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RESEARCH SUBMISSIONS

A phase IV clinical trial of gastrointestinal motility in adult patients with migraine before and after initiation of a calcitonin gene-related peptide ligand (galcanezumab) or receptor (erenumab) antagonist

David Kudrow MD[1] | Linda Nguyen MD[2] | Jack Semler PhD[3] | Chad Stroud RPh[4] | Karen Samaan PharmD[4] | Deirdre B. Hoban PhD[4] | Linda Wietecha MS[4] | Hai-An Hsu PhD[4] | Eric Pearlman MD, PhD[4]

[1]California Medical Clinic for Headache, Santa Monica, California, USA

[2]Division of Gastroenterology, Stanford University, Palo Alto, California, USA

[3]Medtronic, Minneapolis, Minnesota, USA

[4]Eli Lilly and Company, Indianapolis, Indiana, USA

Correspondence
Chad Stroud, Eli Lilly and Company, Indianapolis, IN, USA.
Email: stroud_chad_e@lilly.com

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Abstract

Objective: To compare effects of an initial dose of calcitonin gene-related peptide (CGRP) monoclonal antibody (mAb) antagonists on gastrointestinal (GI) motility in patients with migraine and to explore if the mechanistic difference contributes to GI adverse events (AEs).

Background: Different frequencies of constipation have been observed between CGRP mAbs that target the ligand (galcanezumab [GMB]) or receptor (erenumab [ERE]).

Methods: Patients (n = 65) with migraine without significant GI symptoms were enrolled in a multi-center, single-blind phase IV clinical trial (NCT04294147) and randomized 1:1 to receive GMB (240 mg; n = 33) or ERE (140 mg; n = 32). GI whole and regional transit times were assessed using a wireless motility capsule 1 week before and 2 weeks after mAb administration. The primary endpoint was change from baseline in colonic transit time (CTT) within each treatment group. Other measures included GI Symptom Rating Scale (GSRS), Bristol Stool Form Scale (BSFS), and spontaneous bowel movement (SBM) evaluation. AEs were monitored throughout the study.

Results: Baseline characteristics indicated significant GI transit time variability with minimal GI reported symptoms. While not statistically significant, a numerical mean increase in CTT was observed in ERE patients (n = 28, mean [SD] at baseline: 33.8 [29.4] h; least square [LS] mean [SE] change: 5.8 [5.7] h, 95% confidence interval [CI] −5.7 to 17.2, p = 0.320), while GMB decreased CTT (n = 31, mean [SD] at baseline: 29.3 [24.5] h; LS mean [SE] change: −5.4 [5.4] h, 95% CI −16.2 to 5.5, p = 0.328) compared to baseline. No meaningful changes were observed in other regional transit times. ERE

Abbreviations: AE, adverse event; AMY1, amylin; BSFS, Bristol Stool Form Scale; CGRP, calcitonin gene-related peptide; CTT, colonic transit time; GET, gastric emptying time; GI, gastrointestinal; GSRS, GI symptom rating scale; LS, least squares; mAb, monoclonal antibody; SAE, serious adverse event; SBM, spontaneous bowel movement; SBTT, small bowel transit time; SLBTT, small and large bowel transit time; TEAE, treatment-emergent adverse event; WGTT, whole gut transit time; WMC, wireless motility capsule.

significantly reduced BSFS (LS mean [SE] score −0.5 [0.2], $p = 0.004$) and SBM (LS mean [SE] −1.2 [0.5], $p = 0.0120$), and increased GSRS-constipation compared to baseline (LS mean [SE] score 0.3 [0.1], $p = 0.016$). GMB increased GSRS-constipation (LS mean [SE] score 0.4 [0.1], $p = 0.002$). There were no discontinuations due to or serious AEs. A higher percentage of treatment-emergent AEs were reported with ERE than GMB (ERE: nine of 32 [28.1%] versus GMB: three of 33 [9.1%]), with constipation the most frequently reported (ERE: five of 32 [15.6%] versus GMB one of 33 [3.0%]).

Conclusion: While the primary endpoint of this study was not met, secondary and tertiary endpoints support a within- and between-treatment change in GI effects suggesting possible mechanistic differences between ligand (GMB) and receptor (ERE) antagonism.

KEYWORDS
calcitonin gene-related peptide, colonic transit time, constipation, gastrointestinal motility, migraine, monoclonal antibodies

INTRODUCTION

Calcitonin gene-related peptide (CGRP) is implicated in the development and maintenance of migraine. Modulation of CGRP via receptor or ligand antagonists is a strategy for the prevention of migraine.[1–3] Differences have been observed between reported frequencies of constipation in clinical trials and post-marketing adverse event (AE) reporting of CGRP antagonists that target the ligand (galcanezumab, fremanezumab) or the receptor (erenumab, atogepant).[4–8]

Galcanezumab is a humanized monoclonal antibody (mAb) that binds to CGRP and prevents its biological activity without blocking the CGRP receptor. The efficacy of galcanezumab in the prevention of migraine has been demonstrated in three randomized, double-blind, placebo-controlled phase III trials.[9–11] Across phase II and phase III clinical studies in patients with migraine, galcanezumab exhibited a favorable safety profile at doses up to 300 mg every 4 weeks for 3 months, or 240 mg monthly for up to 1 year.[10–14] The incidences of serious AEs (SAEs) and discontinuations due to AEs were low in the phase III studies, the most commonly reported treatment-emergent AEs (TEAEs) were injection site pain and injection site reactions, generally of mild to moderate severity. In post-marketing experience, hypersensitivity reactions, including anaphylaxis, angioedema, dyspnea, urticaria, and rash, have been reported with galcanezumab.

Erenumab is a human mAb that antagonizes the CGRP receptor. The efficacy of erenumab for the prevention of migraine has been demonstrated in three randomized, double-blind phase III trials.[15–17] The incidences of SAEs and discontinuations due to AEs were low, and the most common AEs were injection site reactions, constipation, and cramps/muscle spasms.[4] Hypersensitivity reactions (including rash, angioedema, and anaphylaxis), constipation with serious complications, and new-onset or worsening of pre-existing hypertension have been reported with erenumab in post-marketing experience.

