Research Submission

Analysis of Initial Nonresponders to Galcanezumab in Patients With Episodic or Chronic Migraine: Results From the EVOLVE-1, EVOLVE-2, and REGAIN Randomized, Double-Blind, Placebo-Controlled Studies

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Objective.—To examine the likelihood of response with continued galcanezumab treatment in patients with episodic or chronic migraine without initial clinical improvement.

Background.—A percentage of patients with migraine may require additional time on pharmacotherapy but discontinue treatment prematurely. Additionally, recognizing when continued treatment is unlikely to provide improvement limits unnecessary exposure.

Methods.—Post hoc analysis of response after continued galcanezumab treatment was conducted in a subset of patients with episodic (N = 879) and chronic (N = 555) migraine who did not achieve "good" early improvement (episodic, ≥50% reduction in baseline migraine headache days [MHD] and chronic, ≥30% reduction) after 1 month of dosing (NR-1; episodic, n = 450 and chronic, n = 306). This subset was categorized by level of reduction in MHD during 1 month of treatment: "modest" (>30% to <50% fewer MHD for episodic and >10% to <30% fewer MHD for chronic), "limited" (episodic only; >10% to ≤30% fewer MHD), or "minimal/no" early improvement (≤10% fewer MHD to ≤10% more MHD), or "worsening" (>10% more MHD). The percentages of patients having "better" (≥75% fewer MHD for episodic and ≥50% for chronic), "good," or "little-to-no" (≤10% fewer MHD) response during the remaining treatment period were calculated for each category. Similarly, the subset of NR-1 patients who did not achieve "good" early improvement after 2 months of treatment (NR-2; episodic, n = 290 and chronic, n = 240) were categorized by level of their average monthly reduction across 1 and 2 months using similar categories.

Results.—Of NR-1 patients with *episodic* migraine having "modest" early improvement, 62% (96/155) achieved "good" and 20% (31/155) achieved "better" responses with continued treatment. A percentage of patients with "limited" (43%; 46/108) or "minimal/no" (34%; 29/85) early improvement, or "worsening" (20%; 20/102) achieved a "good" response after continued treatment. A percentage of NR-1 patients with *chronic* migraine having "modest" early improvement achieved "good" (38%; 44/116) and "better" (13%; 15/116) responses with continued treatment. A "good" response was achieved for a percentage of patients with "minimal/no" early improvement (17%; 23/133). Similar patterns were observed for the NR-2 subset, though percentages were lower.

Conclusions.—Galcanezumab-treated patients with episodic or chronic migraine without response following 1 or 2 months of treatment appear to have a reasonable likelihood of continued improvement in months following initial treatment and this opportunity is more likely in patients showing greater early improvements. While a small percentage of patients with episodic or chronic migraine who experienced worsening in the number of MHD following initial treatment responded with continued treatment, most do not show substantial reduction in MHD. Overall benefit of therapy should be determined collaboratively between the patient and physician.

Key words: migraine, episodic, chronic, preventive, initial response, continued treatment

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INTRODUCTION

Migraine, both episodic and chronic, is a prevalent disease and is associated with medical and psychiatric comorbidities and disability that greatly impact quality of life.[1–4] Despite the preventive treatment options available, many patients are untreated or discontinue treatment[5–8] and most often for reasons of lack of efficacy and/or tolerability.[6–10] Patients with episodic migraine are at risk of their headache frequency increasing to chronic migraine, known as chronification.[11] However, adherence to preventive medications is associated with a reversion.[12] Patients who are taking preventive therapies for migraine should be routinely evaluated for both efficacy and tolerability. Therapy changes should be considered for patients not achieving efficacy within a reasonable time period or for tolerability issues, with the overall goal of reducing the migraine burden.

Galcanezumab is a humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) and prevents its biological activity without blocking the CGRP receptor and is under development for the prevention of migraine. Three randomized, double-blind, placebo-controlled Phase 3 studies of galcanezumab (120 and 240 mg/month) in patients with episodic (EVOLVE-1 and EVOLVE-2 parallel studies) or chronic (REGAIN study) migraine

examined the efficacy of galcanezumab.[13–15] In those studies, the percentage of patients with episodic or chronic migraine who achieved the threshold response criteria of reduction in the number of monthly migraine headache days (MHD) by ≥50% from baseline during the 6-month (episodic) or 3-month (chronic) double-blind period was measured. Higher thresholds of response were also evaluated. In both the episodic and chronic migraine trials, the percentage of patients achieving clinically meaningful differences (≥50% reduction of MHD) for either galcanezumab group was superior to placebo for patients with episodic migraine (60%) and patients with chronic migraine (27%).[13-15]

Results from these studies also suggested that some patients who did not initially meet threshold response criteria (subthreshold) stayed below the threshold for a month and then gained a response greater than the threshold. Additionally, some patients may not have reached the response threshold until the end of the treatment period. To examine the likelihood of response in this galcanezumab-treated patient population with episodic or chronic migraine that did not achieve threshold response criteria after 1 or 2 months of treatment, the response rates in the months following initial galcanezumab treatment and after continued treatment were evaluated.

METHODS

Study Design.—Detailed descriptions of the study designs have been reported separately.[13-15] Briefly, in both episodic migraine (6 months)[13,14] and in the chronic migraine (3 months)[15] double-blind studies, adult patients were randomized 1:1:2 and received subcutaneous injections of galcanezumab 120 mg/month (after a 240-mg initial loading dose) or 240 mg/month or placebo. Episodic migraine was defined as having between 4 and 14 MHD and at least 2 migraine attacks per month.[16] Chronic migraine was defined as having headache 15 or more days per month for more than 3 months and having features of migraine headache 8 or more days per month.[17] The study protocols were reviewed and approved by the appropriate institutional review board for each of the study sites. The studies were conducted according to Good Clinical Practice and the Declaration of Helsinki guidelines. Patients provided written informed consent before undergoing study procedures. The trials were registered with ClinicalTrials.gov (NCT02614183, NCT02614196, and NCT02614261). Data for the galcanezumab 120 mg and 240 mg groups were pooled from episodic and chronic migraine trials of galcanezumab-treated patients and were the basis of this post hoc analysis.

