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Title: A Multicenter, Prospective, Randomized, Open-label Study to Compare the Efficacy, Safety, and Tolerability of BOTOX® and Topiramate for Headache Prophylaxis in Adults with Chronic Migraine

Protocol Date: May 27, 2014


Statistical Analysis Plan (SAP) Date: July 17, 2017

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## **FORWARD Study Evaluating Preventive Treatment Options for Chronic Migraine**

### **A Multicenter, Prospective, Randomized, Open-label Study to Compare the Efficacy, Safety, and Tolerability of BOTOX<sup>®</sup> and Topiramate for Headache Prophylaxis in Adults with Chronic Migraine**

Protocol Number:	GMA-US-NEU-0206
Amendment:	1
Phase:	4
Name of Investigational Product(s):	BOTOX <sup>®</sup> and topiramate
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Numbers; name, address, and statement of qualifications of each investigator; name of each  
subinvestigator working under the supervision of the investigator; name and address of the  
research facilities to be used; name and address of each reviewing IRB; US 21 CFR 312.23  
section 6(iii)b.

## INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

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Investigator Printed Name

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Signature

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Date

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## Protocol Summary

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**Study Compound(s):** BOTOX<sup>®</sup> (onabotulinumtoxinA) Botulinum Toxin Type A Purified Neurotoxin Complex (hereafter referred to as BOTOX) and topiramate (Topamax<sup>®</sup>; Janssen Pharmaceuticals, Inc.)

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**Phase:** 4

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**Study Objective(s):** To compare the efficacy, safety, and tolerability of prophylactic treatment with BOTOX and topiramate in adults with chronic migraine

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### Clinical Hypotheses

BOTOX is more effective than topiramate as measured by the difference between treatment groups in a 50% responder rate (defined as the proportion of patients with a  $\geq 50\%$  reduction from baseline in the number of headache days over a 28-day period).

BOTOX has a superior tolerability profile than topiramate as measured by the difference between treatment groups in the rates of adverse events and discontinuations due to adverse events.

BOTOX has an acceptable safety profile.

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### Study Design

*Structure:* Multicenter, randomized, open-label, parallel-group, post-authorization, prospective study

*Duration:* Up to 54 weeks (includes a 28-day run-in period within a 6-week window, followed by up to 36 weeks of study treatment, followed by up to 12 weeks of posttreatment follow up)

*Study Treatment Groups:* BOTOX or topiramate

*Controls:* None, as this is an open-label study of 2 active treatments

*Dosage/Dose Regimen:* BOTOX 155 U will be administered approximately every 12 weeks as 31 fixed-site, fixed-dose intramuscular injections across 7 specific head/neck muscle areas for up to 36 weeks. Patients randomized to BOTOX will receive 3 treatment sessions of BOTOX. The final/exit visit for these patients will be at week 36 (or approximately 12 weeks after the last injection).

Topiramate will be administered as oral tablets given daily for up to 36 weeks. The topiramate dose will be titrated to a minimum of 50 mg/day and maximum of 100 mg/day taken twice daily. The final/exit visit for patients who complete topiramate treatment will be at week 36. Patients who discontinue topiramate treatment on or before week 36 will return to the office at the next scheduled office visit and approximately every 12 weeks up to and including the week 36 visit to receive BOTOX 155 U, for a maximum of 3 BOTOX treatment sessions in the study. The final/exit visit for these patients who discontinue topiramate and subsequently receive BOTOX will be at week 48 (or approximately 12 weeks after the last injection).

*Randomization/Stratification:* On day 1, qualified patients will be randomly assigned with 1:1 treatment allocation ratio to receive either BOTOX or topiramate. There is no stratification factor.

*Visit Schedule:* Up to 6 office visits and up to 4 electronic clinical outcome assessments (eCOA) at home are planned for each patient:

- 1) Screening (Office Visit): Visit occurs within 6 weeks prior to day 1. The time period between screening and day 1 will include a 28-day run-in period.
- 2) Day 1 (Office Visit): Randomization and first administration of study drug (BOTOX or topiramate)
- 3) Week 6 (eCOA)
- 4) Week 12 (Office Visit)
- 5) Week 18 (eCOA)
- 6) Week 24 (Office Visit)

- 7) Week 30 (eCOA)
- 8) Week 36 (Office Visit/Study Exit\*)
- 9) Week 42 (eCOA; only for patients remaining in the study)\*
- 10) Week 48 (Office Visit; only for patients remaining in the study)\*

\*For patients randomized to topiramate who receive BOTOX injection(s) in the study, an additional eCOA will be made at week 42 and the final/exit visit will occur in the office at week 48.

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**Study Population Characteristics**

*Number of Patients:* Approximately 400 patients (200 patients per arm) will be enrolled at approximately 40 US sites

*Condition/Disease:* Diagnosis of chronic migraine

*Inclusion Criteria:*

1. Male or female 18 to 65 years of age on the day that informed consent is signed
2. Medical history of chronic migraine, diagnosed according to the adult chronic migraine diagnostic criteria listed in the International Classification of Headache Disorders, 3<sup>rd</sup> edition (ICHD-3 beta)
3. Fifteen (15) or more headache days during the 28-day run-in period, with each headache day consisting of either or both of the following criteria: a total of 4 or more hours of headache and/or headache of any duration with the use of prescription migraine-specific acute headache medication(s) (ie, ergot alkaloids, ergot combinations, opioids, serotonin receptor agonists ["triptans"], combination analgesics [simple analgesics combined with opioids or barbiturates with or without caffeine])

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] y.

*Exclusion Criteria:*

1. [REDACTED]
2. Patient who is taking opioid-containing products for acute headache treatment more than 8 days during the 28-day run-in period
3. [REDACTED]
4. Previous treatment or immunization with botulinum toxin of any serotype for any reason
5. Previous treatment with topiramate for any reason

[REDACTED]

7 [REDACTED]

[REDACTED]

9. Patient who is on a ketogenic diet (eg, a diet high in fat and low in carbohydrates)
10. Patient has a history of acute myopia or increased intraocular pressure for any reason or a syndrome consisting of acute myopia associated with secondary angle closure glaucoma

[REDACTED]

12. Any medical condition that may put the patient at increased risk with exposure to BOTOX, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis or any other significant disease that might interfere with neuromuscular function

[REDACTED]

[REDACTED]

15. Treatment of study target muscles using acupuncture, transcutaneous electrical stimulation (TENS), cranial traction, dental splints for headache, or injection of anesthetics/steroids within 4 weeks prior to the screening visit

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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## Response Measures

### Efficacy Measures:

Primary Efficacy Measure: The proportion of patients with a  $\geq 50\%$  decrease from baseline in the frequency of headache days.

A headache day will be defined as a calendar day (00:00 to 23:59) with 4 or more hours of headache and/or headache of any duration with the use of migraine-specific acute headache medication(s) (ie, ergot alkaloids, ergot combinations, opioids, triptans, combination analgesics [simple analgesics combined with opioids or barbiturate with or without caffeine])

### Secondary Efficacy Measures:

- Frequency of headache days
- Headache Impact Test (HIT-6™)
- Proportion of patients with a  $\geq 70\%$  decrease from baseline in the frequency of headache days

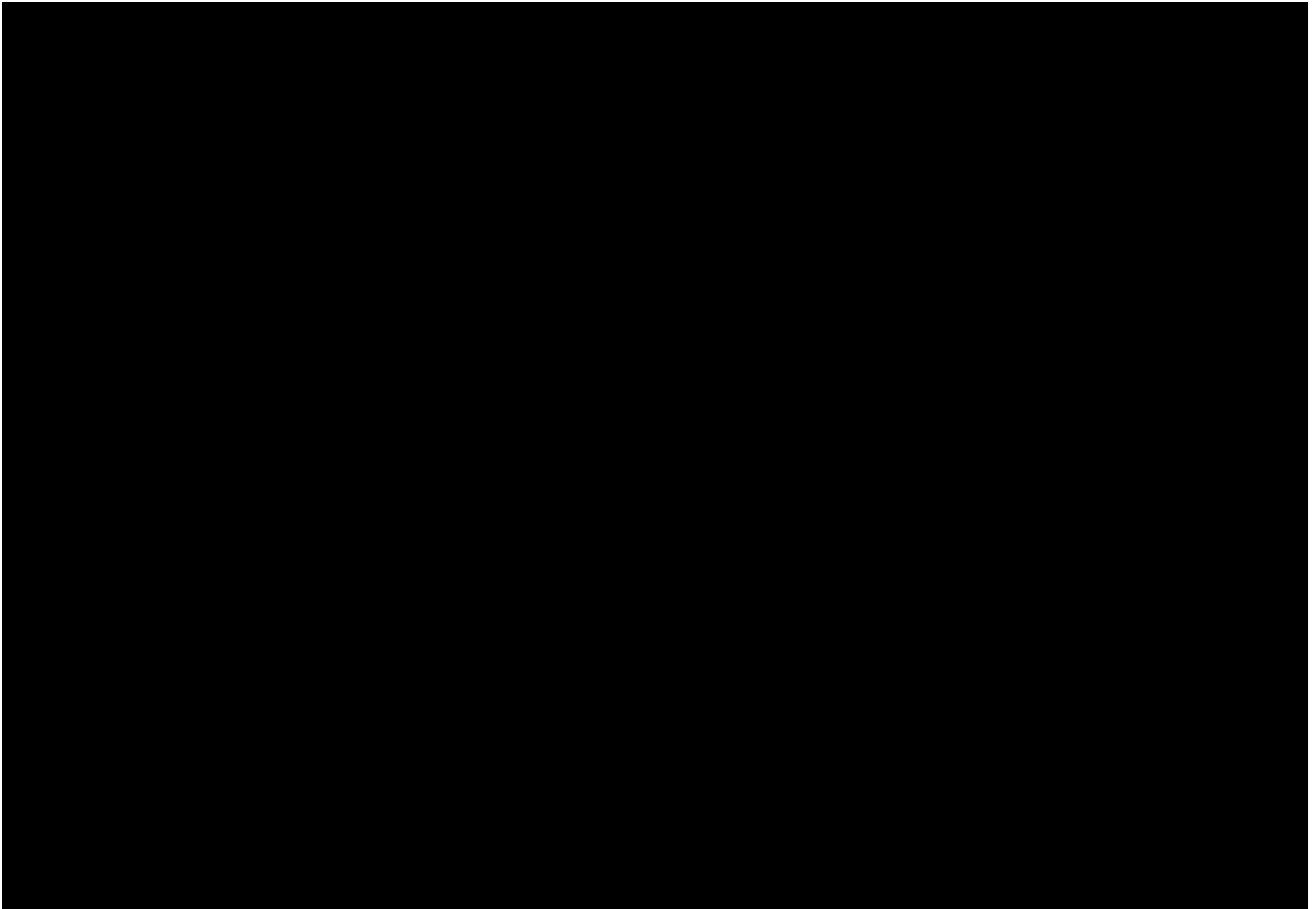
**General Statistical Methods and Types of Analyses:** Efficacy analysis will be performed on the Intent-to-Treat (ITT) analysis set. A sensitivity analysis will be performed using a subset of the ITT analysis set. Patients will be analyzed according to the treatment arm to which they were randomized for all efficacy analyses. The primary efficacy endpoint (proportion of patients with a  $\geq 50\%$  responder rate at week 32) is a dichotomous variable, and this will be analyzed using a logistic regression model with treatment as a factor, and baseline value as a covariate. A worst case imputation method will be utilized to impute missing values for this analysis. This type of imputation replaces the missing value (ie, frequency of headache days during the 28-day run-in period) with the baseline value. Thus, if a patient has a missing responder value at week 32 for any reason (eg, discontinuation due to adverse events, loss to follow-up, lack of efficacy), then the patient will be considered as a nonresponder and baseline value data will be utilized. Patient(s) randomized to topiramate who discontinue treatment and subsequently cross over to BOTOX will be considered nonresponder(s) for the efficacy analyses thus baseline value data will be utilized. A two-sided test with p-value less than or equal to 0.05 will be considered as statistically significant. If there are convergence issues with the logistic regression due to small cell counts, the same logistic regression model will be implemented using exact (conditional) logistic regression analysis.

