Statistical Analysis Plan: I5Q-MC-CGBC (v2)

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

NCT04294147

Approval Date: 29-Sep-2020

1. Statistical Analysis Plan
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

Galcanezumab-gnlm (LY2951742) Migraine

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 a single-blind treatment period with post–study treatment WMC test.

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Protocol I5Q-MC-CGBC

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 12 March 2020
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 29-Sep-2020 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Figure **Page**

Table of Contents

Appendix **Page**

3. Revision History

Statistical Analysis Plan Version 1 was approved prior to the first patient visit.

Statistical Analysis Plan Version 2 was approved prior to the first patient visit. The following updates were made to coincide with a protocol amendment:

- Section 5.1 and throughout, updated to single-blind study as the protocol was updated to a single-blind study design.
- Section 5.3 and throughout, updated stratification factors. Removed concurrent migraine preventive treatment (Yes/No) and migraine classification of episodic or chronic; and replaced with body mass index category ($<30 kg/m^2$, ≥ 30 kg/m^2), and by baseline migraine frequency (<8 migraine headache days, ≥8 migraine headache days).
- Section 6.2, with the removal of chronic migraine patients, the derivation of chronic versus episodic has been removed.
- Section 6.3 was updated to include language about adjustments due to COVID-19.
- Section 6.8, substance use, medical history, and preexisting conditions were added to patient characteristics.
- Section 6.11, vital signs bullet was added, and a description of models used for safety analyses was provided.
- Section 6.11.2, treatment compliance was moved to this section.
- Section 6.11.6, analyses for vital sign data were added; previously no analyses were planned.
- Section 6.12, section on blinding was added since study design switched from open-label to single-blind.
- General formatting and grammatical edits were made throughout the document that did not change the meaning.

4. Study Objectives

4.1. Primary Objective

The primary objective is 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. The primary outcome measure is CTT in hours. The primary endpoint is the change from baseline in CTT after administration of galcanezumab or erenumab within each treatment group in hours at the end of Week 2.

4.2. Secondary and Tertiary Objectives

Table CGBC.4.1 shows the secondary and tertiary objectives and endpoints.

Table CGBC.4.1. Secondary and Tertiary Objectives and Endpoints

Objectives	Endpoints
Secondary Objectives 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: • whole gut • gastric emptying • small intestine, and • 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: • whole gut transit time (WGTT), in hours • gastric emptying time (GET), in hours • small intestine bowel transit time (SBTT), in hours, and • 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 colonic transit time (CTT) results.	Changes in pressure parameters from baseline: • contraction freq/min • motility index = ln (# of contractions × ∑pressure amplitudes +1), and • Area under the pressure curve (AUC).
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 post-treatment.
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 post-treatment.
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 post-treatment.