Statistical Method.—For this analysis, data included only galcanezumab-treated patients (dose groups pooled), 879 with *episodic* migraine (n = 444 for galcanezumab 120 mg; n = 435 for galcanezumab 240 mg) and 555 with *chronic* migraine (n = 278 for galcanezumab 120 mg; n = 277 for galcanezumab 240 mg). Only patients with both baseline and Month 1 MHD values were included in the post hoc analysis. In both the episodic and chronic migraine trials, there were no statistically significant differences between the galcanezumab 120-mg and 240-mg dose groups on primary and key secondary endpoints which justified pooling of the galcanezumab dose groups. Likewise, for the 2 episodic migraine trials, given the identical trial designs, it was expected that the corresponding dose groups from each trial performed similarly and could be pooled. Patients who did not achieve "good" early improvement after Month 1 of dosing (NR-1) were examined. Good early improvement was defined for episodic migraine as at least a 50% reduction from baseline in MHD and for patients with chronic migraine, at least a 30% reduction from baseline

in MHD. Responder rates have been traditionally defined in migraine as ≥50% reduction, but in the chronic migraine population, a reduction ≥30% in MHD can be clinically meaningful and was adopted for this analysis.[18] This subset of patients was then categorized based on the level of MHD reduction seen during 1 month of treatment. The categories of early improvement were as follows: "modest," "limited" (for episodic only), "minimal/no," or "worsening" response; definitions are further described in Table 1. The outcomes of the percentages of patients having "better," "good," or "little-to-no" response for the remaining treatment period (Months 2 through 6 for episodic trials and Months 2 and 3 for the chronic trial and derived based on average monthly reductions for the remaining months) were calculated for each of these categories; definitions are further described in Table 1. In a similar fashion, the subset of NR-1 patients who also did not have "good" early improvement after Month 1 or Month 2 of treatment (NR-2) were classified based on their average monthly reduction achieved across 1 and 2 months using the same categories given in Table 1, and the percentages of patients achieving "better," "good," or "little-to-no" responses were further summarized. The percentages of patients who met protocol-defined threshold response and the percentages of patients meeting the early improvement categories are illustrated in Figure 1 for patients with episodic migraine and in Figure 2 for patients with chronic migraine. Missing MHD values were replaced with the corresponding posterior mean condition on the data observed for the corresponding patient. This posterior mean is from a Bayesian hierarchical regression (via SAS Proc MI[19]) with non-informative (Jeffreys) priors assumed for the underlying mean vectors and variance matrices. The use of a Bayesian hierarchical regression with non-informative prior is commonly leveraged when conducting multiple imputation. However, in this case, we are only using the corresponding mean values. This, in essence, is similar to using a large number of imputations and replacing the missing values with the mean imputed value.

RESULTS

Patient Disposition.—Data from 879 galcanezumab-treated patients with episodic migraine and 555 patients

Table 1.—Definitions of Patient Categorization by Early Improvement, and Outcome Response

	Episodic	Chronic
Duration of initial treatment		
NR-1	Subthreshold or no response after Month 1 of treatment	
NR-2	Subthreshold or no response after either Month 1 or Month 2 of treatment	
Protocol threshold response	≥50% fewer MHD	≥30% fewer MHD[†]
Early improvement categories		
Modest	>30% to <50% fewer MHD	>10% to <30% fewer MHD
Limited	>10% to ≤30% fewer MHD	NA
Minimal/no	≤10% fewer MHD to ≤10% more MHD	≤10% fewer MHD to ≤10% more MHD
Worsening	>10% more MHD	>10% more MHD
Duration of continuing treatment period through double-blind treatment period		
NR-1	5 months	2 months
NR-2	4 months	1 month
Outcome response		
Better	≥75% fewer MHD	≥50% fewer MHD
Good	≥50% fewer MHD	≥30% fewer MHD
Little-to-no	≤10% fewer MHD	≤10% fewer MHD

MHD = migraine headache days; NA = not applicable.
[†]The key protocol-defined secondary response endpoint was ≥50%; however, patients with ≥30% were considered to have responded.
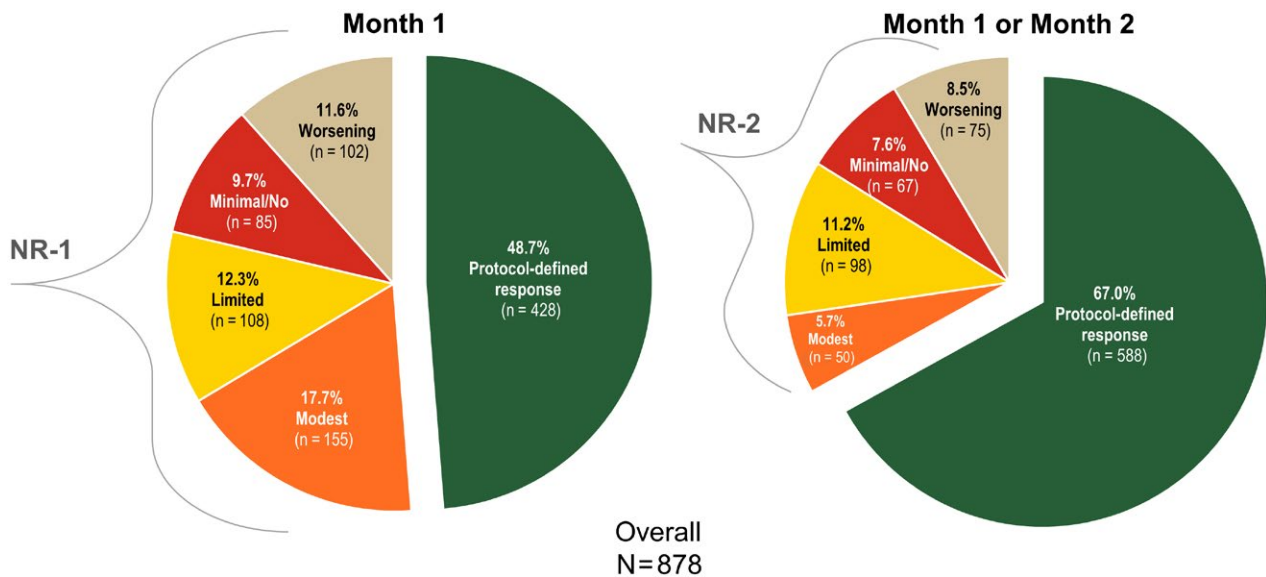