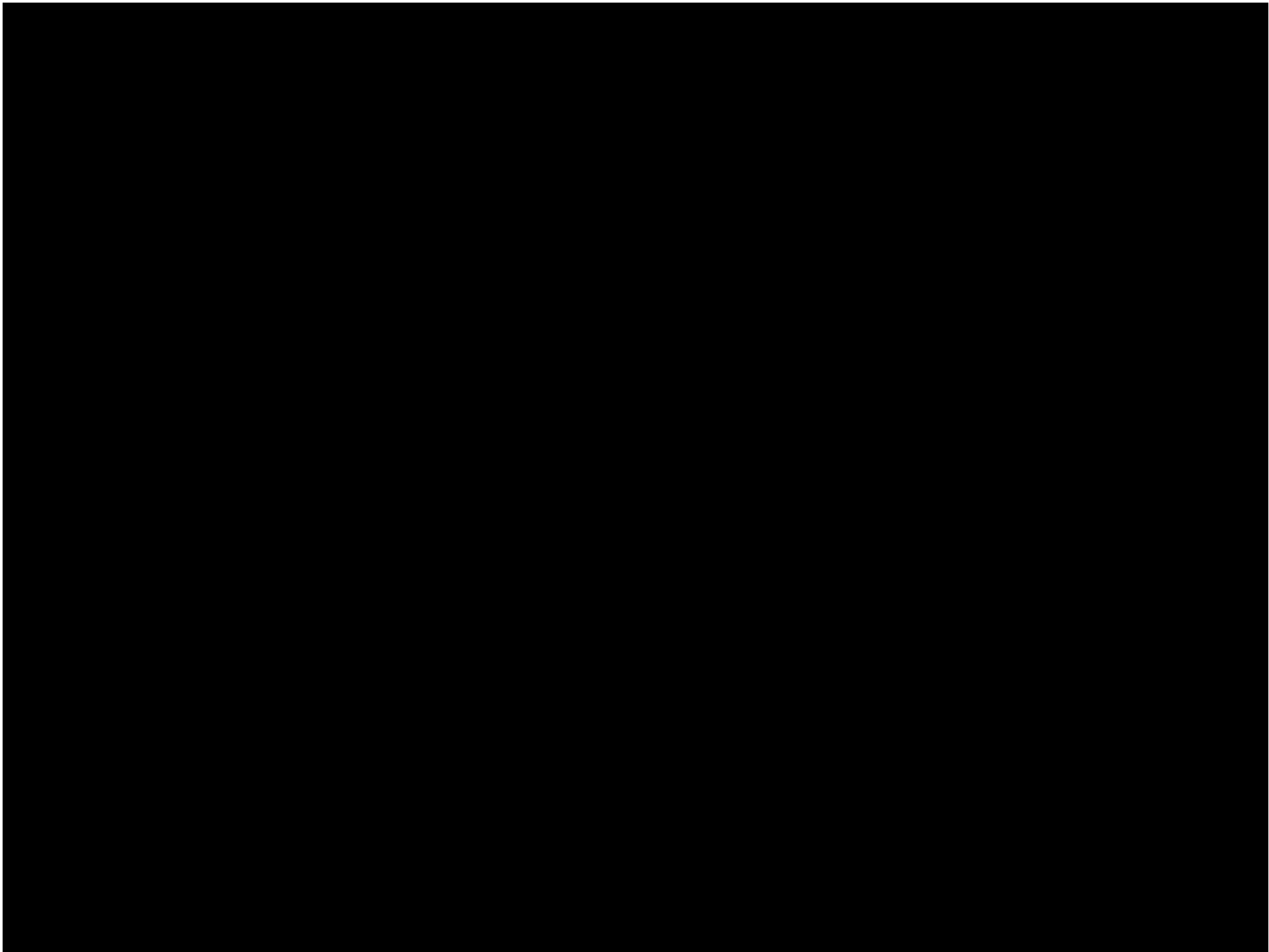
The 3 secondary efficacy variables are ranked in a hierarchical order of clinical importance. To control for Type I error rate for multiple secondary endpoints, a hierarchical testing gatekeeping procedure will be used, starting with the first secondary endpoint in the ranking order, followed by the next, and so on, in a sequential fashion. The change from baseline in frequency of headache days will be compared between BOTOX and topiramate groups via analysis of covariance (ANCOVA) with baseline headache day count as the covariate. The HIT-6 score will be compared between treatment groups using a nonparametric rank analysis of covariance (rank ANCOVA), with treatment as a factor, and adjusting for the baseline value. The proportion of patients with  $\geq 70\%$  responder rate will be analyzed similarly as the primary endpoint, using a logistic regression model adjusted by the baseline frequency of headache days.

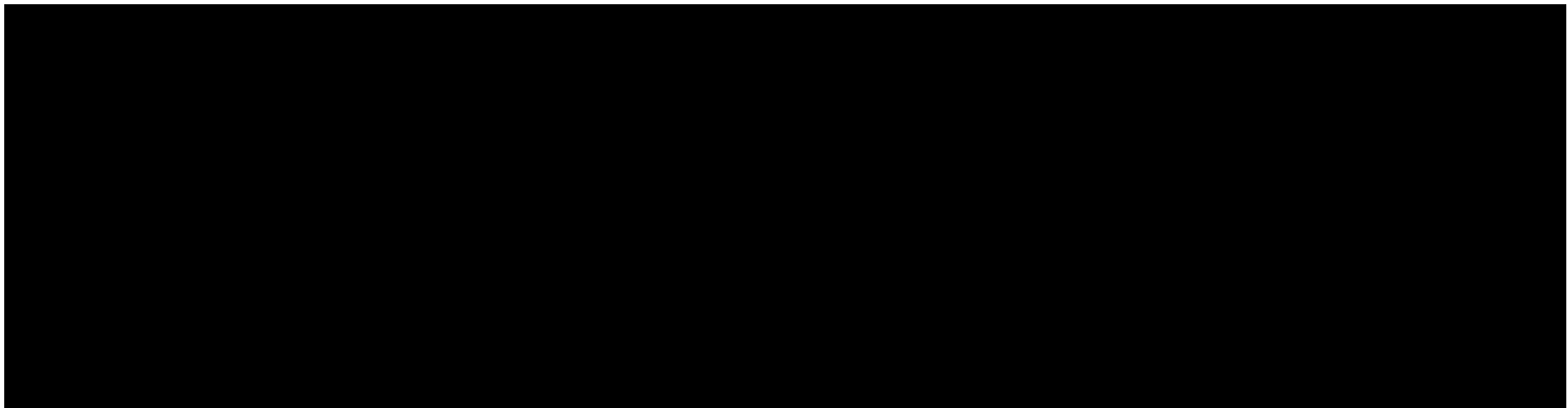
All safety analyses will be performed using the safety population, consisting of all patients who received at least one dose of either study medication. Safety data will be summarized by treatment actually received.

*Sample Size Calculation:* Approximately 400 patients (200 per group) are required to provide 90% statistical power to detect an expected treatment difference of 16%. This calculation assumes a topiramate responder rate of 28% and a BOTOX responder rate of 44% at the primary timepoint of week 32. A responder is defined as having a  $\geq 50\%$  decrease from baseline in the frequency of headache days per 28-day period. The above calculations were based on a two-sided test at  $\alpha = 0.05$ , using the commercial software nQuery Advisor version 6.01 ([Elashoff, 2005](#)), procedure PTT1 for a two-group continuity corrected Chi-squared test of equal proportions, with equal sample sizes.

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## 1. Background and Clinical Rationale

Migraine is a debilitating headache disorder. Because there are no biological markers for migraine, diagnosis is based on clinical history and the exclusion of other headache disorders. Chronic migraine (CM) is recognized as a complication of migraine, and CM sufferers experience  $\geq 15$  headache days per month (Olesen et al, 2006). CM is a disabling, underdiagnosed, and undertreated disorder (Bigal et al, 2008). Approximately 1.3% of the US population ( $\sim 3$  million people) and 1.3% to 2.4% of the European population suffer from CM. Females are 2.5 to 6.5 times more likely to suffer from the disorder than males (Scher et al, 1998; Castillo et al, 1999; Lanteri-Minet et al, 2003; Natoli et al, 2010). Studies have established that those suffering from CM have impaired quality of life and that they suffer substantial socio-economic burden due to increased medical needs, referral to medical specialists, drug utilization, work absenteeism, and reduced effectiveness at work (Blumenfeld et al, 2011; Munataka et al, 2009).

BOTOX<sup>®</sup> (Botulinum Toxin Type A Purified Neurotoxin Complex [US Adopted Name is onabotulinumtoxinA], henceforth referred to as BOTOX) has been approved by the United States Food and Drug Administration (US FDA) and global regulatory agencies for prophylaxis of headaches in adult patients with CM and is increasingly included in guidelines globally as a prophylactic option in this difficult to treat chronic migraine population. Results from 2 phase 3 multicenter, double-blind, placebo-controlled pivotal trials demonstrated that BOTOX treatment resulted in significant improvements compared with placebo for multiple headache symptom measures, including the frequency of headache-free days (Aurora et al, 2010; Diener et al, 2010). Intramuscular (IM) administration of BOTOX at doses of 155 to 195 U every 12 weeks for 56 weeks resulted in clinically meaningful and statistically significant improvements in functioning, vitality, psychological distress, and overall quality of life. Repeat treatment with BOTOX was safe and well tolerated with few systemic adverse effects. The most frequently reported adverse events (occurring in  $\geq 5\%$  of patients) following injection of BOTOX were neck pain and headache (BOTOX<sup>®</sup> US package insert, 2013).

