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Protocol for Study M21-307

Episodic Migraine: Phase 3 Study of BOTOX (Botulinum Toxin Type A) for the Prevention of Migraine in Subjects with Episodic Migraine

VERSION:	6.0	DATE:	03 April 2024
SPONSOR:	AbbVie	PLANNED NUMBER OF SITES:	Approximately 125
ABBVIE INVESTIGATIONAL PRODUCT:	BOTOX (Botulinum Toxin Type A)	EudraCT:	2021-001979-16

FULL TITLE: Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study of BOTOX (Botulinum Toxin Type A) for the Prevention of Migraine in Subjects with Episodic Migraine

Incorporating Versions 1.0, 2.0, 3.0, 3.1 (Regional VHP), 3.2 (Germany Only), 4.0, 4.1 (United Kingdom Only), 5.0, and 6.0 and Administrative Changes 1, 2, 3, 4, 5, and 6 (United Kingdom Only).

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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1 SYNOPSIS

Title: Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study of BOTOX (Botulinum Toxin Type A) for the Prevention of Migraine in Subjects with Episodic Migraine	
Background and Rationale:	Botulinum Toxin Type A Purified Neurotoxin Complex (United States and Canada adopted name is onabotulinumtoxinA; referred to hereafter as BOTOX) for injection is currently indicated for the prophylaxis of headaches in adults with chronic migraine (CM). Episodic migraine (EM) and CM are both part of the migraine disease spectrum that is nonbinary and manifests as a continuum of disease severity; this is evidenced by frequent and spontaneous fluctuations between CM and EM and similar levels of disability associated with CM and high frequency EM. Given the economic burden of migraine, the overall impact of migraine on quality of life, and the continued need for treatment alternatives, AbbVie is evaluating BOTOX for the prophylaxis of EM, which has the potential to expand treatment options available to patients in the pursuit of headache freedom.
Objective(s) and Endpoint(s):	The objective of this study is to evaluate the efficacy and safety of 2 dose levels of BOTOX compared with placebo as migraine prevention in subjects with EM. The primary endpoint is the change from baseline in the frequency of monthly migraine days across Months 5 and 6. The secondary endpoints will be as follows (and will be evaluated in the stated order): 1. Change from baseline in the frequency of monthly headache days across Months 5 and 6 2. Responder status of 50% reduction from baseline in the frequency of monthly migraine days across Months 5 and 6 3. Change from baseline in the frequency of monthly acute headache medication days across Months 5 and 6 4. Change from baseline in Migraine-Specific Quality-of-Life Questionnaire version 2.1 Role Function – Restrictive domain score at Month 6 5. Change from baseline in the Activity Impairment in Migraine – Diary Physical Impairment domain score across Months 5 and 6 (6-item Headache Impact Test [HIT-6] in Europe) Safety assessments: adverse event (AE) monitoring, clinical laboratory testing (hematology, chemistry, and urinalysis), vital sign measurements, and Columbia-Suicide Severity Rating Scale (C-SSRS) scores
Investigator(s):	Multicenter
Study Site(s):	Approximately 125 sites in multiple countries, including, but not limited to, Canada, Czech Republic, Germany, Israel, Poland, Spain, Sweden, the United Kingdom (UK), and the United States

Study Population and Number of Subjects to be Enrolled:	Approximately 777 adult subjects with EM are planned for enrollment.
Investigational Plan:	This is a multicenter, randomized, double-blind placebo-controlled, parallel-group study with an open-label extension phase in adults with EM.
Key Eligibility Criteria:	Eligible subjects are adults with a history of migraine headache disorder meeting International Classification of Headache Disorders (ICHD)-3 diagnostic criteria for migraine with aura or migraine without aura (1.1 and 1.2) for ≥ 12 months, with onset of migraine before 50 years of age, who have a history of 6 to 14 migraine days and < 15 headache days per month in each of the 3 months prior to Visit 1 and experience 6 to 14 migraine days and < 15 headache days during the 4-week screening/baseline phase.
Study Drug and Duration of Treatment:	Eligible subjects will be randomized 1:1:1 to receive BOTOX 195 U, BOTOX 155 U, or placebo. BOTOX (195 or 155 U) or matching placebo will be administered by a trained investigator (or designee) at Day 1 (Visit 2) and Week 12 (Visit 5) of the double-blind phase. All subjects who are eligible to continue to the open-label treatment phase of the study will receive open-label BOTOX 195 U at 12-week intervals, i.e., at Week 24 (Visit 8) and Week 36 (Visit 11), for up to 2 treatment cycles.
Date of Protocol Synopsis:	03 April 2024

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Migraine is a multifactorial, disabling neurological disease characterized by recurrent and often debilitating headaches of moderate to severe intensity and accompanied by symptoms that can include nausea, vomiting, and/or sensitivity to light or sound.[1] It is one of the most common neurologic disorders, affecting 12% of the general population, and ranked second among the causes of disability worldwide.[2,3]

Migraine with/without aura can be further categorized according to the frequency of attacks as episodic migraine (EM) or chronic migraine (CM).[1] The definition of CM and EM is based on the frequency of days with headache; however, this does not cover the complexity of the disorder.[1] In fact, EM and CM are both part of the migraine disease spectrum that is nonbinary and manifests as a continuum of disease severity; this is evidenced by frequent and spontaneous fluctuations between CM and EM and similar levels of disability associated with CM and high frequency EM.[4,5]

Botulinum Toxin Type A Purified Neurotoxin Complex (United States and Canada adopted name is onabotulinumtoxinA; referred to hereafter as BOTOX) for injection is currently indicated for the prophylaxis of headaches in adults with CM.[6] Individuals who experience less frequent migraines, including those categorized as having EM, are not covered in the current indication.

The economic burden of migraine, the overall impact of migraine on quality of life, and the continued need for treatment alternatives, support the rationale to develop appropriate management and treatment choices for the population suffering from EM. Therefore, AbbVie is evaluating BOTOX for the prophylaxis of EM, which has the potential to expand treatment options available to patients in the pursuit of headache freedom.

2.2 Benefits and Risks to Subjects

BOTOX is approved in over 90 countries for the prophylaxis or symptom relief of headaches in adults with CM. The similar disease characteristics, along with the established efficacy of BOTOX in adults with CM, supports the assumption that the benefit/risk profile in EM will be favorable.

The results of the safety analyses of the Phase 3 CM population support the known safety and tolerability profile of BOTOX seen in a large number of other clinical applications, when BOTOX is administered every 12 weeks. Overall, no safety findings emerged from the CM safety database, or from Phase 4 studies and the postmarketing database, that raise concerns over the use of BOTOX at doses of 155 or 195 U administered intramuscularly every 12 weeks in the target population of adults with migraine.

In the Phase 3 CM studies, the most frequently reported adverse drug reactions occurring in ≥ 5% of patients following injection of BOTOX were neck pain reported in 8.7% of patients. Additional adverse drug reactions that were reported in ≥ 2% of BOTOX-treated patients were headache (4.7%), migraine

(3.8%), eyelid ptosis (3.6%), musculoskeletal stiffness (3.6%), muscular weakness (3.5%), injection site pain (3.3%), myalgia (3.1%), musculoskeletal pain (2.6%), and facial paresis (2.2%).

The doses and dosing paradigm confirmed in the Phase 3 CM studies will be utilized in this Phase 3 EM Study, M21-307.

Known risks associated with BOTOX administration are pre-existing neuromuscular disorders, immunogenicity, distant spread of toxin, and dysphagia in chronic migraine patients.

Based on the collective evidence from the Phase 3 CM studies, observational studies, and clinical experience, international consensus guidelines recommend BOTOX as both effective and safe in subjects with CM.[7-9] The lack of need for slow dose escalation, the relatively rapid onset of therapeutic benefits, and the positive tolerability of injectable therapies such as BOTOX contribute to a favorable benefit-risk profile.[10]

Further details, including findings from completed studies and other safety data, are provided in the current Investigator's Brochure for BOTOX.

Considering the coronavirus disease 2019 (COVID-19) pandemic, the benefit and risk to subjects participating in this study have been re-evaluated. Based on the limited information to date, no additional risk to study subjects is anticipated with the use of BOTOX. Based on the population and disease being studied and the anticipation that COVID-19 related risks are not expected to differ substantially between study subjects and the broader population of subjects receiving treatment for migraine, no change to the benefit/risk balance for subjects in this study is expected.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The objective of this study is to evaluate the efficacy and safety of 2 dose levels of BOTOX compared with placebo as migraine prevention in subjects with EM.

