

Protocol: I5Q-MC-CGBC (a)

A Phase 4 Single-Blind Study of Gastrointestinal Transit Time in Adult Patients with Migraine Before and After Initiation of a mAb CGRP Antagonist.

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**Protocol I5Q-MC-CGBC
A Phase 4 Single-Blind Study of Gastrointestinal Transit
Time in Adult Patients with Migraine Before and After
Initiation of a mAb CGRP Antagonist**

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galcanezumab-gnlm (LY2951742)

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1. Synopsis

Title of Study:

A Phase 4 single-blind study of gastrointestinal transit time in adult patients with migraine before and after initiation of a mAb CGRP antagonist.

Rationale:

Differences have been observed between reported frequencies of constipation in clinical trials and postmarketing adverse event (AE) reporting among calcitonin gene-related peptide (CGRP) antagonists. In particular, these differences have been observed between CGRP monoclonal antibodies (mAb) that target the ligand (galcanezumab, fremanezumab) or the receptor (erenumab) for the prevention of migraine (Stauffer et al. 2018b; Ashina et al. 2019; FDA [WWW] 2019; Robbins 2019; Silberstein et al. 2019; Aimovig package insert, 2020). Preclinical animal studies suggest that differences in the mechanism of action of these agents may contribute to the different frequencies of constipation (Hargreaves and Olesen 2019). The purpose of Study I5Q-MC-CGBC (CGBC) is to measure gastrointestinal (GI) transit time in adult patients with migraine who have been initiated on preventive treatment with a CGRP antagonist (galcanezumab or erenumab), and explore whether there is a mechanistic difference that contributes to GI AEs in humans.

A wireless motility capsule (WMC) technology will be used to evaluate total GI transit time as well as segmental transit time. The US Food and Drug Administration has approved the WMC (SmartPill™) for the evaluation of adult patients with suspected delayed gastric emptying and the evaluation of colonic transit time (CTT) and combined small and large bowel transit time (SLBTT) in patients with chronic constipation (Saad and Hasler 2011; Medtronic 2017).

Components to the WMC system include a WMC (SmartPill™ Motility Capsule), a wearable data recorder (SmartPill™ Motility Recorder), and a software program (MotiliGI™). 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). The American and European Neurogastroenterology and Motility Societies recognized the WMC technology as a validated, standardized, objective measure of GI transit time and recommended its use for testing in individuals with suspected alterations of GI motility (Rao et al. 2011).

Objectives/Endpoints:

Objectives	Endpoints
<p><u>Primary Objective</u></p> <p>To evaluate colonic transit time (CTT) in patients with migraine 1 week prior to and 2 weeks after administration of an initial loading dose of galcanezumab 240 mg or erenumab 140 mg.</p>	<p>Change from baseline in CTT after administration of galcanezumab or erenumab within each treatment group in hours at the end of Week 2.</p>
<p><u>Secondary Objectives</u></p> <p>To evaluate transit time of the following segments of the gastrointestinal (GI) tract 1 week prior to and 2 weeks after administration of galcanezumab or erenumab:</p> <ul style="list-style-type: none"> • whole gut • gastric emptying • small bowel • combined small and large bowel. 	<p>Change from baseline in GI transit time in each of the following segments after administration of galcanezumab or erenumab within each treatment group at the end of Week 2:</p> <ul style="list-style-type: none"> • Whole gut transit time (WGTT) in hours • Gastric emptying time (GET), in hours • Small bowel transit time (SBTT), in hours • Combined small and large bowel transit time (SLBTT), in hours.
<p>To evaluate the frequency of contractions, motility index, and area under the pressure curve (AUC) by quartile in the colon to assess for correlation with CTT results.</p>	<p>Changes in pressure parameters from baseline:</p> <ul style="list-style-type: none"> • Contraction Freq/Min • Motility Index = $\ln(\# \text{ of contractions} \times \sum \text{pressure amplitudes} + 1)$ • Area under the Pressure Curve.
<p>To evaluate number of weekly spontaneous bowel movements (un-aided by laxatives, enemas, or suppositories) prior to and after administration of galcanezumab or erenumab.</p>	<p>Change from baseline in number of weekly spontaneous bowel movements after administration of galcanezumab or erenumab within each treatment group at Weeks 2 and 4.</p>
<p>To evaluate GI symptom rating scale (GSRS) prior to and after administration of galcanezumab or erenumab.</p>	<p>Change from baseline in GSRS after administration of galcanezumab or erenumab within each treatment group at Weeks 2 and 4.</p>
<p>To evaluate the Bristol stool form scale (BSFS) prior to and after administration of galcanezumab or erenumab.</p>	<p>Change from baseline in BSFS after administration of galcanezumab or erenumab within each treatment group at Weeks 2 and 4.</p>
<p><u>Tertiary/Exploratory Objectives</u></p> <p>To evaluate the transit time between galcanezumab and erenumab for</p> <ul style="list-style-type: none"> • whole gut • gastric emptying • small bowel • colon • combined small and large bowel. 	<p>Change from baseline in transit time after administration of galcanezumab or erenumab between treatment groups at the end of Week 2 for</p> <ul style="list-style-type: none"> • WGTT, in hours • GET, in hours • SBTT, in hours • CTT, in hours • combined SLBTT, in hours.
<p>To evaluate number of weekly spontaneous bowel movements (un-aided by laxatives, enemas, or suppositories) prior to and after administration of galcanezumab or erenumab.</p>	<p>Change from baseline in number of weekly spontaneous bowel movements after administration of galcanezumab or erenumab between each treatment group at Weeks 2 and 4.</p>

Objectives	Endpoints
To evaluate GSRS prior to and after administration of galcanezumab or erenumab.	Mean change difference from baseline in GSRS scores after administration of galcanezumab or erenumab between treatment groups at Weeks 2 and 4 post-treatment.
To evaluate the BSFS prior to and after administration of galcanezumab or erenumab.	Mean change difference from baseline in BSFS scores after administration of galcanezumab or erenumab between treatment groups at Weeks 2 and 4 post-treatment.

Summary of Study Design:

Study CGBC is a multicenter, randomized, single-blind study with 2 study periods in patients with migraine deemed eligible for preventive treatment by the study physician. Within the 2 study periods, there are a total of 5 onsite patient visits:

Visit	Description
Visit 1	Informed consent and screening
Visit 2	First WMC administration and lead-in
Visit 3	Randomization and dosing
Visit 4	Second WMC administration
Visit 5	Exit visit

Treatment Arms and Duration:

Two treatment arms: galcanezumab (240-mg loading dose) and erenumab 140 mg.

At Visit 1, the study investigators will screen patients to determine their eligibility and administer study-specific questionnaires if the patients are deemed eligible. At Visit 2, administration of the WMC will occur. At Visit 3, patients will be randomized 1:1 to receive single-blind galcanezumab (240-mg loading dose) or erenumab 140 mg, which will be administered by onsite study staff. At Visit 4, approximately 14 days following study treatment administration (Visit 3), patients will be administered their second WMC upon return to site. Patients will return to the study site approximately 14 days following ingestion of the second WMC for Visit 5 exit visit.

Number of Patients:

The study will screen an estimated 75 potential study participants to ensure randomization of approximately 60 eligible patients.

Statistical Analysis:

Unless otherwise specified, analyses will be conducted on an intent-to-treat (ITT) population, which include all patients who are randomized and receive at least 1 dose of study treatment. Patients in the ITT population will be analyzed according to the treatment group to which they are randomized. When change from baseline is assessed, the patient will be included in the analysis only if the patient has baseline and postbaseline measurements.

The primary analysis will evaluate the changes in CTT between pre- and post-drug administration within each treatment group. The primary analysis will be performed using an analysis of covariance (ANCOVA) model. The analysis will include the categorical effects of treatment and all randomization stratification factors, as well as the continuous baseline CTT. Least squares mean (LSMean) change from baseline in each treatment group will be tested to detect any change in CTT between pre- and post-drug administration.