A number of other drug classes have been used clinically for the prevention of headache in patients suffering from chronic migraine, despite not being specifically labeled for use in this patient population, eg, antiepileptic drugs, antihypertensive agents, antidepressants, and calcium channel blockers. Topiramate (Topamax<sup>®</sup>, Janssen Pharmaceuticals, Inc., Titusville, NJ), an antiepileptic agent, is approved by the US FDA for adults for the prophylaxis of migraine headaches. Topiramate has shown efficacy in several clinical trials with daily oral doses of 100 to 200 mg (Brandes et al, 2004; Silberstein et al, 2007; Diener et al, 2007;

[Silberstein et al, 2012](#)). The 100 mg daily dose was used in the pivotal clinical trials for topiramate and is the FDA-approved dose for migraine prophylaxis ([Topamax® US package insert, 2012](#)). However, despite being listed in a number of guidelines as a first line therapy option for prophylaxis in patients with chronic migraine, topiramate has been associated with systemic adverse events such as paresthesia, anorexia, weight decrease, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, difficulty with memory, concentration, and attention, cognitive problems, and confusion. Adverse events most often associated with the use of topiramate relate to the central nervous system. Clinical studies with topiramate have demonstrated high discontinuation rates due to adverse events and low tolerability. Many patients who begin migraine prophylaxis with antiepileptics are no longer taking these medications at 6 months ([Berger et al, 2012](#)).

Two double-blind randomized studies of headache prophylaxis compared BOTOX (maximum 200 U) and topiramate (maximum 200 mg/day) in 119 CM patients ([Mathew and Jaffri, 2009](#); [Cady et al, 2011](#)). Both studies demonstrated positive benefit for both BOTOX and topiramate in the reduction of headache days from baseline. In the 9-month study by Mathew and Jaffri, patients receiving BOTOX had fewer adverse events than topiramate, and fewer patients in the BOTOX group discontinued the study due to adverse events.

## **2. Study Objectives and Clinical Hypotheses**

### **2.1 Study Objectives**

To compare the efficacy, safety, and tolerability of prophylactic treatment with BOTOX and topiramate in adults with CM

### **2.2 Clinical Hypotheses**

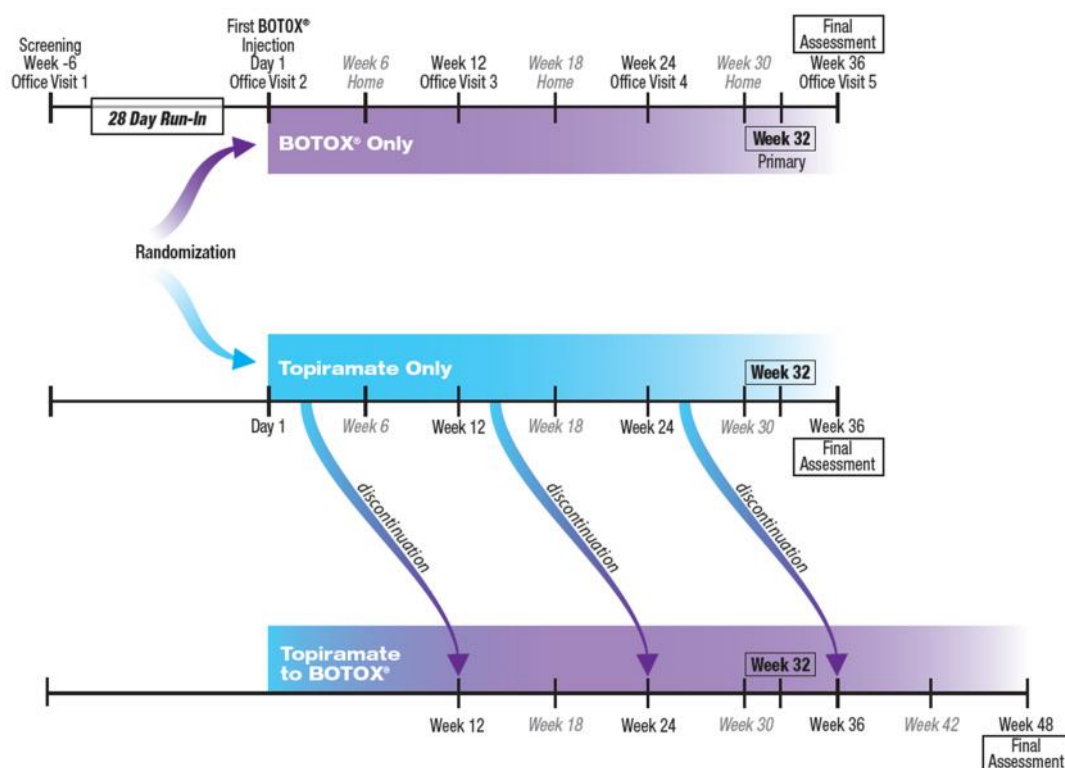
- BOTOX is more effective than topiramate as measured by the difference between treatment groups in a 50% responder rate (defined as the proportion of patients with a  $\geq 50\%$  reduction from baseline in the number of headache days over a 28-day period).
- BOTOX has a superior tolerability profile than topiramate as measured by the difference between treatment groups in the rates of adverse events and discontinuations due to adverse events.
- BOTOX has an acceptable safety profile.

### 3. Study Design

#### 3.1 Structure

This is a prospective, multicenter, randomized, open-label, parallel-group, post-authorization study to evaluate the efficacy, safety, and tolerability of BOTOX versus topiramate in adult patients with CM. The study consists of a pretreatment period lasting 4 weeks, a treatment period with BOTOX or topiramate treatment lasting up to 36 weeks, and a posttreatment follow-up period lasting 12 weeks (for patients receiving BOTOX) (Figure 1). All randomized patients are to remain in the study until week 36. However, patients who discontinue topiramate treatment on or before week 36 will crossover to treatment with BOTOX and remain in the study until week 48. Therefore, a patient could remain in the study for a maximum of 54 weeks. Patients are required to maintain a daily electronic headache diary (e-diary) the during the entire study period (ie, screening visit to exit visit).

**Figure 1 Study Design**



The pretreatment period consists of a screening visit that occurs within 6 weeks prior to day 1 and a prospective 28-day run-in period. The prospective run-in period should begin as soon as the patient completes the screening procedures. Patients who complete the run-in period

and meet the prespecified entry criteria will be randomized on day 1 in a 1:1 ratio to receive BOTOX or topiramate. For data analysis purposes, the number of headache days during the first 28 continuous days of the run-in period will serve as the “baseline” for calculating change from baseline for 28-day periods subsequent to each office visit.

The treatment period consists of patients receiving either IM injections of BOTOX 155 U approximately every 12 weeks or up to 100 mg/day of oral topiramate administered daily up to week 36. Patients randomized to BOTOX will receive 3 treatment sessions of BOTOX 155 U (at day 1, week 12  $\pm$  7 days, and week 24  $\pm$  7 days) according to the fixed-site, fixed-dose injection paradigm. The final/exit visit for these patients will be at week 36 (or approximately 12 weeks after the last injection) (see Section 5.4.1 for details).

Patients randomized to receive topiramate treatment will receive up to 36 weeks of daily topiramate treatment. A stable topiramate dose of at least 50 mg/day is required (maximum 100 mg/day) (see Section 5.4.2 for details). The final/exit visit for patients who complete topiramate treatment will be at week 36. Patients who discontinue topiramate treatment before the week 36 visit will return to the office approximately every 12 weeks up to and including the week 36 visit to receive BOTOX 155 U, for a maximum of 3 BOTOX treatment sessions in the study. The final/exit visit for these patients who discontinue topiramate and subsequently receive BOTOX will be at week 48 (or approximately 12 weeks after the last injection).

## **3.2 Visit Schedule**

Up to 6 office visits and up to 4 electronic clinical outcomes assessment (eCOAs) at home are planned for each patient:

- 1) Screening (Office Visit): Visit occurs within 6 weeks prior to day 1. The time period between screening and day 1 will include a 28-day run-in period.
- 2) Day 1 (Office Visit): Randomization and first administration of study drug (BOTOX or topiramate)
- 3) Week 6 (eCOA)
- 4) Week 12 (Office Visit)
- 5) Week 18 (eCOA)
- 6) Week 24 (Office Visit)
- 7) Week 30 (eCOA)
- 8) Week 36 (Office Visit/Study Exit\*)

9) Week 42 (eCOA; only for patients remaining in the study)\*

10) Week 48 (Office Visit; only for patients remaining in the study)\*

\*For patients randomized to topiramate who receive BOTOX injection(s) in the study, an additional eCOA will be made at week 42 and the final/exit visit will occur in the office at week 48.

The primary efficacy timepoint is the 28-day period ending at week 32.

### 3.3 Study Treatments

Study medication will be administered for up to 48 weeks. Following a 28-day run-in period, patients meeting the inclusion/exclusion criteria will receive their first treatment on day 1. Patients will be randomized in a 1:1 ratio to receive IM injections of BOTOX 155 U administered approximately every 12 weeks, or topiramate administered orally at doses up to 100 mg/day (minimum 50 mg/day), until week 36. Patients who discontinue topiramate treatment on or before the end of the week 36 visit will crossover to BOTOX treatment for the remainder of the study. All patients receiving BOTOX will be followed for approximately 12 weeks after the last injection.

Patients randomized to receive BOTOX treatment will receive 3 treatment sessions of BOTOX over the course of the treatment period, ie, at day 1, week  $12 \pm 7$  days, and week  $24 \pm 7$  days. During each of the treatment sessions, each patient will receive a dose of 155 U BOTOX administered as 31 fixed-site, fixed-dose IM injections across 7 specific head/neck muscle areas (ie, the US labeled injection paradigm; [BOTOX® US package insert, 2013](#)). The follow-the-pain injection paradigm should not be used. Patients who complete BOTOX treatment at week 24 will be exited from the study at the week 36 visit.

Patients randomized to receive topiramate will receive up to 36 weeks of daily treatment. There will be a 4-week titration phase starting on day 1, followed by a dose maintenance phase for the remainder of topiramate treatment. At the day 1 office visit, patients will receive an initial dose of topiramate 25 mg/day and will be instructed to continue this dose for 1 week. Patients will be instructed that, during the next 3 weeks of the titration phase, the topiramate dose should be increased in weekly increments of 25 mg/day until a dose of 100 mg/day (or a lower maximum tolerated dose) is reached. Upon discussion with the investigator, the patient may also decrease the dose until the topiramate dose is optimized. Starting at week 2, topiramate will be administered in 2 divided doses. Starting at week 4 (ie, the maintenance phase), a stable topiramate dose of at least 50 mg/day is required. As per the recommended topiramate dose for migraine prophylaxis, the topiramate dose must

not exceed 100 mg/day ([Topamax<sup>®</sup> US package insert, 2012](#)). At the next scheduled office visit (ie, week 12), the investigator, at his/her discretion, may adjust the topiramate dose (upward or downward) to be within the range of 50 to 100 mg/day; the patient should remain on this dose for the remainder of topiramate treatment in the study. For all patients completing topiramate treatment or those who discontinue from treatment, a dose taper period of up to 2 weeks is recommended. Refer to Section 5.4.2 for further details.

