14]

Table 2 shows known groups validity results. Patients with worse severity levels of illness as assessed using the PGI-S had lower RFP and EF domain scores. Significant differences ($p < 0.0001$) in mean RFP and EF domain scores at baseline were observed between patients in nearly all of the PGI-S levels (RFP: $\delta = 0.02$ to 1.67; EF: $\delta = 0.03$ to 1.65); however, no significant differences were observed between mean scores of patients with PGI-S levels of "normal/borderline" versus "mildly ill" or "moderately ill" groups. The groups with fewer monthly migraine headache days had higher mean RFP and EF domain scores in all three studies (RFP: $p \leq 0.001$, $\delta = -0.24$ to -0.36; EF: $p \leq 0.001$, $\delta = -0.33$ to -0.41; Table 2).

Responsiveness

Patients who had ≥1 level improvement in MIDAS, PGI-S, or PGI-I and/or experienced at least 50% fewer monthly migraine headache days from baseline to Month 3 had significant improvements ($p \leq 0.0001$) in their RFR, RFP, and EF domain mean scores versus patients with no categorical improvements in respective measures/outcomes (RFR: all $p < 0.001$, $\delta = 0.55$ to 1.40; RFP, all $p < 0.001$, $\delta = 0.40$ to 1.2; EF: all $p \leq 0.001$, $\delta = 0.44$ to 1.13; Figure 1). The correlation between change in the RFR, RFP, and EF domain scores and percent change in monthly migraine headache days were −0.46 to −0.48, −0.33 to −0.36, and −0.34 to −0.35 for EM, respectively, and −0.60, −0.48, and −0.47 for CM, respectively. These results provide strong evidence to support the responsiveness (ability to detect change) of the RFR, RFP, and EF domains in patients with EM and CM.

Meaningful within-patient change threshold

Table 3 shows the median and mean of baseline to Month 3 MSQ v2.1 ePRO domain change scores by PGI-S change group and PGI-I group. The median change on the RFR domain for patients who had a 1-point improvement on the PGI-S was 22.86 for all three studies and the mean change ranged from 22.72 to 24.88. For patients who had a 2-point improvement on the PGI-S, the median change on the RFR domain ranged from 31.43 to 34.29 and the mean change ranged from 32.00 to 32.45. Patients who were "a little better" on the PGI-I had a median RFR score change of 20.00 in all three studies and the mean change ranged from 19.58 to 21.65. For patients who were "much better" the median change ranged from 28.57 to 34.29 and the mean ranged from 30.55 to 34.91. In consideration of these results and the attainable score changes that fall within these anchor estimates, the meaningful within-patient change threshold for baseline to Month 3 for the RFR domain was a 25.71-point change (9-points on the raw scale) for EM and CM.

The median change on the RFP domain for patients who had a 1-point improvement on the PGI-S was 15.00 for all three studies and the mean change ranged from 15.25 to 18.71. For patients who had a 2-point improvement on the PGI-S, the median change on the RFP domain ranged from 20.00 to 25.00 and the mean change ranged from 22.99 to 26.82. Patients who were "a little better" on the PGI-I had a median RFP score change of 15.00 in all three studies and the mean change ranged from 15.02 to 17.01. For patients who were "much better" the median change ranged from 20.00 to 25.00 and the mean ranged from 21.83 to 28.17. The attainable score changes on the RFP domain that fall within these anchor estimates are 15.00, 20.00, and 25.00. Given the results, the meaningful within-patient change threshold for baseline to Month 3 for the RFP domain was a 20.00-point change (4-points on the raw scale) for EM and CM.

The median change on the EF domain for patients who had a 1-point improvement on the PGI-S ranged from 13.33 to 20.00 and the mean change ranged from 19.74 to 21.44. For patients who had a 2-point improvement on the PGI-S, the median change on the EF domain ranged from 26.67 to 33.33 and the mean change ranged from 28.29 to 31.68. Patients who were "a little better" on the PGI-I had a median EF score change ranged from 13.33 to 20.00 and the mean change ranged from 17.32 to 20.69. For patients who were "much better" the median change ranged from 26.67 to 33.33 and the mean ranged from 28.21 to 34.18. In consideration of these results and the attainable score changes that fall within these anchor estimates (13.33, 20.00, 26.67, and 33.33), the meaningful within-patient change threshold for baseline to Month 3 for the EF domain was a 26.67-point change (4-points on the raw scale) for EM and CM. The eCDFs and PDFs for the three domains exhibited clear separation of domain change scores by PGI-S and PGI-I anchor levels (Figure 2).

DISCUSSION

The current retrospective analysis from Phase 3 studies in patients with EM and CM demonstrates the stability of psychometric properties for all three domains of the MSQ v2.1 ePRO with regard to reliability, validity, and responsiveness. The internal consistency reliability exceeded the recommended threshold of ≥0.70, and the test–retest reliability demonstrated almost perfect agreement for all three domains in EVOLVE-1, EVOLVE-2, and REGAIN studies. Across studies, moderate-to-strong correlations in convergent validity for all three domains with MIDAS and PGI-S were observed. The findings are consistent with the hypothesis and prior studies.[8,9,29] These findings are relevant as they signify the benefit of MSQ v2.1 ePRO in measuring the patient's migraine experience that is not captured by measuring monthly migraine headache days alone. The construct validity of the MSQ domains was further confirmed within the framework of known groups validity, with the results demonstrating significant differences between PGI-S levels, and between patients with <8, and ≥8 monthly migraine headache days for both RFP and EF domains. The MSQ v2.1 ePRO was responsive to detect a change between all domains from the three studies using four anchors of change over time.