The estimand corresponding to the primary objective of this study is displayed in the table below. It defines the primary endpoint as the change from baseline in the frequency of monthly migraine days (i.e., migraine or probable migraine headache days) across Months 5 and 6 in the BOTOX groups and the placebo group for subjects in the intent-to-treat (ITT) population, which includes all subjects who are randomized. The primary analysis assumes that missing data are missing completely at random or missing at random.

ESTIMAND	
Target Study Population: Patients with EM as constrained by the study inclusion and exclusion criteria; most notably < 15 headache days and 6 to 14 migraine days during the 28-day baseline period that ends the day before randomization. The population of inference will be further constrained by baseline ranges that are narrower or less inclusive than the eligibility criteria (e.g., too few males compared with the target population epidemiology).	Endpoint of Interest: Change from baseline in the frequency of monthly migraine days across Months 5 and 6, which are defined as the 28-day daily diary periods ending with Days 56 and 84 after the second study treatment intervention day with BOTOX or placebo injections, for subjects in the ITT population.
Intercurrent Events: Study discontinuation, especially those due to lack of efficacy or due to AEs. Also, any significant protocol deviation that could affect the primary endpoint, such as taking rescue medication or not receiving the Week 12 treatment. A sensitivity analysis will impute scores differently for such intercurrent events (e.g., reversion toward baseline) and will be described in the SAP.	Population-Level Summary of Variable: Between-treatment comparison of the change from baseline in monthly migraine days across Months 5 and 6.

Clinical Hypotheses

- At least 1 dose level of BOTOX is more effective than placebo, as measured by the difference between treatment groups in the change from baseline in the frequency of migraine days per 28day period
- BOTOX has an acceptable safety profile

3.2 Primary Endpoint

The primary endpoint is the change from baseline in the frequency of monthly migraine days across Months 5 and 6.

3.3 Secondary Endpoints

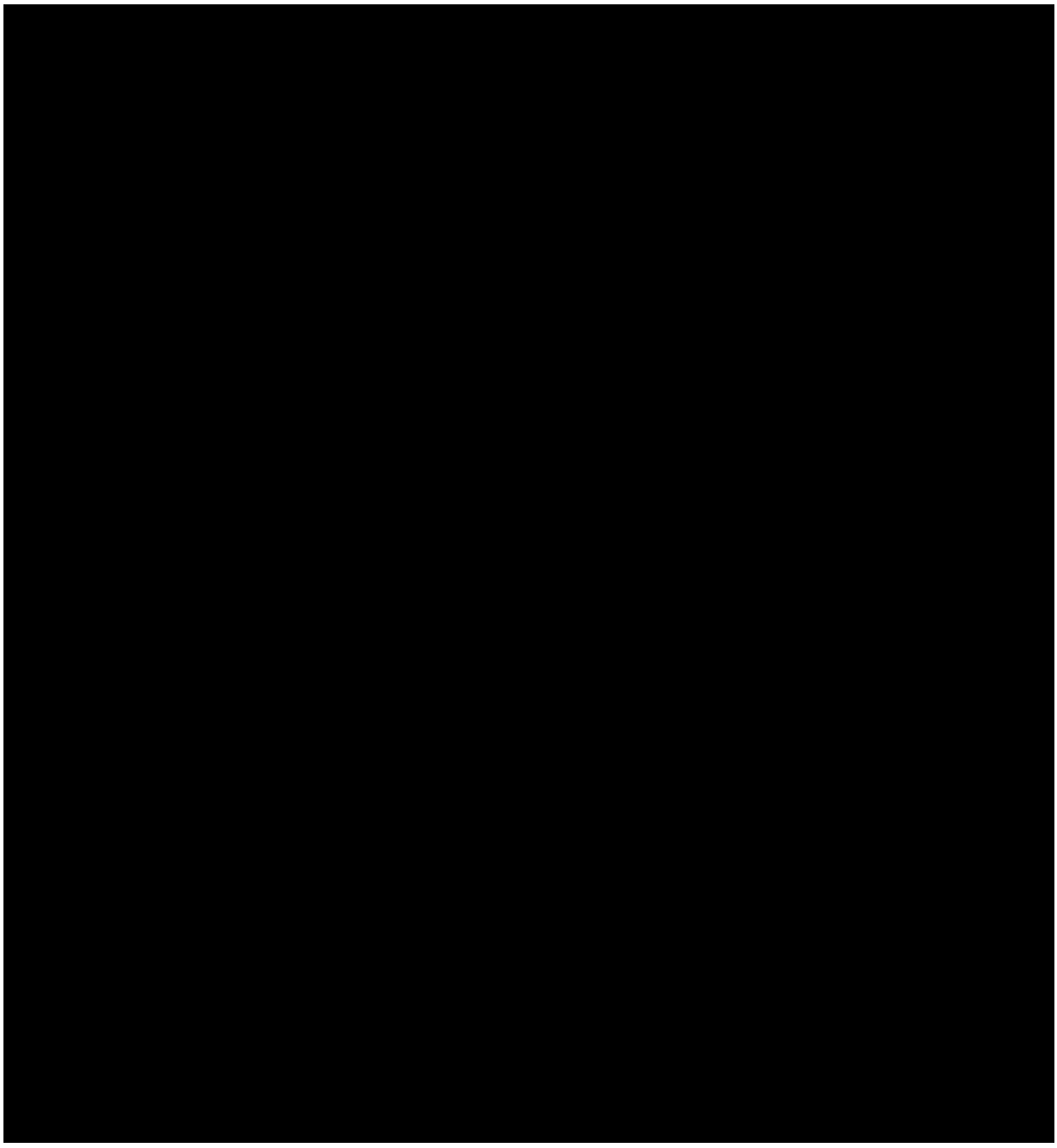
The secondary efficacy endpoints will be as follows (and will be evaluated in the stated order):

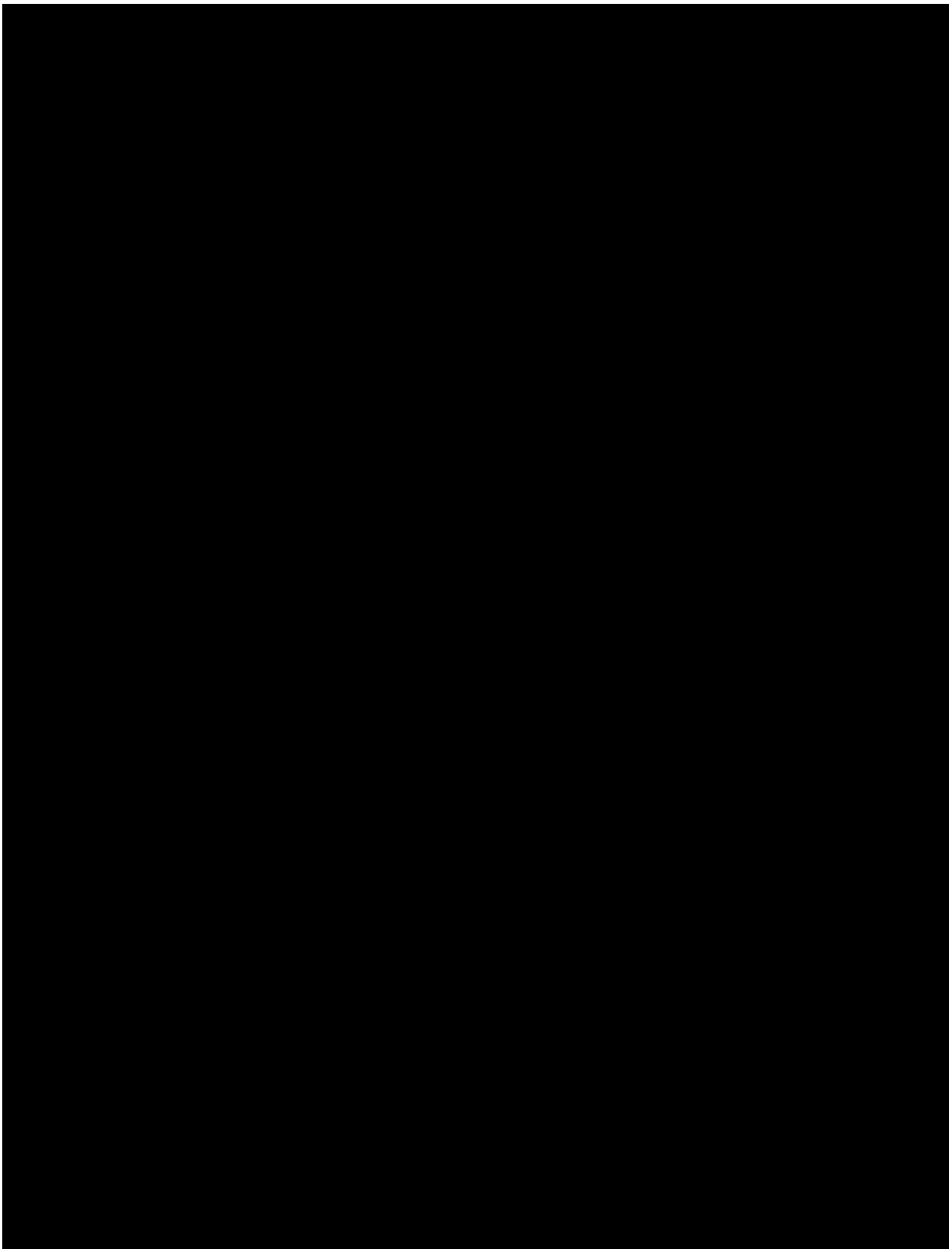
1. Change from baseline in the frequency of monthly headache days across Months 5 and 6
2. Responder status of 50% reduction from baseline in the frequency of monthly migraine days across Months 5 and 6
3. Change from baseline in the frequency of monthly acute headache medication days across Months 5 and 6
4. Change from baseline in Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) Role Function Restrictive (RFR) domain score at Month 6