Secondary and Tertiary Objectives and Endpoints

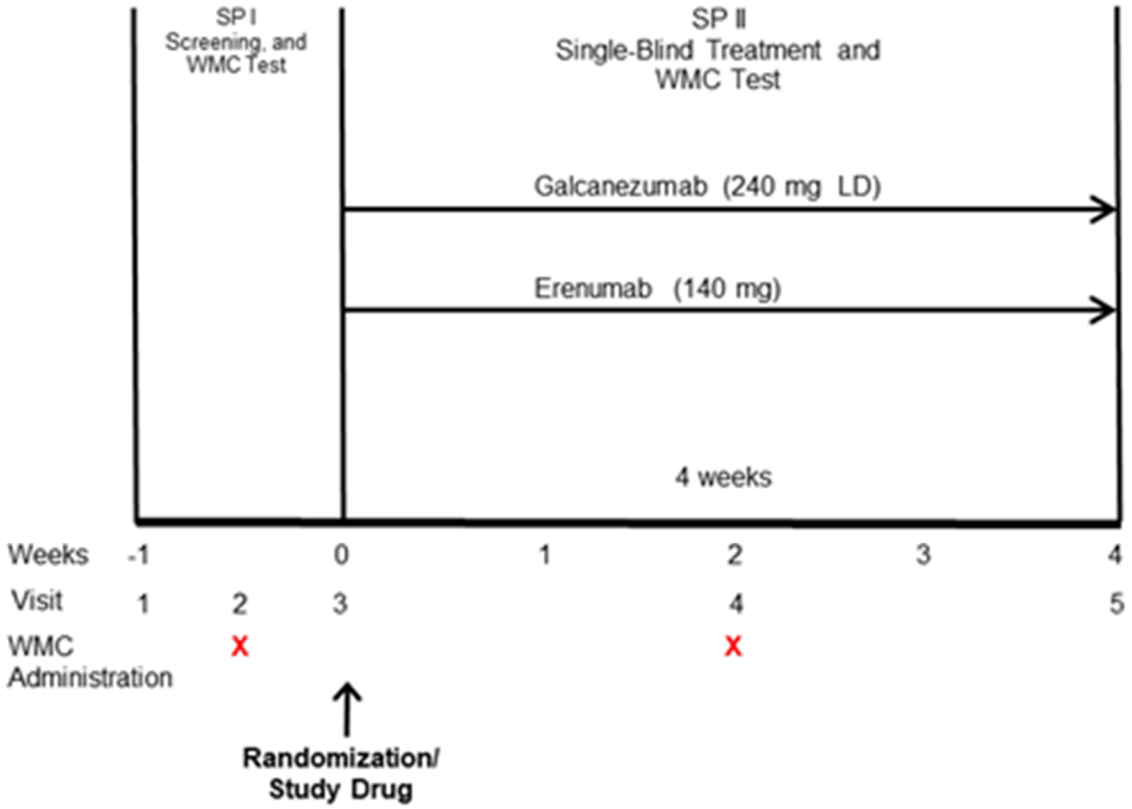
Objectives	Endpoints
Tertiary/Exploratory Objectives To evaluate the transit time between galcanezumab and erenumab for • whole gut • gastric emptying • small bowel • colon, and • combined small and large bowel.	Change from baseline in transit time after administration of galcanezumab or erenumab between treatment groups at the end of Week 2 for • WGTT, in hours • GET, in hours • SBTT, in hours • CTT, in hours, and • 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 post-treatment.
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. Summary of Study Design

Study I5Q-MC-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 wireless motility capsule (WMC) test and a single-blind treatment period with a post-study treatment WMC test.

Figure CGBC.5.1 illustrates the study design.



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

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

5.2. Determination of Sample Size

Assuming that the within-group mean difference in CTT is approximately 4.2 hours with a 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 is 60 patients.

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

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to single-blind treatment at Visit 3 in a 1:1 ratio to galcanezumab or erenumab. To achieve between-group comparability, the randomization will be stratified by site, body mass index (BMI) category (<30kg/m^2, ≥30 kg/m^2), and by baseline migraine frequency (<8 migraine headache days, ≥8 migraine headache days). Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system.

5.4. Measures

5.4.1. Primary Measures

The SmartPill™ WMC technology (Medtronic, Minneapolis, MN, USA) will be used to evaluate total gastrointestinal (GI) transit time and segmental transit time. The WMC 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 in the study, patients will be asked to eat a SmartBar, followed by ingesting the WMC with 120 mL of water. Patients will be instructed to fast for an additional 6 hours after ingesting the WMC and to 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 will be transferred to the wearable external data recorder and displayed and analyzed using Medtronic MotiliGI™ version 3.1 software (Medtronic, Minneapolis, MN, USA).

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

The primary outcome measure is CTT in hours. Secondary transit time outcome measures include the whole gut transit time in hours, gastric emptying time (GET) in hours, small intestine bowel transit time (SBTT) in hours, and small and large bowel transit time (SLBTT) in hours. All transit time outcome measures will be collected at baseline and 2 weeks after study drug administration.

Further secondary outcome measures include contraction, measured as frequency per minute, motility index, and AUC.