Clinical trials with selective CGRP receptor antagonists for migraine prevention reported greater constipation-related AEs[4,8,18] than trials studying antagonists that target the CGRP ligand.[6,7] Preclinical animal studies suggest that the different mechanisms of action of these agents may contribute to the different frequencies of reported constipation.[19] In addition to its agonist activity at the CGRP receptor, CGRP is a potent agonist at the amylin (AMY1) receptor. CGRP receptors are located throughout the gastrointestinal (GI) system of rodents and humans, including both the small and large intestines. CGRP infusion has been reported to cause GI symptoms, including diarrhea, in 93% of human subjects.[20] Additionally, CGRP (administered intraperitoneally) has been shown to cause diarrhea in rodents that can be blocked by a CGRP antibody.[21] AMY1 receptors are found on nerves projecting from the area postrema to the GI tract, activation of which affects motor and secretory drives to induce stasis of the GI system. An antibody that binds to the CGRP receptor (erenumab) will block the effects of CGRP at the CGRP receptor but will not affect CGRP activity at the AMY1 receptor. In theory, by blocking the CGRP receptor, erenumab would decrease the motility-enhancing characteristics of CGRP while not affecting the GI motility-slowing effects via AMY1 receptor activation. In contrast, an antibody that binds to CGRP itself (galcanezumab) will inhibit the pharmacological effects of CGRP at both the CGRP and AMY1 receptors. Consequently, the effect of inhibiting the motility-enhancing and motility-slowing effects of CGRP at the CGRP and AMY1 receptors, respectively, may have no net effect on GI transit time.

In this study, we hypothesized that, because of their differing mechanisms of action, a single dose of erenumab would increase GI transit time whereas a single dose of galcanezumab would not alter GI transit time, compared to baseline, in patients with episodic migraine. Therefore, the purpose of this clinical study was to measure GI transit time in adult patients with episodic migraine who had a single dose of preventive treatment with a CGRP mAb antagonist (galcanezumab or erenumab) and to explore whether this is a mechanistic difference that may contribute to GI AEs in humans.

METHODS

Overall design

This study was a multicenter, randomized, single-blind, phase IV clinical study (NCT04294147) in patients with episodic migraine who were deemed eligible for preventive treatment by the study investigator. The study was performed at three centers (outpatient clinics) in the United States. The study design is outlined in Figure 1, and the trial was conducted according to the original protocol. Briefly, the study had two periods: a screening period to determine patient eligibility, with lead-in with a baseline wireless motility capsule (WMC) test; and a single-blind treatment period with an on-treatment WMC test. Visit 1 consisted of a full clinical assessment and a physical examination. Visit 2 included administration of the baseline WMC to patients who met all eligibility requirements. At the start of the single-blind treatment period (Visit 3), participants were randomized in a 1:1 ratio to receive galcanezumab 240 mg (the initial loading dose per United States Prescribing Information [USPI]) or erenumab 140 mg subcutaneously. Participants were administered two galcanezumab injections of 120 mg each to achieve the 240-mg loading dose or two erenumab injections of 70 mg each to achieve the 140 mg dose. At 2 weeks post-dose (Visit 4), participants repeated the WMC test and completed the study 4 weeks post-dose (Visit 5; Figure 1).

Ethical approval and conduct

The study protocol was reviewed and approved by the appropriate institutional or ethical review board for each site. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki guidelines. Participants provided written informed consent before undergoing the study procedures. Given the phase IV nature of this trial, there was no data safety monitoring board in place, rather patients were monitored by the prescribing physician (principal investigator).

Inclusion and exclusion criteria

Eligible patients were aged 18–55 years with a diagnosis of episodic migraine with or without aura, as determined by the study investigator and in consideration of *International Headache Society International Classification of Headache Disorders*, third edition guidelines.[22] Participants had a frequency of <15 monthly headache days of which up to 14 could be migraine headache days, defined as episodic migraine. Participants were on no more than one other migraine preventive treatment (except for tricyclic antidepressants and verapamil, which were excluded) if that participant had a stable dose of the oral migraine preventive treatment for a minimum of 2 months prior to Visit 1 or participants received a minimum of 2 cycles of onabotulinumtoxinA prior to Visit 1.

Participants were excluded from study enrollment if they had significant GI symptoms: less than three bowel movements in the 7 days prior to Visit 1, had a history of irritable bowel syndrome or chronic constipation, reported history of gastric bezoars, swallowing disorders, severe dysphagia to food or pills, suspected or known strictures, fistulae, or physiological/mechanical GI obstruction. Participants were also excluded if they had a history of GI surgery (except for cholecystectomy, appendectomy, or Nissen fundoplication), any abdominal surgery within the previous 3 months or bariatric surgery or if they were taking certain concomitant medications known to alter GI transit time. Comorbid

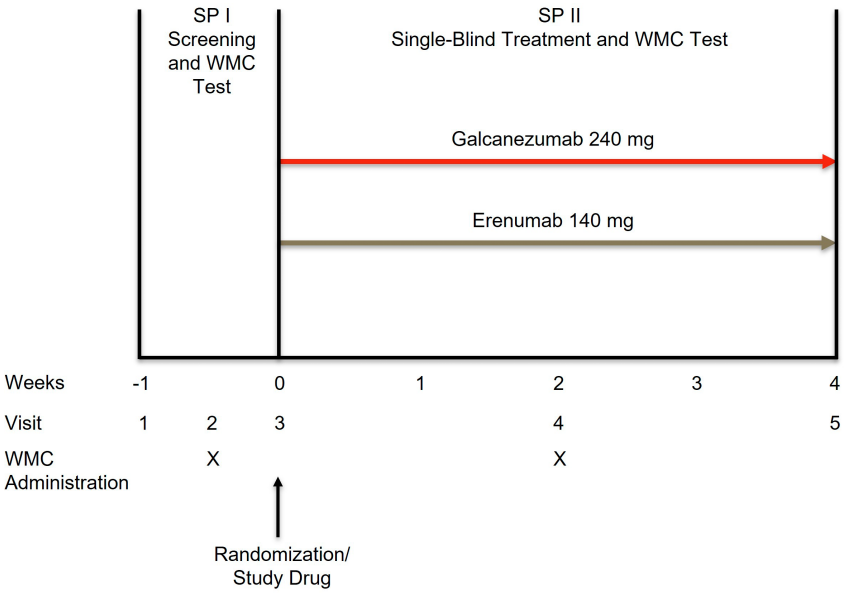

FIGURE 1 Illustration of the clinical study design. SP, study period; WMC, wireless motility capsule. [Color figure can be viewed at wileyonlinelibrary.com]

conditions leading to exclusion from the study included history of Crohn's disease, celiac disease, ulcerative colitis, diverticulitis, and Type 1 or Type 2 diabetes. Patients who were currently receiving or had received a mAb CGRP antagonist within the past 6 months prior to Visit 1, or who had received an oral CGRP antagonist (gepant) 14 days prior to Visit 1 were excluded from the study. A full list of inclusion/exclusion criteria can be found in Supporting Data S3.

Wireless motility capsule

To evaluate whole gut and segmental GI transit time WMC technology was used. The WMC is an orally ingested, nondigestible, data recording capsule that has been approved by the United States Food and Drug Administration to evaluate patients with suspected delayed gastric emptying and to evaluate colonic transit time (CTT) in patients with chronic idiopathic constipation.[23] Components to the WMC system include a WMC (SmartPill™ Motility Capsule), a wearable data recorder (SmartPill™ Motility Recorder), and a software program (MotiliGI™ Version 3.1). The system measures whole gut and regional (stomach, small bowel, and colon) transit time by measuring pressure, pH, and temperature throughout the GI tract (Medtronic 2017). Patients' baseline transit times were measured with the WMC at visit 2 prior to the first dose of the mAb CGRP antagonist (Visit 3) and 2 weeks following study treatment administration (Visit 4) for comparison to baseline (Figure 1) and were read by a blinded reader.