Patients who complete topiramate treatment at week 36 will be exited from the study at week 36. Patients who discontinue topiramate treatment at any time up to or including week 36 will crossover to receive treatment with BOTOX 155 U for the remainder of the study. The first BOTOX treatment will be administered at the next scheduled office visit, and the patient will return every 12 weeks up to and including the week 36 visit to receive BOTOX treatments, with a final exit visit at week 48. BOTOX treatment can be initiated during the topiramate dose tapering period.

All patients receiving BOTOX in the study will be followed for 12 weeks after the last injection.

### **3.4 Schedule for Data Collection**

Office visit data (ie, non-diary data) for this study will be collected using electronic case report forms (eCRFs) or eCOA at the screening visit, the day 1 (randomization/treatment) visit, and at 12-week intervals thereafter, coinciding with each office visit. Patient diary data will be collected daily via an e-diary during the 28-day run-in period and daily throughout the duration of the study. Patient-reported and clinician-reported outcomes will be collected via an eCOA. Follow-up data will be collected up to week 48, or up to 12 weeks after the last BOTOX injection.

## **4. Study Population and Entry Criteria**

### **4.1 Number of Patients**

Approximately 400 patients (200 patients per arm) will be enrolled at approximately 40 US sites.

### **4.2 Study Population Characteristics**

Diagnosis of chronic migraine

### 4.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Male or female 18 to 65 years of age on the day that informed consent is signed
2. Medical history of chronic migraine, diagnosed according to the adult chronic migraine diagnostic criteria listed in the International Classification of Headache Disorders, 3<sup>rd</sup> edition (ICHD-3 beta)
3. Fifteen (15) or more headache days during the 28-day run-in period, with each headache day consisting of either or both of the following criteria: a total of 4 or more hours of headache and/or headache of any duration with the use of prescription migraine-specific acute headache medication(s) (ie, ergot alkaloids, ergot combinations, opioids, serotonin receptor agonists [“triptans”], combination analgesics [simple analgesics combined with opioids or barbiturates with or without caffeine])

#### 4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

2. Patient who is taking opioid-containing products for acute headache treatment more than 8 days during the 28-day run-in period

- [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]
4. Previous treatment or immunization with botulinum toxin of any serotype for any reason
5. Previous treatment with topiramate for any reason
- [REDACTED]  
[REDACTED]
- [REDACTED]  
[REDACTED]  
[REDACTED])
- [REDACTED]  
[REDACTED]
9. Patient who is on a ketogenic diet (eg, a diet high in fat and low in carbohydrates)
10. Patient has a history of acute myopia or increased intraocular pressure for any reason or a syndrome consisting of acute myopia associated with secondary angle closure glaucoma
11. [REDACTED]
12. Any medical condition that may put the patient at increased risk with exposure to BOTOX, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis or any other significant disease that might interfere with neuromuscular function
- [REDACTED]
- [REDACTED]
15. Treatment of study target muscles using acupuncture, transcutaneous electrical stimulation (TENS), cranial traction, dental splints for headache, or injection of anesthetics/steroids within 4 weeks prior to the screening visit
- [REDACTED]  
[REDACTED]  
[REDACTED]



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[REDACTED]

## **4.5 Permissible and Prohibited Medications/Treatments**

### **4.5.1 Permissible Medications/Treatments**

Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact Allergan or Allergan designee. In addition, any concern regarding drug-drug interactions should be addressed with Allergan or designee prior to administering the study treatment.

The use of any concurrent medication including vitamins and herbal remedies, dietary supplements and prescription or over-the-counter (OTC) medication, is to be recorded on the patient's eCRF along with the reason the medication was taken.

Patients may use medication(s) with a known headache prophylactic effect if, in the opinion of the investigator, the dose has been stable and the medication(s) has been well tolerated for at least 12 weeks prior to screening. Any medication with a known headache prophylactic effect used by the patient should be maintained at a stable dose and dosage regimen during the study.

Patients may also take prescription or OTC acute headache pain medications as prescribed and/or directed by the investigator. The specific medication class used each day should be recorded by the patient in the e-diary.

Any concurrent medication should be maintained at a stable dose and dosage regimen during the study.

#### **4.5.1.1 Definition of Females of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods**

Women who are not of childbearing potential are considered as postmenopausal (at least 12 consecutive months without menstruation) or permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy). For women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: 1) the use of 2 of the following methods at the same time: oral contraceptives, patch contraceptives, injection contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device; or 2) surgical sterilization (bilateral tubal ligation); or 3) vasectomized partner; or 4) sexual abstinence.

The investigator and each patient will determine the appropriate methods of contraception for the patient and/or partner during the participation in the study. Patients should be instructed that the maximum topiramate dose of 100 mg/day in the current study has not been shown to cause decreased contraceptive efficacy ([Topamax<sup>®</sup> US package insert, 2012](#)).

If a pregnancy is reported during the study, the investigator will notify the Allergan immediately after the pregnancy is confirmed and the patient will be exited from the study after appropriate safety follow-up. To report a pregnancy, use the Allergan Pregnancy Communication Form. The Pre-Delivery Information Form (initial) (GSE-SIMR-F-005) reports initial information and the Post-Delivery (follow-up) information Form (GSE-SIMR-F-005) reports follow-up information and outcome. These forms are completed following signing of additional informed consents by the patient and partner. Fax the Pregnancy Communication Form to Allergan Safety Information Management and Reporting using the fax number found on the cover page of protocol. The investigator will then (1) notify the patient's physician that the patient was being treated with an investigational drug BOTOX or topiramate, if appropriate, and (2) follow the progress of the pregnancy. The investigator should record the date of the last menstrual period so that the approximate time of completion of the pregnancy can be estimated. Allergan will conduct follow -up.

#### **4.5.2 Prohibited Medications/Treatments**

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan or designee should be notified before the prohibited medication/treatment is administered.

Patients should not receive acupuncture, TENS, cranial traction, dental splints for headache, or injection of steroid or anesthetics into the study target muscles at any time during the study. Coadministration of aminoglycosides or other agents that could interfere with neuromuscular transmission (eg, curare-like agents) should only be used with caution as the effects of toxin theoretically could be potentiated.

Patients should be advised that any of the following medications may interact with topiramate during the study: antiepileptic drugs (eg, phenytoin, carbamazepine, valproic acid, lamotrigine), topical anticholinergic or sympathomimetic dilating drops, tricyclic antidepressants, monoamine oxidase inhibitors, antihistamines, antiparkinsonian drugs, antipsychotic medications, antispasmodic agents, sulfonamide-containing medications, metformin, carbonic anhydrase inhibitors (eg, zonisamide, acetazolamide, dichlorphenamide), lithium, alcohol, and all central nervous system depressants.

Administration of botulinum toxin of any serotype or topiramate for any indication during the study is prohibited, except as directed by the study.

Concurrent enrollment in another clinical investigational medicinal product or device study is prohibited.

### **4.5.3 Special Diet or Activities**

Throughout the study, patients should maintain the same or similar level of caffeine ingestion. Per the exclusion criteria, patients on a ketogenic diet should not be enrolled.

## **5. Study Treatments**

### **5.1 Study Treatments and Formulations**

BOTOX<sup>®</sup> (onabotulinumtoxinA, Formulation Number 9060X) contains 200 U of *Clostridium botulinum* toxin type A, 1 milligram (mg) of albumin (human), and 1.8 mg of sodium chloride in a sterile, vacuum dried form without preservative. One unit corresponds to the calculated median lethal intraperitoneal dose in mice.

BOTOX will be reconstituted with 4 mL sterile, non-preserved 0.9% sodium chloride injection USP for the 200 U vial.

Topiramate will be provided for oral administration as 25 mg tablets in 60 tablet count bottles. Sufficient supply will be provided to ensure a 13-week supply.

## **5.2 Treatment Allocation Ratio and Stratification**

On day 1, qualified patients will be randomly assigned with 1:1 treatment allocation ratio to 1 of 2 treatment arms: 155 U BOTOX given IM or up to 100 mg/day of oral topiramate.

There is no stratification factor.

## **5.3 Method for Assignment to Treatment Groups/Randomization**

At the screening visit, once informed consent is signed, the site staff will log onto the interactive web response system (IWRS) to obtain a unique patient number, which will be used as identification for the electronic patient e-diary, eCRFs, eCOAs, and all source documentation throughout the study.

The IWRS system will provide the site with the treatment assignment to which the patient is assigned. Sites will dispense study medication according to the IWRS instructions. Sites log onto the IWRS at subsequent visits to dispense additional study medication as needed. Sites will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

## **5.4 Treatment Regimen and Dosing**

### **5.4.1 BOTOX Treatment**

During each of the BOTOX treatment sessions, each patient will receive a dose of 155 U BOTOX administered as 31 fixed-site, fixed-dose IM injections across 7 specific head/neck muscle areas (Table 2 and Figure 2). The follow-the-pain injection paradigm should not be used. No dose adjustments will be made.

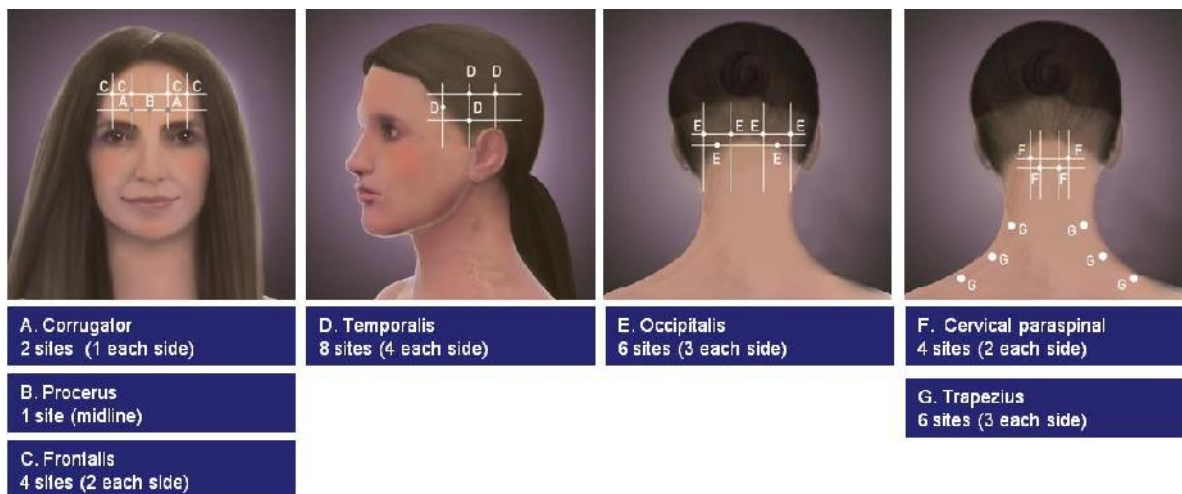
Detailed instructions for the administration of study medication are provided in Attachment 12.1.