5. Change from baseline in the Activity Impairment in Migraine Diary (AIM-D) Physical Impairment domain score across Months 5 and 6 (total 6-item Headache Impact Test [HIT-6] score in Europe)

3.4 Other Endpoints

The other endpoints include the following:





The primary and secondary efficacy measures will also be evaluated at monthly time points.

3.5 Safety Endpoints

Measures of safety and tolerability for the entire study duration include adverse event (AE) monitoring, clinical laboratory testing (hematology, chemistry, and urinalysis), vital sign measurements, and Columbia-Suicide Severity Rating Scale (C-SSRS) scores.

3.6 Biomarker Research

Biospecimens (whole blood DNA, plasma, and serum) will be collected at specified time points (Appendix D) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers in circulation or at tissue sites. All samples will be optional. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. The analyses may include but are not limited to: biomarkers associated with mechanisms of migraine, such as calcitonin gene-related peptide (CGRP) and its degradants. This research may be exploratory in nature and the results may not be included with the clinical study report. Further details regarding the biomarker research rationale and collection time points are located in the Operations Manual, Section 3.9 and Appendix D.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind placebo-controlled, parallel-group study with an open-label extension phase in adults with EM. Approximately 777 subjects who meet study enrollment eligibility criteria will be randomized in this study. Subjects in this study will be male or female adults 18 to 65 years of age at Visit 1 with a history of migraine headache disorder meeting ICHD-3 diagnostic criteria for migraine with aura or migraine without aura (1.1 and 1.2) for ≥ 12 months, with onset before 50 years of age. Specifically, subjects will have 6 to 14 migraine days and < 15 headache days per month in each of the 3 months prior to the screening visit (Visit 1) and during the 4-week screening/baseline phase. See Section 5 for information regarding eligibility criteria.

Randomization will be stratified by [redacted] (yes/no) and ≥[redacted] monthly migraine days at baseline (yes/no). Enrollment will be monitored to target at least [redacted]% of randomized subjects having taken at least [redacted] with proven efficacy (see Section 8.1 of the Operations Manual, Appendix F, for the list of medications) and at least [redacted]% of randomized subjects having ≥[redacted] monthly migraine days during baseline. The population of subjects who have failed [redacted] preventive treatments will be monitored throughout the trial. The target is to enroll no less than [redacted]% of the study population who have failed [redacted] preventive treatments. This may result in enrollment restrictions for subjects who failed fewer than [redacted] preventive treatments. The study will aim to enroll no more than [redacted]% of subjects meeting criteria for medication overuse per the investigator's discretion based on regular overuse of acute headache medication as defined in the Operations Manual Section 8.2 in the 3 months prior to Visit 1 OR history of medication overuse

headache diagnosis per ICHD-3 8.2.[1] The study will aim to enroll approximately [redacted]% males in order to obtain a representative proportion of males with EM.[11] Enrollment restrictions may be implemented in order to achieve these enrollment targets.

Screening/baseline phase

Study participation will begin with a 4-week screening/baseline phase, during which subjects will use an electronic diary (e-Diary). Subjects will complete daily e-Diary entries on a handheld device provided to them at home to report headache data, including the absence of headache, as well as acute medication use. On a weekly basis, the subject will also be asked to enter the number of migraine attacks he or she experienced over the past 7 days. Subjects must complete at least 20 out of 28 days in the e-Diary during the screening/baseline phase to continue in the study.

Subjects who complete the 4-week screening/baseline phase and meet all entry criteria will proceed to the double-blind placebo-controlled treatment phase at Visit 2 (randomization visit). The screening/baseline phase may be extended due to COVID-19-related circumstances (see Section 5.4). Re-screening is permitted in certain situations, such as COVID-19 related circumstances, with permission from AbbVie. However, subjects with a positive result on the urine drug and alcohol test unless explained by permitted concomitant medication use (e.g., opioids prescribed for migraine pain) are not allowed to be re-screened.

Double-blind, placebo-controlled phase

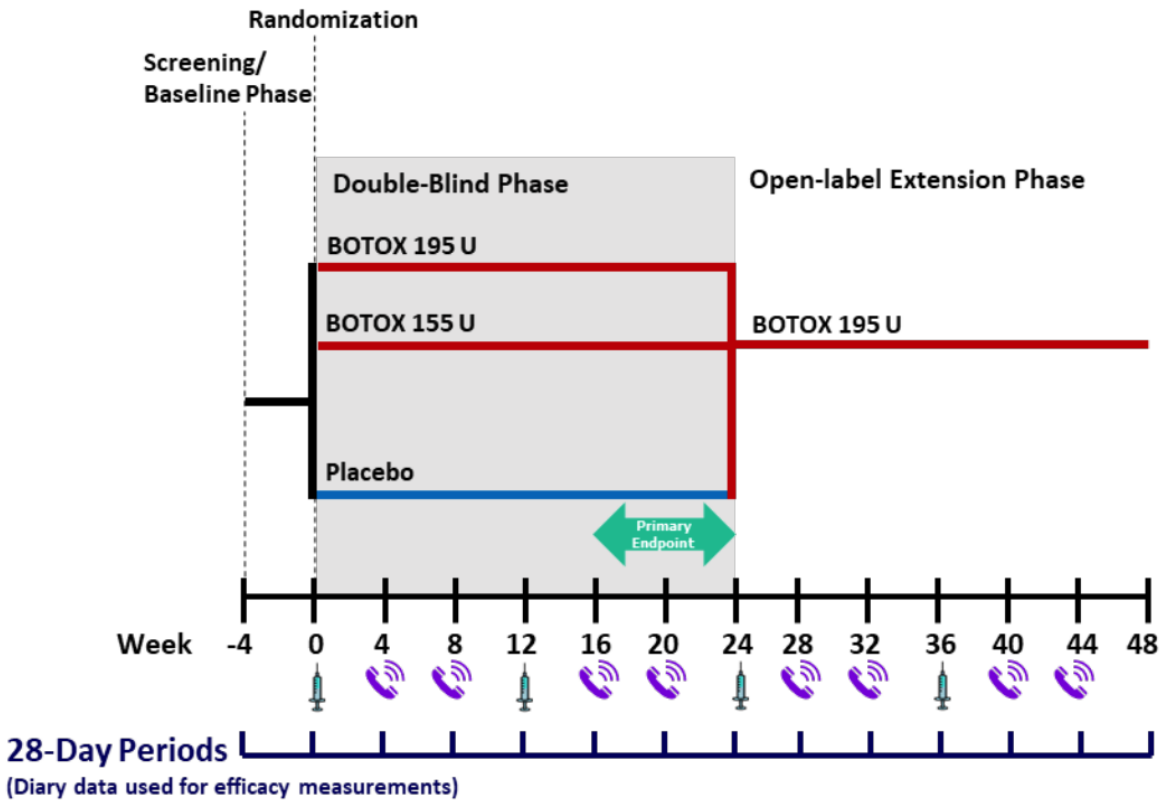
At Visit 2 (Day 1/Randomization Visit), subjects will be randomized 1:1:1 to receive BOTOX 195 U, BOTOX 155 U, or placebo, and will be administered the first treatment. Telephone visits will occur at Week 4 (Visit 3), Week 8 (Visit 4), Week 16 (Visit 6), and Week 20 (Visit 7); clinic visits will occur at Week 12 (Visit 5) and Week 24 (Visit 8). At Week 12 (Visit 5), subjects will be administered the second blinded treatment. Subjects will complete daily e-Diary entries and patient-reported outcome (PRO) questionnaires on the handheld device provided to them.