Endpoint assessments

Gastrointestinal transit time

The primary endpoint was change from baseline in CTT after administration of galcanezumab or erenumab at Week 2. Secondary endpoints included change from baseline in whole gut transit time (WGTT), gastric emptying time (GET), small bowel transit time (SBTT), and combined small and large bowel transit time (SLBTT) after administration of galcanezumab or erenumab at the end of Week 2. All transit times were measured using the WMC. Primary and secondary measures evaluated changes *within* each treatment group whereas tertiary objectives evaluated changes *between* treatment groups.

Gastrointestinal Symptom Rating Scale (GSRS)

The GSRS is a validated 15-item questionnaire that evaluates the five common symptoms of GI disorders: abdominal pain, reflux, indigestion, constipation, and diarrhea. Items ask about the past week using a 7-point categorical response scale from no discomfort to very severe discomfort.[24,25]

Bristol Stool Form Scale (BSFS)

The BSFS is a 7-point ordinal scale of stool types ranging from the hardest (Type 1) to the softest (Type 7). Symptoms of constipation are related to harder stools (Types 1 and 2) and symptoms of diarrhea are related to loose/liquid stools (Types 6 and 7). Overall, stools Type 3 to 5 are considered normal. BSFS provides the patient with a pictorial representation of each type of stool.[26]

Spontaneous bowel movement (SBM)

The SBM was assessed by asking patients to report their number of weekly SBMs (unaided by laxatives, enemas, or suppositories) prior to and after administration of galcanezumab or erenumab. Change from baseline in number of weekly SBMs after administration of galcanezumab or erenumab within each treatment group at Weeks 2 and 4 was assessed.

Safety

The safety measures for this study were collection of spontaneously reported TEAEs, SAEs, and AEs leading to discontinuation. Investigators were responsible for monitoring the overall safety of patients who entered the study including following and reporting AEs that are serious or otherwise medically important, considered related to the study treatment or the study, or that caused the patient to discontinue the study treatment before completing the study. The patient received appropriate follow-up care until the event resolved, stabilized with appropriate diagnostic evaluation, or was reasonably explained.

Statistical methods

Primary and secondary measures evaluated changes *within* each treatment group whereas tertiary objectives evaluated changes *between* treatment groups. For our tertiary objectives of between treatment group analyses, this study examined an equivalence hypothesis, that is testing the equivalence for each treatment group by assessing differences before and after treatment in a single treatment group.

When determining sample size, the assumption was made that within-group mean difference in CTT would be ~4.2 h with a standard deviation (SD) of ~8 h, and a sample of 30 patients in each treatment group would provide 80% power to detect the difference within the treatment group. The total sample size for the study would therefore need to be 60. Assuming 20% screen failure rate, ~75 patients would need to be screened to enroll 60 patients into the study. Eligible patients would be randomized in a 1:1 ratio to galcanezumab or erenumab to have ~30 patients in each treatment group. Assignment to treatment groups was determined

by a computer-generated random sequence using an interactive web-response system (IWRS). Patients were stratified by migraine headache days (<8 and ≥8 days) and by body mass index (BMI; <30 and ≥30 kg/m^2). As this study was single-blind, participants were centrally randomized and only the investigator, site personnel, and sponsor knew the randomized treatment after randomization. There was no advance notice of treatment assignment to study team or site personnel to ensure that patients remain blinded to treatment.

Unless otherwise specified, analyses were conducted on the intent-to-treat population, which included all patients who were randomized and received the study treatment dose. Patients in the intent-to-treat population were analyzed according to the treatment group to which they were randomized. When change from baseline was assessed, the patient was included in the analysis only where the patient had baseline and post-baseline measurements. All tests of within- and between-group comparisons were conducted at a two-sided significance level of $p < 0.05$, unless otherwise stated.

The primary analysis was performed using an analysis of covariance model including the categorical effects of treatment, pooled investigative site, BMI category (<30 and ≥30 kg/m^2), and baseline migraine frequency (<8 and ≥8 migraine headache days), as well as the continuous baseline CTT (in hours). Least squares (LS) mean change from baseline in the primary and secondary outcome whereas tertiary objective were estimated in each treatment group and between-treatment difference. The primary analysis assumed that data were normally distributed. To assess the impact of the normality assumption, a nonparametric sensitivity analysis of the primary endpoint was produced using the Wilcoxon signed-rank test[27] to compare the change from baseline within each treatment group (Table S1).

For continuous measures with repeated post-baseline measurements, change from baseline was analyzed using a restricted maximum likelihood-based mixed effects model for repeated measures (MMRM) technique. The analysis included the fixed categorical effects of treatment, pooled investigative site, BMI category (<30 and ≥30 kg/m^2), baseline migraine frequency (<8 and ≥8 migraine headache days), week, and treatment-by-week interaction, as well as the continuous fixed covariates of baseline value and baseline-by-week interaction.

For all efficacy analyses using the analysis of covariance model, no imputation for missing data and only observed data were used, all patients with a baseline and post-baseline measurement were included in the analyses. For the repeated measures analyses, the model parameters were simultaneously estimated using restricted likelihood estimation incorporating all the observed data. Estimates have been shown to be unbiased when data are missing at random (MAR). Missingness due to coronavirus disease 2019 (COVID-19) does not depend on the outcome measurements and therefore will be considered MAR.

All statistical analyses were performed using the Statistical Analysis System (SAS) Enterprise Guide 7.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Participant disposition and demographics

Of the 65 patients randomized to receive a dose of erenumab (140 mg) or galcanezumab (240 mg), 30/32 (93.8%) and 33/33 (100%) of patients completed the study, respectively (Figure 2). Two patients from the erenumab arm discontinued the study as they tested positive for COVID-19 after Visit 3 dosing, which resulted in an out-of-window deviation for Visit 4.