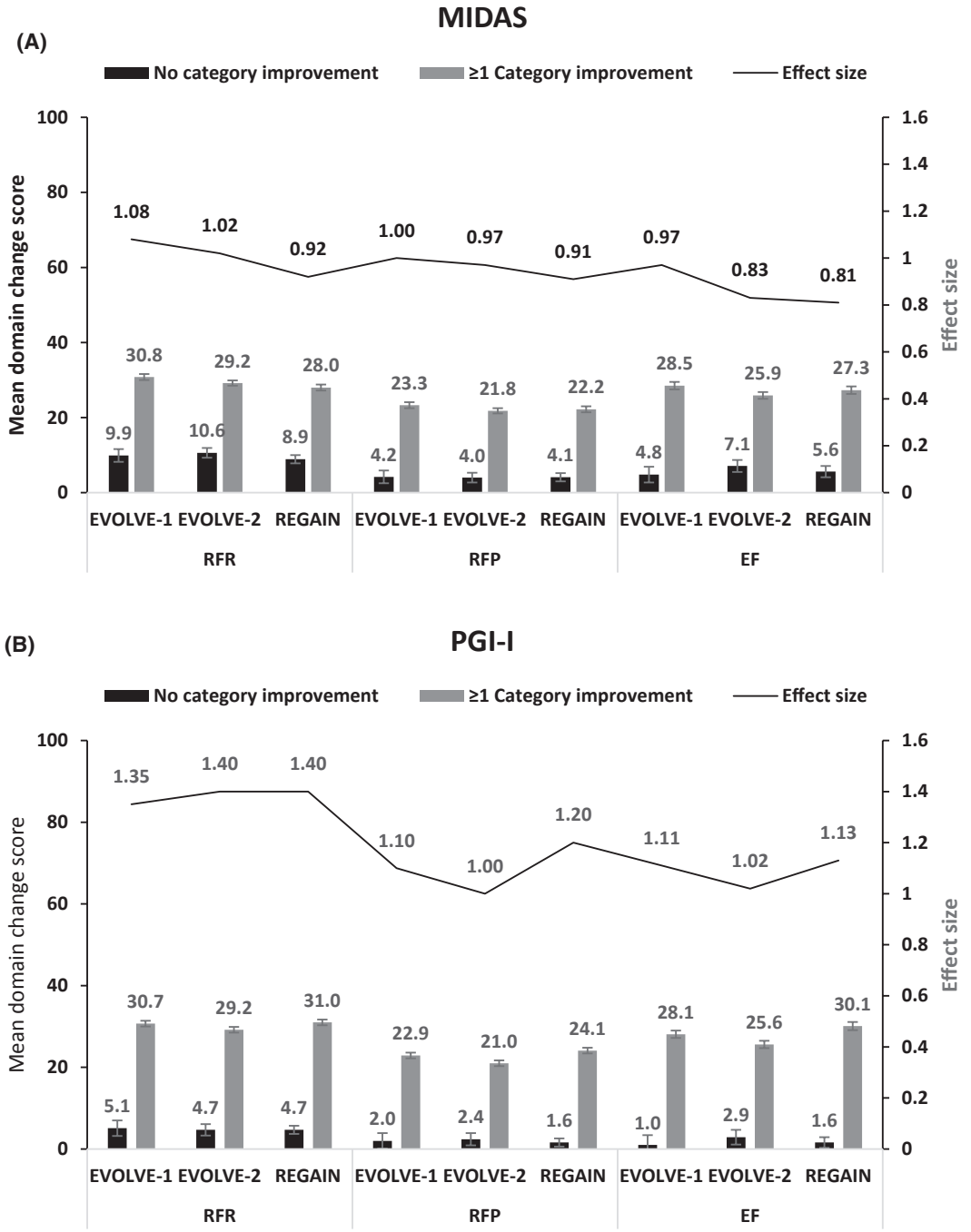


FIGURE 1 Responsiveness: one-way ANOVA with MSQ v2.1 ePRO (RFR, RFP, and EF) among (A) MIDAS, (B) PGI-S, (C) PGI-I, and (D) percent change in monthly migraine headache days improvement groups (Baseline to Month 3). *p*-values for ANOVA all <0.0001. ANOVA, analysis of variance; EF, Emotional Function; MIDAS, Migraine Disability Assessment; MSQv2.1 ePRO, Migraine-Specific Quality of Life questionnaire version 2.1 electronic patient-reported outcome; PGI-I, Patient Global Impression of Improvement; PGI-S, Patient Global Impression of Severity; RFP, Role Function-Preventive; RFR, Role Function-Restrictive; SE, standard error

The MSQ v2.1 ePRO can provide unique information about the functional and emotional effects of treatment. The meaningful within-patient change threshold is an indirect measure, derived from the MSQ v2.1 ePRO, and can serve to contextualize the effects of treatment in clinical studies. Consistent with the US Food and Drug Administration (FDA) Patient Focused Drug Development draft guidance on meaningful within-patient change,[26] we used both static and change anchors and provided a range of estimates based on the 1-point improvement on the PGI-S or "a little better" on the PGI-I and the 2-point improvement on the PGI-S or "much better" on the PGI-I. The rationale for providing a range, was that an estimate consistent with a 1-level change may not be conservative enough