Open-label phase

Subjects who complete the double-blind, placebo-controlled phase may be eligible to continue to the open-label treatment phase of the study at Week 24 (Visit 8). All subjects in the open-label phase will receive BOTOX 195 U at 12-week intervals for up to 2 treatment cycles. Telephone visits will occur at Week 28 (Visit 9), Week 32 (Visit 10), Week 40 (Visit 12), and Week 44 (Visit 13); clinic visits will occur at Week 36 (Visit 11) and Week 48 (Visit 14). Subjects will complete daily e-Diary entries and patient-reported outcome questionnaires on the handheld device provided to them. The total duration of the study will be up to 52 weeks.

The schematic of the study is shown in Figure 1. The study procedures by visit and associated visit windows are listed in the Schedule of Activities (Appendix D). The screening visit window is Day −35 to Day −28 and all post-randomization visits have a window of ± 3 days. Further details regarding study procedures are provided in the Operations Manual.

Figure 1. Study Schematic



4.2 Discussion of Study Design

Choice of Control Group

The double-blind phase of the study is placebo-controlled. Given the substantial placebo effects observed in migraine trials, especially those involving injections, the placebo not only controls for the actual placebo response, it also controls for other nonspecific effects such as natural history and regression to the mean.[12-14]

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with migraine. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Development of the inclusion and exclusion criteria for the Phase 3 EM study were based on the recent guidelines put forth by the International Headache Society for controlled trials of preventive treatment of migraine attacks in adults with EM.[15]

Considering the spontaneous fluctuations in migraine frequency, requiring at least 12 months of attacks meeting ICHD criteria for EM will ensure that subjects enrolled into a clinical trial are less likely to enter a spontaneous remission period.[4,16] Further, since EM with onset after 50 years of age is very unusual, and the risk of secondary headache increases with age of onset, only subjects who have EM prior to this age threshold will be enrolled in this study.

The study will enroll subjects with 6 to 14 migraine days per month in each of the 3 months prior to the screening visit and during the 4-week screening/baseline phase. This population is appropriate based on available evidence from prior studies and the literature, which suggests that subjects with 6 to 14 migraine days per month have a similar response to BOTOX as subjects with CM.

The study will require subjects to have less than 15 headache days per month in each of the 3 months prior to screening and in the 4-week screening/baseline phase.

The study will exclude subjects with CM and other confounding headache disorders as listed above. Subjects who have failed more than 4 prophylactic treatments for migraine, 2 with different mechanisms, will be excluded as these subjects may be treatment-refractory. To reduce potential confounding factors for efficacy, the study will exclude subjects with prior [redacted] treatment in protocol treatment areas, prohibit the concurrent use of prophylactic treatments for migraine (e.g., CGRP monoclonal antibodies), and exclude the use of gepants in the double-blind phase.

Selection of Doses in the Study

The doses of BOTOX for this study in EM (155 U and 195 U) were selected to be consistent with the doses and dosing paradigm that demonstrated efficacy in the Phase 3 CM studies. The selection of the [redacted] dose and dosing paradigm in EM as in CM is considered appropriate as subjects with EM and CM are part of a migraine spectrum with similar disease burden and response to treatment.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects must voluntarily **sign and date an informed consent** approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, 18 to 65 years of age at Visit 1.
- 3. Completed at least 20 out of 28 days in the e-Diary during the screening/baseline phase.

- 4. Able to read, understand, and complete study questionnaires and e-Diary per investigator's judgment.
- 5. Willing and able to comply with procedures required in this protocol.
- 6. Negative result on the urine drug and alcohol screen at Visit 1 unless explained by permitted concomitant medication use (e.g., opioids prescribed for migraine pain).

Disease/Condition Activity

- 7. History of migraine headache disorder meeting ICHD-3 diagnostic criteria for migraine with aura or migraine without aura (1.1 and 1.2) for ≥ 12 months.
- 8. Onset of migraine before 50 years of age.
- 9. History of 6 to 14 migraine days/month in each of the 3 months prior to Visit 1.
- 10. Six to 14 migraine days during the 4-week screening/baseline phase.
- 11. < 15 headache days/month in each of the 3 months prior to Visit 1 and during the 4-week screening/baseline phase.

Subject History

- 12. No current diagnosis of chronic migraine (1.3) according to ICHD-3
- 13. No history of or current diagnosis of the following headache disorders according to ICHD-3:
    a. Migraine with brainstem aura (1.2.2) or retinal migraine (1.2.4)
    b. Complications of migraine (1.4), chronic tension-type headache (2), trigeminal autonomic cephalalgias (3), hypnic headache (4.9), [redacted] (3.4) or new daily persistent headache (4.10)
- 14. No history of headache attributed to another disorder (e.g., cervical dystonia, craniotomy, head/neck trauma) with exception that medication overuse headache per ICHD-3 criteria (8.2) is allowed.
- 15. No history of inadequate response to > 4 prophylactic treatment for migraine, 2 of which have different mechanisms of action (see Section 8.1 of the Operations Manual for the list of medications and criteria for determining inadequate response).
- 16. No unremitting headache lasting continuously throughout the 4-week baseline period.
- 17. No concurrent pain condition that may significantly impact current headache disorder (e.g., fibromyalgia, craniofacial pain, TMD/TMJ).
- 18. Subject must not have Patient Health Questionnaire (PHQ-9) score ≥ 15 at Visit 1 (or potentially confounding depression per the investigator's discretion).

- 19. No significant risk of self-harm, based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator; subject must be excluded if they report suicidal ideation with intent, with or without a plan or suicidal behavior (i.e., yes response to Question 4 or 5 in the suicidal ideation section or yes to any question in the suicidal behavior section of the C-SSRS) in the past 6 months prior to Visit 1.
- 20. No concurrent psychiatric conditions including bipolar disorder, schizophrenia, dementia, or other significant neurological disorders.
- 21. No presence or history of any medical condition that may place the subject at increased risk following exposure to BOTOX or interfere with the study evaluation, including:
    a. Diagnosed myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, or any other significant disease that might interfere with neuromuscular function.
    b. Facial nerve palsy.
    c. Infection or dermatological condition at the site of study intervention injection.
    d. Any significant eyebrow or eyelid ptosis at Day 1 as determined by the investigator.
- 22. No history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within 6 months of Visit 1.
- 23. Must not have a condition or be in a situation which, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.
- 24. No known active Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., polymerase chain reaction [PCR]) test result.
- 25. No unremitting symptoms of "Long COVID" due to prior SARS-CoV-2 infection or any other lasting symptoms that, in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study.
- 26. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:
    a. At least 14 days since first negative PCR test result have passed in asymptomatic patients or 14 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.
- 27. If the subject has received a SARS-CoV-2 vaccination, the subject must have completed their final dose of the vaccine at least 14 days prior to Day 1 (study drug administration). Subjects who receive an initial SARS-CoV-2 vaccine during the screening/baseline period may remain in the study, as long as a minimum 14-day interval between the vaccine administration and study drug administration is maintained. Subjects who are unvaccinated are eligible for this study (see Section 5.4 for additional guidance).