5.4.2. Other Secondary Measures

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 contain questions about

the past week using a 7-point categorical response scale ranging from no discomfort to very severe discomfort (Revicki et. al 1998; Khanna et al. 2017). Based on a factor analysis, the 15 GSRS items are summarized by the 5 scales, which are calculated by taking the mean of the items completed within an individual scale. The GSRS is grouped accordingly by

- abdominal pain – abdominal pain, hunger pains, and nausea
- reflux syndrome – heartburn and acid reflux
- diarrhea syndrome – diarrhea, loose stools, and urgent need to have a bowel movement
- indigestion syndrome – rumbling, bloating, belching, and increased flatus (breaking wind); and
- constipation syndrome – constipation, hard stools, and sensation of not completely emptying the bowels.

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

Spontaneous Bowel Movement Frequency Evaluation: The spontaneous bowel movement (SBM) frequency evaluation is the number of spontaneous (nonintervention induced) bowel movements that a patient has had in the past 7 days. Patients are asked how many SBMs they have had in the past 7 days, and the information is collected on the case report form (CRF) for Visits 1, 3, 4, and 5.

6. A Priori Statistical Methods

6.1. General Considerations

General aspects of statistical analyses are described below.

Unless otherwise specified, analyses will be conducted for the intent-to-treat (ITT) population, which includes 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. The ITT population will be the primary population for which statistical analysis are performed. When mean change from baseline is assessed, only patients with baseline and postbaseline measurements will be included in the analysis.

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.

6.2. Adjustments for Covariates

The analysis of covariance (ANCOVA) model will include the categorical effects of treatment, pooled investigative site, BMI category (<30kg/m^2, ≥30 kg/m^2), and baseline migraine frequency (<8 migraine headache days, ≥8 migraine headache days), as well as the continuous baseline value. Rules for pooling of investigative sites are described in Section 6.4.

For continuous measures with repeated postbaseline measurements, change from baseline will be analyzed using a restricted maximum likelihood (REML)–based mixed effects model for repeated measures (MMRM) technique. The analysis will include the fixed categorical effects of treatment, pooled investigative site, BMI category (<30kg/m^2, ≥30 kg/m^2), baseline migraine frequency (<8 migraine headache days, ≥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.

6.3. Handling of Dropouts or Missing Data

For the repeated measures analyses, the model parameters are simultaneously estimated using restricted likelihood estimation incorporating all of the observed data. Estimates have been shown to be unbiased when data are missing at random (MAR). Missingness due to COVID-19 does not depend on the outcome measurements and therefore will be considered MAR.

6.4. Multicenter Studies

Investigative sites with fewer than 4 randomized patients per treatment group will be pooled for analyses. If a pooled site has fewer than 4 randomized patients per treatment group, the site will be pooled with the next smallest site, determined to be the site with the smallest number of randomized patients, or if more than one site meets that criterion, the smallest site with the lowest investigator number. This process will continue until all pooled sites have 4 or more randomized patients per treatment group.

All analyses that are prespecified to include investigative site will use this pooled investigative site. The investigative site numbers will be included in the listings.

6.5. Multiple Comparisons/Multiplicity

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

6.6. Analysis Populations

Intent-to-treat (ITT) population: 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.

Safety population: All patients who are randomized and receive at least 1 dose of study treatment. Patients in the safety population will be analyzed according to the treatment they receive.

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.

6.7. Patient Disposition

The number and percentage of patients in the ITT population 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 the ITT population. Patient allocation by investigative site will also be listed.

6.8. Patient Characteristics

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

- demographics (age, gender, ethnic origin, height, weight, and BMI)
- medical history and preexisting conditions
- total gut and segmental transit times
- GI symptom rating scale, SBM frequency, and BSFS, and
- alcohol, tobacco, caffeine, and nicotine consumption.

Medical history and preexisting conditions will be summarized by descending frequency of Preferred Term (PT) nested within System Organ Class (SOC). Medical history is defined as illness(es) that ended prior to the signing of informed consent. Preexisting conditions and adverse events (AEs) at baseline are those AEs occurring during the baseline/screening visits for the study period.

The percentage of patients who report a change in alcohol, tobacco, caffeine, or nicotine consumption during the study will be summarized.

6.9. Concomitant Therapy

The proportion of patients who received concomitant medication recorded on the general concomitant medication electronic case report form (eCRF) will be summarized for the ITT population. Treatment group comparisons, if needed, will be done using Fisher's exact test.