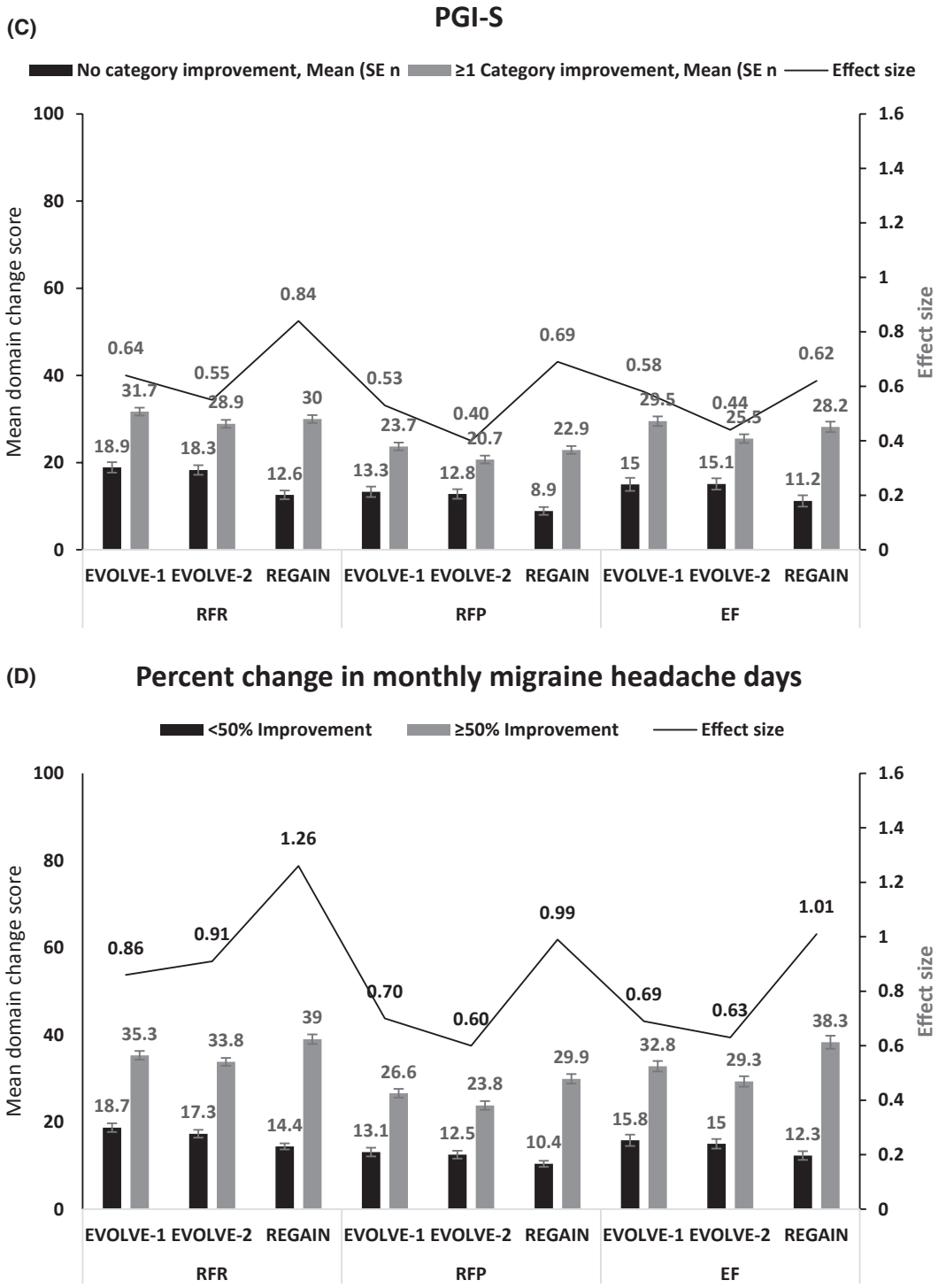


FIGURE 1 (Continued)

and truly meaningful, whereas an estimate consistent with a 2-level change could be overly conservative for evaluating global improvements, though a meaningful patient-reported anchoring level.[30]

For the RFP and EF domains, the derived meaningful within-patient change thresholds were within the range of observed median score changes for the 2-level PGI-S and PGI-I anchor groups. For the RFR domain, a threshold between the 1-level and 2-level change groups was derived because the 2-level estimates were potentially overconservative, specifically for the CM population, and the eCDFs and PDFs show clear separation from the no change and worsen groups at the derived threshold. In addition, a measurement of functional restrictions due to migraine is expected to be more sensitive to the differences between patients with EM and CM as patients with migraine often choose to continue their daily activities

TABLE 3 Anchor-based meaningful within-patient change estimates.