- 28. Subject has not received any investigational product within 30 days or 5 half-lives of the drug (whichever is longer) before the first dose of study drug or is currently enrolled in another clinical study. This will be confirmed via Verified Clinical Trials (VCT) for US subjects only. Simultaneous enrollment in a non-interventional study not for a headache or migraine condition, may be permitted as long as the study is not overly burdensome, is not anticipated to impact performance on key study endpoints, and is unlikely to trigger subject discontinuation pending approval by AbbVie.
- 29. No known allergy or sensitivity to the study medication or its components.

Contraception

- 30. For all females of childbearing potential; a **negative serum pregnancy test** at Visit 1 and a negative urine pregnancy test at Visit 2 prior to the first dose of study drug.
- 31. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is effective from Visit 1 through at least 90 days after the last dose of study drug. Female subjects of nonchildbearing potential do not need to use birth control.
- 32. Female who is not **pregnant, breastfeeding, or considering becoming pregnant** during the study or within 90 days after the last dose of study drug.

Concomitant Medications

- 33. No use of any opioids or barbiturates > [redacted] days/month or any gepant in the 3 months prior to Visit 1 per investigator's judgment, or during the baseline or screening phase.
- 34. No prior use of ANY [redacted] injections in the head, face, and/or neck in the subject's lifetime.
- 35. No prior use of ANY botulinum toxin (any serotype, therapeutic or cosmetic), regardless of location, in the 6 months prior to Visit 1.
- 36. No concurrent use or use of any migraine prophylactic treatment in the 4 weeks prior to Visit 1 nor during the baseline or screening phase.
- 37. No use of CGRP monoclonal antibody in the 6 months prior to Visit 1.
- 38. No concurrent use or use of acupuncture, TENS (e.g., Cefaly Dual), cranial traction, nociceptive trigeminal inhibition or occipital nerve block treatments, or injection of anesthetics or steroids into the study target muscles in the 4 weeks prior to Visit 1.
- 39. Euthyroid based on investigator review of relevant medical information at screening, laboratory results, physical exam, concomitant medication, and medical history. Thyroid medication must be stable for at least 3 months prior to Visit 1 and remain unchanged during the study.
- 40. Subject must not have received immunization for any botulinum toxin serotype nor have a history of botulism.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
     - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
  2. Postmenopausal female
     - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
     - Postmenopausal, Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone level > 30 IU/L.

- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy during the study and for at least 90 days after the last dose of study drug.
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study baseline Day 1.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS).
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence

[e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Contraception recommendations related to the use of concomitant therapies prescribed should be based on the local label.

5.3 Prohibited Medications and Therapy

In addition to the medications listed in the eligibility criteria, the following medications/therapies are prohibited during the study:

- Monoclonal antibodies blocking the CGRP pathway (e.g., erenumab, fremanezumab, galcanezumab, eptinezumab)
- Oral CGRP antagonists (e.g., rimegepant and atogepant; during the double-blind and open-label phases) except ubrogepant, which is prohibited during the double-blind phase but allowed during the open-label phase with restricted use of no more than [redacted] days per month
- Medications with demonstrated efficacy for the prophylactic treatment of migraine (e.g., amitriptyline, topiramate, propranolol) (see Section 8.1 of the Operations Manual for the list of medications)
- Benzodiazepines
- Botulinum toxin type A or other serotypes except for the investigational product
- Homeopathic or herbal remedies for migraine headaches (e.g., feverfew, valerian, belladonna)
- Marijuana, CBD oil, or other cannabinoid derivatives
- Any therapy intended for preventive treatment of migraine

Opioids and barbiturates are allowed but their use is restricted to no more than [redacted] days/month. Therapy considered necessary for the subject's welfare may be given at the discretion of the investigator. The decision to administer a prohibited medication/treatment is made with the safety of the study subject as the primary consideration. When possible, AbbVie should be notified before the prohibited medication/treatment is administered.

Coadministration of aminoglycosides or agents that could interfere with neuromuscular transmission (e.g., curare-like agents) or muscle relaxants should be used with caution, as the effects of the toxin could be potentiated.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study from 6 months prior to study drug administration through the exit visit (Week 48) must be recorded.

Concomitant prophylactic medications are not allowed in the study; however, the following medications for the acute treatment of migraine are allowed during the study and use of these medications must be documented in the e-Diary:

- Acute migraine-specific medication (any triptan, ditan, or ergot)
- Any other form of analgesic (including acetaminophen)
- Any NSAID agent
- Any antiemetic agent
- Any opioid ≤ [redacted] days/month
- Any barbiturate ≤ [redacted] days/month

Ubrogepant is an acute migraine-specific medication and is allowed during the open-label phase only with restricted use of no more than [redacted] days per month. Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with BOTOX can be located in the Investigator's Brochure.

COVID 19 Pandemic Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during the treatment period, as long as components of the vaccine are not contraindicated. The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject. The potential impact of BOTOX on SARS-CoV-2 vaccination is unknown.

If the subject has received a SARS-CoV-2 vaccination prior to screening, the subject must have completed their final dose of the vaccine at least 14 days prior to Day 1 (study drug administration). Subjects who receive an initial SARS-CoV-2 vaccine during the screening/baseline period may remain in the study, as long as a minimum 14-day interval between the vaccine administration and study drug administration is maintained. If this is not possible, the timing of the Day 1 visit for eligible subjects may be extended by a maximum of 14 days or the subject may need to withdraw from the study and be re-screened after receiving their final dose of vaccine, pending approval by the Sponsor.

Throughout the study, study drug, when possible, is preferred to be given at least 14 days before or after SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete treatment course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine electronic case report form (eCRF). Refer to Section 4.2 of the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- The subject responds "Yes" to questions 4 or 5 in the suicidal ideation section or to any question in the suicidal behavior section of the C-SSRS.
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie medical contact.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation is noted after the subject started study drug and continuation of the study drug may place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug may place the subject at risk.
- The subject is significantly noncompliant with study procedures, which may put the subject at risk for continued participation in the trial.
- Any female subject who becomes pregnant while participating in the study will not be eligible to receive further study intervention. However, the subject should remain in the study to ensure adequate follow-up of safety and efficacy data through the end of the respective treatment cycle, and then be exited from the study. See "Pregnancy" subsection under Section 6.1 for more information.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made, and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at their site if they have safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID 19 Pandemic Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix F.

The investigator should contact the AbbVie medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

Refer to the Operations Manual in Appendix F for details on how to handle study activities/procedures.

Interruption/Discontinuation of Study Drug Due to COVID 19 Infection

During the study drug dosing period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- Asymptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation (PD) from the study drug dosing period. Follow subsequent protocol Section 5.6 for subjects who discontinue study drug. Frequency or timing of COVID-19 testing and intervals between testing for the above viral clearance criteria may be adjusted to account for epidemiologic trends, updated information regarding infectivity, and local/institutional guidelines.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the exit/PD visit (Week 48/Visit 14) should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs (TEAEs)/SAEs have been resolved.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed the patient has withdrawn and no longer wishes biomarker samples research to continue, samples will not be analyzed, and no new biomarker analysis data will be collected for the withdrawn subject or added to the existing

data or database(s). Data generated from biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

BOTOX (195 U or 155 U) or matching placebo will be administered by a trained injector at Day 1 (Visit 2) and Week 12 (Visit 5) of the double-blind phase.

All subjects who continue to the open-label treatment phase of the study will receive open-label BOTOX 195 U at Week 24 (Visit 8) and Week 36 (Visit 11).

Each site will keep an accurate record that specifies the amount of study drug administered to each subject and the date of administration. This information will be recorded in the subject's eCRF.

AbbVie provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

BOTOX 100 U and matching placebo vials manufactured by AbbVie will be packaged in quantities sufficient to accommodate the study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Study drug will only be used for the conduct of this study.

An independent drug reconstitutor (IDR) will add preservative-free saline to each vial and draw the study drug into syringes to be injected. Instructions for drug preparation are provided in the Pharmacy Manual, which will be provided separately from the protocol and operations manual.

Digital Health Tools Accountability

The investigator or their representative will verify that the digital health tools are received intact and in the correct amounts. A proof of receipt or similar document will be kept in the site files as a record of what was received.

In addition, sites will maintain records of traceability, accountability, and return including but not limited to date received/dispensed/returned, subject number, and the identification of the person dispensing/returning the digital health tools.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule at Visit 2.