**Table 2 Required BOTOX Dose Using Fixed-site, Fixed-dose Injection Paradigm**

Head/Neck Area	<b>LEFT</b> Number of units per muscle (number of injection sites <sup>a</sup> )	<b>RIGHT</b> Number of units per muscle (number of injection sites <sup>a</sup> )	<b>TOTAL</b> Number of units per muscle (number of injection sites <sup>a</sup> )
Procerus	-	-	5 (1 site)
Corrugator	5 (1 site)	5 (1 site)	10 (2 sites)
Frontalis	10 (2 sites)	10 (2 sites)	20 (4 sites)
Temporalis	20 (4 sites)	20 (4 sites)	40 (8 sites)
Occipitalis	15 (3 sites)	15 (3 sites)	30 (6 sites)
Cervical Paraspinal Muscle Group	10 (2 sites)	10 (2 sites)	20 (4 sites)
Trapezius	15 (3 sites)	15 (3 sites)	30 (6 sites)
<b>Total Dose</b>	-	-	<b>155 U (31 sites)</b>

<sup>a</sup> 1 injection site = 0.1 milliliter (mL) = 5 U of BOTOX

**Figure 2 Fixed-site, Fixed-dose BOTOX Injection Site Locations: (A) Corrugators, (B) Procerus, (C) Frontalis, (D) Temporalis, (E) Occipitalis, (F) Cervical Paraspinal, and (G) Trapezius Muscle Injection Sites**



## 5.4.2 Topiramate Treatment

Patients randomized to topiramate treatment will receive daily oral administration of topiramate tablets.

Because of the bitter taste, topiramate tablets should not be broken. Topiramate can be taken without regard to meals.

There will be a 4-week titration phase starting on day 1, followed by a dose maintenance phase for the remainder of topiramate treatment.

### 5.4.2.1 Dose Titration

At the day 1 office visit, patients will receive an initial dose of topiramate 25 mg/day taken once daily and will be instructed to continue this dose for 1 week. Patients will be instructed that, during the next 3 weeks, the topiramate dose should be increased in weekly increments of 25 mg/day until a dose of 100 mg/day (or a lower maximum tolerated dose) is reached. Upon discussion with the investigator, the patient may also decrease the dose until the topiramate dose is optimized. Starting at week 2, topiramate will be administered in 2 divided doses. As per the recommended topiramate dose for migraine prophylaxis, the topiramate dose must not exceed 100 mg/day ([Topamax<sup>®</sup> US package insert, 2012](#)).

The recommended topiramate dose titration schedule is presented in Table 3.

**Table 3 Recommended Topiramate Dose Titration Schedule**

	Morning Dose	Evening Dose
Week 1	None	25 mg
Week 2	25 mg	25 mg
Week 3	25 mg	50 mg
Week 4	50 mg	50 mg

Source: Topamax<sup>®</sup> US package insert, 2012

Note, during the 4-week titration period, the topiramate dose should be increased or decreased in weekly increments of 25 mg/day until a dose of 100 mg/day (or a lower maximum tolerated dose) is reached.

### 5.4.2.2 Dose Maintenance

Starting at week 4 (ie, the maintenance phase), the patient should remain on a stable topiramate dose of at least 50 mg/day. As per the recommended topiramate dose for migraine prophylaxis, the topiramate dose must not exceed 100 mg/day (Topamax<sup>®</sup> US package insert, 2012). At the next scheduled office visit (ie, week 12), the investigator, at

his/her discretion, may adjust the topiramate dose (upward or downward) to be within the range of 50 to 100 mg/day; the patient should remain on this dose for the remainder of topiramate treatment in the study.

For all patients who complete topiramate treatment or who discontinue from treatment, a dose taper period of up to 2 weeks is recommended. The investigator will determine the duration of the taper, which is based on the maximum dose received during the maintenance phase.

Patients who discontinue topiramate at any time up to or including week 36 will crossover to receive treatment with BOTOX 155 U for the remainder of the study. The first BOTOX treatment will be administered at the next scheduled office visit, and the patient will return every 12 weeks up to and including the week 36 visit to receive BOTOX treatments, with a final exit visit at week 48. BOTOX treatment can be initiated during the topiramate dose tapering period.

## **5.5 Storage of Study Medications**

The study medications must be stored in a secure area and administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol.

Upon receipt, BOTOX MUST be stored immediately in a refrigerator at 2° to 8° Celsius (°C) until used. Reconstituted BOTOX that is not administered immediately should not be withdrawn from the vial, and the vial must be stored in a refrigerator (2° to 8°C). If not used within 4 hours of reconstitution, study medication vials may not be used.

## **5.6 Preparation of Study Medications**

BOTOX will be reconstituted with 4 mL sterile, non-preserved 0.9% sodium chloride injection USP for the 200 U vial. Detailed instructions for the preparation of study medication are provided in the Pharmacy Manual.

## **5.7 Treatment Administration**

Following a 28-day run-in period, patients meeting the inclusion/exclusion criteria will receive their first treatment at visit 2 (day 1). On day 1, patients will be randomized in a 1:1 ratio to receive IM BOTOX 155 U administered approximately every 12 weeks or up to 100 mg/day oral topiramate administered daily, up to week 36. Patients who discontinue topiramate treatment on or before the week 36 visit will receive treatment with BOTOX for the remainder of the study.

Patients randomized to receive BOTOX treatment will receive 3 treatment sessions of BOTOX according to the US labeled injection paradigm (see Section 5.4.1) over the course of the study, ie, at day 1, week  $12 \pm 7$  days, and week  $24 \pm 7$  days.

Patients randomized to receive topiramate treatment will receive up to 36 weeks of topiramate administered orally at doses starting at 25 mg/day given once daily and tapered up to 100 mg/day given twice daily. Patients will continue to receive daily doses of topiramate until week 36 or early discontinuation (with dose tapering to commence at the time of discontinuation).

Patients who discontinue topiramate treatment prior to week 36 will be asked to return to the office at the next scheduled visit to receive treatment with BOTOX. These patients will receive IM injections of BOTOX 155 U approximately every 12 weeks up to and including the week 36 visit, for a maximum of 3 BOTOX treatment sessions during the course of the study. BOTOX treatment can initiated during the topiramate dose tapering period.

All patients receiving BOTOX in the study will be followed for approximately 12 weeks after the last injection.

## **6. Response Measures and Summary of Data Collection Methods**

### **6.1 Efficacy Measures**

Data required for the evaluation of the primary and some secondary efficacy measures will be recorded by patients using an e-diary. Patients are required to maintain the daily e-diary for the entire duration of the study, ie, from the screening visit to the exit visit. The following efficacy parameters will be collected with the daily e-diary. Patient instructions and training for completion of e-diary will be provided.

- Frequency of headache days
- Headache duration (ie, whether the headache lasted more than 4 hours)
- Frequency of severe headache days
- Days of acute headache pain medication use
- Migraine Interictal Burden Scale (MIBS-4)



The following patient-reported and clinician-reported outcome measures will be collected via eCOA:

- Headache Impact Test (HIT-6™)
- Assessment of Chronic Migraine – Impact (ACM-I)
- Controlled Oral Word Association Test (COWAT)
- Patient Health Questionnaire (PHQ-9) Quick Depression Assessment
- Work Productivity and Activity Impairment Questionnaire – Specific Health Problem (WPAI-SHP)
- Patient Treatment Satisfaction (PTS)
- Clinician Treatment Satisfaction (CTS)

### **6.1.1 Primary Efficacy Measure**

The primary efficacy measure is the proportion of patients with a  $\geq 50\%$  decrease from baseline in the frequency of headache days.

A headache day will be defined as a calendar day (00:00 to 23:59) with 4 or more hours of headache and/or headache of any duration with the use of migraine-specific acute headache medication(s) (ie, ergot alkaloids, ergot combinations, opioids, triptans, combination analgesics [simple analgesics combined with opioids or barbiturate with or without caffeine]).

A worst case imputation (WCI) method will be utilized to impute missing values for this analysis. This type of imputation replaces the missing value (ie, frequency of headache days during the 28-day run-in period) with the baseline value. Thus, if a patient has a missing responder value at week 32 for any reason (eg, discontinuation due to adverse events, loss to follow-up, lack of efficacy), then the baseline value data will be utilized and the patient will be considered a nonresponder. Patient(s) randomized to topiramate who discontinue treatment and subsequently cross over to BOTOX will be considered nonresponder(s) for the primary and secondary analyses thus baseline value data will be utilized.

### 6.1.2 Secondary Efficacy Measures

- Frequency of headache days
- Headache Impact Test (HIT-6):

The HIT-6 is a valid disease-targeted measure used to assess the impact of headaches (Yang et al, 2011). It is a reliable measure that is also responsive to changes in physical activity, irritability, and limitations in daily activities due to headaches. The HIT-6 comprises 6 items that assess pain, role functioning, social functioning, cognitive functioning, vitality, and psychological distress. A total score is created by summing across all items, and ranges from 36 (no impact) to 78 (severe impact) reflecting a “best to worst” scoring. Score categories are based on the total score and include “little to no impact” (total score 36 to 49), “some impact” (total score 50 to 55), “substantial impact” (total score 56 to 59) and “severe impact” (total score 60 to 78).

The HIT-6 questionnaire will be completed by the patient at day 1 and weeks 6, 18, and 30. Data will additionally be completed at week 42 for patients who discontinue topiramate and cross over to BOTOX. The developer’s scoring algorithm will be used.

- Proportion of patients with a  $\geq 70\%$  decrease from baseline in the frequency of headache days



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### **6.3 Examination Procedures, Tests, Equipment, and Techniques**

Study evaluations and treatment should be performed by the same investigator or sub-investigator throughout the study whenever possible. If it is not possible to use the same individual to follow the patient, then an attempt should be made to have visits overlap (examine the patient together and discuss findings) for at least 1 visit. Study treatment with BOTOX must be administered by a clinician investigator or clinician sub-investigator who has been trained on the protocol injection paradigm.

### **6.4 Other Study Supplies**

The following may be provided by Allergan or Allergan designee:

- Laboratory kits for the collection and shipment of blood samples, urine pregnancy kits, and urine illicit drug test kits will be provided by a vendor (eg, central laboratory) contracted by Allergan or Allergan designee.

- Shipping materials for shipment of laboratory samples to central laboratory
- Calibrated temperature recorder for monitoring freezer and refrigerator temperatures (if not already present at the site).

The following will be provided by the investigator:

- Needles for study treatment reconstitution (22 gauge, 1.5 inch) and injection (30 gauge, 0.5 inch)
- Syringes for study treatment reconstitution (5 cc) and injection (1 mL tuberculin type with 0.1 mL gradations, plastic, disposable with removable needles)
- Alcohol swabs
- Preservative-free 0.9% 0.9% sodium chloride injection USP for study treatment reconstitution
- Surgical gloves for study treatment reconstitution and study treatment administration
- Adhesive bandages
- Refrigerator to store dry/reconstituted study medication at a temperature of 2°C to 8°C
- Access to a computer with internet connection (high-speed connection for eCRF completion)
- Body weight scale with height measure
- Centrifuge for processing laboratory samples
- Covered hazardous medical waste container

## **6.5 Summary of Methods of Data Collection**

An IWRS will be used to randomize patients and manage study medication inventory. All office visit data (ie, non-diary data) for this study will be collected using eCRFs via an electronic data capture system. Source documents will be used at the sites and may include a patient's medical record, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as laboratory tests, X-rays, etc. A centralized clinical laboratory will be used for the analysis of all blood samples. Additional information on the collection and handling of samples is detailed in the Lab Procedure Manual.