Overall, the treatment groups were generally similar regarding patient demographics and baseline characteristics (Table 1). The mean regional GI transit times exhibited a baseline variability larger than expected with a higher percentage of patients having values

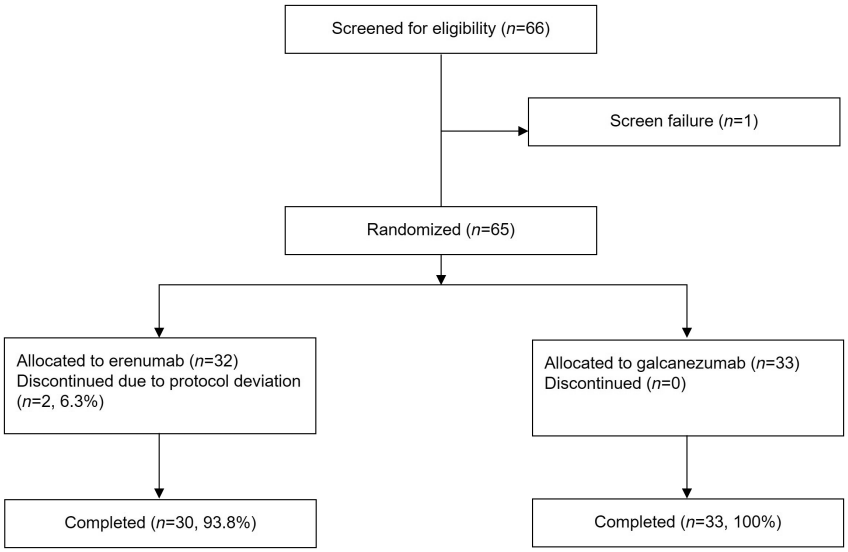

FIGURE 2 Participant disposition. *n*, number of participants.

TABLE 1 Baseline demographics and clinical characteristics

Demographic	Erenumab (*n* = 32)	Galcanezumab (*n* = 33)	Total (*n* = 65)
Sex, *n* (%)			
Female	27 (84.4)	28 (84.8)	55 (84.6)
Male	5 (15.6)	5 (15.2)	10 (15.4)
Age, years, mean (SD)	40.7 (11.4)	38.0 (9.5)	39.3 (10.5)
Race, *n* (%)			
White	23 (76.7)	26 (78.8)	49 (77.8)
Black or African American	4 (13.3)	6 (18.2)	10 (15.9)
American Indian or Alaska native	2 (6.7)	0 (0.0)	2 (3.2)
Asian	0 (0.0)	1 (3.0)	1 (1.6)
Native Hawaiian or other Pacific Islander	1 (3.3)	0 (0.0)	1 (1.6)
Ethnicity			
Hispanic or Latino	12 (38.7)	15 (45.5)	27 (42.2)
Not Hispanic or Latino	19 (61.3)	18 (54.5)	37 (57.8)
BMI, kg/m^2, mean (SD)	29.0 (6.0)	29.0 (6.1)	29.0 (6.0)
Clinical characteristics			
Monthly migraine headache days, mean (SD)	6.8 (3.2)	6.1 (3.1)	6.4 (3.1)
Monthly migraine headache frequency, *n* (%)			
<8 days	20 (62.5)	20 (60.6)	40 (61.5)
≥8 days	12 (37.5)	13 (39.4)	25 (38.5)
Days of opioid use in past 30 days, mean (SD)	0.1 (0.4)	0.0 (0.0)	0.0 (0.2)
Colonic transit time, h, mean (SD)[a]	31.5 (28.1)	28.3 (24.1)	29.9 (26.0)
Whole gut transit time, h, mean (SD)[a]	41.9 (30.3)	42.3 (29.8)	42.1 (29.8)
Gastric emptying time, h, mean (SD)[a]	5.3 (6.3)	9.3 (17.4)	7.3 (13.2)
Small bowel transit time, h, mean (SD)[a]	5.1 (1.6)	4.7 (2.2)	4.9 (1.9)
Combined small and large bowel transit time, h, mean (SD)[a]	36.6 (28.6)	33.0 (24.7)	34.8 (26.6)
Number of weekly spontaneous bowel movements, mean (SD)	8.6 (3.7)	9.2 (5.7)	8.9 (4.8)
GSRS-constipation score, mean (SD)	1.1 (0.1)	1.1 (0.2)	1.1 (0.2)
Bristol Stool Form Scale score, mean (SD)	3.6 (0.9)	3.8 (1.1)	3.7 (1.0)

Note: Demographics are shown as *n* (%) unless otherwise noted. Clinical characteristics are shown as mean (SD) unless otherwise noted.
Abbreviations: BMI, body mass index; GSRS, Gastrointestinal Symptom Rating Scale; h, hours; *n*, number of participants; SD, standard deviation.
[a]Normative transit time (converted to decimal hours) for colonic transit time: ≥4.5 to ≤58.75 h; whole gut transit time: ≥10.75 to ≤68.75 h; gastric emptying time: ≥1.75 to <5.0 h; small bowel transit time: ≥2.25 to ≤6.0 h; and combined small and large bowel transit time: ≥8.25 to ≤65.25 h.[26]

outside the established normative range when compared with transit times in healthy volunteers[28] (Figure 3). The mean weekly bowel frequency and BSFS appeared normal at baseline and mean scores on the GSRS-constipation measured close to no discomfort (Table 1).

Efficacy outcomes

Gastrointestinal transit times

The primary endpoint of LS mean change from baseline in CTT (in hours) within each treatment group at 2 weeks post-administration was not statistically significant. A mean change increase of 5.8 h ($p = 0.320$) from baseline (mean [SD] 33.8 [29.4] to 38.7 [38.3] h) was observed for erenumab, while a mean change decrease of 5.4 h ($p = 0.328$) from baseline (mean [SD] 29.3 [24.5] to 24.8 [19.5] h) was observed for galcanezumab. The tertiary objective of LS mean change difference in CTT between treatment groups (−11.1 h, 95% confidence interval [CI] −25.4 to 3.2, $p = 0.125$) was not statistically significant (Table 2). Secondary transit time endpoints of LS mean change from baseline in WGTT, GET, SBTT and SLBTT (in hours) within each treatment group at 2 weeks post-administration was not statistically significant, except for SBTT in the galcanezumab treatment group, measuring a LS mean change decrease of 0.7 h ($p = 0.018$). There were no statistically significant differences in WGTT, GET, SBTT, and SLBTT between treatment groups (Table 2).