Fig. 1.—Percentage of patients with episodic migraine by improvement after 1 month and 2 months of galcanezumab treatment. MHD = migraine headache days; NR-1 = patients without response (with response defined as ≥50% reduction of MHD) after Month 1 of galcanezumab treatment; NR-2 = patients without response (with response defined as ≥50% reduction of MHD) after Month 1 or Month 2 of galcanezumab treatment.

with chronic migraine were evaluated. One patient in the episodic group was excluded because of missing Month 1 MHD values. Baseline demographics and disease characteristics of the pooled dose groups for the episodic and chronic migraine populations show that overall, over 80% were female and over 74% were white. The mean age was 40 years and the mean migraine disease duration was 20 years (Table 2). At baseline, the mean MHD/month was 9.1 for patients with episodic migraine and 19.3 for patients with chronic migraine. Protocol-defined response (≥50% fewer MHD) was met by 48.7% (NR-1) and
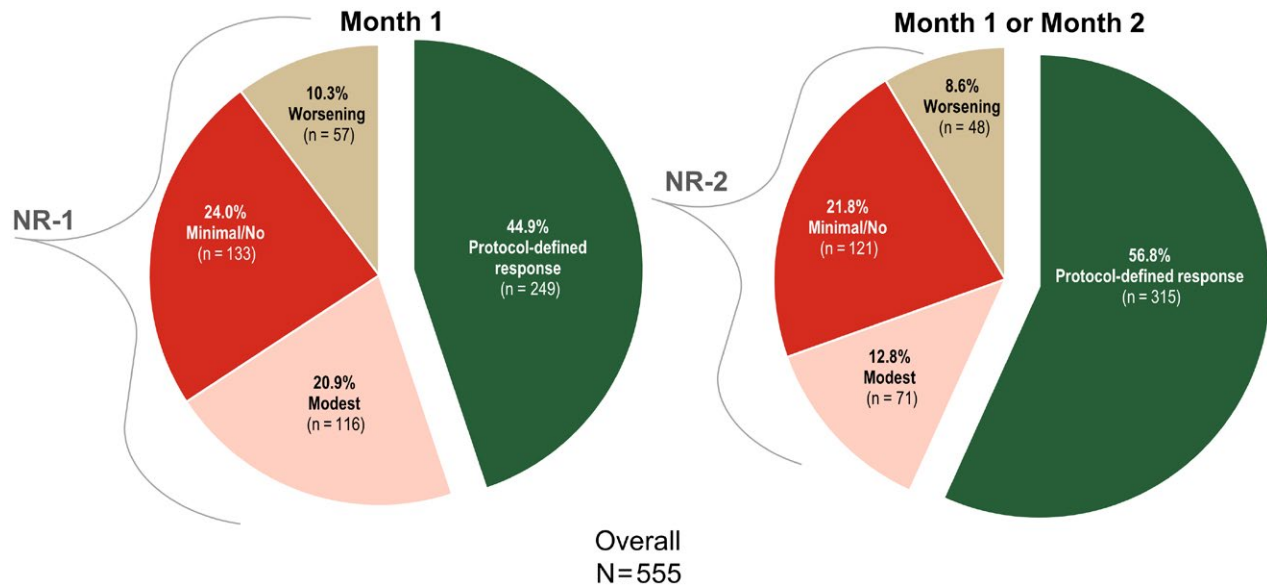
Fig. 2.—Percentage of patients with chronic migraine by improvement after 1 month and 2 months of galcanezumab treatment. MHD = migraine headache days; NR-1 = patients without response (with response defined as ≥30% reduction of MHD) after Month 1 of galcanezumab treatment; NR-2 = patients without response (with response defined as ≥30% reduction of MHD) after Month 1 or Month 2 of galcanezumab treatment.

67.0% (NR-2) of patients with *episodic* migraine (Fig. 1) and 44.9% (NR-1) and 56.8% (NR-2) of patients with *chronic* migraine (Fig. 2); these patients were not subject to further analysis. The analysis set included patients who did not meet protocol-defined response at Month 1 (NR-1; episodic, n = 450 and chronic, n = 306) and Month 1 or Month 2 (NR-2; episodic, n = 290 and chronic, n = 240) (Figs. 1 and 2).

Results for Galcanezumab-Treated Patients Without Initial Treatment Response at Month 1 (NR-1).—Of NR-1 patients with *episodic* migraine, more patients having "modest" early improvement with treatment achieved a "good" response (62% with ≥50% fewer MHD) or a "better" response (20% with ≥75% fewer MHD) response with continued treatment relative to other early improvement categories. Further, the percentage of patients who achieved a "good" response after continued treatment was 43% for those with "limited" and 34% with "minimal/no" early improvement, and 20% for those with "worsening." Overall, patients with "limited" or "minimal/no" early improvement or "worsening" ~10% of patients achieved a "better" response (Table 3, Fig. 3).