Data required for the evaluation of the primary and some secondary efficacy measures will be recorded by patients using a daily e-diary. Patients will be asked to report data at approximately the same time each day, preferably at the beginning and end of the day, during the 28-day baseline period and throughout the study duration. The following data will be collected with the e-diary (patient instructions and training for completion of the e-diary will be provided):

- Estimated total duration of all headache(s) that day (if no headache, patient will report 0 hours)
- Maximum severity of headache(s) that day (mild, moderate or severe) (only for patients who report a headache duration of > 0)
- Any acute headache pain medication(s) used that day
- The dose of topiramate taken that day (only for patients receiving topiramate)
- MIBS-4 (only for patients who report a headache duration of 0)

Questionnaire data required to be directly collected from patients will be obtained at protocol-specified study visits using an electronic device. Questionnaires are to be completed by the patient and the answers to the questions on the questionnaires should come from the patients directly, not from family, friends, or the study support personnel. The patient may elect not to answer some or all of the questions. The patient questionnaires for a specific study visit should only be completed at that specific study visit. The patient will not have access to previously completed questionnaires.

Questionnaire data required to be directly collected from clinicians will be obtained at protocol-specified office visits and recorded on the eCOA.

If the patient reports an AE of cognitive impairment, in addition to completing the detailed questions on the AE eCRF, the clinician should indicate the patient's response on the Global Cognitive Impairment Assessment (GCIA) eCRF. This assessment aims to provide context for the complex symptoms associated with cognitive impairment.

The C-SSRS will be conducted as a clinical interview at each office visit, and the scores will be collected from the designated site staff via an electronic device.

## 7. Statistical Procedures

A detailed statistical analysis plan (SAP) describing analyses for all study endpoints will be developed subsequent to study launch and content finalized prior to database lock. The SAP will include a more technical and detailed elaboration of the principal features stated in the protocol and detailed procedures for executing the statistical analysis of the primary and secondary variables and other data as appropriate (ICH E9 [Statistical Principles for Clinical Trials], 1998). All analyses will be completed in accordance with the finalized SAP. A clinical summary will be prepared when all patients have completed the primary timepoint at week 32 (or exited the study prior to such completion). A final analysis will also be conducted after completion of all planned data analyses following the final posttreatment follow-up visit.

### 7.1 Analysis Populations

Four analysis populations are defined for this study.

- The intent-to-treat (ITT) population will consist of all randomized patients and analysis based on ITT will be the primary evidence of efficacy.
- A subset of the ITT population (ssITT) will exclude patients who discontinue treatment for any reason other than: adverse events, loss to follow-up, lack of efficacy, C-SSRS response of “yes” to questions 4 or 5 in the suicidal ideation section or “yes” to any question in the suicidal behavior section, or noncompliance with the study treatment regimen. Sensitivity analysis of the primary and secondary efficacy endpoints will be performed with the ssITT population. All efficacy endpoints will analyze patients according to the treatment to which they were randomized.
- The per protocol (PP) population will include all patients who had no major protocol deviations during the study. This will be determined prior to the final database lock following the completion of the final posttreatment follow-up visit. This population may be used in further exploratory analyses of some specified efficacy variables, and patients will be analyzed as-treated and without any imputation for missing data. Details will be provided in the SAP.
- The safety population will consist of all patients who received at least one dose of study medication. All safety analyses will be performed using the safety population and patients will be analyzed as treated.

## **7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments**

Data required for the evaluation of efficacy measures will be recorded for the duration of the study using e-diary, eCRFs, and eCOA, which includes patient- and clinician-reported assessments.

Each patient will establish a baseline frequency of headache days in the e-diary system daily during the baseline period. Additionally, over the course of active treatment, headache frequency, severity, and duration, as well as days of use of acute headache pain medications and dose of topiramate treatment will be recorded daily. Should a patient skip a day of an e-diary entry, the patient will be able to provide the missed information for up to 1 calendar day. This is defined as a 1-day “missing-recall” window. Responses reported during missing-recall time windows will be treated identically to responses reported on the intended reporting day. The e-diary should not be completed on the day of the office visit; the last e-diary entry for the preceding period should be completed the day prior to the office visit.

If total hours of headache and/or severity are recorded more than once for the same calendar day, the maximum number of reported hours for that day and the maximum severity reported for that day will be used as the patient’s data for analysis. For example, if the patient reported 4 total hours of headache yesterday and within the 1-day “missing-recall” window reports 6 total hours of headache for yesterday, then the report of 6 hours will be used as the patient’s response. This is allowed in case the patient had additional hours of headache after making an e-diary report yesterday.

The primary efficacy variable is the proportion of patients with a  $\geq 50\%$  decrease from baseline in the frequency of headache days per 28-day period ending with week 32. This variable is derived from the e-diary reports of total duration of all headaches for a given day. It is based on the count of days with at least 4 hours total duration of headaches and/or headache of any duration with the use of migraine-specific acute headache medication(s). The primary timepoint is week 32, encompassing the last 28-day period ending with week 32 (ie, day 198 to day 225 inclusive following the day 1 office visit).

Following study treatment at day 1, where the randomization and administration of BOTOX or topiramate take place, there are 8 more assessments (both in-office and eCOAs at home) at 6-week intervals, including 5 visits ending at week 30 (just prior to the primary timepoint of week 32) and 3 other visits (where the last 2 visits at weeks 42 and 48 only apply to topiramate patients who receive BOTOX during the study). However, in practice, there may or may not be an exact 6-week (ie, 42-day) duration between 2 consecutive visits.

For data analysis purposes, the number of headache days during the first 28 continuous days of the run-in period will serve as the “baseline” for calculating change from baseline for 28-day periods subsequent to each office visit. If the run-in period (starting with the screening visit and preceding the first study treatment on day 1) exceeds 28 days, then the run-in period will only include the first 28 days. In order to be randomized, a patient must have been in the run-in period for at least 28 continuous days and must have reported e-diary data for at least 20 days (including “missing recall”) during the 28-day run-in period.

Baseline assessments for non-daily e-diary data (eg, HIT-6, ACM-1, COWAT) will be collected at the day 1 office visit.

### **7.2.1 Primary Efficacy Variable**

The primary efficacy variable is the proportion of patients with a  $\geq 50\%$  decrease from baseline in the frequency of headache days per 28-day period, at the primary timepoint of week 32 (defined as the 28-day period ending with week 32).

#### **7.2.1.1 Imputation for Missing Diary Entries**

The primary efficacy endpoint is a dichotomous variable (responder /nonresponder), and a WCI method will be utilized to impute missing values. If a patient has a missing responder value at week 32 for any reason (ie, discontinuation), the patient will be considered as a nonresponder.

Other types of imputation for the analysis of secondary efficacy variables or in sensitivity/supportive analysis of the primary variable will be detailed in the SAP.

### **7.2.2 Secondary Efficacy Variables**

- Change from baseline in the frequency of headache days per 28-day period. This variable will be derived from the daily e-diary reports. It will be based on the count of days with at least 4 continuous hours in total duration of headaches, and/or headache of any duration with the use of migraine-specific acute headache medication(s).
- Change from baseline in total HIT-6 score per 28-day period
- Proportion of patients with a  $\geq 70\%$  decrease from baseline in the frequency of headache days per 28-day period. This responder variable will be derived from the underlying primary variable of headache days.

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[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### **7.2.3.1 Imputation for Missing Values and Scoring Algorithms**

For validated questionnaires, scoring will follow the guidelines set forth by the instrument developers and missing data handled per developer instructions. Imputation methods for missing values and scoring algorithms for other outcome measures will be detailed in the SAP.

Over the course of active treatment, each patient receiving topiramate will record the total daily dose taken in the e-diary system. If a patient skips a dose(s) or fails to take the specific maintenance dosing regimen, the patient will still be able to continue in the study.

Topiramate dosing compliance will be calculated based on the e-dairy data and if necessary, corresponding pill counts (number of pills actually taken, number of pills retrieved/returned, and the number of pills expected to have been taken by the patient while in the topiramate arm of the study). Topiramate dosing compliance details will be provided in the SAP. If the patient indicates that no topiramate treatment was taken in the e-dairy system and treatment discontinuation is reported at the subsequent office visit, then date of last dose taken will be the reported as date of discontinuation.

## **7.3 Hypothesis and Methods of Analysis**

### **7.3.1 Primary Efficacy Analyses**

The primary efficacy analysis is based on the proportion of responders (patients with a  $\geq 50\%$  decrease from baseline in the frequency of headache days per 28-day period), and the primary timepoint is defined as the 28-day diary period ending with week 32 (ie, weeks 29 to 32). The primary null hypothesis is that BOTOX and topiramate are equally effective, as measured by the proportion of patients with a  $\geq 50\%$  decrease from baseline in the frequency of headache days per 28-day period at week 32. The alternative hypothesis is that BOTOX has a different effect than topiramate.

The primary comparison between treatment groups will be performed using a simple logistic regression model, adjusted by the baseline number of headache days as a covariate. Missing values will be estimated according to the imputation method provided in the SAP. All centers will be pooled for this analysis. A two-sided test with p-value less than or equal to 0.05 will be considered as statistically significant, with the exception that treatment-by-subgroup interactions will be examined at the 0.10 level. If there are convergence issues with the simple logistic regression due to small cell counts, the same logistic regression model will be implemented using exact (conditional) logistic regression analysis.

### 7.3.2 Secondary Efficacy Analyses

A sensitivity analyses of the primary variable will be performed using (1) Fisher's exact test based on the imputation method discussed in the SAP, and (2) using a similar logistic regression analysis but applying another imputation scheme (to be discussed in the SAP) to impute for missing values when there are less than 20 days of reported data in the e-diary. Other sensitivity analyses will be described in the SAP.

The 3 secondary efficacy variables (Section 7.2.2) are ranked in a hierarchical order of clinical importance. To control for Type I error rate for multiple secondary endpoints, a hierarchical testing gatekeeping procedure will be used, starting with the first secondary endpoint in the ranking order, followed by the next, and so on, in a sequential fashion. If the test of the first secondary endpoint shows statistical significance at the 0.05 level (2-sided), then there is justification to proceed to test the next endpoint in the ranking order; this stepwise process continues for all the endpoints listed in the hierarchical order. However, if no statistical significance is shown at the 0.05 level (2-sided) for the test of any specified endpoint in the hierarchical order, then that endpoint and all subsequent endpoints below this in the ranking order should not be considered statistically significant, regardless of their nominal p-value.