2. Schedule of Activities

Table CGBC.2.1. Schedule of Activities

Study Period	SP I Screening and Baseline GI Transit Time		SP II Single-Blind Treatment and Post WMC Evaluation			Notes
	V1	V2	V3	V4	V5	
Day	-8 ± 2	-7 ± 2	0	14 ± 3	28 ± 3	
Patient education regarding WMC	X					
Calibrate Medtronic WMC		X		X		
WMC administration		X ^a		X		<ul style="list-style-type: none"> • Fasting is defined as no food or drink, except water, for at least 8 hours prior to testing. • No alcohol consumption for 24 hours prior to ingesting the WMC and 6 hours after ingestion. • Tobacco use should also be avoided for 8 hours before ingestion and 6 hours after ingestion of the WMC. • Patients will consume a SmartBar immediately before ingesting WMC and will fast for 6 hours following WMC ingestion. • Patients should not sleep for 6 hours after ingesting the WMC.
Assessment that WMC has been expelled			X ^b	X ^b		The recorder will be returned to the site and data will be uploaded and evaluated to confirm WMC expulsion at Visit 3 and between Visits 4 and 5.
Study treatment administered			X			
Procedures						
Informed consent	X					
Inclusion and exclusion criteria	X					
Concomitant medication review	X	X	X	X	X	

Study Period	SP I Screening and Baseline GI Transit Time		SP II Single-Blind Treatment and Post WMC Evaluation			Notes
	V1	V2	V3	V4	V5	
Urine pregnancy test, performed locally	X				X	
Eligible patient randomized via IWRS			X			
Physical examination	X					
Height	X					
Weight	X					
Medical history	X					
Substance use	X		X	X		Substances: alcohol, caffeine, nicotine, tobacco.
Vital signs	X		X	X	X	Includes body temperature, sitting blood pressure, and pulse.
Assessment of migraine and headache days	X					Will be done retrospectively for the previous month.
GI Symptom Rating Scale (GSRS)	X		X	X	X	
Bristol Stool Form Scale	X		X	X	X	
Spontaneous Bowel movement (SBM) frequency evaluation	X		X	X	X	
Adverse events	X	X	X	X	X	

Abbreviations: GI = gastrointestinal; IBS = irritable bowel syndrome; IWRS = interactive web-response system; SP = study period; TT = transit time; V = visit; WMC = wireless motility capsule.

- ^a If the patient meets the requirement of fasting at Visit 1, then Visit 1 and Visit 2 could be combined. Sites must not instruct patients to fast prior to signing the ICF
- ^b An x-ray may be obtained in the event that the expulsion of the WMC cannot be confirmed.

3. Introduction

3.1. Study Rationale

Differences have been observed between reported frequencies of constipation in clinical trials and postmarketing adverse event (AE) reporting among calcitonin gene-related peptide (CGRP) antagonists. In particular, these differences have been observed between CGRP monoclonal antibodies (mAb) that target the ligand (galcanezumab, fremanezumab) or the receptor (erenumab) for the prevention of migraine (Stauffer et al. 2018b; Ashina et al. 2019; Robbins 2019; Silberstein et al. 2019; Aimovig package insert, 2020). Preclinical animal studies suggest that the different mechanisms of action of these agents may contribute to the different frequencies of constipation (Hargreaves and Olesen 2019). The purpose of Study I5Q-MC-CGBC (CGBC) is to measure gastrointestinal (GI) transit time in adult patients with migraine who have been initiated on preventive treatment with a CGRP antagonist (galcanezumab or erenumab), and explore whether there is a mechanistic difference that contributes to GI AEs in humans.

Medtronic's wireless motility capsule (WMC) technology, which is commercially available, will be used to evaluate total GI transit time as well as segmental transit time. The Medtronic WMC technology includes a WMC (SmartPill™ Motility Capsule), a wearable data recorder (SmartPill™ Motility Recorder), and a software program (MotiliGI™). 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). The US Food and Drug Administration has approved the system for the evaluation of adult patients with suspected delayed gastric emptying and the evaluation of colonic transit time (CTT) and combined small and large bowel transit time (SLBTT) in patients with chronic constipation (Saad and Hasler 2011; Medtronic 2017). The American and European Neurogastroenterology and Motility Societies recognized the WMC technology as a validated, standardized, objective measure of GI transit time and recommended its use for testing in individuals with suspected alterations of GI motility (Rao et al. 2011). Patients' baseline transit times will be measured with the WMC prior to first dose of the CGRP antagonist in patients with migraine deemed eligible by the study investigator. Two weeks following study treatment administration, a second WMC will be administered to obtain comparative transit time values to one's baseline for those patients in each treatment group.

3.2. Background

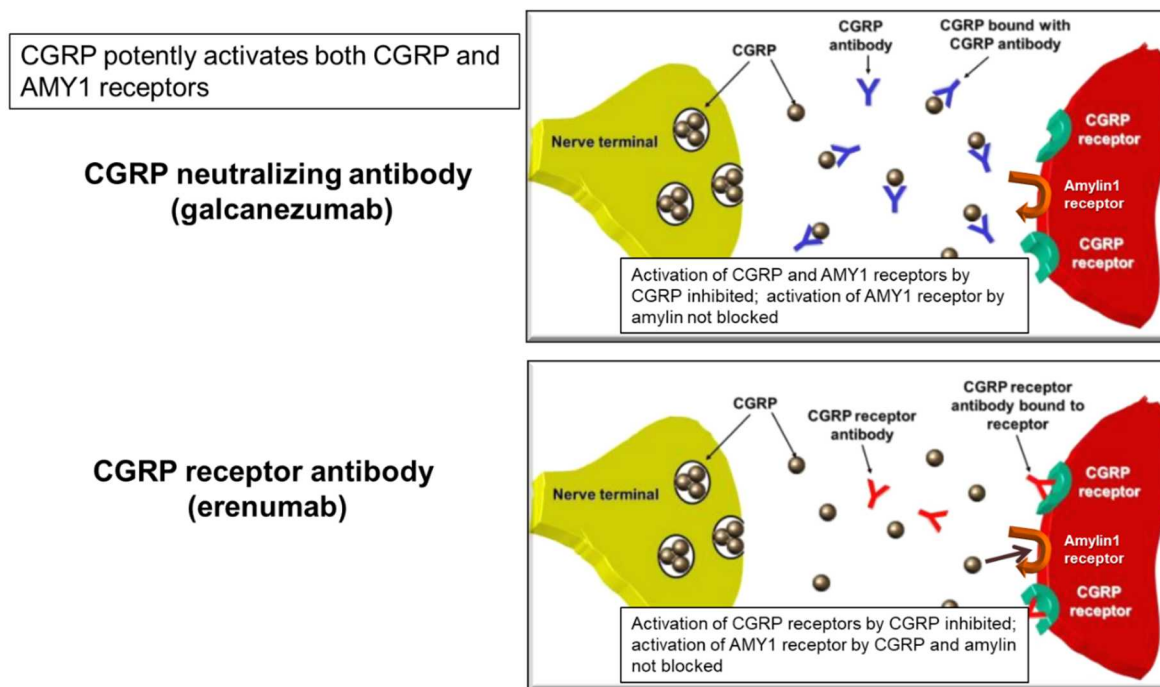
Recent publications have illustrated that CGRP can induce pharmacological effects at the CGRP receptor, as well as being a potent agonist at the amylin 1 (AMY1) receptor. As such, an antibody that binds to the CGRP receptor (erenumab) will block the effects of CGRP at the CGRP receptor, but will not inhibit the effects of CGRP at the AMY1 receptor. In contrast, an antibody that binds to CGRP itself (galcanezumab) will inhibit the pharmacological effects of CGRP at both the CGRP and AMY1 receptors (Figure CGBC.3.1). Amylin is an agonist at the AMY1 receptor, but is a very weak activator of the CGRP receptor (Hay 2017; Hay et al. 2018;

Hargreaves and Olesen 2019). The effects of amylin at the AMY1 receptor will persist in the presence of either antibody.