Of NR-1 patients with *chronic* migraine, more patients having "modest" early improvement with treatment achieved a "good" response (38% with ≥30% fewer MHD) or a "better" response (13% with ≥50%

fewer MHD) response with continued treatment relative to other early improvement categories. Further, the percentage of patients who achieved a "good" response after continued treatment was 17% for those with "minimal/no" early improvement and 11% for those with "worsening." Overall, patients with "minimal/no" early improvement or "worsening" few (~4%) achieved a "better" response (Table 4, Fig. 4).

Results for Galcanezumab-Treated Patients Without Initial Treatment Response at Month 1 or Month 2 (NR-2).—Similar to the patterns observed with the NR-1 groups, response with continued treatment followed a decreasing trend based on the category of early improvement, though in general, the percentages of patients were lower for each response outcome. Specifically, of NR-2 patients with *episodic* migraine, among those having "modest" early improvement with treatment, 50% achieved a "good" response (≥50% fewer MHD) and 12% achieved a "better" (≥75% fewer MHD) response with continued treatment. The percentages of patients with initial "limited" or "minimal/no" early improvement or "worsening" responses who achieved a "good" response after continued treatment were 41%, 18%, and 9%, respectively. The small percentage of patients with "limited" early improvement who achieved a "better" response (14%) was similar to that of those with

Table 2.—Patient Demographics and Disease Characteristics of Galcanezumab[†]-Treated Patients From Episodic and Chronic Migraine Trials

Variables	Episodic[‡] N = 879	Chronic[§] N = 555
Age, years, mean (SD)	40.7 (11.4)	40.4 (12.2)
Female, n (%)	744 (84.6)	463 (83.4)
Race white, n (%)	652 (74.2)	447 (80.7)
Body mass index, kg/m^2, mean (SD)	27.6 (5.5)	26.5 (5.4)
Migraine disease duration, years, mean (SD)	20.1 (12.2)	20.2 (12.7)
Migraine headache days (MHD)/month, mean (SD)	9.1 (2.9)	19.3 (4.4)
MHD/month with acute medication use, mean (SD)	7.4 (3.4)	14.8 (6.3)
Headache days/month, mean (SD)	10.7 (3.7)	21.3 (4.0)
Migraine headache hours/month, mean (SD)	55.0 (39.7)	135.4 (83.0)
Headache hours/month, mean (SD)	61.7 (51.9)	145.3 (89.4)
Migraine with aura, n (%)	467 (53.1)	294 (53.0)
Prior preventive treatment in past 5 years, n (%)	559 (63.6)	431 (77.7)
Failed ≥2 preventives in past 5 years, n (%)	88 (10.0)	165 (29.7)
MIDAS total, mean (SD)	33.1 (28.2)	65.8 (57.3)
MSQ RF-R, mean (SD)	51.1 (16.1)	39.1 (17.3)
MSQ RF-P, mean (SD)	66.7 (19.7)	56.3 (21.3)
MSQ EF, mean (SD)	59.2 (24.0)	45.5 (26.6)
PGI-S, mean (SD)	4.3 (1.2)	4.8 (1.3)

EF = Emotional Function; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire version 2.1; PGI-S = Patient Global Impression of Severity; RF-P = Role Function-Preventive; RF-R = Role Function-Restrictive; SD = standard deviation.
[†]Combined 120 mg/month and 240 mg/month galcanezumab-treated patient groups.
[‡]Pooled data from two 6-month trials in patients with episodic migraine. Note: 1 patient did not have MHD values at Month 1 and was excluded from further analyses.
[§]Three-month trial.

"modest" early improvement, while few patients with "minimal/no" early improvement or "worsening" were able to achieve the "better" response categorization (Table 3, Fig. 5).

Of the NR-2 group with *chronic* migraine, the pattern of percentages of patients with response with continued treatment based on their early improvement categorization (Table 4, Fig. 6) was very similar to that seen with the NR-1 group (Fig. 4).

Results for Placebo-Treated Patients Without Initial Treatment Response at Month 1 (NR-1) or Month 1 or Month 2 (NR-2).—Table 5 presents results for patients with episodic and chronic migraine treated with placebo categorized by NR-1 and NR-2 groupings. In both groups of patients with episodic or chronic migraine, the pattern of percentages of patients with response with continued placebo treatment followed a decreasing trend based on the category of early improvement. However, it is important to note that formal comparisons between placebo and galcanezumab treatment groups were not made and would not be appropriate.

DISCUSSION

A proportion of patients with episodic or chronic migraine who had lower than protocol-defined responses within the first month or two of galcanezumab treatment were able to achieve clinically meaningful response with continued galcanezumab treatment. This opportunity was greatest for those patients who, in the initial month of treatment, had early improvement closer to the threshold response (ie, "modest" early improvement).