Concomitant therapies are defined those that were stopped during Study Period II or continued in Study Period II. If a medication was started and stopped on the same day as the first injection, it will be counted as a concomitant medication. If a medication was started before the first day of injection but was stopped on the same day of injection, it will not be counted as a concomitant medication.

6.10. Efficacy Analyses

6.10.1. Primary Outcome and Methodology

The primary analysis will evaluate the change from baseline in CTT (hours) after administration of an initial loading dose of galcanezumab 240 mg or erenumab 140 mg at the end of Week 2.

The primary analysis will be performed using an ANCOVA model including the categorical effects of treatment, pooled investigative site, BMI category ($<30 kg/m^2$, ≥ 30 kg/m^2), and baseline migraine frequency (<8 migraine headache days, ≥8 migraine headache days), as well as the continuous baseline CTT (hours).

The primary endpoint of this study for galcanezumab 240 mg and erenumab 140 mg will be estimated as the least squares (LS) mean change from baseline to Week 2 from the ANCOVA model. The type I error rate for the study will be controlled at a 2-sided 0.05 level.

6.10.2. Secondary and Tertiary Efficacy Analyses

The LS mean change from baseline to Week 2 in CTT (hours) between galcanezumab 240 mg and erenumab 140 mg will be compared to detect any between-group differences in the primary model described above.

For continuous secondary/tertiary measures with a 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. The LS mean change from baseline in each treatment group will be tested to detect any changes between pre- and post-treatment administration. The LS mean change from baseline in the 2 treatment groups will also be compared to detect any between-group differences.

For continuous efficacy measures with repeated postbaseline measurements, change from baseline will be analyzed using a REML-based MMRM technique. The analysis will include the fixed categorical effects of treatment, pooled investigative site, BMI category ($<30 kg/m^2$, ≥ 30 kg/m^2), baseline migraine frequency (<8 migraine headache days, ≥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.

An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger (Kenward and Roger 1997) approximation will be used to estimate the denominator degrees of freedom. If the model does not converge, with both the Hessian and the G matrix being positive definite under the default fitting algorithm used by PROC MIXED, the Fisher scoring algorithm will be implemented by specifying the SCORING option in SAS®. If the model still fails to converge, the model will be fit using covariance matrices of the following order specified by a decreasing number of covariance parameters until convergence is met:

- heterogeneous Toeplitz
- heterogeneous first-order autoregressive
- Toeplitz, and
- first-order autoregressive.

When the unstructured covariance matrix is not utilized, the sandwich estimator (Diggle and Kenward 1994) will be used to estimate the standard errors of the fixed-effects parameters. The sandwich estimator is implemented by specifying the EMPIRICAL option in SAS. When the sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom (Kenward and Roger 1997) cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions by the DDFM=BETWITHIN option in SAS. SAS PROC MIXED will be used to perform the analysis.

6.10.3. Sensitivity Analyses

The primary analysis assumes that data are normally distributed. To assess the impact of the normality assumption, a nonparametric sensitivity analysis of the primary endpoint will be produced using the Wilcoxon signed rank test (Wilcoxon 1945) to compare the change from baseline within each treatment group.

6.10.4. Exploratory Analyses

If the within-treatment analyses of change from baseline in GET and SBTT are statistically significant for either treatment, the changes in pressure parameters (frequency of contractions, motility index, and AUC) will be assessed for both treatments for the stomach, antrum, duodenum, ileum, caecum, sigmoid, and small bowel (by quartile) using the ANCOVA model described in Section 6.10.2.

Colonic transit time (hours) for patients with treatment-emergent (TE) constipation versus those without TE constipation will be explored. Treatment-emergent constipation is defined as reporting a treatment-emergent adverse event (TEAE) of constipation and/or score of ≥4 for constipation syndrome from the GSRS assessment. Descriptive statistics and boxplots will be provided by TE constipation category (Yes vs No) for change from baseline in CTT (hours) by treatment separately. Furthermore, if 10 or more patients have TE constipation for each treatment, then ANCOVA analyses will be performed to evaluate the change from baseline in CTT (hours) between TE constipation categories at the end of Week 2 for each treatment. The ANCOVA analyses will include the categorical effects of TE constipation, pooled investigative

site, BMI category (<30kg/m^2, ≥30 kg/m^2), and baseline migraine frequency (<8 migraine headache days, ≥8 migraine headache days), as well as the continuous baseline CTT (hours).