Calcitonin gene-related peptide receptors are located throughout the GI system of rodents and humans, including both the small and large intestines. Calcitonin gene-related peptide infusion has been reported to cause GI symptoms in 93% of human subjects (Falkenberg and Olesen 2019). Additionally, CGRP (administered intraperitoneally) has been shown to cause diarrhea in rodents that can be blocked by a CGRP antibody (Kaiser et al. 2017). Investigators have reported constipation with treatment for migraine prevention in clinical trials of selective CGRP receptor antagonists that are higher (Ho et al. 2014; ClinicalTrials.gov 2018; Ashina et al. 2019; Aimovig package insert, 2020) than the CGRP antagonists at the ligand (Stauffer et al. 2018b; Silberstein et al. 2019).

Alternatively, activation of amylin receptors induces stasis of the GI system. Amylin receptors are found on nerves projecting to the GI tract. The amylin analog, pramlintide, slows gastric emptying and is contraindicated in patients with gastroparesis. An amylin antagonist (AC187) accelerates gastric emptying in rats.

One possible explanation for the differences between reported frequencies of constipation in Phase 2 and 3 clinical trials, postmarketing clinician observation, and postmarketing AE reporting for monoclonal antibodies that act at the CGRP ligand versus the CGRP receptor could involve the effects of CGRP at the AMY1 receptor (Hay et al. 2018; Stauffer et al. 2018b; Aimovig package insert, 2020; Ashina et al. 2019; Hargreaves and Olesen 2019; Robbins 2019; Silberstein et al. 2019). By blocking the CGRP receptor, the CGRP receptor antagonist (erenumab) would decrease the motility-enhancing characteristics of CGRP while maintaining, or perhaps increasing, the GI motility-slowing effects via AMY1 receptor activation. Alternatively, the CGRP antagonist acting at the ligand would inhibit the motility-enhancing and motility-slowing effects of CGRP at the CGRP and AMY1 receptors, respectively, with the net effect being little to no change in GI transit time. This hypothesis will be studied in this clinical trial.



Abbreviations: AMY1 = amylin 1; CGRP = calcitonin gene-related peptide.

Figure CGBC.3.1. Mechanism of action of CGRP monoclonal antibodies.

3.3. Benefit/Risk Assessment

Galcanezumab is a humanized monoclonal antibody that potently and selectively 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 Phase 3 randomized, double-blind, placebo-controlled trials, which found statistically significant and clinically meaningful mean reduction of monthly migraine headache days and improvement in patient function compared with placebo in patients with episodic and chronic migraine (Detke et al. 2018; Skljarevski et al. 2018; Stauffer et al. 2018a). Across Phase 2 and Phase 3 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 (Camporeale et al. 2018; Dodick et al. 2014; Oakes et al. 2018; Skljarevski et al. 2018; Stauffer et al. 2018a). The incidences of serious adverse events (SAEs) and discontinuations due to AEs were low, and treatment-emergent adverse events (TEAEs) were generally of mild to moderate severity. In the Phase 3 studies, the most commonly reported TEAEs were injection site pain and injection site reactions, also generally of mild to moderate severity. There was no evidence of an effect on cardiovascular function. Additionally, in postmarketing experience, hypersensitivity reactions, including anaphylaxis, angioedema, dyspnea, urticaria, and rash, have been reported with galcanezumab.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of galcanezumab are to be found in the Investigator's Brochure (IB).

Erenumab is a human monoclonal antibody that antagonizes the CGRP receptor. The efficacy of erenumab for the prevention of migraine has been demonstrated in three Phase 3 randomized, double-blind trials (Goadsby et al. 2017; Tepper et al. 2017; Dodick et al. 2018). Erenumab 70 and 140 mg were both found to be effective in reducing the number of monthly migraine days in patients with episodic and chronic migraine. No serious safety concerns were identified with a clear causal relationship to erenumab. The incidences of SAEs and discontinuations due to AEs were low, and the most common adverse reactions (with an incidence of at least 2% for either dose of erenumab and at least 2% greater than placebo) were injection site reactions, constipation, and cramps/muscle spasms (Ashina et al. 2019; Aimovig package insert, 2020). 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 postmarketing experience.

The risks of WMC include capsule retention and aspiration, which rarely and very rarely are reported. With regard to the cases of capsule retention, they resolved either without intervention or with endoscopy/colonoscopy. Surgery was required for resolution in one instance of capsule small bowel retention that led to identification of a stricture.

To minimize these risks, patients with a history of GI surgery, a self-reported history of gastric bezoars, swallowing disorders, severe dysphagia to food or pills, suspected or known strictures, fistulas, or physiological/mechanical GI obstruction are excluded to participate in the study.

Patients should not undergo a magnetic resonance imaging (MRI) test until capsule passage is confirmed by review of the MotiliGI™ graph or x-ray of kidneys, ureter, and bladder. If a WMC is in the body during an MRI test, there is a risk of damage to the GI tract.

4. Objectives and Endpoints

Table CGBC.4.1 shows the objectives and endpoints of the study.

Table CGBC.4.1. Objectives and Endpoints

Objectives	Endpoints
<p><u>Primary Objective</u> To evaluate colonic transit time (CTT) in patients with migraine 1 week prior to and 2 weeks after administration of an initial loading dose of galcanezumab 240 mg or erenumab 140 mg.</p>	Change from baseline in CTT after administration of galcanezumab or erenumab within each treatment group in hours at the end of Week 2.
<p><u>Secondary Objectives</u> To evaluate transit time of the following segments of the gastrointestinal (GI) tract 1 week prior to and 2 weeks after administration of galcanezumab or erenumab:</p> <ul style="list-style-type: none"> • whole gut • gastric emptying • small bowel • combined small and large bowel. 	Change from baseline in GI transit time in each of the following segments after administration of galcanezumab or erenumab within each treatment group at the end of Week 2: <ul style="list-style-type: none"> • Whole gut transit time (WGTT), in hours • Gastric emptying time (GET), in hours • Small bowel transit time (SBTT), in hours • Combined small and large bowel transit time (SLBTT), in hours.
To evaluate the frequency of contractions, motility index, and area under the pressure curve (AUC) by quartile in the colon to assess for correlation with CTT results.	Changes in pressure parameters from baseline: <ul style="list-style-type: none"> • Contraction Freq/Min • Motility Index = $\ln(\# \text{ of contractions} \times \sum \text{pressure amplitudes} + 1)$ • Area under the Pressure Curve.
To evaluate number of weekly spontaneous bowel movements (un-aided by laxatives, enemas, or suppositories) prior to and after administration of galcanezumab or erenumab.	Change from baseline in number of weekly spontaneous bowel movements after administration of galcanezumab or erenumab within each treatment group at Weeks 2 and 4.
To evaluate GI symptom rating scale (GSRS) prior to and after administration of galcanezumab or erenumab.	Change from baseline in GSRS after administration of galcanezumab or erenumab within each treatment group at Weeks 2 and 4.
To evaluate the Bristol stool form scale (BSFS) prior to and after administration of galcanezumab or erenumab.	Change from baseline in BSFS after administration of galcanezumab or erenumab within each treatment group at Weeks 2 and 4.
<p><u>Tertiary/Exploratory Objectives</u> To evaluate the transit time between galcanezumab and erenumab for</p> <ul style="list-style-type: none"> • whole gut • gastric emptying • small bowel • colon • combined small and large bowel. 	Change from baseline in transit time after administration of galcanezumab or erenumab between treatment groups at the end of Week 2 for <ul style="list-style-type: none"> • WGTT, in hours • GET, in hours • SBTT, in hours • CTT, in hours • combined SLBTT, in hours.
To evaluate number of weekly spontaneous bowel movements (un-aided by laxatives, enemas, or suppositories) prior to and after administration of galcanezumab or erenumab.	Change from baseline in number of weekly spontaneous bowel movements after administration of galcanezumab or erenumab between each treatment group at Weeks 2 and 4.