For patients with episodic migraine, the best indicator of a good treatment response over time was the achievement of limited-to-modest early improvement by 2 months. However, even patients with

Table 3.—Galcanezumab-Treated Patients With Episodic Migraine: Response in NR-1 and NR-2 Groups After Continued Galcanezumab Treatment (Remaining Months 2 Through 6)

Patient Category for Type of Early Improvement	Response Outcome Across Remaining 6 Months With Continued Galcanezumab Treatment, n (%)			
	N = 878	Better (≥75% Fewer MHD)	Good (≥50% Fewer MHD)	Little-To-No (≤10% Fewer MHD)
NR-1[†]				
Protocol-threshold[‡]	n = 428	NA	NA	NA
Modest[§]	n = 155	31 (20.0)	96 (61.9)	10 (6.5)
Limited[¶]	n = 108	13 (12.0)	46 (42.6)	17 (15.7)
Minimal/no[††]	n = 85	11 (12.9)	29 (34.1)	17 (20.0)
Worsening[‡‡]	n = 102	8 (7.8)	20 (19.6)	48 (47.1)
NR-2[†]				
Protocol-threshold[‡]	n = 588	NA	NA	NA
Modest[§]	n = 50	6 (12.0)	25 (50.0)	2 (4.0)
Limited[¶]	n = 98	14 (14.3)	40 (40.8)	14 (14.3)
Minimal/no[††]	n = 67	3 (4.5)	12 (17.9)	20 (29.9)
Worsening[‡‡]	n = 75	1 (1.3)	7 (9.3)	49 (65.3)

MHD = migraine headache days; NA = not applicable; NR-1 = patients without response (with response defined as ≥50% reduction of MHD) after Month 1 of galcanezumab treatment; NR-2 = patients without response (with response defined as ≥50% reduction of MHD) after Month 1 or Month 2 of galcanezumab treatment.
[†]Combined 120 mg/month and 240 mg/month galcanezumab-treated patient groups. Note: 1 patient did not have MHD values at Month 1 and was excluded from further analyses.
[‡]Defined as reduction from baseline ≥50% in monthly MHD. These patients were not subject to further post hoc analysis.
[§]Defined as fewer MHD by >30% to <50%.
[¶]Defined as fewer MHD by >10% to ≤30%.
[††]Defined as ≤10% fewer MHD to ≤10% more MHD.
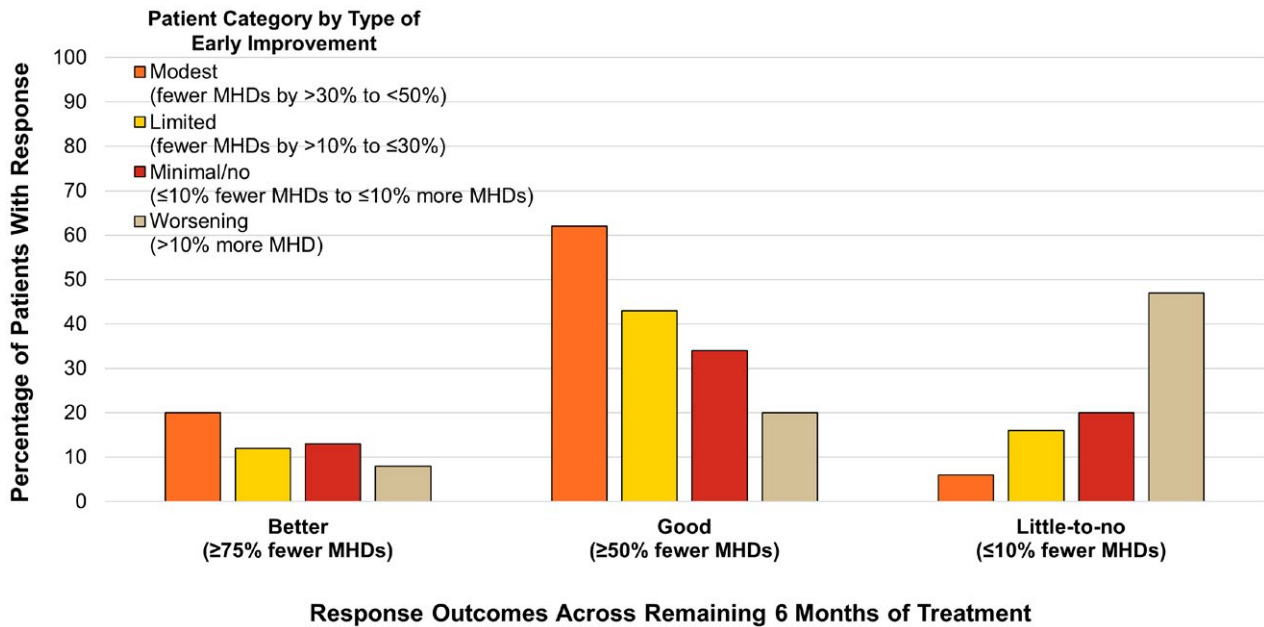[‡‡]Defined as >10% more MHD.

Fig. 3.—Response of patients with episodic migraine (NR-1) after continued galcanezumab treatment (remaining months 2-6). MHD = migraine headache days; NR-1 = patients without response (with response defined as ≥50% reduction of MHD) after Month 1 of galcanezumab treatment.

Table 4.—Galcanezumab-Treated Patients With Chronic Migraine: Response in NR-1 and NR-2 Groups After Continued Galcanezumab Treatment (Remaining Months 2 Through 3)

Patient Category for Type of Early Improvement	Response Outcome Across Remaining 3 Months With Continued Galcanezumab Treatment, n (%)			
	N = 555	Better (≥50% Fewer MHD)	Good (≥30% Fewer MHD)	Little-To-No (≤10% Fewer MHD)
NR-1[†]				
Protocol-threshold[‡]	n = 249	NA	NA	NA
Modest[§]	n = 116	15 (12.9)	44 (37.9)	35 (30.2)
Minimal/no[¶]	n = 133	6 (4.5)	23 (17.3)	71 (53.4)
Worsening[††]	n = 57	2 (3.5)	6 (10.5)	42 (73.7)
NR-2[†]				
Protocol-threshold[‡]	n = 315	NA	NA	NA
Modest[§]	n = 71	12 (16.9)	25 (35.2)	20 (28.2)
Minimal/no[¶]	n = 121	7 (5.8)	16 (13.2)	74 (61.2)
Worsening[††]	n = 48	1 (2.1)	5 (10.4)	41 (85.4)

MHD = migraine headache days; NA = not applicable; NR-1 = patients without response (with response defined as ≥30% reduction of MHD) after Month 1 of galcanezumab treatment; NR-2 = patients without response (with response defined as ≥30% reduction of MHD) after Month 1 or Month 2 of galcanezumab treatment.
[†]Combined 120 mg/month and 240 mg/month galcanezumab-treated patient groups.
[‡]Defined as reduction from baseline ≥30% in monthly MHD. These patients were not subject to further post hoc analysis.
[§]Defined as fewer MHD by >10% to <30%.
[¶]Defined as ≤10% fewer MHD to ≤10% more MHD.
[††]Defined as >10% more MHD.