	PGI-S baseline to Month 3 change groups									
	Worsened		No change		1-Point improvement		2-Point improvement		≥3-Point improvement	
MSQv2.1 ePRO	*N*	Median, mean (SE)	*N*	Median, mean (SE)	*N*	Median, mean (SE)	*N*	Median, mean (SE)	*N*	Median, mean (SE)
RFR										
EVOLVE-1	55	17.1, 15.2 (2.6)	216	17.1, 19.8 (1.3)	240	22.9, 24.9 (1.2)	142	31.4, 32.3 (1.6)	116	42.9, 45.3 (1.8)
EVOLVE-2	74	14.3, 14.9 (2.2)	254	18.6, 19.3 (1.2)	257	22.9, 22.8 (1.2)	144	31.4, 32.0 (1.6)	108	40.0, 39.2 (1.8)
REGAIN	112	5.7, 9.9 (1.9)	361	11.4, 13.5 (1.1)	266	22.9, 22.7 (1.2)	137	34.3, 32.5 (1.7)	124	44.3, 43.0 (1.8)
RFP										
EVOLVE-1	55	10.0, 11.2 (2.6)	216	10.0, 13.8 (1.3)	240	15.0, 18.7 (1.2)	142	20.0, 23.0 (1.6)	116	35.0, 34.9 (1.8)
EVOLVE-2	74	10.0, 7.4 (2.2)	254	15.0, 14.4 (1.2)	257	15.0, 15.3 (1.2)	144	25.0, 23.7 (1.6)	108	30.0, 29.5 (1.8)
REGAIN	112	5.0, 6.8 (1.9)	361	10.0, 9.5 (1.1)	266	15.0, 16.4 (1.2)	137	25.0, 26.8 (1.7)	124	30.0, 32.5 (1.8)
EF										
EVOLVE-1	55	13.3, 11.3 (3.2)	216	13.3, 15.9 (1.6)	240	20.0, 21.4 (1.5)	142	30.0, 30.4 (2.0)	116	40.0, 45.2 (2.2)
EVOLVE-2	74	13.33, 12.0 (2.7)	254	13.3, 16.0 (1.4)	257	13.33, 19.7 (1.4)	144	26.7, 28.3 (1.9)	108	33.3, 35.6 (2.2)
REGAIN	112	6.7, 9.4 (2.5)	361	13.3, 11.8 (1.4)	266	13.3, 20.4 (1.6)	137	33.3, 31.7 (2.3)	124	40.0, 41.1 (2.4)
PGI-I Month 3 groups										
	Very much worse/much worse/a little worse		No change		A little better		Much better		Very much better	
	N	Median, mean (SE)	*N*	Median, mean (SE)	*N*	Median, mean (SE)	*N*	Median, mean (SE)	*N*	Median, mean (SE)
RFR										
EVOLVE-1	23	−2.9, −4.5 (3.6)	81	2.9, 7.8 (1.9)	209	20.0, 19.7 (1.2)	268	31.4, 31.4 (1.1)	188	40.0, 41.8 (1.3)
EVOLVE-2	31	−5.7, −3.1 (2.9)	122	5.7, 6.7 (1.5)	231	20.0, 19.6 (1.1)	251	28.6, 30.6 (1.0)	202	37.1, 38.6 (1.1)
REGAIN	75	0.0, 2.3 (2.0)	274	2.9, 5.4 (1.0)	311	20.0, 21.7 (1.0)	221	34.3, 34.9 (1.1)	118	48.6, 48.1 (1. 6)
RFP										
EVOLVE-1	23	0.0, −1.1 (3.8)	81	5.0, 2.8 (2.0)	209	15.0, 15.5 (1.3)	268	25.0, 23.9 (1.1)	188	25.0, 29.6 (1.3)
EVOLVE-2	31	−5.0, −3.6 (3.3)	122	5.0, 3.9 (1.6)	231	15.0, 15.0 (1.2)	251	20.0, 21.8 (1.2)	202	25.0, 26.8 (1.3)
REGAIN	75	−5.0, −3.3 (2.1)	274	5.0, 3.0 (1.1)	311	15.0, 17.0 (1.0)	221	25.0, 28.2 (1.2)	118	32.5, 35.3 (1.6)
EF										
EVOLVE-1	23	0.0, −6.7 (4.83)	81	0.0, 3.1 (2.6)	209	13.3, 17.4 (1.6)	268	26.7, 29.7 (1.4)	188	33.3, 37.7 (1.7)
EVOLVE-2	31	−6.7, −8.0 (3.9)	122	6.7, 5.6 (2.0)	231	13.3, 17.3 (1.4)	251	26.7, 28.2 (1.4)	202	26.7, 31.9 (1.5)
REGAIN	75	0.0, −1.2 (2.8)	274	6.7, 2.4 (1.4)	311	20.0, 20.7 (1.4)	221	33.3, 34.2 (1.6)	118	46.7, 47.5 (2.2)

Abbreviations: EF, Emotional Function; MSQv2.1 ePRO, Migraine-Specific Quality of Life questionnaire version 2.1 electronic patient-reported outcome; PGI-I, Patient Global Impression of Improvement; PGI-S, Patient Global Impression of Severity; RFP, Role Function-Preventive; RFR, Role Function-Restrictive.

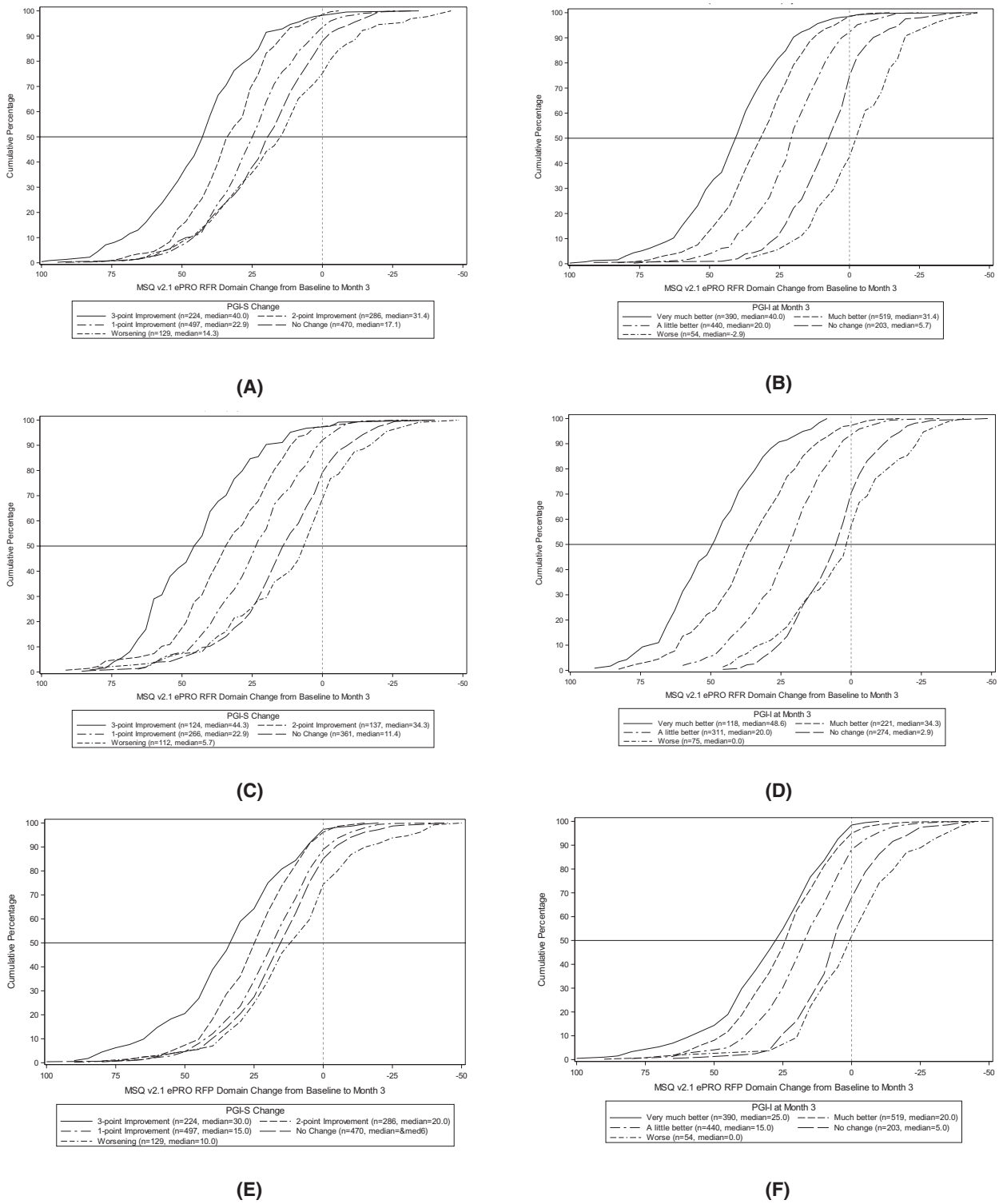
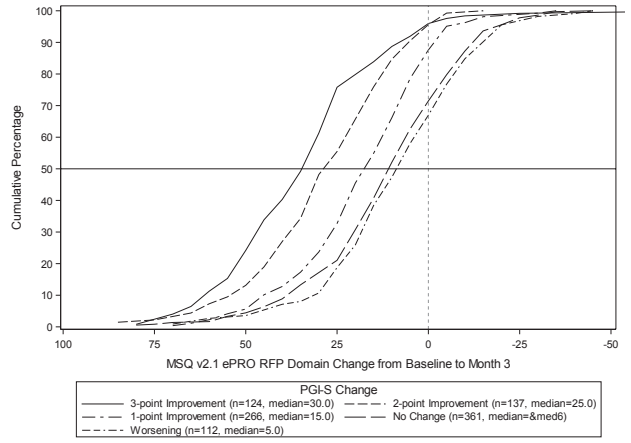