Objectives	Endpoints
To evaluate GSRS prior to and after administration of galcanezumab or erenumab.	Mean change difference from baseline in GSRS scores after administration of galcanezumab or erenumab between treatment groups at Weeks 2 and 4 post-treatment.
To evaluate the BSFS prior to and after administration of galcanezumab or erenumab.	Mean change difference from baseline in BSFS scores after administration of galcanezumab or erenumab between treatment groups at Weeks 2 and 4 post-treatment.

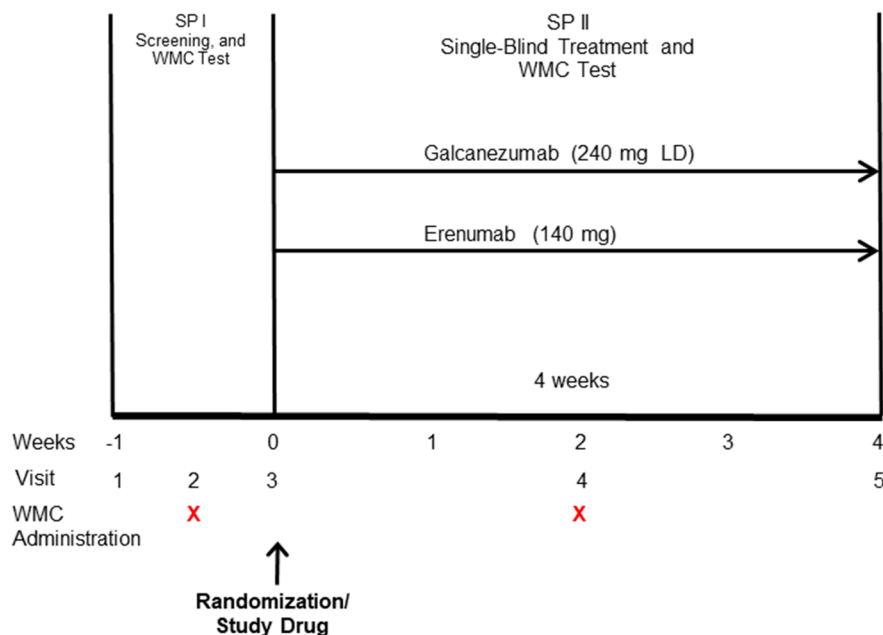
5. Study Design

5.1. Overall Design

Study CGBC is a multicenter, randomized, single-blind, Phase 4 study with 2 study periods in patients with migraine who are deemed eligible for preventive treatment by the study investigator. The study has 2 periods: a screening period to determine patient eligibility and lead-in with a baseline WMC test; and an single-blind treatment period with a post-study treatment WMC test.

Study governance considerations are described in detail in [Appendix 2](#).

Figure CGBC.5.1 illustrates the study design.



Abbreviations: LD = loading dose; Single-Blind = only the investigator, site personnel, and sponsor will know the randomized treatment after randomization; SP = study period; WMC = wireless motility capsule.

Figure CGBC.5.1. Illustration of study design for Clinical Protocol I5Q-MC-CGBC.

Study Period I: The study and potential risks will be explained to the patient at Visit 1. The informed consent form (ICF) must be signed before any study procedures are performed.

The screening and baseline GI transit time visit (Visit 1) will consist of a full clinical assessment, including a comprehensive medical evaluation documenting medical history, and a physical examination (see Schedule of Activities, Section 2) to confirm eligibility. Visit 2 includes administration of the WMC and receipt of recorder to patients meeting all eligibility requirements.

Study Period II: At the start of the single-blind treatment period (Visit 3), patients will be randomized in a 1:1 ratio to receive galcanezumab 240 mg loading dose or erenumab 140 mg. Patients will be administered 2 galcanezumab injections of 120 mg each to achieve the 240-mg loading dose or 2 erenumab injections of 70 mg each to achieve the 140-mg dose. At Visit 4, an additional WMC and recorder will be given to patients following calibration. Patients will exit the study at Visit 5.

5.2. Number of Participants

The study will screen an estimated 75 potential study participants to ensure randomization of approximately 60 patients with migraine.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

Refer to Section 3.1 for further information.

5.5. Justification for Dose

A galcanezumab 240-mg loading dose (2 consecutive injections of 120 mg each) or a dose of 140 mg erenumab (2 consecutive injections of 70 mg each) will be administered by subcutaneous injection because both galcanezumab and erenumab have been approved in the US at these respective doses for migraine prevention.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening:

Patient and Disease Characteristics

- [1] Patients are 18 to 55 years of age (inclusive) at the time of screening.
- [2] Have a diagnosis of migraine (1.1 and 1.2 ICHD), with or without aura, as determined by the study investigator and in consideration of International Headache Society International Classification of Headache Disorders – 3rd edition guidelines (ICHD-3 2018).
- [3] Have a frequency of less than 15 monthly headache days of which up to 14 can be migraine headache days.
- [4] Patients can be on no more than 1 other migraine preventive treatment (except for tricyclic antidepressants and verapamil) as long as:
 - that patient has had a stable dose of the oral migraine preventive treatment for a minimum of 2 monthsor
 - patients that have received onabotulinumtoxinA for a minimum of 2 cycles prior to Visit 1.

Informed Consent and Patient Agreements

- [5] Are able and willing to give signed informed consent.
- [6] Are reliable and willing to follow study procedures.
- [7] Male patients must agree to use a reliable method of birth control during the study as well as for 5 months after dosing with study treatment.
- [8] Women of childbearing potential must test negative for pregnancy at the time of enrollment based on a urine pregnancy test.
- [9] Women of childbearing potential who are abstinent from sexual intercourse must agree to remain abstinent during the study as well as for 5 months after dosing with study treatment.

- [10] Otherwise, women of childbearing potential must agree to use 1 highly effective method of contraception (including a male partner who has had a vasectomy), or a combination of 2 effective methods of contraception during the study as well as for 5 months after dosing with study treatment. Birth control is not required if the female is infertile due to surgical sterilization (hysterectomy, or at least 6 weeks after surgical bilateral oophorectomy or tubal ligation) confirmed by medical history or menopause.
- [11] Agree not to post any personal medical data related to the study or information related to the study on any website or social media site (e.g., Facebook, Twitter, LinkedIn, Google+, etc.) until the entire trial has completed.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

Medical Conditions

- [12] Prior to Visit 1, less than 3 bowel movements in the previous 7 days.
- [13] Patients with a history of irritable bowel syndrome (IBS) or chronic constipation.
- [14] Patients with a self-reported history of gastric bezoars, swallowing disorders, severe dysphagia to food or pills, suspected or known strictures, fistulas, or physiological/mechanical GI obstruction.
- [15] History of GI surgery with the exception of cholecystectomy, appendectomy, or Nissen fundoplication.
- [16] History of any abdominal surgery within the past 3 months.
- [17] History of bariatric surgery.
- [18] History of Crohn's disease, celiac disease, ulcerative colitis, or diverticulitis.
- [19] Patients with type 1 or type 2 diabetes.
- [20] Patients with cardiac pacemakers or other implanted or portable electromechanical device.
- [21] Patients with a body mass index (BMI) of ≥ 40 kg/m².
- [22] Women who are pregnant or nursing.
- [23] History of drug or alcohol abuse/dependence within 1 year prior to Visit 1 (excessive or compulsive use as judged by the investigator), or currently using drugs of abuse (including opioids, barbiturates, and marijuana), or any prescribed or over-the-counter medication in a manner that the investigator considers indicative of abuse/dependence.

- [24] Have an acute, serious, or unstable medical condition that, in the judgment of the investigator, indicates a medical problem that would preclude study participation.
- [25] Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, stroke, deep vein thrombosis, or pulmonary embolism within 6 months of screening, or have planned cardiovascular surgery or percutaneous coronary angioplasty.
- [26] Patients who, in the clinician's judgment, are actively suicidal and therefore deemed to be at significant risk for suicide, or have had clinically significant suicidal ideation within the past month (e.g., includes some plan or intent to act), or have had any suicidal behavior within the past month.