Fig. 4.—Response of patients with chronic migraine (NR-1) after continued galcanezumab treatment (remaining months 2-3). MHD = migraine headache days; NR-1 = patients without response (with response defined as ≥30% reduction of MHD) after Month 1 of galcanezumab treatment.

Fig. 5.—Response of patients with episodic migraine (NR-2) after continued galcanezumab treatment (remaining months 3-6). MHD = migraine headache days; NR-2 = patients without response (with response defined as ≥50% reduction of MHD) after Month 1 or Month 2 of galcanezumab treatment.
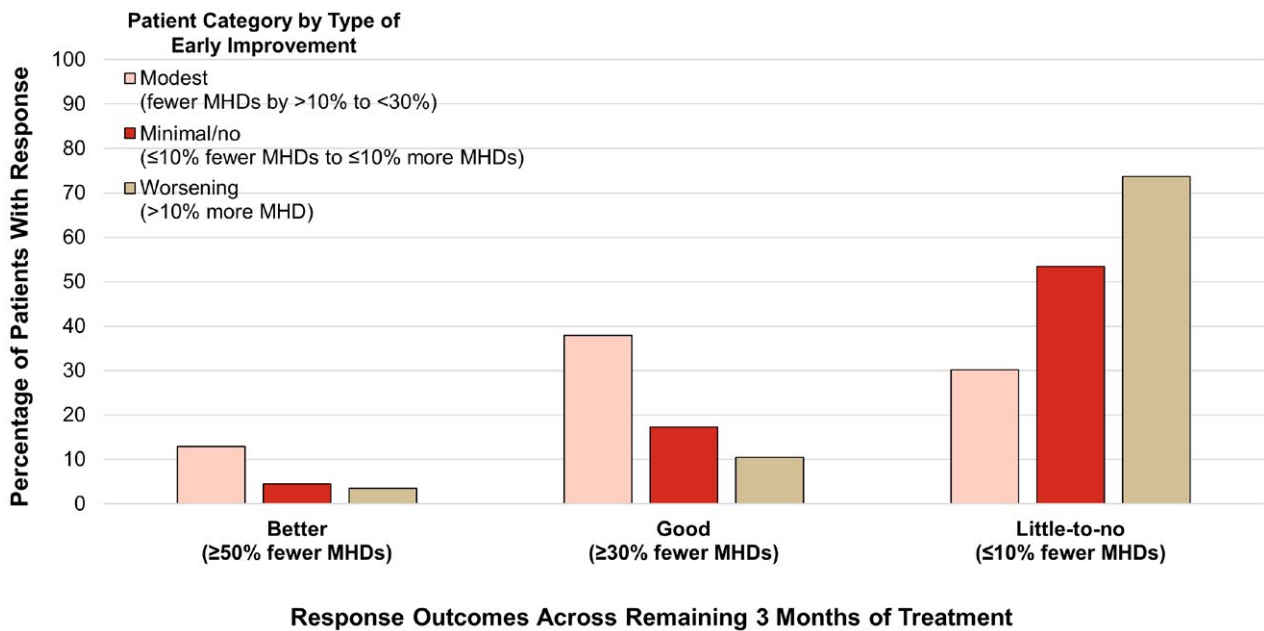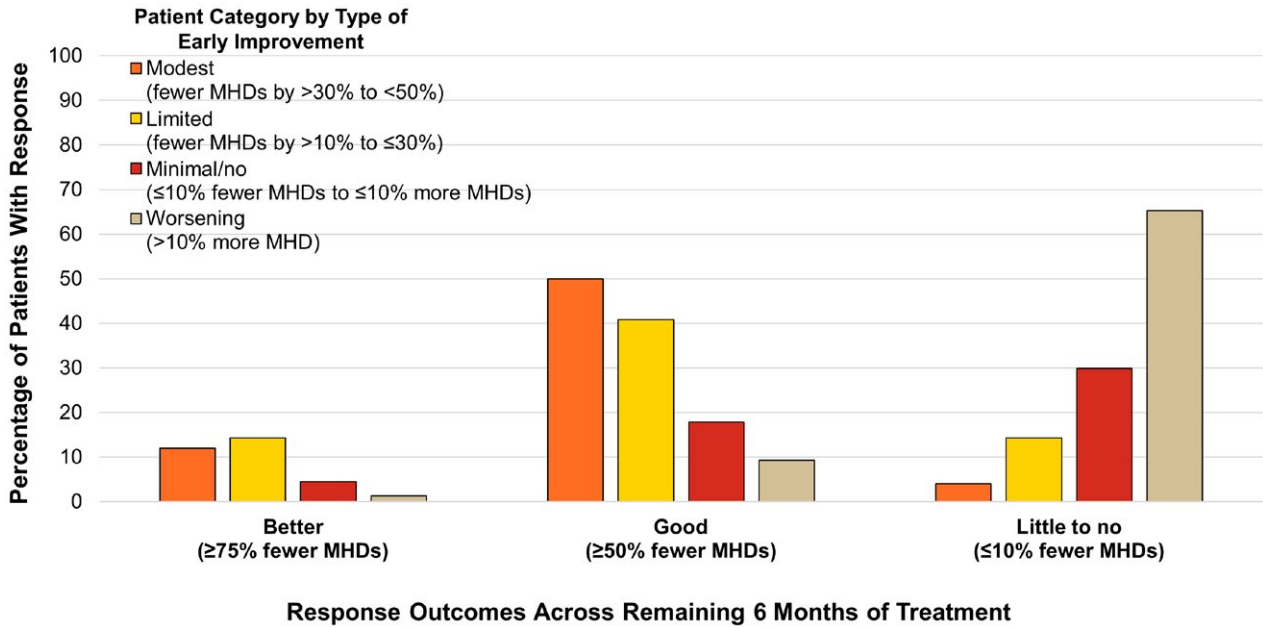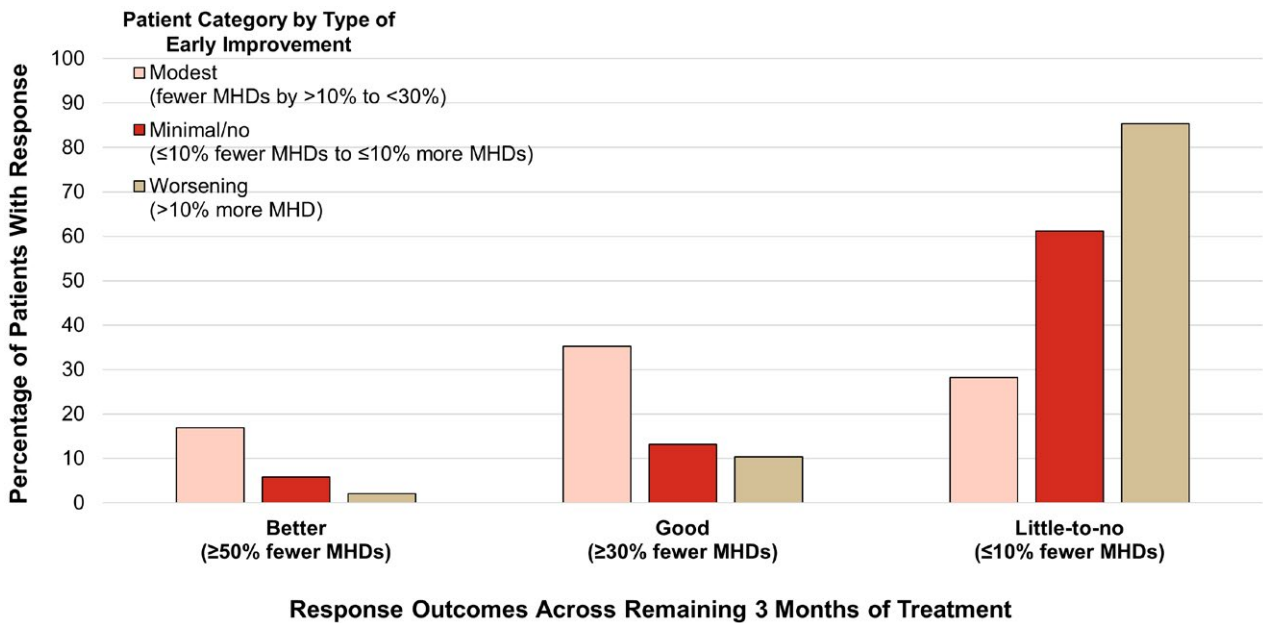