The change from baseline in frequency of headache days will be compared between BOTOX and topiramate groups via analysis of covariance (ANCOVA) with baseline headache day count as the covariate. A treatment-by-investigator site interaction will also be investigated in a separate ANCOVA model.

The HIT-6 score will be compared between treatment groups using a nonparametric rank analysis of covariance (rank ANCOVA) ([Stokes et al, 2000](#)), with treatment as a factor, and adjusting for the baseline value.

The  $\geq 70\%$  responder rate will be analyzed similar to the primary endpoint, using a logistic regression model adjusted by the baseline frequency of headache days. The exact conditional logistic regression analysis will be performed if there are convergence issues with the default unconditional analysis.

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## 7.4 Subgroup Analyses

Subgroup analyses of efficacy and/or safety variables will be detailed in the SAP.

## 7.5 Sample Size Calculation

Approximately 400 patients (200 per group) are required to provide 90% statistical power to detect an expected treatment difference of 16%. This calculation assumes a topiramate responder rate of 28% and a BOTOX responder rate of 44% at the primary timepoint of week 32. A responder is defined as having a  $\geq 50\%$  decrease from baseline in the frequency of headache days per 28-day period. The above calculations were based on a two-sided test at  $\alpha = 0.05$ , using the commercial software nQuery Advisor version 6.01 (Elashoff, 2005), procedure PTT1 for a two-group continuity corrected Chi-squared test of equal proportions, with equal sample sizes.

The assumed responder rates for BOTOX were estimated from 2 Allergan phase 3 double-blind placebo-controlled studies which reported the observed rates as 43.5% (113/260), 50.5% (141/279), and 47.1% (254/539) for study 191622-079, study 191622-080, and the pooled/combined data, respectively, at the primary timepoint of week 24 ([Aurora et al, 2010](#);



[Diener et al, 2010](#)). At week 32, the observed rates were 55.7% (141/253), 61.7% (161/261), and 58.8% (302/514), respectively, for these studies. The corresponding rates for an ITT analysis where patients terminating the study are treated as failures are obtained as 41.3% (141/341), 46.4% (161/347), and 43.9% (302/688), respectively. Based on these studies, the BOTOX responder rate for an ITT analysis at week 32 ranges from 41.3% to 46.4%, and the value of 44% was chosen as reasonable for the purposes of sample size calculation for the current study.

The topiramate responder rate was estimated from 2 published articles. A double-blind placebo-controlled study with combination therapies, topiramate + placebo (n = 95) and topiramate + propranolol (n = 96) is described in [Silberstein et al, 2012](#). The observed responder rates for  $\geq 50\%$  decrease in headache days from baseline reported at week 24 were 28% (23/82) and 31% (26/84), respectively, for the 2 groups. These correspond to 24% and 27%, respectively, for an ITT analysis where patients terminating the study are treated as failures. [Rothrock et al, 2005](#) also describes an open-label study involving topiramate (n = 170), where a responder rate ( $\geq 50\%$  reduction from baseline) of 38.8% (45/116) was reported. This rate also corresponds to 29.4% for an ITT analysis where patients terminating the study are treated as failures. Thus, the ITT rates for topiramate ranges from 24% to 29.4%, and the value of 28% is deemed reasonable for sample size calculation purposes.

## **7.6 Interim Analysis**

No interim analysis is planned for this study.

## **8. Study Visit Schedule and Procedures**

Please see Table 1 for a schematic of the schedule of visits and procedures.

### **8.1 Patient Entry Procedures**

#### **8.1.1 Overview of Entry Procedures**

Prospective patients as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

#### **8.1.2 Informed Consent and Patient Privacy**

The study will be discussed with the patient and a patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The patient must also give authorization and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related

procedures or change in treatment. If a patient or partner of a patient becomes pregnant, then appropriate follow-up forms should be completed following signing of additional informed consents by the patient and partner (see Section 4.5.1.1).

## 8.2 Washout Intervals/Run-in

There is no protocol-specified washout interval for this study. Patients will be screened at the screening visit and eligible patients will commence with the 28-day prospective run-in period.

### 8.3 Procedures for Final Study Entry

At the screening and day 1 (randomization) visits, patients must meet all of the inclusion criteria and must not meet any of the exclusion criteria. Also, all females of childbearing potential must have negative results on the urine pregnancy test on day 1 (prior to the first administration of study medication).

See Section 5.3 for the method for assignment to treatment groups/randomization.

## 8.4 Visits and Associated Procedures

The study procedures are listed for each visit below.

- [REDACTED]
  - [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
- I [REDACTED]
  - [REDACTED]
  - [REDACTED]
- I [REDACTED]
  - [REDACTED]
- I [REDACTED]
- [REDACTED] [REDACTED]
- I [REDACTED]
  - [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
  - [REDACTED]
- I [REDACTED]
  - [REDACTED]
- I [REDACTED]
- I [REDACTED]

[illegible]

- [illegible]

Row	Bar Length (approx. % of total width)
1	25
2	75
3	85
4	98
5	10
6	60
7	65
8	100
9	35
10	90
11	45
12	95
13	55
14	75
15	40
16	55
17	98
18	10
19	45
20	30
21	75
22	85
23	60
24	90
25	50
26	25
27	70
28	85

- A horizontal bar chart with 20 rows. Each row consists of a small vertical bar on the left and a longer horizontal bar on the right. The vertical bars are black, and the horizontal bars are white with black outlines. The horizontal bars represent percentages, with some reaching 100% and others being shorter. The categories are not labeled, but the bars are arranged in descending order of length.

Category	Percentage
1	100%
2	100%
3	100%
4	100%
5	100%
6	100%
7	100%
8	100%
9	100%
10	100%
11	100%
12	100%
13	100%
14	100%
15	100%
16	100%
17	100%
18	100%
19	100%
20	100%

## 8.5 Instructions for the Patients

At approximately the same time (preferably at the beginning and end of the day) on a daily basis during the 28-day run-in period and throughout the study duration, patients are to report information, using an e-diary, on the total duration of all headaches (in hours), maximum severity of headaches that occurred that day (as mild, moderate or severe), any acute headache pain medication(s) used that day, and for those patients taking topiramate, the dose of topiramate that day. Patients will be able to report headache data, including absence of headache, for the day of the e-diary report and for the previous day(s). Patients will be asked to complete the MIBS-4 questionnaire only on the specific day(s) when a duration of 0 headache hours are reported in the e-diary.

Patient-reported outcome questionnaires (ie, HIT-6, ACM-I, PHQ-9, COWAT, WPAI-SHP, and PTS) are to be completed by the patient via the eCOA on days specified in the visit schedule (Table 1), and the answers to the questions on the questionnaires should come from the patients directly, not from family, friends, or the study support personnel. Patient instructions and training for completing the e-diary and eCOA will be provided to the site.

Patients receiving topiramate will be instructed on the daily dosing schedule. At the day 1 office visit, patients will receive an initial topiramate dose of 25 mg/day and will be instructed to continue this dose for 1 week. Patients will be instructed that, during the next 3 weeks, the topiramate dose should be increased in weekly increments of 25 mg/day until a dose of 100 mg/day (or a lower maximum tolerated dose) is reached. Upon discussion with the investigator, the patient may also decrease the dose until the topiramate dose is optimized. At the next scheduled office visit (ie, week 12), the investigator may adjust the topiramate dose (upward or downward) at his/her discretion and the patient will be instructed to remain on this dose for the remainder of topiramate treatment in the study. Patients should report in the daily e-diary the doses of topiramate taken each day. Patients should consult with the investigator regarding any changes made to their instructed topiramate dosing schedule. If the patient decides to stop taking topiramate, for any reason, they should contact their investigator to ensure an appropriate tapering regimen and unused pills should be returned at next visit. The patient should continue to complete their daily diary and the treatment discontinuation eCRF can be completed at the subsequent office visit. The patient treatment discontinuation eCRF must be completed to determine reason for discontinuation.

Patients may use medication(s) with a known headache prophylactic effect and take prescription or OTC acute headache pain medications, as prescribed and/or directed by the investigator. Any medication with a known headache prophylactic effect used by the patient should be maintained at a stable dose and dosage regimen during the study. Patients should



not receive acupuncture, TENS, cranial traction, dental splints for headache, or injection of steroid or anesthetics into the study target muscles at any time during the study. Patients should be advised of the use of medications that may interact with topiramate during the study (see Section 4.5.2).

Females of childbearing potential will be counseled on using reliable methods of contraception during the study. The investigator and each patient will determine the appropriate methods of contraception for the patient and/or partner (see Section 4.5.1.1).

Throughout the study, patients should maintain the same or similar level of caffeine ingestion.

## **8.6            Unscheduled Visits**

All procedures and evaluations necessary for the well-being of the patient should be performed, if necessary at an unscheduled visit, and eCRFs should be completed if appropriate.

## **8.7            Compliance with Protocol**

Patients will be scheduled for follow-up visits in a timely manner and these should occur as close as possible to the day specified in the visit schedule (Table 1). At each visit, the patient will be asked if the patient changed the dose/regimen of any existing concomitant medications, initiated the use of any new concomitant medications, or had any concurrent procedures since the last visit to ensure compliance with the protocol. Both BOTOX and topiramate study treatments should be administered per protocol. Given topiramate is self-administered, patients will also record in the daily e-diary if the topiramate treatment was taken and the specific dose each day to ensure compliance with titration and maintenance dosing. If the specified dose is not recorded, the patient will be able to continue in the study and criteria for adequate topiramate compliance will be detailed in the SAP.

## **8.8            Early Discontinuation of Patients**

Patients may voluntarily withdraw consent from the study at any time. If the patient withdraws consent due to any reasons other than treatment discontinuation (eg, patient moved, patient does not complete visits), all of the final measurements should be performed at the exit visit and recorded on the appropriate eCRF. The eCRF for patient treatment discontinuation should be completed to document patient withdrawal of consent.

If a patient discontinues topiramate treatment, the eCRF for patient treatment discontinuation should be completed to document the reason for discontinuation. The patient should not be

exited from the study, but should be administered BOTOX at the next scheduled office visit (ie, week 12, 24, or 36).

If a patient discontinues BOTOX treatment, the eCRF for patient treatment discontinuation should be completed to document the reason for discontinuation. The patient should then be exited from the study and all of the final measurements should be performed at the exit visit and recorded on the appropriate eCRFs.

If a patient is determined as a loss to follow-up, the eCRF for patient treatment discontinuation should be completed to document the reason for discontinuation.

If a patient must exit the study due to pregnancy or the C-SSRS (ie, the patient answers “yes” to questions 4 or 5 in the suicidal ideation section or “yes” to any question in the suicidal behavior section), the eCRF for patient treatment discontinuation should be completed to document the reason for discontinuation. The patient should then be exited from the study and all of the final measurements should be performed at the exit visit and recorded on the appropriate eCRF.

Notification of early patient discontinuation from the study and the reason for discontinuation will be made to Allergan or Allergan designee and will be clearly documented on the appropriate eCRF.