Prior/Concomitant Therapy

- [27] Patients currently receiving a mAb CGRP antagonist or have received a mAb CGRP antagonist within the past 6 months prior to Visit 1.
- [28] Have received an oral CGRP antagonist (gepant) 14 days prior to Visit 1.
- [29] Known hypersensitivity to monoclonal antibodies or other therapeutic proteins, or to galcanezumab.
- [30] Known allergy to SmartBar ingredients including granola (rolled oats, evaporated cane juice, expeller pressed canola oil, defatted wheat germ, oat flour, brown rice syrup, molasses, salt, natural flavor, soy lecithin), whey crisp, rice syrup, corn syrup, whey protein isolate, invert sugar, puffed wheat, apples, maltodextrin, sorbitol, apple juice concentrate, partially hydrogenated vegetable oil (cottonseed, soybean), honey, natural and artificial flavor, salt, gluten, vanilla.
- [31] Medications known to alter GI transit times including opioids, tricyclic antidepressants, verapamil, and medications that can affect the WMC test such as proton pump inhibitors, are excluded from the study 1 week prior to Visit 2 and at any time after Visit 2. See medication exclusion list for a full list of excluded medications.

Prior/Concurrent Clinical Trial Experience

- [32] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

Other Exclusions

- [33] In the opinion of the investigator, have other issues that would interfere with compliance with the study requirements and completion of evaluations required for this study.

- [34] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- [35] Are Lilly employees or are employees of Medtronic.
- [36] Are unwilling or unable to comply with the use of a data collection device to directly record data from the subject.

6.3. Lifestyle Restrictions

No vigorous exercise, such as sit-ups, abdominal crunches, or prolonged extreme exercises, should be performed throughout the duration of the WMC test, which is approximately 5 days.

Patients should maintain consistent dietary habits throughout the duration of the study (from Visit 1 to Visit 5).

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreen once, with approval from Lilly Medical for only the criteria shown below. The interval between screening and rescreening must be at least 45 days or longer if required for the specified time frames in the inclusion/exclusion criteria or concomitant medication list. If rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

- Inclusion criterion 1: If patients are less than 18 years old at the time of informed consent, they may be rescreened when they reach 18 years of age during the study enrollment period.
- Exclusion criterion 27, 28, and 31: Patients using a concomitant medication that requires a stable dose for a specific duration prior to Visit 1 may be rescreened if additional time is needed to meet the duration requirement.

7. Treatments

7.1. Treatments Administered

This study involves an evaluation of GI transit time in patients who receive galcanezumab 240 mg administered by subcutaneous injection and erenumab 140 mg administered by subcutaneous injection. Both galcanezumab and erenumab will be administered by site staff once with an autoinjector (AI) pen at Visit 3 of the study. [Table CGBC.7.1](#) shows the treatment regimens.

Table CGBC.7.1. Treatment Regimens

Regimen	Dose Day 7 ± 2
Galcanezumab 240 mg	240 mg (2 × 120-mg SC injection)
Erenumab 140 mg	140 mg (2 × 70-mg SC injection)

Abbreviation: SC = subcutaneous.

The investigator or his/her designee is responsible for

- verifying that instructions are followed properly
- maintaining accurate records of study treatment dispensing and collection, and
- at the end of the study, returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed that all unused medications are to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labeling

Galcanezumab and erenumab will be supplied as an injectable solution in 1-mL, single-dose, prefilled, disposable AI pen. Each AI pen of galcanezumab is designed to deliver 120 mg/mL, and each AI pen of erenumab is designed to deliver 70 mg/mL. All AI pens will be supplied in single pen cartons, with the site to select the appropriate quantity of AI pens, specific to the planned treatment schedule. Two galcanezumab AI pens are needed for the galcanezumab (240 mg) treatment. Two erenumab AI pens are needed for the erenumab (140 mg) treatment.

The commercial products being provided will be labeled with a commercially approved product label. Each commercial product package is to have a “For CT use only” label.

7.1.2. Medical Devices

The commercial medical devices provided for use in the study are AI pens and the SmartPill™ system. The SmartPill™ motility testing system includes the SmartPill™ motility capsule (WMC), the MotiliGI™ software, and the SmartPill™ motility recorder.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to single-blind treatment at Visit 3. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

To achieve between-group comparability, the randomization will be stratified by site, BMI category ($<30 \text{ kg/m}^2$, $\geq 30 \text{ kg/m}^2$), and by baseline migraine frequency (<8 migraine headache days versus ≥ 8 migraine headache days).

7.2.1. Selection and Timing of Doses

The study treatment will be administered only once at Visit 3.

7.3. Blinding

This is a single-blind study. Only the investigator, site personnel, and sponsor will know the randomized treatment after randomization. Site Personnel are responsible to ensure patients remain blinded to treatment (i.e., patients must not see the AI pens before, during, or after the drug administration). See the Manual of Operations for further details regarding blinding.

7.4. Dosage Modification

Not applicable.

7.5. Preparation/Handling/Storage/Accountability

The investigator or his/her designee is responsible for the following:

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

The study treatment must be stored according to the storage requirements printed onto the commercial label.

To administer the galcanezumab or erenumab injections, the investigational sites are to refer to the commercial package insert for the preparation and handling instructions of each study treatment.

7.6. Treatment Compliance

Patient compliance with study medication will be assessed at the dosing visit. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

7.7. Concomitant Therapy

The list of excluded medications and procedures is provided in the Manual of Operations. Any changes in the list of allowed/not allowed medications will be communicated to investigators and will not constitute a protocol amendment.

7.8. Treatment after the End of the Study

Study treatment will not be made available to patients after conclusion of the study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. *Permanent Discontinuation from Study Treatment*

Possible reasons leading to permanent discontinuation of study treatment:

- **Subject Decision**
 - the patient requests to discontinue study treatment.
- In addition, patients will be discontinued from the study treatment in the following circumstances:
 - WMC retention or aspiration

Patients discontinuing from the study prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. *Temporary Discontinuation from Study Treatment*

Not applicable.

8.1.3. *Discontinuation of Inadvertently Enrolled Patients*

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue study treatment. If the investigator and the sponsor clinical research physician (CRP)/clinical research scientist (CRS) agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without study treatment. Safety follow-up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an study treatment or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP)
- investigator decision

- the investigator decides that the patient should be discontinued from the study
- if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- patient decision
 - the patient requests to be withdrawn from the study
- patient becomes pregnant.

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not receive study treatment. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

9.1. Efficacy Assessments

9.1.1. Primary Assessment of GI Transit Time

The WMC (Medtronic 2017) measures whole gut and regional gut (stomach, small bowel, and colon) transit times through measurement of pH, pressure, and temperature throughout the GI tract. Once enrolled into study, the patient will be asked to eat a SmartBar, followed by ingesting the WMC with 120 mL of water. The patient will then be instructed to fast for an additional 6 hours after the WMC is administered and wear an external data recorder for up to 5 days. The WMC is a 4.5-g indigestible single-use, 27 × 12 mm cylindrical capsule. Data are transferred to the accompanied wearable external data recorder and displayed and analyzed using MotiliGI™ version 3.1 software (Medtronic 2017).

The baseline and postbaseline WMC test will be assessed by expert readers who are blind to treatment assignment.

9.1.2. Secondary Assessment Scales

Gastrointestinal Symptom Rating Scale. The Gastrointestinal Symptom Rating Scale (GSRS) is a validated 15-item questionnaire that evaluates the 5 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 (Revicki et.al 1998; Khanna 2017).

Bristol Stool Form Scale. The Bristol Stool Form Scale (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, stool Type 3 to 5 are considered normal. BSFS provides the patient with a pictorial representation of each type of stool (Blake et al. 2016).