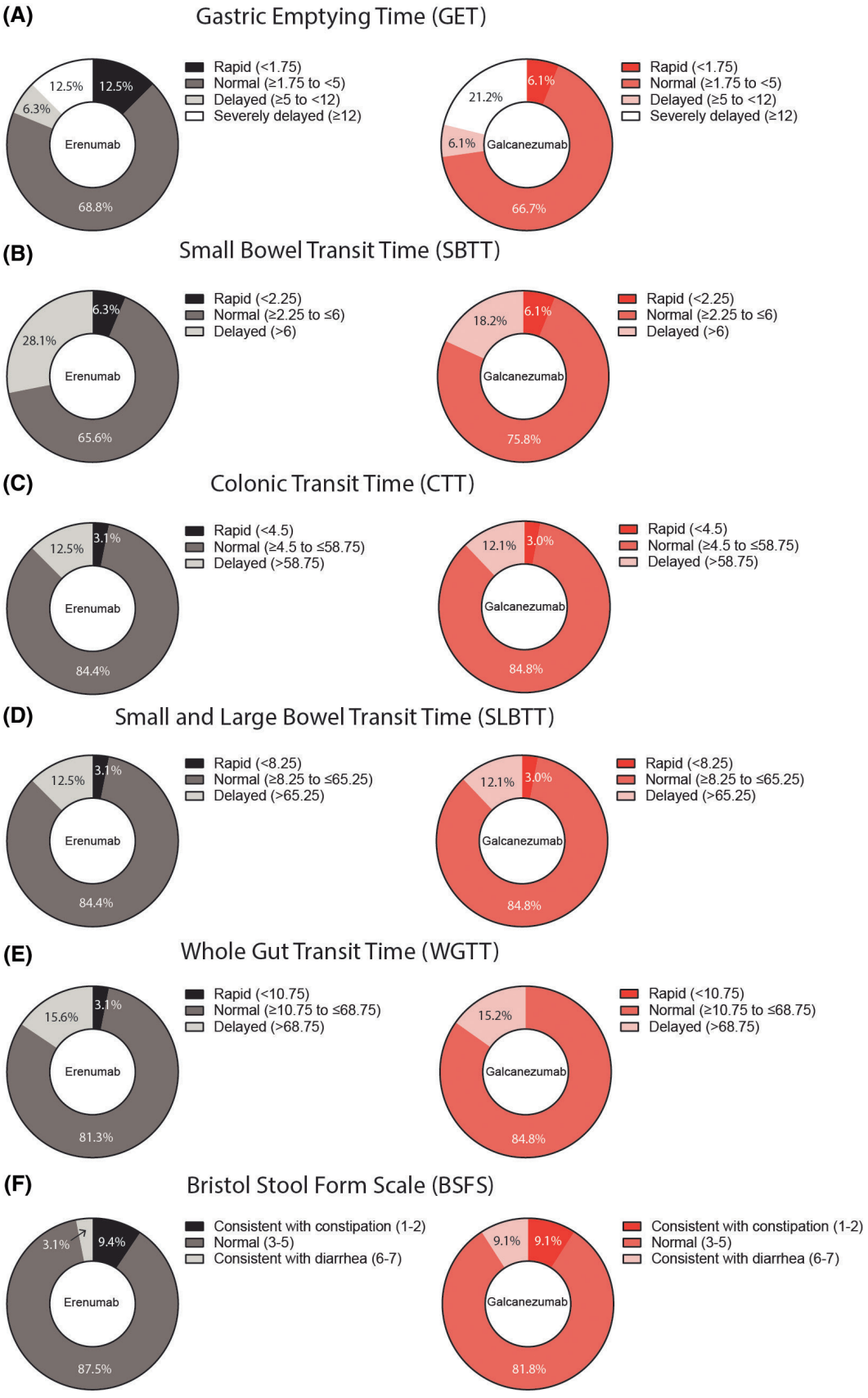

FIGURE 3 Baseline prevalence of GI disturbances. Transit time shown in hours. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 . Changes from baseline in gastrointestinal transit time

Variable (h)	Primary/secondary endpoints											Tertiary endpoints		
	Erenumab (n = 28)						Galcanezumab (n = 31)						Galcanezumab versus erenumab		
	LS mean change (SE)	Q1	Median	Q3	95% CI	p	LS mean change (SE)	Q1	Median	Q3	95% CI	p	LS mean change difference (SE)	95% CI	p
CTT	5.8 (5.7)	−15.3	2.7	17.9	(−5.7, 17.2)	0.320	−5.3 (5.4)	−13.5	−1.4	7.4	(−16.2, 5.5)	0.328	−11.1 (7.1)	(−25.4, 3.2)	0.125
WGTT	4.1 (6.0)	−19.3	2.2	23.0	(−7.9, 16.1)	0.494	−7.0 (5.6)	−18.1	−1.6	4.5	(−18.3, 4.3)	0.217	−11.2 (7.4)	(−26.0, 3.7)	0.138
GET	−1.3 (1.0)	−0.8	0.1	1.0	(−3.4, 0.7)	0.206	−0.6 (1.0)	−1.2	0.0	1.0	(−2.5, 1.4)	0.551	0.7 (1.3)	(−1.8, 3.3)	0.567
SBTT	−0.6 (0.3)	−1.3	−0.8	0.0	(−1.2, 0.1)	0.085	−0.7 (0.3)	−2.2	−0.3	0.8	(−1.3, −0.1)	0.018	−0.2 (0.4)	(−0.9, 0.6)	0.665
SLBTT	5.2 (5.7)	−15.4	2.2	16.2	(−6.2, 16.5)	0.367	−6.0 (5.4)	−13.0	−1.6	5.1	(−16.7, 4.8)	0.271	−11.1 (7.0)	(−25.2, 3.0)	0.120

Abbreviations: CI, confidence interval; CTT, colonic transit time; GET, gastric emptying time; LS, least squares; n, number of subjects with a baseline and post-baseline result for a specific parameter; Q1, 25th percentile; Q3, 75th percentile; SBTT, small bowel transit time; SE, standard error; SLBTT, small and large bowel transit time; WGTT, whole gut transit time.

Spontaneous bowel movements and BSFS

No statistically significant changes from baseline were seen for either SBM or BSFS scale within the galcanezumab treatment group. In the erenumab treatment group, patients reported a statistically significant reduction from baseline in the weekly frequency of SBMs at Weeks 2 and 4 post-erenumab dose (Table 3). As this decrease in SBM was not observed in the galcanezumab treatment group, this resulted in a statistically significant difference in the number of weekly SBM between treatment groups at Week 2 and Week 4 (Table 3). Using the BSFS, a statistically significant LS mean decrease in the observed stool type score was reported in the erenumab treatment group at both Week 2 and Week 4, indicating hardening of the stool form. A statistically significant LS mean change difference in the BSFS score of 0.5 was also observed between treatment groups at Week 4 (Table 3).

Gastrointestinal Symptom Rating Scale

The five symptom domains of GSRS were evaluated and results are provided for the secondary and tertiary endpoints in Tables 3 and S2. In the Constipation domain, a small but statistically significant increase in the score measuring patient discomfort was observed within each treatment group at Week 2, and within the galcanezumab treatment group at Week 4 (Table 3). Additionally, small but statistically significant within-treatment group changes from baseline were observed in the galcanezumab treatment group in the Reflux and Indigestion domains at Week 4, and in the erenumab treatment group in the Diarrhea domain at Week 2 (Table S2). However, no statistically significant difference between treatment groups was observed at Week 2 or Week 4 in all five symptom domains (Table S2). Finally, a statistically significant increase in the GSRS total score was also observed in the galcanezumab group at Week 4 (Table 3); however, a change this small is unlikely to be clinically meaningful, and there was no difference between treatment groups.