Eligible subjects will be randomized to BOTOX 155 U, BOTOX 195 U, or placebo in a 1:1:1 ratio. Randomization in this study will be performed at the country level, and randomization stratification factors will include [redacted] (yes/no), and ≥ [redacted] monthly migraine days at baseline (yes/no). [redacted] is based on medical history and patient interview. The monthly migraine days count at baseline is generated in the full eligibility report using e-Diary data of the 28 days prior to Visit 2; no manual calculation is required.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the BOTOX and placebo vials provided for the study will be identical in appearance. In addition, an IDR will add preservative-free saline to each vial and draw the study drug into syringes to be injected. To further facilitate blinding, all subjects will receive 39 injections in the prespecified injection sites at all treatment cycles during the double-blind phase (BOTOX 155 U: 31 sites with active study drug and 8 sites with placebo; BOTOX 195 U: 39 sites with active study drug; placebo: 39 sites with placebo).

When necessary for the safety and proper treatment of the subject, the investigator can unmask the subject's treatment assignment to determine which treatment was assigned and institute appropriate follow-up care. The IRT will provide unrestricted and immediate access to unblinded subject treatment information. The responsibility to break the treatment code in emergency situations resides solely with the investigator. The investigator should inform the AbbVie medical contact of the unmasking. The reason for breaking the code must be recorded in the subject's eCRF.

All subjects who are eligible to continue to the open-label treatment phase of the study at Week 24 (Visit 8) will receive open-label BOTOX 195 U at 12-week intervals for up to 2 treatment cycles.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol, except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

5.10 Data Monitoring Committee

No data review committee is planned for this study.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events: BOTOX

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has

been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as a serious AE within 24 hours of the site being made aware of the serious AE (or sooner, depending on local requirements; refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event along with any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. Examples of such 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.

All AEs reported from the time of consent through the last study visit (i.e., 12 weeks after the last study drug administration) or through 30 days after the last study drug administration (for subjects who discontinue prematurely) will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information), and meets one of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

All AEs will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

Possible distant spread of toxin (PDSOT) is defined as a possible pharmacologic effect of botulinum toxin at sites noncontiguous and distant from the site of injection. Utilizing a standardized methodology to assess for PDSOT, Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) that may be associated with botulinum toxin effects have been prospectively identified (see the statistical analysis plan [SAP] for a complete list of these PTs). Adverse events reporting any of these terms will be medically reviewed on a regular basis throughout the duration of the study and will be summarized in the study CSR.

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE as mild, moderate, or severe.

The investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator will use the following definitions to assess the relationship of the AE to the use of study treatment:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected. While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Any female subject who becomes pregnant while participating in the study will not be eligible to receive further study intervention but should remain in the study to ensure adequate follow-up of safety and efficacy data through the end of the respective treatment cycle, and then be exited from the study.

The study subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the study subject and the neonate, and the information will be forwarded to the Sponsor. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure. The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Other Safety Data Collection

Columbia Suicide Severity Rating Scale (C SSRS)

The C-SSRS reports the severity of both suicidal ideation and behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than one classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts. Any subject who has suicidal ideation with intent (with or without plan), either via answering "yes" to question 4 and/or question 5 to the suicidal ideation section or "yes" to any question in the suicidal behavior section of the C-SSRS, or via clinical interview, will be evaluated immediately by the investigator and discontinued from the study. The AbbVie medical contact will also be notified. The subject should receive appropriate follow-up as in routine clinical practice. In addition, if the subject expresses suicidal ideation at any time during the study, the

investigator and the AbbVie medical contact should be notified immediately. Under no circumstances should a subject who has positively endorsed or expressed suicidal ideation be left alone, be allowed to exit the site, or go home before a qualified medical professional has evaluated the subject's risk.

The C-SSRS is administered by the clinician or trained personnel via subject interview in person or over the telephone, as applicable, at all study visits. At Visit 1 (screening), the C-SSRS will be completed for the subject's lifetime history and for the 6 months prior to screening. At all other visits the C-SSRS will be completed for ideation and behavior since the previous visit.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and key secondary analyses. Complete and specific details of the statistical analysis will be described in the SAP, which must be in place before randomization codes are unmasked for any analysis.

A primary analysis will be performed at the end of the double-blind phase and a final analysis at the end of the open-label phase. A database lock will occur, and randomization data will be released when all subjects have completed the double-blind phase through the Week 24 visit. The planned primary analysis will be performed at that time. The final database will be locked when all subjects have completed the open-label phase of the study. For analysis purposes, subjects who complete the Week 24 visit and remain in the study regardless of whether or not they receive further treatment, will be considered as having entered the open-label phase. The planned final analysis will be performed after the final database is locked. The final analysis will include data from both the double-blind phase and the open-label phase of the study.

7.2 Definition for Analysis Populations

The following analysis populations are defined for this study:

- The intent-to-treat (ITT) population includes all subjects who are randomized. This will be used as the full analysis set (FAS) population. Subjects will be summarized according to their randomization assignment (i.e., as randomized), regardless of study intervention received. (All subjects will have non-missing baseline data for the primary efficacy variable because it is a condition of randomization, and therefore, the ITT population is not being modified with such a constraint.)
- The safety population includes all randomized subjects who have at least 1 study treatment intervention (i.e., BOTOX or placebo). Subjects will be summarized according to the study intervention received (i.e., as treated), regardless of their randomization assignment.

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The estimand corresponding to the primary objective of this study is displayed in Section 3.1. Among intercurrent events, it includes study discontinuations, especially if due to lack of efficacy or due to AEs. Also included are any significant protocol deviations that could affect the primary endpoint, such as taking rescue medication or not receiving the Week 12 treatment. A sensitivity analysis will impute scores differently for such intercurrent events (e.g., reversion toward baseline).

The primary analysis assumes that missing data are missing completely at random or missing at random. A sensitivity analysis will use the same model as the primary analysis after imputation of missing data by the modified last observation carried forward (mLOCF) rate-change method, which adjusts the most recent observation by the average change since that observation within the same treatment regimen. An additional sensitivity analysis, which is aimed at intercurrent events, will instead impute missing data by reversion toward baseline for subjects who have intercurrent events that could affect the primary endpoint. These sensitivity analyses will be described in more detail in the SAP.

7.4 Statistical Analyses for Efficacy

The efficacy analyses will be based on the ITT population, in general. Baseline for efficacy analyses is defined as the last non-missing efficacy assessment before randomization. For the primary efficacy variable and similar variables based on headache diary data, baseline will be the count of affected days during the 4 weeks ending the day before randomization.

Summary and Analysis of the Primary Endpoint

The primary efficacy endpoint is defined in Section 3.2. The primary efficacy analysis will test the null hypothesis that BOTOX (each dose group separately) and placebo are equally effective, as measured by the change from baseline in monthly migraine days across Months 5 and 6.

A mixed model repeated measures (MMRM) analysis will be used for the primary analysis, using data for baseline and each month of the double-blind, placebo-controlled phase (i.e., months ending with Weeks 4, 8, 12, 16, 20, and 24).[17] The statistical model will include treatment (BOTOX 195 U, BOTOX 155 U, and placebo), month, country, strata of [redacted], and treatment group-by-month interaction as fixed effects, with the baseline number of monthly migraine days as a covariate, included as a continuous variable rather than as the binomial stratification variable. Subject and residual errors will be random effects. The primary comparisons of interest will be the pairwise comparisons of each BOTOX dose (195 U and 155 U) versus placebo across Months 5 and 6.

Each dose comparison will be analyzed across primary and secondary endpoints in the order described in Section 7.7, using a ranked-order serial gatekeeping approach to control the overall type I (false-positive) error rate. For each BOTOX dose versus placebo, each variable/dose pair will be examined for significance only if significance was determined for all variable/dose pairs ranked ahead of it.

The primary analysis assumes that missing data are missing completely at random or missing at random. Details of the sensitivity analyses will be provided in the SAP. A 2-sided test with a *P* value ≤ 0.05 will be

considered as statistically significant for the treatment group comparisons of each BOTOX dose (195 U and 155 U) versus placebo.

Interaction effects will be examined at the 0.10 level by including treatment group-by-country interaction in a separate expansion of the primary MMRM model. If there is a significant interaction ($P \leq 0.10$) in the expanded MMRM model, the relevant reduced model will be examined for interpretation (i.e., by country).