9.1.3. Appropriateness of Assessments

The efficacy and safety assessments used in this study have been well documented and are generally regarded as reliable, accurate, and are relevant for use in this study.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, 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 should be followed up until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

The investigator will record all relevant AE and SAE information in the eCRF. After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure and study treatment, via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause-and-effect relationship between the study treatment, study device, and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's study treatment is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e., immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- when a condition related to the AI pen necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of “required intervention” will be assigned.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed by official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient disposition eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he or she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the galcanezumab IB or the erenumab US package insert (USPI) and that the investigator identifies as related to study treatment or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

Lilly collects product complaints on study treatment and drug delivery systems used in clinical studies to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study treatment (galcanezumab or erenumab) or device (AI or WMC) so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the IB for galcanezumab and the Product Label for erenumab.

9.4. Safety

9.4.1. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

9.4.2. Laboratory Tests

For each patient, the local urine pregnancy test should be conducted according to the Schedule of Activities (Section 2).

9.4.3. Immunogenicity Assessments

Not applicable.

9.4.4. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

9.4.4.1. Hepatic Safety Monitoring

Not applicable.

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

Not applicable.

9.8. Biomarkers

Not applicable.

9.9. Health Economics

Health Economics and Medical Resource Utilization parameters are not evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

Assuming within-group mean difference in CTT is about 4.2 hours with standard deviation of approximately 8, a sample of 30 patients in each treatment group will provide 80% power to detect the difference within the treatment group. The total sample size for the study would be 60.

Assuming 20% screen failure rate, approximately 75 patients may be screened to enroll 60 patients into the study. Eligible patients will be randomized in a 1:1 ratio to galcanezumab or erenumab to have about 30 patients in each treatment group.

10.2. Populations for Analyses

For purposes of analysis, the intent-to-treat (ITT) population will be used. The ITT population includes all patients who are randomized and received study treatment. Other populations may be explored if appropriate, such as the ITT population excluding patients taking prohibited medications that are known to have an effect on GI motility or the WMC test.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Details of statistical analysis methods will be described in the statistical analysis plan (SAP).

Unless otherwise specified, analyses will be conducted on the ITT population, which will include all patients who are randomized and receive at least 1 dose of study treatment. Patients in the ITT population will be analyzed according to the treatment group to which they are randomized. When change from baseline is assessed, the patient will be included in the analysis only if the patient has baseline and postbaseline measurements.

Investigative sites with fewer than 4 randomized patients per treatment group will be pooled for statistical analysis purposes.

All tests of within-group and between-group comparisons will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP or the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

The number and percentage of ITT patients who complete the study or discontinue early will be summarized for both treatment groups. A detailed description of patient disposition will be provided at the end of the study.

Patient allocation by investigative site will be summarized for ITT population. Patient allocation by investigative site will also be listed.

10.3.2.2. Patient Characteristics

The following patient characteristics at baseline will be summarized by treatment group for ITT population:

- demographics (age, gender, ethnic origin, height, weight, body mass index)
- medical history and pre-existing condition
- total gut and segmental transit times, and
- GI symptom rating scale, SBM frequency, and Bristol stool form scale.

10.3.2.3. Concomitant Therapy

The proportion of patients who received concomitant medication will be summarized for all ITT patients.

10.3.2.4. Treatment Compliance

Not applicable.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary objective is to assess changes in CTT between pre- and post-drug administration within each treatment group. The primary measure is the mean change from baseline in the CTT 2 weeks after drug administration within each treatment group.

The primary analysis will be performed using an analysis of covariance (ANCOVA) model. The analysis will include the categorical effects of treatment and all randomization stratification factors (site, baseline migraine frequency, and BMI category; see Section 7.2), as well as the continuous baseline CTT. Least squares mean change from baseline in each treatment group will be tested to detect any change in CTT between pre- and post-drug administration.

10.3.3.2. Secondary Analyses

For continuous secondary measures with single postbaseline measurement, analysis will be performed using an ANCOVA model. The analysis will include the categorical effects of treatment and all randomization stratification factors, as well as the continuous baseline value. Least squares mean change from baseline in each treatment group will be tested to detect any changes between pre- and post-drug administration. Least squares mean change from baseline in 2 treatment groups will be compared to detect any between-group differences.

10.3.3.3. Tertiary/Exploratory Analyses

For continuous measures with repeated postbaseline measurements, change from baseline will be analyzed using a restricted maximum likelihood-based mixed effects model for repeated measures technique (MMRM). The analysis will include the fixed categorical effects of treatment, all randomization stratification factors, investigative site, week, and treatment-by-week interaction, as well as the continuous fixed covariates of baseline value and baseline-by-week interaction. Details of MMRM model are described in the SAP, and further details regarding tertiary analyses are summarized in the SAP.

10.3.4. Safety Analyses

The safety analyses will be conducted for the single-blind treatment phase.

Safety data will be summarized by treatment group.

The safety and tolerability of treatment will be assessed by summarizing adverse events:

- TEAEs
 - by Preferred Term (PT)
 - by System Organ Class (SOC)
 - by maximum severity
 - considered to be related to study treatment by investigator
- SAEs, and
- AEs leading to discontinuation.

Treatment-emergent adverse events are defined as the reported AEs that first occurred or worsened during the postbaseline phase compared with baseline phase. For each TEAE, the severity level of the event (mild, moderate, or severe) will be determined by patient or physician opinion. The Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term will be used in the treatment-emergent computation. For each Lowest Level Term, the maximum severity at baseline will be used as the baseline severity. If the maximum severity during postbaseline is greater than the maximum baseline severity, the event is considered to be treatment emergent for the specific postbaseline period. For each patient and TEAE, the maximum severity for the MedDRA level being displayed (PT, High Level Term, or SOC) is the maximum postbaseline severity observed from all associated Lowest Level Terms mapping to that MedDRA level.

For events that are gender specific, the denominator and computation of the percentage will include only patients from the given gender.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

10.3.6. Evaluation of Immunogenicity

Not applicable.

10.3.7. Other Analyses

Not applicable.

10.3.7.1. Health Economics

Not applicable.

10.3.7.2. Subgroup Analyses

Not applicable.

10.3.8. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (study) drug, whether or not related to the medicinal (study) drug.
AI	autoinjector
AMY1	amylin 1
ANCOVA	analysis of covariance
blinding/masking	A single-blind study is one in which the investigator and/or staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/or staff and the patient are not.
BSFS	Bristol Stool Form Scale
CGRP	calcitonin gene-related peptide
CIOMS	Council for International Organizations of Medical Sciences
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRS	clinical research scientist
CSR	clinical study report
CTT	colonic transit time
eCOA	electronic clinical outcome assessment is a method of capturing data electronically in clinical trials.
eCRF	electronic case report form

Term	Definition
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	Good Clinical Practice
GET	gastric emptying time
GI	gastrointestinal
GSRS	Gastrointestinal Symptom Rating Scale
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
mAb	monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model for repeated measures
MRI	magnetic resonance imaging
PT	Preferred Term
SAE	serious adverse event
SAP	statistical analysis plan

Term	Definition
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SBTT	small bowel transit time
SBM	spontaneous bowel movement
SLBTT	combined small and large bowel transit time
SOC	System Organ Class
study treatment	Any treatment(s), in this case marketed product(s), intended to be administered to a study participant according to the study protocol
SUSAR	suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
WGTT	whole gut transit time
WMC	wireless motility capsule or the SmartPill™

Appendix 2. Study Governance Considerations

Appendix 2.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 2.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of study treatment.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 2.1.2. Recruitment

Lilly is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 2.1.3. Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with

- the protocol and related amendments and addenda, current Investigator's Brochure for galcanezumab, US Product Information for erenumab, and updates during the course of the study
- ICF, and

- other relevant documents (e.g., curricula vitae, advertisements).

Appendix 2.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines, and
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 2.1.5. Investigator Information

Investigators in this clinical trial should be neurologists, headache specialists, or other specialists with experience in headache clinical trials and treating patients with migraine.

Appendix 2.1.6. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 2.1.7. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

An investigator selected by the study team will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 2.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the case report forms (CRFs), and study procedures.

- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection, and
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 2.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system. Investigator sites will have continuous access to the electronic clinical outcome assessment (eCOA) source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the eCOA instruments record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data will be encoded and stored in a clinical trial database. eCOA data read by a central reader, such as the WMC test, will be stored electronically. Subsequently, these data will be transferred from the central reader to the Lilly data warehouse.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome measures (e.g., a rating scale).

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 2.3. Study and Site Closure***Appendix 2.3.1. Discontinuation of Study Sites***

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 2.3.2. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 2.4. Publication Policy

The publication policy for Study I5Q-MC-CGBC is described in the Clinical Trial Agreement.

**Appendix 3. Protocol Amendment
I5Q-MC-CGBC(a) Summary
A Phase 4 Single-Blind Study of Gastrointestinal Transit
Time in Adult Patients with Migraine Before and After
Initiation of a mAb CGRP Antagonist**

Overview

Protocol I5Q-MC-CGBC(a) A Phase 4 Single-Blind Study of Gastrointestinal Transit Time in Adult Patients with Migraine Before and After Initiation of a mAb CGRP Antagonist has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol I5Q-MC-CGBC Amendment (a)

Section # and Name	Description of Change	Brief Rationale
Global	The study has been amended from an open-label study to a single-blind study.	This change was made to reduce potential for patient bias, as the frequency and consequences of constipation for erenumab and galcanezumab are not the same based on a recent USPI update for erenumab regarding constipation.
	Minor editorial changes	Minor editorial changes were made to improve clarity.
Title	CGRP Antagonist has been clarified to mAb CGRP Antagonist.	This clarification was made due to the recent approval of oral CGRP antagonists.
Section 2 Schedule of Activities	Vital sign assessments have been added to Visits 3, 4, and 5.	The additional vital sign assessments were added due to the April 2020 update to the erenumab USPI with Warning and Precautions language for new-onset or worsening of pre-existing hypertension based on postmarketing information.
Section 6.1 Inclusion Criteria	Chronic migraine has been removed from Inclusion Criterion [2].	The chronic migraine diagnosis was removed because this patient population has a higher frequency of headaches per month, which can be associated with more comorbidity. Therefore, this change was made to reduce variation in the population due to the small sample size and the exploratory nature of the study. Chronic migraine was also removed from Inclusion Criterion [4] due to this change.
	Inclusion Criterion [3] has been added.	The Inclusion Criterion [3] (that patients must have a frequency of less than 15 monthly migraine headache days of which up to 14 can be migraine headache days) was added in response to the removal of chronic migraine from Inclusion Criterion [2].
Section 6.2 Exclusion Criteria	Exclusion Criterion [21] has been changed from “Patients with a body mass index of $\geq 50 \text{ kg/m}^2$ ” to “Patients with a body mass index (BMI) of $\geq 40 \text{ kg/m}^2$.”	The BMI criteria was amended to be consistent with the BMI thresholds in the previously conducted Phase 3 trials. This change will limit the potential for outliers.
	Exclusion Criterion [28] has been added.	Having received oral CGRP antagonists has been added as an exclusion criterion due to their recent approval for the acute treatment of migraine. The half-lives of oral CGRP antagonists are in the range of 5 to 12 hours, so a 14-day washout period was considered appropriate to ensure a complete washout before a patient enters the study.

Section # and Name	Description of Change	Brief Rationale
Section 6.4 Screen Failures	Exclusion Criterion [27] and [28] has been added to the statement, “Patients using a concomitant medication that requires a stable dose for a specific duration prior to Visit 1 may be rescreened if additional time is needed to meet the duration requirement.”	These Exclusion Criterion were added so that patients may be rescreened if additional time is needed to meet the specific medication duration requirement.
Section 7.1 Treatments Administered	The 140 mg/mL dose of erenumab has been updated to 2 consecutive doses of 70 mg/mL each.	This change was made to support the patient blinding so that each patient receives 2 injections. This change also occurs in Section 7.1.1 (Packaging and Labeling).
Section 7.2 Method of Treatment Assignment	Stratification of randomization has been amended from migraine classification of episodic or chronic and concurrent migraine preventive treatment to baseline migraine frequency and BMI category.	Baseline migraine frequency was added, as chronic migraine has been removed from the inclusion criteria. Since chronic migraine is excluded, it is expected that fewer patients will be on a concurrent migraine preventive treatment. Therefore, migraine preventive treatment has been removed as a stratification factor. BMI category (<30 kg/m ² , ≥30 kg/m ²) was added to reduce any imbalance of outliers across the 2 treatment groups. This change has also been made in Section 10.3.3.1 (Primary Analyses).
	The statement, “The study treatment will be administered only once at Visit 3 after expulsion of the WMC has been confirmed” has been amended to “The study treatment will be administered only once at Visit 3.”	This statement was amended because administering the study treatment is not dependent on the expulsion of the WMC.
Section 7.3 Blinding	This section has been amended to clarify that Study CGBC is now single blind.	Additions were made to this section due to Study CGBC changing from an open-label to a single-blind study so that the patient does not know treatment randomization.
Section 9.1.1 Primary Assessment of GI Transit Time	The statement, “Once enrolled into study, the patient will be asked to eat a SmartBar with 120 mL water, followed by ingesting the WMC with 50 mL of water” has been amended to “Once enrolled into study, the patient will be asked to eat a SmartBar, followed by ingesting the WMC with 120 mL of water.”	This statement was amended due to a discrepancy with the SmartPill Manual. The correction was made to align with the manual (Medtronic 2017).

Section # and Name	Description of Change	Brief Rationale
Section 9.2.1 Serious Adverse Events	The statement, "Patients with a serious hepatic AE should have additional data collected using the eCRF" has been removed.	This statement was removed because hepatic laboratory values are not being collected in this study.
Section 9.2.1.1 Suspected Unexpected Serious Adverse Reactions	The statement, "Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study treatment or procedure" has been amended to "Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the galcanezumab IB or the erenumab US package insert (USPI) and that the investigator identifies as related to study treatment or procedure."	This statement was amended to clarify what will be considered a SUSAR for both galcanezumab and erenumab.

Revised Protocol Sections

Note: Deletions have been identified by ~~strikethroughs~~.
 Additions have been identified by the use of underscore.
 “open-label” is replaced by “single-blind” throughout the document and each instance is not identified with strikethrough/underscore.
 Minor formatting and editorial changes have been made throughout the document and each instance is not identified with strikethrough/underscore.

Protocol I5Q-MC-CGBC A Phase 4 ~~Open-Label~~Single-Blind Study of Gastrointestinal Transit Time in Adult Patients with Migraine Before and After Initiation of a mAb CGRP Antagonist

2. Schedule of Activities

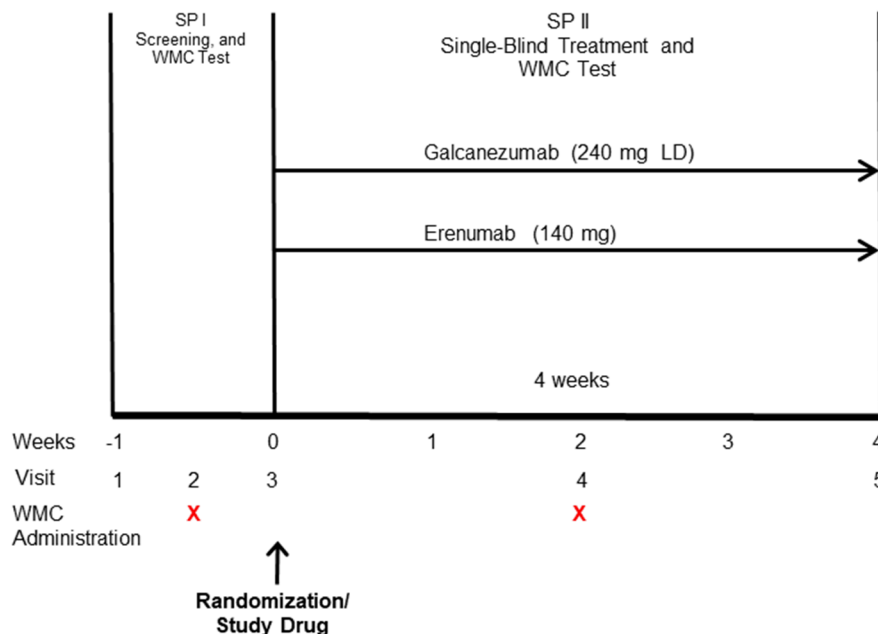
Table CGBC.2.1. Schedule of Activities

Study Period	SP I Screening and Baseline GI Transit Time		SP II Single-Blind <u>Open-Label</u> Treatment and Post WMC Evaluation			Notes
	V1	V2	V3	V4	V5	
Vital signs	X		<u>X</u>	<u>X</u>	<u>X</u>	Includes body temperature, sitting blood pressure, and pulse.