Baseline shift in gastrointestinal transit times

Using both normative transit times published previously,[28] and transit times in this population, the percentage of participants shifting from one transit time category at baseline to another at Week 2 was calculated in post hoc analyses (CTT: Figure 4 and secondary transit times: Figure S1). For CTT, most of the erenumab- and galcanezumab-treated participants had normal CTT at baseline and Week 2 (Figure 4A: 65.63% and Figure 4B: 72.73%, respectively). Of note, 6.25% of erenumab-treatment participants moved from normal to delayed CTT, compared to 3.03% of galcanezumab-treated participants. Of erenumab-treatment participants who had delayed CTT at baseline, 9.38% were still categorized as such at Week 2, while the 9.09% of galcanezumab-treated participants who had delayed CTT at baseline were categorized as normal at Week 2.

TABLE 3 Change from baseline in key secondary and tertiary endpoints

	Secondary endpoints								Tertiary endpoints		
	Erenumab ($n = 32$)				Galcanezumab ($n = 33$)				Galcanezumab versus erenumab		
Variable Time	*N*	LS mean change (SE)	95% CI	*p*	*N*	LS mean change (SE)	95% CI	*p*	LS mean change difference (SE)	95% CI	*p*
SBM											
Week 2	32	−1.3 (0.5)	(−2.4, −0.2)	0.020	33	0.3 (0.5)	(−0.7, 1.3)	0.557	1.6 (0.7)	(0.2, 3.0)	0.028
Week 4	30	−1.1 (0.5)	(−2.2, −0.1)	0.031	33	0.5 (0.5)	(−0.4, 1.5)	0.267	1.7 (0.7)	(0.4, 3.0)	0.014
Overall	32	−1.2 (0.5)	(−2.1, −0.3)	0.012	33	0.4 (0.4)	(−0.5, 1.3)	0.342	1.6 (0.6)	(0.4, 2.8)	0.008
BSFS											
Week 2	32	−0.4 (0.2)	(−0.8, −0.1)	0.008	33	0.0 (0.2)	(−0.4, 0.3)	0.798	0.4 (0.2)	(−0.0, 0.8)	0.059
Week 4	30	−0.5 (0.2)	(−0.8, −0.1)	0.011	33	0.0 (0.2)	(−0.3, 0.4)	0.895	0.5 (0.2)	(0.0, 1.0)	0.040
Overall	32	−0.5 (0.2)	(−0.8, −0.2)	0.004	33	0.0 (0.1)	(−0.3, 0.3)	0.952	0.5 (0.2)	(0.1, 0.8)	0.022
GSRS - constipation											
Week 2	32	0.4 (0.2)	(0.1, 0.7)	0.009	33	0.4 (0.1)	(0.1, 0.7)	0.013	0.0 (0.2)	(−0.4, 0.4)	0.856
Week 4	30	0.3 (0.2)	(−0.1, 0.6)	0.126	33	0.4 (0.2)	(0.1, 0.7)	0.006	0.2 (0.2)	(−0.2, 0.6)	0.389
Overall	32	0.3 (0.1)	(0.1, 0.6)	0.016	33	0.4 (0.1)	(0.2, 0.7)	0.002	0.1 (0.2)	(−0.3, 0.4)	0.668
GSRS - total											
Week 2	32	0.1 (0.1)	(−0.1, 0.2)	0.336	33	0.1 (0.1)	(−0.1, 0.2)	0.290	0.0 (0.1)	(−0.2, 0.2)	0.963
Week 4	30	0.0 (0.1)	(−0.1, 0.2)	0.557	33	0.2 (0.1)	(0.1, 0.3)	0.007	0.2 (0.1)	(−0.0, 0.3)	0.126
Overall	32	0.1 (0.1)	(−0.1, 0.2)	0.361	33	0.1 (0.1)	(0.0, 0.2)	0.025	0.1 (0.1)	(−0.1, 0.2)	0.319

Abbreviations: BSFS, Bristol Stool Form Scale; CI, confidence interval; GSRS, gastrointestinal symptom rating scale; LS, least squares; *N*, number of participants; SBM, spontaneous bowel movement; SE, standard error.