Secondary analyses of covariance (ANCOVAs) of the primary efficacy variable (monthly migraine days) will be made for each month of the double-blind, placebo-controlled phase (i.e., months ending with Weeks 4, 8, 12, 16, 20, and 24), using the same model as for the primary MMRM analysis, but without repeat measures (i.e., omitting fixed effect of month and treatment group-by-month interaction).

A sensitivity analysis will use the same MMRM model after imputation of missing data by the mLOCF rate-change method, which adjusts the most recent observation by the average change since that observation within the same treatment regimen. This method has been chosen for consistency with methods used for the Phase 3 CM studies of BOTOX. Additional sensitivity analyses, including those using other imputation methods, will be described in the SAP (e.g., reversion toward baseline).

Subgroup Analysis of the Primary Endpoint

The primary effectiveness analysis (MMRM of change in monthly migraine days without the fixed effect of the corresponding subgroup variable) will be repeated for subgroups defined by each randomization stratification subgroup (monthly migraine days at baseline ≥ [redacted] [yes/no] and [redacted] [yes/no]), for medication overuse subgroup [yes/no] (see Section 8.2 in the Operations Manual), for each gender, and for each country. Additional subgroup analyses will be described in the SAP.

Summary and Analysis of Secondary Endpoints

The secondary efficacy endpoints are defined in Section 3.3; Each dose comparison will be analyzed across primary and secondary endpoints in the order described in Section 7.7, using a ranked-order serial gatekeeping approach to control the overall type I (false-positive) error rate. For each BOTOX dose versus placebo, each variable/dose pair will be examined for significance only if significance was determined for all variable/dose pairs ranked ahead of it.

The comparisons of interest for each of these secondary endpoints will be the pairwise comparisons of each BOTOX dose (195 U and 155 U) versus placebo, with no statistical comparison between the BOTOX doses.

The analysis results of the change from baseline in monthly headache days, MSQ v2.1 RFR domain score, monthly acute headache medication days, and AIM-D Physical Impairment domain score (or HIT-6 score [for Europe]) across Months 5 and 6 will come from the same type of MMRM analysis of observed data used for the primary efficacy endpoint, except that the baseline covariates will be monthly headache days, MSQ v2.1 RFR domain score, monthly acute headache medication days, and AIM-D Physical Impairment domain score (or HIT-6 score [for Europe]), respectively.

Logistic regression will be used to analyze responder variables using the same ANCOVA analysis model described for the primary variable (i.e., the MMRM model used for the primary analysis, but without repeat measures). The proportion of subjects with 50% reduction in the change from baseline in monthly migraine days across Months 5 and 6 will be summarized, along with p-values from the logistic regression. The primary assessment will be the pairwise comparison of each BOTOX dose versus placebo. A sensitivity analysis will use the same logistic model after imputation of missing data for the underlying primary variable by the mLOCF rate-change method, as described above. Alternatively, GLIMMIX models for repeated measures of binary data might be used in place of MMRM models; if so, the methodology will be described in the SAP.

Summary and Analysis of Other Endpoints

The other endpoints are defined in Section 3.4. These endpoints are not planned to be included in the multiplicity control. Hence, results will be considered descriptive and potentially supportive of the results for the primary and secondary endpoints.

The comparisons of interest for each of the other endpoints will be the pairwise comparisons of each BOTOX dose (195 U and 155 U) versus placebo, with no statistical comparison between the BOTOX doses. Specific details of the statistical analysis of other efficacy endpoints will be described in the SAP.

In general, though, for continuous and ordinal variables, the change from baseline analysis will be done with the same type of MMRM or ANCOVA analyses described for the primary efficacy endpoint, except that the baseline covariate will be for the variable being analyzed. For [redacted] which is recorded as change score postbaseline, the [redacted] baseline score will be used as a surrogate baseline covariate, to adjust for variation in response that is due to baseline differences between treatment groups.

In general, for responder variables, analysis of the responder status will be done with the same methods described for the secondary variable of 50% responder status.

For [redacted], the change from baseline analysis will be done with the same type of MMRM or ANCOVA analyses described for the primary efficacy endpoint, except that the model will use [redacted]. The counts for a given week will be prorated to 28-day counts before calculating the change from baseline.

7.5 Statistical Analyses for Safety

The safety analysis will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include AEs, clinical laboratory test results (hematology, chemistry, and urinalysis), vital signs, C-SSRS, and concomitant medications and procedures. The safety endpoints will be summarized using response frequencies and descriptive statistics, as applicable.

Any AEs that may occur before randomization will be listed but not summarized. An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first study intervention. An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criterion.

The incidence of TEAEs will be presented for each BOTOX dose group and the placebo group by the following:

- descending order of incidence rate
- primary system organ class (SOC) and PT
- primary SOC, PT, and maximum severity
- primary SOC, PT, and maximum duration

The number and percentage of subjects with treatment-related TEAEs in the treatment and placebo groups will similarly be tabulated by descending order of incidence rate, by SOC and PT and, separately, by SOC, PT, and severity.

If more than 1 AE is coded to the same PT for the same subject, the subject will be counted only once for that PT using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

Summary tables will be provided separately for subjects with TESAEs, for subjects with TEAEs leading to discontinuation, and for subjects with AEs of special interest (e.g., PDSOT, as defined in Section 6.1) if 5 or more subjects report such events. Note that MedDRA PTs for PDSOT will be provided in the SAP. Listings of all AEs, SAEs, and AEs leading to discontinuation by subject will be presented.

The analyses described above for treatment versus placebo groups will be for AEs occurring during the 24-week double-blind, placebo-controlled phase. The analyses will be repeated to summarize AE results for treated subjects over the open-label phase for subjects who receive open-label BOTOX.

All safety endpoints and analyses will be fully defined in the SAP.

Subgroup Analysis of Key Safety Endpoint(s)

The analysis of treatment-related TEAEs (by descending order of PT incidence) will be repeated for subgroups defined by each randomization stratification group (monthly migraine days at baseline ≥ [redacted] [yes/no] and [redacted] [yes/no]), for medication overuse subgroup [yes/no] (see Section 8.2 in the Operations Manual), for each gender, and for each country. Additional subgroup analyses will be described in the SAP.

7.6 Interim Analysis

There is no interim analysis planned for this study. However, to assess the validity of the assumptions for powering this Phase 3 trial, a blinded sample size re-estimation will be performed when approximately 33% of the subjects have reached the Week 24 visit (i.e., with diary data available for the primary endpoint of migraine days during Months 5 and 6). This will allow for a potential increase to the study sample size if the assumptions around data variability are inaccurate. Sample size adjustment within 25% of the current sample size per treatment arm of 259 participants per group is allowed without the need for a protocol amendment.

7.7 Overall Type I Error Control

All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise.

To control the overall type I error rate at the 0.05 level, multiple comparisons are accommodated for the 2 BOTOX dose comparisons to placebo across each of the primary efficacy endpoint and the 5 secondary variables in the multiplicity control by serial gatekeeping, as illustrated in Figure 2. Specifically, the hypotheses will be tested in a stepwise manner, with endpoints analyzed in the order illustrated in the figure. The testing process will be terminated for subsequent hypotheses whenever a statistical test indicates that a higher ranked hypothesis is not significant at the 0.05 level (i.e., all subsequent tests of any of the dose/variable combinations ranked in the remaining steps will be considered not significant). Results from the analyses that are not included in this gatekeeping algorithm will be considered supportive and exploratory.

Figure 2. Schematic of the Multiplicity Method to Control Overall Type I Error Rate

Key
- Primary - Change from baseline in the frequency of monthly migraine days across Months 5 and 6
- S1 - Change from baseline in the frequency of monthly headache days across Months 5 and 6
- S2 - Responder status of 50% reduction from baseline in the frequency of monthly migraine days across Months 5 and 6
- S3 - Change from baseline in the frequency of monthly acute headache medication days across Months 5 and 6
- S4 - Change from baseline in MSQ v2.1 RFR domain score at Month 6
- S5 - Change from baseline in AIM-D physical impairment score across Months 5 and 6 *[Europe: Change from baseline in HIT-6 score across Months 5 and 6]*

7.8 Sample Size Determination

For the primary endpoint of change from baseline in the frequency of monthly migraine days to the primary time point (8 weeks ending with Week 24), power and sample size calculations assume a 2-sided false-positive error level of alpha = 0.05, with multiple comparisons accommodated by gatekeeping.