6.11. Safety Analyses

Unless specified otherwise, safety analyses outlined in the following subsections will be conducted for the safety population.

The safety and tolerability of treatment will be assessed by summarizing

- TEAEs
  - by PT
  - by PT nested within SOC
  - by maximum severity
  - by investigator classification of related to study treatment
- serious adverse events (SAEs) by PT
- AEs leading to discontinuation by PT, and
- vital signs.

Baseline for all safety measures includes all data prior to injection of study treatment. Postbaseline includes all data in Study Period II from injection of study treatment to completion of Study Period II.

For safety categorical variables and categorical variables of demographics and baseline characteristics, comparisons between treatment groups will be performed using Fisher's exact test. For continuous variables of demographics and baseline characteristics, an analysis of variance (ANOVA) with treatment as an independent variable in the model will be performed.

6.11.1. Extent of Exposure

Patients will receive study treatment at the beginning of Visit 3.

The following information will be recorded on the eCRF for each dose:

- confirmation that the patient received study treatment (including reason if study treatment was not administered), and
- date and time of administration.

A listing of patient exposure will be produced.

6.11.2. Treatment Compliance

A by-patient listing of doses received will be generated, including dose date, number of injections, and location of injection.

6.11.3. Adverse Events

Treatment-emergent AEs are defined as reported AEs that first occurred or worsened during the postbaseline phase compared with the baseline phase. For each TEAE, severity (mild, moderate, or severe) will be determined by patient or physician opinion. The Medical Dictionary for Regulatory Activities (MedDRA) lowest level term (LLT) will be used in the TE computation. For each LLT, the maximum severity at baseline will be used as the baseline severity. If the maximum postbaseline severity is greater than the maximum baseline severity, the event will be considered TE for the specific postbaseline period.

For each patient and TEAE, the maximum severity for the specified MedDRA level (PT, high level term, or SOC) will be the maximum postbaseline severity observed from all associated LLTs mapping to that MedDRA level.

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

6.11.4. Serious Adverse Events and Other Notable Adverse Events

An SAE is any AE that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of death)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect, or
- 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 autoinjector (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 SAEs will be summarized by PT.

6.11.5. Clinical Laboratory Evaluation

Investigators are responsible for the appropriate medical care of patients during the study and must document their review of each laboratory safety report. Local urine pregnancy tests should be conducted according to the Schedule of Activities (see Section 2 of Protocol CGBC).

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE.

No analyses of clinical laboratory evaluations will be produced.

6.11.6. Vital Signs and Other Physical Findings

Vital signs collected during the study include systolic (SBP) and diastolic blood pressure (DBP), pulse, and temperature. Blood pressure and pulse measurements will be taken when the patient is in a sitting position.

The number and percent of patients meeting criteria for categorical changes of interest in vital signs at any time during study will be summarized. Treatment group comparisons will be performed using Fisher's exact test.

Table CGBC.6.1 displays the criteria for categorical changes of interest in vital signs. The last column of the table displays the patient populations defined by baseline categories.

The criteria to identify patients with TE abnormal changes generally consist of 2 parts: an absolute threshold and a change from baseline amount.

- The absolute threshold in the criteria is based on 1) minimum postbaseline when the direction is low; 2) maximum postbaseline when the direction is high.
- The change from baseline amount in the criteria is 1) decrease from baseline to minimum postbaseline when the direction is low, and 2) increase from baseline to maximum postbaseline when the direction is high.

The baseline for SBP, DBP, pulse, and temperature is defined as the last non-missing baseline value during the baseline period. This baseline definition for SBP, DBP, pulse, and temperature applies to all analyses (both continuous and categorical) for SBP, DBP, pulse, and temperature.