3.3. Benefit/Risk Assessment

Erenumab is a human monoclonal antibody that antagonizes the CGRP receptor. The efficacy of erenumab for the prevention of migraine has been demonstrated in three Phase 3 randomized, double-blind trials (Goadsby et al. 2017; Tepper et al. 2017; Dodick et al. 2018). Erenumab 70 and 140 mg were both found to be effective in reducing the number of monthly migraine days in patients with episodic and chronic migraine. No serious safety concerns were identified with a clear causal relationship to erenumab. The incidences of SAEs and discontinuations due to AEs were low, and the most common adverse reactions (with an incidence of at least 2% for either dose of erenumab and at least 2% greater than placebo) were injection site reactions, constipation, and cramps/muscle spasms (~~Aimovig package insert, 2019~~; Ashina et al. 2019; Aimovig package insert, 2020). Hypersensitivity reactions, (including rash, angioedema, and anaphylaxis), ~~as well as constipation with serious complications, and new-onset or worsening of pre-existing hypertension~~ have been reported with erenumab in postmarketing experience.

5.1. Overall Design



Abbreviations: GI = gastrointestinal; LD = loading dose; Single-Blind = only the investigator, site personnel, and sponsor will know the randomized treatment after randomization; SP = study period; ~~TT~~ WMC = wireless motility capsule transit time.

Figure CGBC.5.1. Illustration of study design for Clinical Protocol I5Q-MC-CGBC.

Study Period II: At the start of the ~~single-blind~~ open-label treatment period (Visit 3), patients will be randomized in a 1:1 ratio to receive galcanezumab 240 mg loading dose or erenumab 140 mg. Patients will be administered 2 galcanezumab injections of 120 mg each to achieve the 240-mg loading dose or ~~a single~~ 2 erenumab injections of 70 mg each to achieve the 140-mg dose. At Visit 4, an additional WMC and recorder will be given to patients following calibration. Patients will exit the study at Visit 5.

5.5. Justification for Dose

A galcanezumab 240-mg loading dose (2 consecutive injections of 120 mg each) or a dose of 140 mg erenumab (2 consecutive injections of 70 mg each) will be administered by subcutaneous injection because both galcanezumab and erenumab have been approved in the US at these respective doses for migraine prevention.

6.1. Inclusion Criteria

- [2] Have a diagnosis of migraine (1.1 and 1.2 ICHD), with or without aura, ~~or chronic migraine~~, as determined by the study investigator and in consideration of International Headache Society International Classification of Headache Disorders – 3rd edition guidelines (ICHD-3 2018).
- [3] Have a frequency of less than 15 monthly headache days of which up to 14 can be migraine headache days.

[43] Patients can be on no more than 1 other migraine preventive treatment (except for tricyclic antidepressants and verapamil) as long as:

- that patient has had a stable dose of the oral migraine preventive treatment for a minimum of 2 months

or

- patients ~~with chronic migraine~~ that have received onabotulinumtoxinA for a minimum of 2 cycles prior to Visit 1.

6.2. Exclusion Criteria

[210] Patients with a body mass index (BMI) of ≥ 50 –40 kg/m².

[276] Patients currently receiving a mAb CGRP antagonist ~~on CGRP antagonists~~ or have ~~taken~~ received a mAb CGRP antagonist within the past 6 months prior to Visit 1.

[28] Have received an oral CGRP antagonist (gepant) 14 days prior to Visit 1.

6.4. Screen Failures

- Exclusion criterion 27, 28, and 31: Patients using a concomitant medication that requires a stable dose for a specific duration prior to Visit 1 may be rescreened if additional time is needed to meet the duration requirement.

7.1. Treatments Administered

Table CGBC.7.1. Treatment Regimens

Regimen	Dose
	Day 7 ± 2
Galcanezumab 240 mg	240 mg (2 × 120-mg SC injection)
Erenumab 140 mg	140 mg (2 × 70 140-mg SC injection)

Abbreviation: SC = subcutaneous.

7.2. Packaging and Labeling

Galcanezumab and erenumab will be supplied as an injectable solution in 1-mL, single-dose, prefilled, disposable AI pen. Each AI pen of galcanezumab is designed to deliver 120 mg/mL, and each AI pen of erenumab is designed to deliver ~~140~~ 70 mg/mL. All AI pens will be supplied in single pen cartons, with the site to select the appropriate quantity of AI pens, specific to the planned treatment schedule. Two galcanezumab AI pens are needed for the galcanezumab (240 mg) treatment. ~~One~~ Two erenumab AI pens are needed for the erenumab (140 mg) treatment.

7.2. Method of Treatment Assignment

To achieve between-group comparability, the randomization will be stratified by site, ~~concurrent migraine preventive treatment~~ BMI category (Yes/No $<30 \text{ kg/m}^2$, $\geq 30 \text{ kg/m}^2$), and by baseline migraine frequency (<8 migraine headache days versus ≥ 8 migraine headache days) ~~migraine classification of episodic or chronic~~.

7.2.1. Selection and Timing of Doses

The study treatment will be administered only once at Visit 3 ~~after expulsion of the WMC has been confirmed~~.

7.3. Blinding

This is an ~~open-label~~ single-blind study. Only the investigator, site personnel, and sponsor will know the randomized treatment after randomization. Site Personnel are responsible to ensure patients remain blinded to treatment (i.e., patients must not see the AI pens before, during, or after the drug administration). See the Manual of Operations for further details regarding blinding.

9.1.1. Primary Assessment of GI Transit Time

The WMC (Medtronic 2017) measures whole gut and regional gut (stomach, small bowel, and colon) transit times through measurement of pH, pressure, and temperature throughout the GI tract. Once enrolled into study, the patient will be asked to eat a SmartBar ~~with 120 mL water~~, followed by ingesting the WMC with 120 mL of water ~~with 50 mL of water~~. The patient will then be instructed to fast for an additional 6 hours after the WMC is administered and wear an external data recorder for up to 5 days. The WMC is a 4.5-g indigestible single-use, 27×12 mm cylindrical capsule. Data are transferred to the accompanied wearable external data recorder and displayed and analyzed using MotiliGI™ version 3.1 software (Medtronic 2017).

9.2.1. Serious Adverse Events

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed by official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. ~~Patients with a serious hepatic AE should have additional data collected using the eCRF.~~

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the galcanezumab IB or the erenumab US package insert (USPI) and that the investigator identifies as related to study treatment or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has

procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

10.3.3.1. Primary Analyses

The primary analysis will be performed using an analysis of covariance (ANCOVA) model. The analysis will include the categorical effects of treatment and all randomization stratification factors (site, ~~concurrent use of migraine preventive treatment Yes vs No, and migraine classification of episodic or chronic~~ baseline migraine frequency, and BMI category; see Section 7.2), as well as the continuous baseline CTT. Least squares mean change from baseline in each treatment group will be tested to detect any change in CTT between pre- and post-drug administration.

Appendix 1. Abbreviations and Definitions

Term	Definition
<u>blinding/masking</u>	<u>A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not.</u>
<u>mAb</u>	<u>monoclonal antibodies</u>

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