Under a 1:1:1 randomization ratio, 259 subjects in each of the BOTOX dose groups and the placebo group at the primary time point will provide 90% power to detect a mean difference of [redacted] days between the groups for tests at alpha 0.05 and to detect a mean difference of [redacted] days for any tests done at alpha 0.025. These power calculations used a standard deviation estimate of [redacted], based on data for the month ending with Day 180 in EM Phase 2 studies for the subgroup of subjects with 8 to 14 migraine/probable migraine days at baseline (AbbVie data on file, Study 191622-037/509). Thus, the sample size is based on an effect size of [redacted].

With approximately 125 investigational sites planned, it is recommended that no site randomize more than approximately 12 subjects (i.e., twice the proportional share of 1 more site = 2 × [777/126]).

Calculations were done by using the commercial software nQuery Advisor® version 7.0, using a 2-sample Student's t-test with equal variances.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local laboratory instead of a central laboratory), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). In the event of a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat), remote review/verification of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit.

12 REFERENCES

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
AIM-D	Activity Impairment in Migraine – Diary
ANCOVA	Analysis of covariance
[redacted]	[redacted]
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CM	Chronic migraine
COVID-19	Coronavirus disease – 2019
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
eCOA	Electronic clinical outcome assessment
eCRF	Electronic case report form
EDC	Electronic data capture
e-Diary	Electronic diary
EM	Episodic migraine
ePRO	Electronic patient-reported outcomes
[redacted]	[redacted]
FAS	Full analysis set
GCP	Good clinical practice
HIT-6	6-item Headache Impact Test
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICHD	International Classification of Headache Disorders
IDR	Independent drug reconstitutor
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat

MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
mLOCF	Modified last observation carried forward
MMRM	Mixed model repeated measures
MSQ v2.1	Migraine-Specific Quality of Life Questionnaire version 2.1
NSAID	Nonsteroidal anti-inflammatory drug
PCR	Polymerase chain reaction
PD	Premature discontinuation
PDSOT	Possible distant spread of toxin
[redacted]	[redacted]
[redacted]	[redacted]
PHQ-9	Patient Health Questionnaire
PP	Per-protocol
PRO	Patient-reported outcome
PT	Preferred term
RFR	Role Function – Restrictive domain of the MSQ
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
UK	United Kingdom
VAS	Visual analogue scale
VCT	Verified Clinical Trials
[redacted]	[redacted]

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M21-307: Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study of BOTOX (Botulinum Toxin Type A) for the Prevention of Migraine in Subjects with Episodic Migraine

Protocol Date: 03 April 2024

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Neuroscience Data and Statistical Sciences

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the 14 subject encounters. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed within Section 5.4 of the Protocol and Section 2.1 of the Operations Manual. Treatment visits, specifically Visits 5, 8, and 11, should be scheduled approximately 12 weeks from the previous treatment visit date.

Study Activities Table

	Double Blind Phase							Open Label Phase						
	Visit 1: Screening	Visit 2: Randomization	Visit 3 (Telephone Visit)	Visit 4 (Telephone Visit)	Visit 5: Treatment 2	Visit 6 (Telephone Visit)	Visit 7 (Telephone Visit)	Visit 8: Treatment 3	Visit 9 (Telephone Visit)	Visit 10 (Telephone visit)	Visit 11: Treatment 4	Visit 12 (Telephone Visit)	Visit 13 (Telephone Visit)	Visit 14: Exit/Premature Discontinuation
Activity	Day –28 to Day –1	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48
Visit Window	Day –35 to Day –28	N/A	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
INTERVIEWS & QUESTIONNAIRES														
Informed consent	✓													
Eligibility criteria	✓	✓												
Demography	✓													
Medical/surgical history	✓													
Migraine headache history	✓													
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
C SSRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Provide handheld device, e Diary instructions, and training	✓													
[redacted]	✓													
[redacted]	✓													
Headache diary (e Diary)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[redacted]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

	Double Blind Phase							Open Label Phase						
	Visit 1: Screening	Visit 2: Randomization	Visit 3 (Telephone Visit)	Visit 4 (Telephone Visit)	Visit 5: Treatment 2	Visit 6 (Telephone Visit)	Visit 7 (Telephone Visit)	Visit 8: Treatment 3	Visit 9 (Telephone Visit)	Visit 10 (Telephone visit)	Visit 11: Treatment 4	Visit 12 (Telephone Visit)	Visit 13 (Telephone Visit)	Visit 14: Exit/Premature Discontinuation
Activity	Day –28 to Day –1	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48
Visit Window	Day –35 to Day –28	N/A	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
MSQ v.2.1		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AIM D (e Diary)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HIT 6		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[redacted]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[redacted]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[redacted]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[redacted]		✓			✓			✓			✓			✓
[redacted]		✓			✓			✓			✓			✓
[redacted]	✓	✓			✓			✓			✓			✓
[redacted]								✓						
Collect handheld device														✓
LOCAL LABS & EXAMS														
Height (screening only) and weight	✓							✓						✓
Vital signs (sitting BP and pulse rate)	✓	✓			✓			✓			✓			✓
Physical examination (abbreviated)	✓													
Urine drug screen	✓													
Urine pregnancy test		✓			✓			✓			✓			
CENTRAL LABS														
Serum pregnancy test	✓													
Laboratory assessments	✓							✓						✓
Urine alcohol screen	✓													

	Double Blind Phase							Open Label Phase						
	Visit 1: Screening	Visit 2: Randomization	Visit 3 (Telephone Visit)	Visit 4 (Telephone Visit)	Visit 5: Treatment 2	Visit 6 (Telephone Visit)	Visit 7 (Telephone Visit)	Visit 8: Treatment 3	Visit 9 (Telephone Visit)	Visit 10 (Telephone visit)	Visit 11: Treatment 4	Visit 12 (Telephone Visit)	Visit 13 (Telephone Visit)	Visit 14: Exit/Premature Discontinuation
Activity	Day –28 to Day –1	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48
Visit Window	Day –35 to Day –28	N/A	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
Optional biomarker sample: whole blood DNA		✓												
Optional biomarker sample: serum		✓						✓						
Optional biomarker sample: plasma		✓						✓						
℞ TREATMENT														
Randomization/drug assignment		✓												
Administer study drug		✓			✓			✓			✓			

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	18 May 2021
Version 2.0	13 July 2021
Version 3.0	16 August 2021
Administrative Change 1	01 October 2021
Version 3.1 (Regional VHP)	06 October 2021
Version 3.2 (Germany Only)	04 November 2021
Administrative Change 2	09 November 2021
Version 4.0	11 February 2022
Version 4.1 (UK only)	10 June 2022
Administrative Change 3	23 November 2022
Administrative Change 4	16 December 2022
Administrative Change 6 (UK only)	21 February 2023
Administrative Change 5	22 February 2023
Version 5.0	04 April 2023

The purpose of this version is to correct minor clerical errors for consistency in addition to the following changes made to align with SAP version 2:

- Protocol title page and Operation Manual Section 1 and Section 4.2 Updated the emergency medical contact with the information of the current personnel.
- Protocol Section 3.3 Moved the last secondary endpoint of [redacted] to Section 3.4 "Other Endpoints" due to the exploratory nature of this endpoint.
- Protocol Section 3.4 Added additional analysis of [redacted] in participants who report at least 1 day of [redacted] during baseline. Removed medication class analysis from change from baseline in the frequency of monthly acute headache medication days endpoint due to too few participants taking these medication classes at baseline. Added a statement that all primary and secondary endpoints will also be analyzed at monthly time points to further evaluate efficacy throughout the study.
- Protocol Section 7.4 Added additional subgroup analyses to align with regulatory guidelines.
- Protocol Section 7.7 Updated schematic of the multiplicity method to control overall Type I error rate to reflect changes in secondary endpoints.

- Protocol Section 9 Replaced COVID-19 pandemic with significant disaster/crisis events to clarify that remote verification may be considered for other significant disasters in addition to COVID-19 pandemic.
- Operation Manual Section 1 and Section 4.2 SAE reporting contact information was updated.

APPENDIX F. OPERATIONS MANUAL