Any clinically significant finding from vital sign measurements that results in a diagnosis and that occurs after the patient receives the first dose of study treatment should be reported as an AE via eCRF to Eli Lilly and Company or its designee.

Other physical findings will be collected at Visit 1. No analyses of other physical findings will be produced.

Table CGBC.6.1. Criteria for Categorical Changes of Interest in Vital Signs

Parameter	Direction	Criteria	Patient Population defined by Baseline Categories
Systolic BP (mm Hg) (sitting)	Low	≤90 and decrease ≥20	All patients; >90; ≤90
	High	≥140 and increase ≥20	All patients; <140, ≥140
	PCS High	≥180 and increase ≥20	All patients; <180; ≥180
	Sustained Elevation	≥140 and increase ≥20 at 2 consecutive visits	All patients; < 140; ≥140
Diastolic BP (mm Hg) (sitting)	Low	≤50 and decrease ≥10	All patients; >50; ≤50
	High	≥90 and increase ≥10	All patients; <90; ≥90
	PCS High	≥105 and increase ≥15	All patients; <105; ≥105
	Sustained Elevation	≥90 and increase ≥10 at 2 consecutive visits	All patients; < 90; ≥90
Systolic BP or Diastolic BP (mm Hg) (sitting)	Sustained Elevation	Meeting criteria for systolic BP for 2 consecutive visits or meeting criteria for diastolic BP for 2 consecutive visits or both	All patients
Pulse (bpm) (sitting)	Low	<50 and decrease ≥15	All patients; ≥50; <50
	High	>100 and increase ≥15	All patients; ≤100; >100
	Sustained Elevation	>100 and increase ≥15 at 2 consecutive visits	All patients; ≤100; >100
Temperature (°F)	Low	<96°F and decrease ≥2°F	≥96°F
	High	≥101°F and increase ≥2°F	<101°F

Abbreviations: BP = blood pressure; PCS = potentially clinically significant.

6.11.7. Electrocardiograms

Not applicable.

6.12. 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 for ensuring that patients remain blinded to treatment (that is, patients must not see the AI pens before, during, or after the drug administration). See the Manual of Operations for further details regarding blinding.

6.13. Subgroup Analyses

Not applicable.

6.14. Important Protocol Deviations

Important protocol deviations that potentially compromise data integrity or patients' rights or safety will be summarized by treatment group for the ITT population. Tables and listings of

important protocol deviations for the ITT population during all study phases will be provided by randomized treatment group.

Appendix 1 lists the categories, subcategories, and study-specific terms of important protocol deviations, as well as the source and method used to identify each deviation. Per the study team's discretion, for non-programmable protocol deviations, additional categories can be added to the final non-programmable protocol deviations list as deemed necessary.

6.15. Annual Report Analyses

Not applicable.

6.16. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

- A summary of AEs will be provided as a dataset, which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA PT.
- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - number of participants at risk of an event
    - number of participants who experienced each event, and
    - number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in less than 5% of patients in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures (for example, the CSR and manuscripts).

7. References

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8. Appendices

Appendix 1. Description of Important Protocol Deviations

Table CGBC.APP.1.1. Description of Important Protocol Deviations

Category	Subcategory	Study-Specific	Source	Comments
Informed consent	Informed Consent Not Obtained	No reconsent for safety update	Non-programmable – Monitor identified	
		Procedure done prior to or without consent	Programmable – Statistics	Check that Visit 1 date is not before informed consent date
Eligibility	Inclusion/Exclusion	Age <18 or >55 years old at study entry	Programmable – Statistics	
		No diagnosis of migraine	Non-programmable – Monitor identified	
		On >1 other migraine preventive medication	Non-programmable – Study team identified	1) Stats will create the list of patients who meet this IPD criteria based on a list of medications from Medical. 2) Among those, the true IPDs will be manually added into a non-programmable excel sheet.
		Number of headache days ≥15 per 30 day period at baseline	Non-programmable – Monitor identified	
		Female patients with positive urine pregnancy test	Non-programmable – Monitor identified	
		<3 bowel movements in the 7 days prior to Visit 1	Programmable – Statistics	
		History of IBS or chronic constipation	Programmable – Statistics	
		Hx bezoar, dysphagia, stricture, fistula, GI obst	Programmable – Statistics	
		History of GI surgery	Non-programmable – Monitor identified	
		History of abdominal surgery in past 3 months	Non-programmable – Monitor identified	
		History of bariatric surgery	Non-programmable – Monitor identified	
		History of Crohn's, celiac, UC, or diverticulitis	Programmable – Statistics	