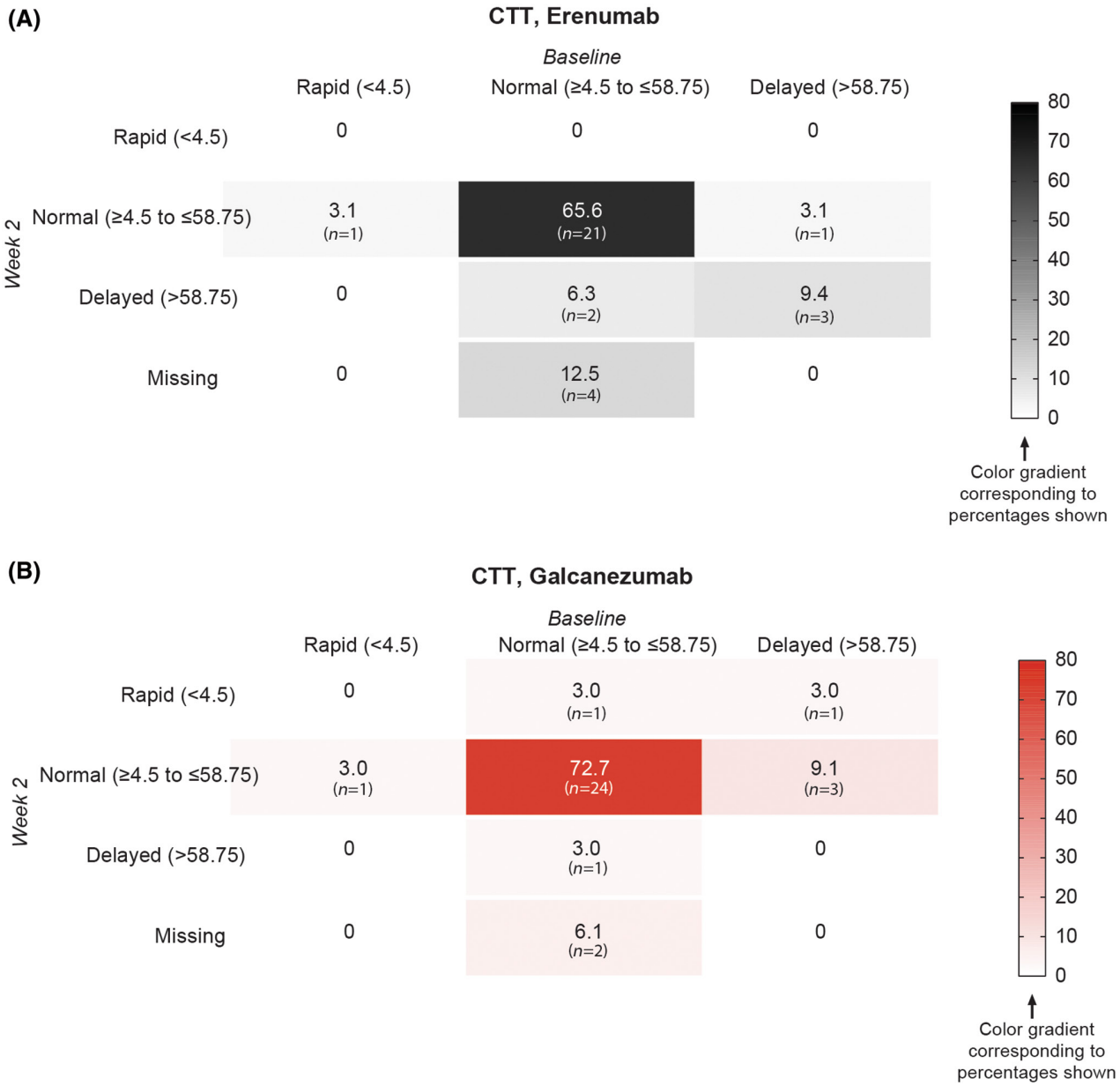

FIGURE 4 Baseline shift in CTT from baseline to Week 2. Movement of (A) erenumab-treated patients and (B) galcanezumab-treated patients between rapid, normal, or delayed categories from baseline to Week 2. Data are shown as percentages of participants with *n* numbers below. CTT, colonic transit time; *n*, number of subjects. [Color figure can be viewed at wileyonlinelibrary.com]

Safety outcomes

No deaths, SAEs, or discontinuations due to an AE were reported in this study. A summary of the reported TEAEs is provided in Table 4. Although no significant between-group changes were observed for any TEAE, more patients in the erenumab treatment group reported TEAEs than in the galcanezumab treatment group, with the most reported TEAE of constipation reported in 15.6% (five patients) of erenumab-treated patients and 3.0% (one patients) of galcanezumab-treated patients. All reported TEAEs were mild in severity except for one report of constipation of moderate severity in the galcanezumab-treatment group. There were no reports of TEAEs rated as severe.

DISCUSSION

The study did not demonstrate a statistically significant within treatment mean change from baseline in CTT (h) at 2 weeks post-treatment in either erenumab- or galcanezumab-treated patients. While numeric differences in mean change in CTT were seen within erenumab-treated patients (increase of 5.75 h) and galcanezumab-treated patients (decrease of 5.35 h), the SDs observed at baseline and Week 2 were too large to detect significance with the final sample size. Categorical shifts in CTT (rapid, normal, delayed) from baseline to Week 2 in erenumab- and galcanezumab-treated patients were consistent with the changes seen in mean change in CTT; however, the numbers of patients in each treatment group

TABLE 4 Summary of treatment-emergent adverse events

Preferred term	Erenumab (*N* = 32), *n* (%)	Galcanezumab (*N* = 33), *n* (%)	Total (*N* = 65), *n* (%)
Participants with ≥1 TEAE	9 (28.1)	3 (9.1)	12 (18.5)
Gastrointestinal disorders			
Abdominal pain upper	0 (0.0)	2 (6.1)	2 (3.1)
Diarrhea	0 (0.0)	1 (3.0)	1 (1.5)
Nausea	1 (3.1)	0 (0.0)	1 (1.5)
Constipation	5 (15.6)	1 (3.0)	6 (9.2)
Abdominal distension	1 (3.1)	0 (0.0)	1 (1.5)
Infections and infestations			
COVID-19	2 (6.3)	0 (0.0)	2 (3.1)
General disorders and administration site conditions			
Injection site reaction	1 (3.1)	0 (0.0)	1 (1.5)

Abbreviations: COVID-19, coronavirus disease 2019; *N*, number of subjects in the analysis population; *n*, number of subjects in the specified category; TEAE, treatment-emergent adverse event.

shifting from one category at baseline to another category at Week 2 were small.

Eligibility criteria for the study were developed to recruit adult patients with migraine excluding those patients with historical procedures or pre-existing conditions affecting GI motility and/or who were taking concomitant medication known to affect GI motility or pH. Given these eligibility criteria and no prior studies using the WMC to measure GI transit times specifically in a migraine population, the study sample size was calculated with the assumption that baseline GI transit times of enrolled patients would be within normative ranges and similar to previously studied healthy volunteers.[28] However, in addition to the aforementioned larger than expected variability, a high percentage of baseline GI transit time abnormalities including CTT were observed. Furthermore, these abnormalities were observed despite minimal to no baseline GI symptoms reported on the GSRS or abnormalities in weekly reported stool frequency or stool form. While these baseline abnormalities in GI transit times support the evidence of a relationship between migraine and gastric motility,[29] further evaluation of the lack of associated baseline GI symptoms and/or bowel abnormalities in frequency or form is needed.

Other WMC measures, including WGTT, GET, SBTT, and SLBTT did not result in clinically meaningful mean changes from baseline within either treatment group, with the numeric differences observed in WGTT and SLBTT primarily due to the mean changes in CTT. Small mean change increases from baseline were observed within both the erenumab- and galcanezumab-treatment groups in the GSRS Constipation domain (secondary objective), indicating an increase in the reported discomfort level in constipation-related symptoms; however, no difference was observed between the treatment groups. Other secondary and tertiary endpoints in the galcanezumab-treatment group did not show any changes in patient-reported bowel habits or stool form consistent with constipation, whereas a statistically significant reduction in the number of patient-reported weekly SBM and a hardening of stools as measured by the BSFS was observed in the erenumab-treatment group. Hardening of stools in the erenumab-treated group may be a result of less fluid, due to increased transit time with a colonic adsorption rate of 2.7 ml/h.[30] Other possibilities include greater AMY1 receptor activation at the area postrema by CGRP,[19] or uncontested receptor activation given that the CGRP receptor has been blocked. Overall, there appears to be a discrepancy in the subjective and objective measures in this study. It is possible that the rates of constipation observed with each treatment are related to other mechanisms of constipation than transit time, such as altered rectal compliance and sensation,[31] and as such there may be differential effects of a ligand versus receptor blocker in visceral nociception. Overall, galcanezumab 240 mg or erenumab 140 mg were not associated with any SAEs, deaths, or discontinuations due to an AE. The most reported AE was constipation. TEAEs were predominantly rated mild in severity. A single TEAE of constipation of moderate severity was reported in the galcanezumab-treatment group. No severe TEAEs were reported.

Limitations

While there were numerically reduced transit times for galcanezumab and numerically increased transit times for erenumab, these changes did not reach statistical significance. Powering of the study assumed transit time SDs would be in line with the general population (given the exclusion of patients with GI symptoms from the study); however, the degree of variability observed and the percentage of subjects with subclinical (below the level of awareness of the individual) transit time abnormalities led to high SDs for whole gut and regional transit times. There were a small number of failed WMC tests, with these patients being excluded from the efficacy analyses; however, the incidence of this was low (two participants per group) and had minimal effect on the overall results. In addition, no placebo group was included making it difficult to draw conclusions on the variability of transit times in the population. Finally, it is likely that the patients' own perception of change in transit times may not have been captured by the CTT endpoint as +/− 5 h might be perceived as a change in the patient experience in terms of predictable timing of bowel movements. Finally, as transit times in the migraine population specifically may be delayed compared to normal ranges, and little has been reported to this effect, this makes it somewhat difficult to know if the study population examined here is generalizable to the migraine population overall.