FIGURE 2 (Continued)

despite impairment due to their migraine headache attacks.[31] The previously reported threshold for the RFR domain for CM was lower (17.14; 6-points on the raw scale)[14]; however, this was derived utilizing the preferred methods at the time, specifically discriminative cut point analyses utilizing receiver operating characteristic curves and Youden Index values in addition to anchor-based methods.

It should be noted that across all three studies some patients who reported that they "stayed the same" or had a "worsening" in their illness also experienced improvements in domain scores; however, these improvements were not sizable, and the eCDFs clearly display that the proportion of these patients is minimal. A lower correlation at baseline between migraine headache days and the RFR



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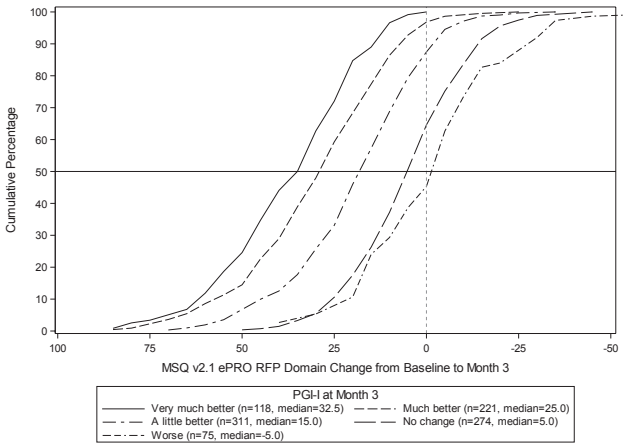

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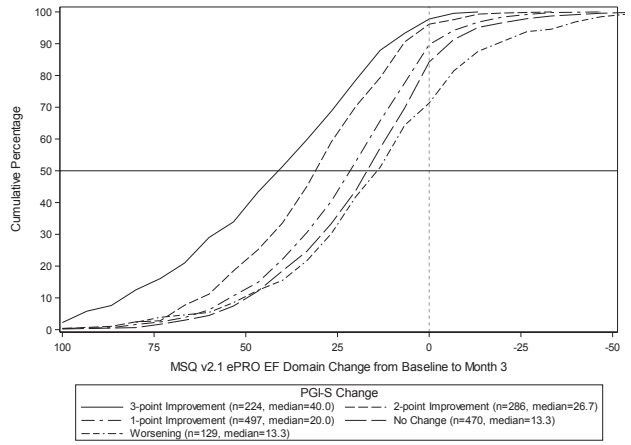

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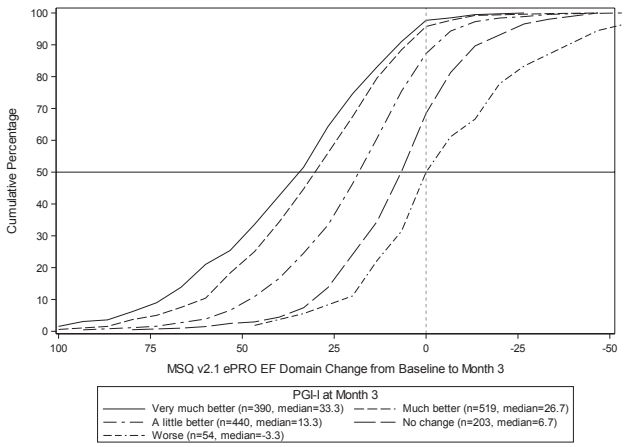

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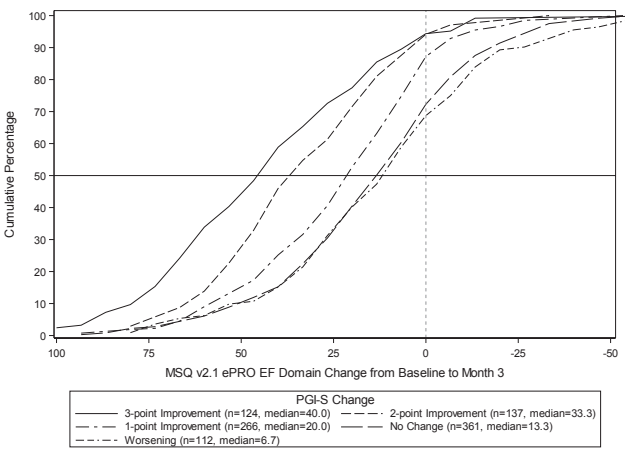