Description of Important Protocol Deviations

Category	Subcategory	Study-Specific	Source	Comments
Eligibility	Inclusion/Exclusion	Diagnosed with type 1 or type 2 diabetes	Programmable – Statistics	
		Have pacemakers or other electromechanical devices	Programmable – Statistics	
		BMI ≥ 40 kg/m^2	Programmable – Statistics	
		Women who are pregnant or nursing	Non-programmable – Monitor identified	
		Drug/alcohol abuse within 1 year prior to Visit 1	Non-programmable – Monitor identified	
		Acute, serious, or unstable medical condition	Non-programmable – Monitor identified	
		History of cardiovascular events in past 6 months	Non-programmable – Monitor identified	
		Suicidal or at significant risk for suicide	Non-programmable – Monitor identified	
		Taken mAb CGRP antagonist within past 6 months	Non-programmable – Study team identified	1) Stats will create the list of patients who meet this IPD criteria based on a list of medications from Medical. 2) Among those, the true IPDs will be manually added into a non-programmable excel sheet.
		Taken oral CGRP antagonist within 14 days	Non-programmable – Study team identified	1) Stats will create the list of patients who meet this IPD criteria based on a list of medications from Medical. 2) Among those, the true IPDs will be manually added into a non-programmable excel sheet.
		Allergy to therapeutic proteins or CGRP antagonist	Non-programmable – Monitor identified	
		Allergic to SmartBar ingredients	Non-programmable – Monitor identified	
		Other inadvertent enrollment	Non-programmable – Monitor identified	
Safety	SAEs	SAEs not reported in 24 hours	Non-programmable – Monitor identified	
Administrative/ Oversight	Suspected Misconduct	Suspected fraud	Non-programmable – Monitor identified	
		Privacy breach	Non-programmable – Monitor identified	

Description of Important Protocol Deviations

Category	Subcategory	Study-Specific	Source	Comments
Administrative/ Oversight	Other	Quality issue at site or vendor	Non-programmable – Monitor identified	
Study Procedures	Excluded Conmeds	Taking agents that affect GI motility	Non-programmable – Study team identified	1) Stats will create the list of patients who meet this IPD criteria based on a list of medications from Medical. 2) Among those, the true IPDs will be manually added into a non-programmable excel sheet.
		Taking CGRP antagonists	Non-programmable – Study team identified	1) Stats will create the list of patients who meet this IPD criteria based on a list of medications from Medical. 2) Among those, the true IPDs will be manually added into a non-programmable excel sheet.
		Taking medications that affect gastric pH	Non-programmable – Study team identified	1) Stats will create the list of patients who meet this IPD criteria based on a list of medications from Medical. 2) Among those, the true IPDs will be manually added into a non-programmable excel sheet.
	Equipment	WMC patient education	Non-programmable – Monitor identified	
		WMC calibration	Non-programmable – Monitor identified	
		WMC assessment of expulsion	Non-programmable – Monitor identified	
	Other	Study treatment administration	Non-programmable – Monitor identified	
Investigational Product	Patient took medication not fit for use	Patient received drug declared “Not Fit for Use”	Non-programmable – Monitor identified	
	Unblinding	Unjustified unblinding of patient treatment assignment	Non-programmable – Monitor identified	

Abbreviations: BMI = body mass index; CGRP = calcitonin gene-related peptide; GI = gastrointestinal; Hx = history; IBS = irritable bowel syndrome; IPD = important protocol deviation; mAb = monoclonal antibody; obst = obstruction; SAE = serious adverse event; Stats = Statistics; UC = ulcerative colitis; WMC = wireless motility capsule.

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