Fig. 6.—Response of patients with chronic migraine (NR-2) after continued galcanezumab treatment (remaining 1 month). MHD = migraine headache days; NR-2 = patients without response (with response defined as ≥30% reduction of MHD) after Month 1 or Month 2 of galcanezumab treatment.

episodic migraine who demonstrated "minimal/no" early improvement or "worsening" after 1 month had a chance to achieve a "good" response with continued galcanezumab treatment.

The results in patients with chronic migraine were encouraging given that this group is the most disabled migraine population. In the REGAIN study, 27% of patients with chronic migraine met the key protocol-defined secondary response endpoint of ≥50% fewer MHD.[15] For this analysis, a protocol-defined response of ≥30% was used and 45% of the patients achieved this response after 1 month. The possibility

Table 5.—Placebo-Treated Patients: Response in NR-1 and NR-2 Groups After Continued Placebo Treatment in Patients With Episodic Migraine (Remaining Months 2-6) and Chronic Migraine (Remaining Months 2-3)

Patient Category for Type of Early Improvement	Episodic Migraine				Chronic Migraine			
		Response Outcome Across Remaining 6 Months With Continued Placebo Treatment, n (%)				Response Outcome Across Remaining 3 Months With Continued Placebo Treatment, n (%)		
	N = 893	Better (≥75% fewer MHD)	Good (≥50% fewer MHD)	Little-to-No (≤10% fewer MHD)	N = 557	Better (≥50% fewer MHD)	Good (≥30% fewer MHD)	Little-to-No (≤10% fewer MHD)
NR-1								
Protocol-threshold[†]	n = 213	NA	NA	NA	n = 150	NA	NA	NA
Modest[‡]	n = 165	25 (15.2)	75 (45.5)	12 (7.3)	n = 135	20 (14.8)	52 (38.5)	36 (26.7)
Limited[§]	n = 144	12 (8.3)	42 (29.2)	29 (20.1)	n = 160	NA	NA	NA
Minimal/no[¶]	n = 150	6 (4.0)	25 (16.7)	55 (36.7)	n = 160	9 (5.6)	25 (15.6)	85 (53.1)
Worsening[††]	n = 221	3 (1.4)	17 (7.7)	135 (61.1)	n = 112	3 (2.7)	7 (6.3)	91 (81.3)
NR-2								
Protocol-threshold[†]	n = 371	NA	NA	NA	n = 240	NA	NA	NA
Modest[‡]	n = 78	5 (6.4)	26 (33.3)	4 (5.1)	n = 77	5 (6.5)	17 (22.1)	26 (33.8)
Limited[§]	n = 137	8 (5.8)	28 (20.4)	19 (13.9)	n = 160	NA	NA	NA
Minimal/no[¶]	n = 135	0 (0.0)	11 (8.2)	70 (51.9)	n = 147	7 (4.8)	14 (9.5)	89 (60.5)
Worsening[††]	n = 172	2 (1.2)	9 (5.2)	126 (73.3)	n = 93	1 (1.1)	2 (2.2)	84 (90.3)