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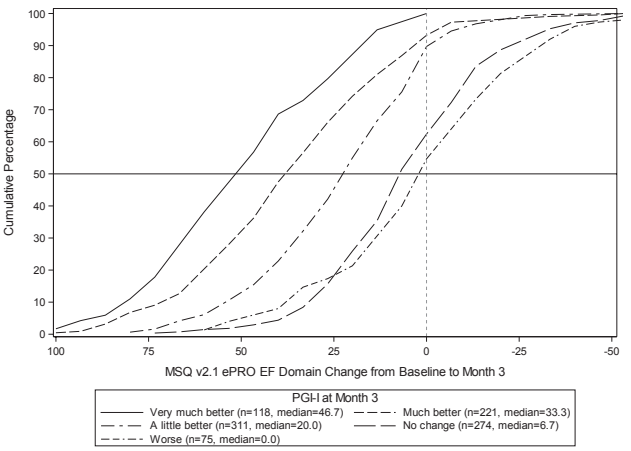
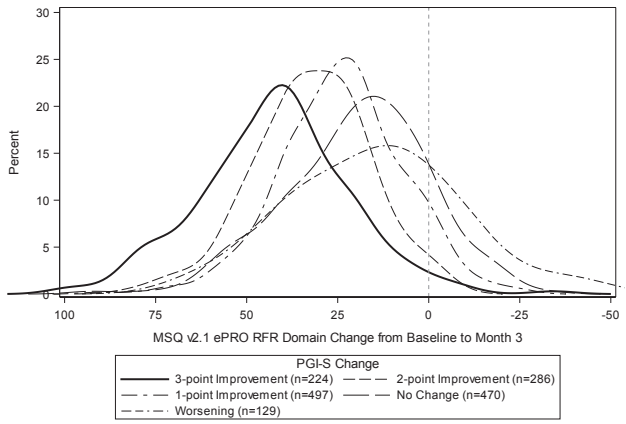


(L)

FIGURE 2 (Continued)

domain was observed, which may suggest that this measure captures aspects of the migraine experience not captured by migraine headache days alone, such as interictal burden.

The MSQ v2.1 ePRO is consistent with FDA guidance on the use of PRO scores in medicinal product development, and is robust and appropriate for inclusion in future clinical studies.[26,32] The primary limitation of this work was with regard to generalizability. Specifically, EVOLVE-1 included patients from the United States and Canada, and EVOLVE-2 and REGAIN enrolled patients from the United States (including Puerto Rico) and 12 other countries. Hence,



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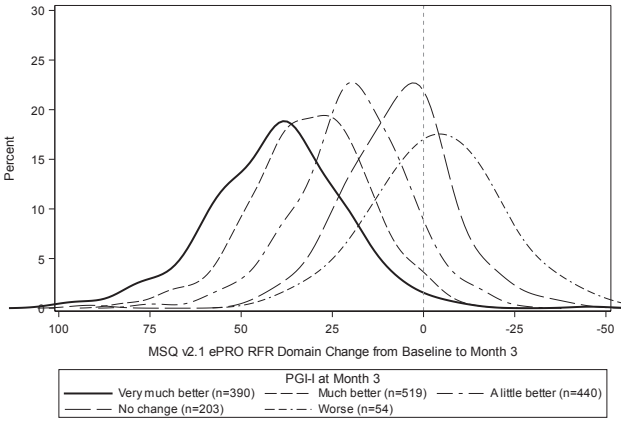

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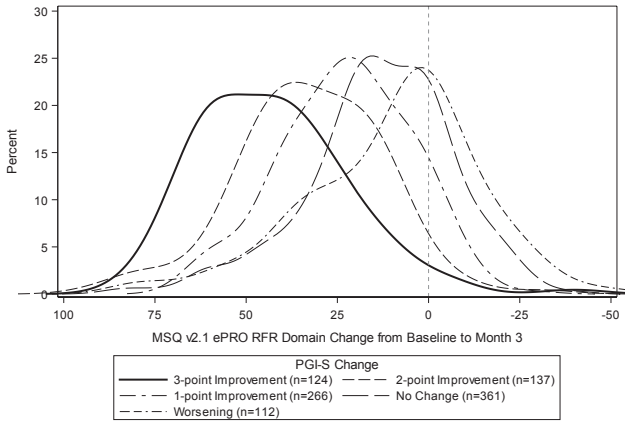

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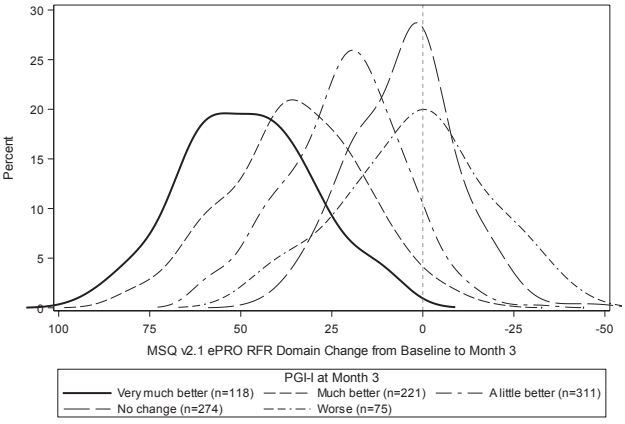

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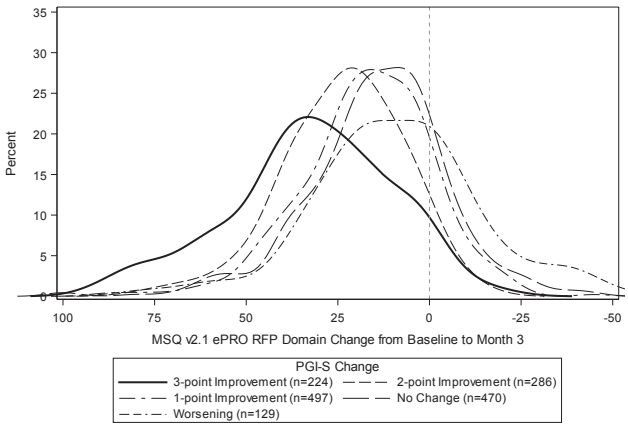