CONCLUSION

While the primary endpoint of this exploratory study did not show a statistically significant change in CTT within treatment groups, the

secondary and tertiary endpoints do support a within- and between-treatment change in GI effects and suggest a possible mechanistic difference between receptor (erenumab) versus ligand (galcanezumab) antagonism to GI effects in patients.

AUTHOR CONTRIBUTIONS

Conception: Linda Nguyen, Karen Samaan, Linda Wietecha, Eric Pearlman. *Design of the work*: Linda Nguyen, Karen Samaan, Linda Wietecha, Eric Pearlman. *Acquisition of data*: David Kudrow, Jack Semler, Karen Samaan. *Analysis of data*: Jack Semler, Hai-An Hsu, Eric Pearlman. *Interpretation of data*: David Kudrow, Linda Nguyen, Jack Semler, Chad Stroud, Karen Samaan, Deirdre B. Hoban, Linda Wietecha, Eric Pearlman. *Drafting of the work*: Chad Stroud, Karen Samaan, Deirdre B. Hoban, Hai-An Hsu. *Critical revision of the work for important intellectual content*: David Kudrow, Linda Nguyen, Jack Semler, Chad Stroud, Deirdre B. Hoban, Linda Wietecha, Eric Pearlman. All authors provided input and gave final approval for the work to be published.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, except for pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union 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.

CLINICAL TRIAL REGISTRATION

NCT04294147 (ClinicalTrials.gov).

ORCID

Chad Stroud https://orcid.org/0000-0002-8374-1212
Deirdre B. Hoban https://orcid.org/0000-0002-9608-8398

REFERENCES

1. Raddant AC, Russo AF. Calcitonin gene-related peptide in migraine: intersection of peripheral inflammation and central modulation. *Expert Rev Mol Med*. 2011;13:e36.
2. Russo AF. Calcitonin gene-related peptide (CGRP): a new target for migraine. *Annu Rev Pharmacol Toxicol*. 2015;55:533-552.
3. Silberstein S, Lenz R, Xu C. Therapeutic monoclonal antibodies: what headache specialists need to know. *Headache*. 2015;55:1171-1182.
4. Ashina M, Kudrow D, Reuter U, et al. Long-term tolerability and nonvascular safety of erenumab, a novel calcitonin gene-related peptide receptor antagonist for prevention of migraine: a pooled analysis of four placebo-controlled trials with long-term extensions. *Cephalalgia*. 2019;39:1798-1808.
5. Robbins L. Erenumab side effects. *Headache*. 2019;59:1088-1089.
6. Silberstein SD, McAllister P, Ning X, et al. Safety and tolerability of fremanezumab for the prevention of migraine: a pooled analysis of phases 2b and 3 clinical trials. *Headache*. 2019;59:880-890.
7. Stauffer VL, Wang S, Bangs ME, Oakes T, Carter J, Aurora SK. Safety data from phase 3 clinical studies comparing galcanezumab and placebo in patients with episodic and chronic migraine. *J Headache Pain*. 2018;19:77.
8. Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the preventive treatment of migraine. *N Engl J Med*. 2021;385:695-706.
9. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018;91:e2211-e2221.
10. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia*. 2018;38:1442-1454.
11. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. *JAMA Neurol*. 2018;75:1080-1088.
12. Camporeale A, Kudrow D, Sides R, et al. A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine. *BMC Neurol*. 2018;18:188.

13. Dodick DW, Goadsby PJ, Spierings EL, Scherer JC, Sweeney SP, Grayzel DS. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. *Lancet Neurol*. 2014;13:885-892.
14. Oakes TMM, Skljarevski V, Zhang Q, et al. Safety of galcanezumab in patients with episodic migraine: a randomized placebo-controlled dose-ranging Phase 2b study. *Cephalalgia*. 2018;38:1015-1025.
15. Dodick DW, Ashina M, Brandes JL, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia*. 2018;38:1026-1037.
16. Goadsby PJ, Reuter U, Hallstrom Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med*. 2017;377:2123-2132.
17. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol*. 2017;16:425-434.
18. Ho TW, Connor KM, Zhang Y, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. *Neurology*. 2014;83:958-966.
19. Hargreaves R, Olesen J. Calcitonin gene-related peptide modulators - the history and renaissance of a new migraine drug class. *Headache*. 2019;59:951-970.
20. Falkenberg K, Bjerg HR, Olesen J. Two-hour CGRP infusion causes gastrointestinal hyperactivity: possible relevance for CGRP antibody treatment. *Headache*. 2020;60:929-937.
21. Kaiser EA, Rea BJ, Kuburas A, et al. Anti-CGRP antibodies block CGRP-induced diarrhea in mice. *Neuropeptides*. 2017;64:95-99.
22. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38:1-211.
23. Saad RJ, Hasler WL. A technical review and clinical assessment of the wireless motility capsule. *Gastroenterol Hepatol*. 2011;7:795-804.
24. Khanna D, Hays RD, Shreiner AB, et al. Responsiveness to change and minimally important differences of the patient-reported outcomes measurement information system gastrointestinal symptoms scales. *Dig Dis Sci*. 2017;62:1186-1192.
25. Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the gastrointestinal symptom rating scale in patients with gastroesophageal reflux disease. *Qual Life Res*. 1998;7:75-83.
26. Blake MR, Raker JM, Whelan K. Validity and reliability of the Bristol Stool Form Scale in healthy adults and patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther*. 2016;44:693-703.
27. Wilcoxon F. Individual comparisons by ranking methods. *Biom Bull*. 1945;1:80-83.
28. Wang YT, Mohammed SD, Farmer AD, et al. Regional gastrointestinal transit and pH studied in 215 healthy volunteers using the wireless motility capsule: influence of age, gender, study country and testing protocol. *Aliment Pharmacol Ther*. 2015;42:761-772.
29. Aurora SK, Shrewsbury SB, Ray S, Hindiyeh N, Nguyen L. A link between gastrointestinal disorders and migraine: insights into the gut-brain connection. *Headache*. 2021;61:576-589.
30. Palma R, Vidon N, Bernier JJ. Maximal capacity for fluid absorption in human bowel. *Dig Dis Sci*. 1981;26:929-934.
31. Sloots CE, Felt-Bersma RJ. Rectal sensorimotor characteristics in female patients with idiopathic constipation with or without paradoxical sphincter contraction. *Neurogastroenterol Motil*. 2003;15:187-193.

SUPPORTING INFORMATION

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

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