MHD = migraine headache days; NA = not applicable; NR-1 = patients without response (with response defined as ≥50% reduction of MHD) after Month 1 of placebo treatment; NR-2 = patients without response (with response defined as ≥50% reduction of MHD) after Month 1 or Month 2 of placebo treatment.
[†]Defined as reduction from baseline ≥50% in monthly MHD for episodic migraine and reduction from baseline ≥30% in monthly MHD for chronic migraine. These patients were not subject to further post hoc analysis.
[‡]Defined as fewer MHD by >30% to <50% for episodic migraine and fewer MHD by >10% to <30% for chronic migraine.
[§]Defined as fewer MHD by >10% to ≤30%.
[¶]Defined as ≤10% fewer MHD to ≤10% more MHD.
[††]Defined as >10% more MHD.

that a treatment effect over time was occurring was most discernible in the patients showing "modest" early improvement at 1 and 2 months, with a notable percentage of those patients achieving a clinically meaningful response. For patients with chronic migraine, the probability of a "good" response by 3 months was low if the patient was not showing at least "modest" early improvements by 2 months of treatment. Patients with chronic migraine who showed "minimal/no" early improvement or "worsening" by 2 months were unlikely to show a meaningful response with continued treatment. It is important to note that the criteria for a "good" response for chronic migraine was lowered to ≥30% fewer MHD. The group analyzed had a baseline mean of 19 MHD per month and thus, a reduction of at least ~6 MHD is clinically meaningful and generally accepted as a valid clinical bar.[18] It is important to consider that these results may be a reflection of the shorter duration of the chronic migraine study. Regardless, recognizing when continued treatment is unlikely to provide improvement is important to limit unnecessary exposure.

With both episodic and chronic migraine, it is important to consider that other factors may contribute to measuring effectiveness of preventive treatment. Reductions in acute medication use, reduced severity of attacks, and improved interictal periods are examples of efficacy that should be taken into account along with overall reduction of MHD when considering continuation or cessation of preventive therapy. Overall effectiveness of therapy, taking into account all aspects of treatment efficacy, should be determined collaboratively between the patient and physician.[20,21]

While the results here are intended to characterize results observed in the pivotal EVOLVE-1 and -2 and REGAIN galcanezumab trials, certain limitations should be noted. First, the post hoc nature of the analysis is an inherent limitation. Second, the short duration of the trials included in the analysis precludes drawing conclusions beyond 3 (chronic migraine) and 6 (episodic migraine) months. In particular, for patients with chronic migraine, it is possible that an additional 2 months of treatment beyond the first month is insufficient to see clinical improvement. Planned, longer term open-label clinical trials may address this issue and potentially identify trends in response. Third, establishing the threshold at ≥30% reduction of MHD in patients with chronic

migraine may be interpreted by some as not clinically meaningful enough. However, when considering the known treatment challenges in the chronic migraine population, this level of response is clinically relevant.[18] Again, longer-term trials may further parse out response distinctions. Fourth, while estimates were calculated based on all available data, sample sizes in some categories were small given that the numbers of patients with subthreshold response at early months were small. Fifth, use of reduction in MHD as the only measure of benefit may limit understanding the full scope of continued treatment in patients without initial threshold response. Finally, the analysis was wholly descriptive in nature and no differential treatment conclusions were made. Formal comparisons with placebo within each of the levels of early improvement are not meaningful in that the populations are likely different (eg, the population of patients showing "modest" early improvement with galcanezumab is likely not the same population that would show "modest" early improvement with placebo). To elaborate, for placebo-treated patients, the expectations of eventual response were conditioned on the level of improvement seen in early months. This result, however, is mainly due to the conditional nature of what is being examined. To illustrate, using the episodic migraine trials and the percentage of patients eventually having a "good" response given that they showed "worsening" at Month 1, as an example, the percentage for placebo-treated patients was 7.7% (compared to the 19.6% of galcanezumab-treated patients). What is not taken into account in this type of analysis is the percentage of patients meeting the criteria (24.7% of placebo patients worsen at Month 1 compared to 11.6% of galcanezumab patients). While interesting, such comparisons should not be made to those observed with galcanezumab treatment due to population differences. Some of the improvements in the galcanezumab groups observed in this trial were likely, in part, due to regression to the mean as well as the known variability of this neurological disorder. Thus, the improvements may have still been observed had the patient not received any treatment at all.

CONCLUSIONS

Galcanezumab-treated patients with episodic or chronic migraine who have not responded following

1 or 2 months of treatment appear to have a reasonable likelihood of continued improvement in months following initial treatment, with greater likelihood seen in patients showing greater early improvement. While a small percentage of patients with episodic or chronic migraine who experienced worsening of MHD following initial treatment responded with continued dosing, most patients do not show substantial response with continued treatment. Factors contributing to response/nonresponse have yet to be elucidated and clinical judgment should be exercised when deciding whether to discontinue treatment.

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