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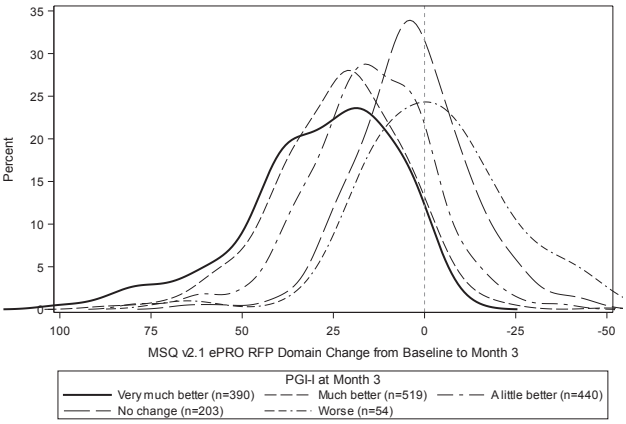

(R)

FIGURE 2 (Continued)

generalizability of these results to other patient populations outside of these countries is not known. The patient-reported outcome measures used in this analysis had various recall periods, for which the implications to the results are unknown. For example, the recall period of migraine days is daily, the MIDAS is 3 months, and the PGI-I is back to the point of randomization. The ability of a patient to recall accurately is surely to be different among those three measures, affecting how each may perform as an anchor. In addition, global patient-ratings serve as a suitable anchor to evaluate meaningful change from the individual perspective; however, have limitations given the complexity of various context and research has not been completed specially in patients with migraine (EM and CM) to more

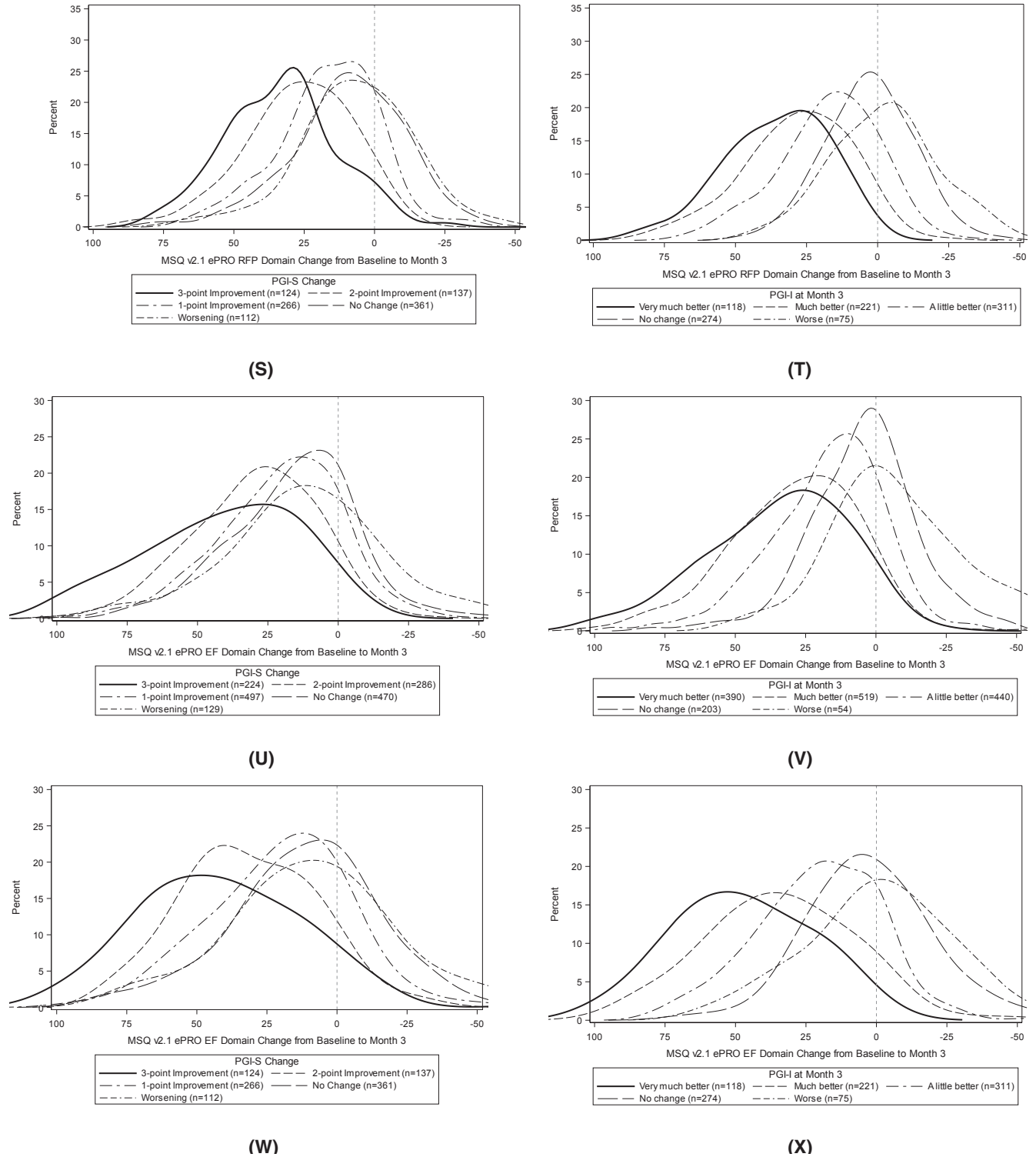

FIGURE 2 (Continued)

fully understand how many levels of improvement would be meaningful to patients.[30]

CONCLUSION

This study examined the psychometric measurement properties and meaningful within-patient change thresholds for all three domains of the ePRO version of the MSQ v2.1 instrument using data from three Phase 3 studies. The findings substantiate the reliability, validity, and responsiveness of the instrument to measure the impact of EM and CM on the functional and emotional aspects based on patient's perspective. The meaningful within-patient change thresholds, ascertained through anchor-based methods supplemented by eCDFs and PDFs, are appropriate for inclusion in future preventive migraine clinical studies to evaluate the impact of study drugs on

FIGURE 2 Empirical cumulative distribution function and probability density function plots: change in MSQ v2.1 ePRO RFR, RFP, and EF domains. (A) Cumulative distribution function of MSQ v2.1 ePRO RFR domain change from baseline to Month 3 (EVOLVE-1 and EVOLVE-2 studies) by PGI-S. (B) Cumulative distribution function of MSQ v2.1 ePRO RFR domain change from baseline to Month 3 (EVOLVE-1 and EVOLVE-2 studies) by PGI-I. (C) Cumulative distribution function of MSQ v2.1 ePRO RFR domain change from baseline to Month 3 (REGAIN study) by PGI-S. (D) Cumulative distribution function of MSQ v2.1 ePRO RFR domain change from baseline to Month 3 (REGAIN study) by PGI-I. (E) Cumulative distribution function of MSQ v2.1 ePRO RFP domain change from baseline to Month 3 (EVOLVE-1 and EVOLVE-2 studies) by PGI-S. (F) Cumulative distribution function of MSQ v2.1 ePRO RFP domain change from baseline to Month 3 (EVOLVE-1 and EVOLVE-2 studies) by PGI-I. (G) Cumulative distribution function of MSQ v2.1 ePRO RFP domain change from baseline to Month 3 (REGAIN study) by PGI-S. (H) Cumulative distribution function of MSQ v2.1 ePRO RFR domain change from baseline to Month 3 (REGAIN study) by PGI-I. (I) Cumulative distribution function of MSQ v2.1 ePRO EF domain change from baseline to Month 3 (EVOLVE-1 and EVOLVE-2 studies) by PGI-S. (J) Cumulative distribution function of MSQ v2.1 ePRO EF domain change from baseline to Month 3 (EVOLVE-1 and EVOLVE-2 studies) by PGI-I. (K) Cumulative distribution function of MSQ v2.1 ePRO EF domain change from baseline to Month 3 (REGAIN study) by PGI-S. (L) Cumulative distribution function of MSQ v2.1 ePRO EF domain change from baseline to Month 3 (REGAIN study) by PGI-I. (M) Kernel density plot of MSQ v2.1 ePRO RFR domain change from baseline to Month 3 (EVOLVE-1 and EVOLVE-2 studies) by PGI-S. (N) Kernel density plot of MSQ v2.1 ePRO RFR domain change from baseline to Month 3 (EVOLVE-1 and EVOLVE-2 studies) by PGI-I. (O) Kernel density plot of MSQ v2.1 ePRO RFR domain change from baseline to Month 3 (REGAIN study) by PGI-S. (P) Kernel density plot of MSQ v2.1 ePRO RFR domain change from baseline to Month 3 (REGAIN study) by PGI-I. (Q) Kernel density plot of MSQ v2.1 ePRO RFP domain change from baseline to Month 3 (EVOLVE-1 and EVOLVE-2 studies) by PGI-S. (R) Kernel density plot of MSQ v2.1 ePRO RFP domain change from baseline to Month 3 (EVOLVE-1 and EVOLVE-2 studies) by PGI-I. (S) Kernel density plot of MSQ v2.1 ePRO RFP domain change from baseline to Month 3 (REGAIN study) by PGI-S. (T) Kernel density plot of MSQ v2.1 ePRO RFP domain change from baseline to Month 3 (REGAIN study) by PGI-I. (U) Kernel density plot of MSQ v2.1 ePRO EF domain change from baseline to Month 3 (EVOLVE-1 and EVOLVE-2 studies) by PGI-S. (V) Kernel density plot of MSQ v2.1 ePRO EF domain change from baseline to Month 3 (EVOLVE-1 and EVOLVE-2 studies) by PGI-I. (W) Kernel density plot of MSQ v2.1 ePRO EF domain change from baseline to Month 3 (REGAIN study) by PGI-S. (X) Kernel density plot of MSQ v2.1 ePRO EF domain change from baseline to Month 3 (REGAIN study) by PGI-I. EF, Emotional Function; MSQv2.1 ePRO, Migraine-Specific Quality of Life questionnaire version 2.1 electronic patient-reported outcome; PGI-I, Patient Global Impression of Improvement; PGI-S, Patient Global Impression of Severity; RFP, Role Function-Preventive; RFR, Role Function-Restrictive

Role Function-Restrictions and prevention and EF in patients with migraine.

CONFLICT OF INTEREST

DWA, JF, and RB are employees of Eli Lilly and Company. DWA and JF are minority stockholders of Eli Lilly and Company. KWW is a former employee of Eli Lilly and Company. RMS and RY are employees of Evidera, which provides consulting and other research services to pharmaceutical, medical device, and related organizations. In their salaried positions, they work with a variety of companies and organizations and are precluded from receiving payment or honoraria directly from these organizations for services rendered. Evidera received funding from Eli Lilly and Company to work on the study.

AUTHOR CONTRIBUTIONS

Conception and Design: Rebecca M. Speck, David W. Ayer, Janet H. Ford, Kathleen W. Wyrwich. *Acquisition of Data*: David W. Ayer. *Analysis and Interpretation of Data*: Rebecca M. Speck, Ren Yu, David W. Ayer, Janet H. Ford, Rohit Bhandari, Kathleen W. Wyrwich. *Drafting the Manuscript*: Rebecca M. Speck, Rohit Bhandari, Kathleen W. Wyrwich. *Revising It for Intellectual Content*: Rebecca M. Speck, Ren Yu, Janet H. Ford, David W. Ayer, Rohit Bhandari, Kathleen W. Wyrwich. *Final Approval of the Completed Manuscript*: Rebecca M. Speck, Ren Yu, Janet H. Ford, David W. Ayer, Rohit Bhandari, Kathleen W. Wyrwich.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

Table S1-S2

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