## **8.9 Withdrawal Criteria**

Female patients must be withdrawn from the study if they become pregnant (see Section 4.5.1.1). Patients who have replied with “yes” to questions 4 or 5 in the suicidal ideation section or “yes” to any question in the suicidal behavior section of the C-SSRS should not receive any further study treatments, must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice.

## **8.10 Study Termination**

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

## **9. Adverse Events**

Adverse events occurring during the study will be recorded on an adverse event case report form. If adverse events occur, the first concern will be the safety of the study participants.

## **9.1 Definitions**

### **9.1.1 Adverse Event**

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should NOT be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events will be assessed, documented, and recorded in the eCRF throughout the study (ie, after informed consent has been obtained). All adverse events prior to study treatment from the time of informed consent are collected and defined as Pre-Treatment Adverse Event (PTAE). At each visit, the investigator should begin by querying for adverse events by asking each patient a general, non-directed question such as “How have you been feeling since the last visit?” Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate eCRF.

If the patient reports an AE of cognitive impairment, in addition to completing the detailed questions on the AE eCRF, the clinician should indicate the patient’s response on the GCIA eCRF. This assessment aims to provide context for the complex symptoms associated with cognitive impairment.

### **9.1.2 Serious Adverse Event**

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be

life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting a serious adverse event.)

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization is not reportable as a serious adverse event.

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a serious adverse event and reported to Allergan.

### **9.1.3 Severity**

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an adverse event may be an 'all or nothing' finding which cannot be graded.

### **9.1.4 Relationship to Study Drug or Study Procedure**

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug or study procedure.

## **9.2 Procedures for Reporting Adverse Events**

Any adverse event must be recorded on the appropriate eCRF.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board (IRB) as required by the IRB, local regulations, and the governing health authorities. Any adverse event that is marked 'ongoing' at the exit visit must be followed-up as appropriate.

### **9.3 Procedures for Reporting a Serious Adverse Event**

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 12 weeks after the last dose of study drug must be immediately reported but no later than 24 hours after learning of a serious adverse event. Serious adverse events must be reported to Allergan recorded on the Serious Adverse Event Form (GSE-SIMR-F-011). All patients with a serious adverse event must be followed up and the outcomes reported. The investigator must supply Allergan and the IRB with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of a serious adverse event, the investigator must:

1. Notify Allergan immediately by fax or email using the Serious Adverse Event Form (GSE-SIMR-F-011) (contact details can be found on page 1 of the Serious Adverse Event Form); phone numbers and relevant Allergan personnel contacts are also on the front page of protocol.
2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
3. Provide Allergan with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.
4. Promptly inform the governing IRB of the serious adverse event as required by the IRB, local regulations, and the governing health authorities.

## **10. Administrative Items**

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Conference on Harmonisation (ICH) Guideline on GCP.

### **10.1 Protection of Human Patients**

#### **10.1.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations**

Written informed consent is to be obtained from each patient prior to any study-related activities or procedures in the study, and/or from the patient's legally authorized representative. If the patient is under the legal age of consent, the consent form must be signed by the legally authorized representative in accordance with the relevant country and local regulatory requirements.

#### **10.1.2 Compliance With IRB Regulations**

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103). The investigator must obtain approval from a properly constituted IRB prior to initiating the study and re-approval or review at least annually. Allergan or Allergan designee is to be notified immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB correspondence with the investigator should be provided to Allergan or Allergan designee.

#### **10.1.3 Compliance With Good Clinical Practice**

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

#### **10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21CFR Part 11)**

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

### **10.2 Changes to the Protocol**

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to

study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

### **10.3 Patient Confidentiality**

A report of the results of this study may be published, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to the Sponsor of the study, Allergan or Allergan designee, or the governing health authorities or the FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

#### **10.3.1 Patient Privacy**

Written authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ["HIPAA"]).

In accordance with HIPAA requirements, additional purposes of this study may include publishing of anonymous patient data from the study.

### **10.4 Documentation**

#### **10.4.1 Source Documents**

Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a patient's study-related data.

The following information should be entered into the patient's medical record:

- Patient's name
- Patient's contact information
- The date that the patient entered the study and patient number
- The study title and/or the protocol number of the study and the name of Allergan

- A statement that informed consent and/or assent was obtained (including the date).  
A statement that written authorization and local patient privacy required documentation for this study has been obtained (including the date).
- Dates of all patient visits
- Medical history
- All current concomitant medication use, including prescription, OTC, herbal, and illicit drug use
- Past and current headache prophylaxis medication use history, including prescription, OTC, and herbal drug use
- Documentation of all procedures conducted during the course of the study
- Occurrence and status of any adverse events
- The date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation, withdrawal, or loss to follow-up
- The results of laboratory tests performed by the site (eg, urine pregnancy tests)
- Key study variables

#### **10.4.2 Case Report Form Completion**

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRF and related documents. An investigator who has signed the protocol signature page should personally sign for the eCRF to ensure that the observations and findings are recorded on the eCRF correctly and completely. The eCRFs are to be submitted to Allergan or Allergan designee in a timely manner at the completion of the study, or as otherwise specified by Allergan or Allergan designee.

#### **10.4.3 Study Summary**

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB.



#### **10.4.4 Retention of Documentation**

All study related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of case report forms should be maintained on file.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

### **10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments**

#### **10.5.1 Labeling/Packaging**

Investigators will be provided 1 vial of BOTOX 200 Units per participant for each treatment session and the appropriate number of bottles of topiramate 25 mg tablets for each participant dispensed according to the schedule of visits and procedures.

#### **10.5.2 Clinical Supply Inventory**

The investigator must keep an accurate accounting of the number of investigational units of BOTOX or topiramate bottles received from Allergan or Allergan designee, dispensed (administered) to the patients, and the number of units or bottles returned to Allergan or Allergan designee during and at the completion of the study. A detailed inventory must be completed for the study medication. BOTOX must be reconstituted and administered only by an appropriately qualified person to patients in the study. All study medication is to be used in accordance with the protocol and package insert by patients who are under the direct supervision of an investigator.

#### **10.5.3 Return or Disposal of Study Medications/Treatments and/or Supplies**

All clinical study medications/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction.

### **10.6 Monitoring by the Sponsor**

A representative of Allergan or Allergan designee will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or Allergan designee or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

## **10.7 Handling of Biological Specimens**

All urine pregnancy testing will be performed on site. Refer to your local laboratory manual for handling procedures.

Samples of blood for evaluation of chemistry will be analyzed at a centralized clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology or Clinical Laboratory Improvement Amendments certification). See the Study Procedure Manual for details regarding specimen sample collection, processing, and shipment procedures.

All blood samples will be stored at the centralized clinical laboratory until they are analyzed at the direction of Allergan or Allergan designee. All samples will be returned to Allergan or Allergan designee for destruction. Allergan shall have full ownership rights to any biological specimens/samples derived from the study.

## **10.8 Publications**

Allergan, as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

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## **12. Attachments**

### **12.1 BOTOX Treatment Administration**

#### *Standard Injection Methods Regardless of Muscle Location*

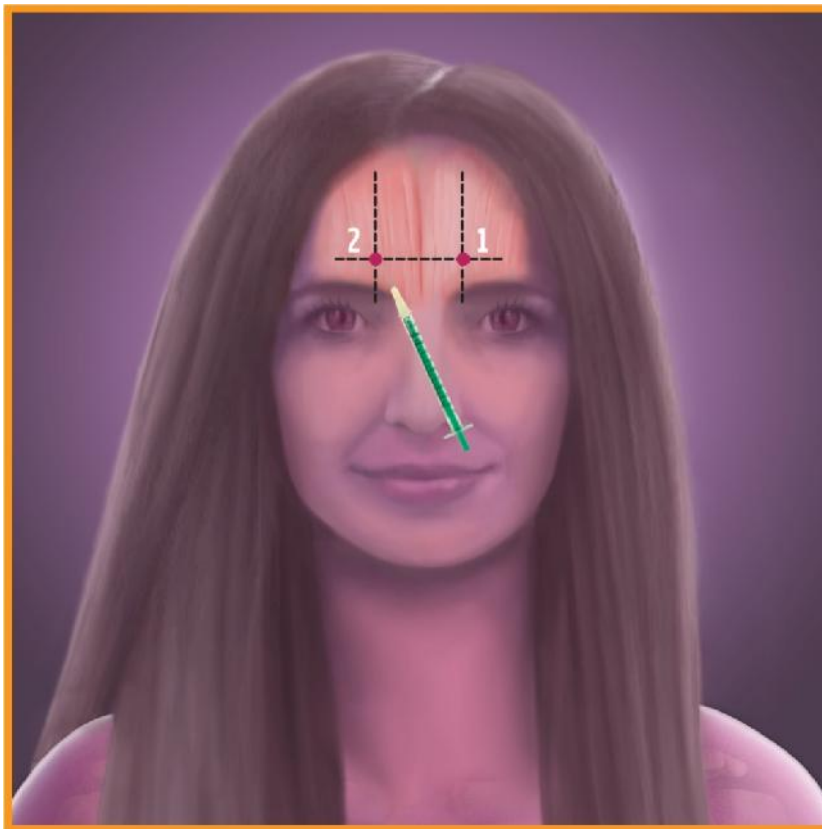
Prior to injection, the injecting clinician should double-check that 30-gauge, 0.5 inch injection needles have been securely fastened to the injection syringes. The skin at the injection sites should be wiped with alcohol prior to the injection. Each injection (ie, each time the needle is inserted into the muscle) the injection volume will be 0.1 mL. Note that each muscle has a fixed total dose, a fixed number of injection sites, and a fixed location of the injection sites. Prior to injecting, palpate the muscle to verify muscle delineation. For bilateral muscles, it is suggested that you inject on the LEFT side first at the specified injection sites, then proceed to the RIGHT side. Always insert the needle into the muscle with the bevel side up, at approximately a 45 degree angle. In the corrugators, procerus and frontalis muscles, keep the needle superficial to avoid hitting the periosteum. After the needle is inserted into the muscle hold the hub of the needle with one hand to ensure that the needle does not twist in the skin, pull the plunger back slightly to ensure no blood return, and then push the plunger with the other hand to administer the study treatment. To reduce pain, do not inject too deep into the cervical paraspinal and trapezius muscles. As a general rule, the hub of a 0.5 inch needle serves as a relatively accurate maximum “depth” guide. Do not rub the area after injection.

Patients should be positioned supine for the injection of the corrugators, procerus, frontalis and temporalis muscles and sitting up for injection of the occipitalis, cervical paraspinal muscle group and trapezius muscles. Further, to ensure that all injections are administered, it is suggested that all patients be injected in a standardized fashion, whereby the “order” of the injection of the muscles should be corrugators, procerus, frontalis, temporalis, occipitalis, cervical paraspinal muscle group and trapezius. In the following sections, specific instructions for injecting each of these muscles are provided. After the injection, the patient should be observed for any immediate post-injection adverse events.

### *Corrugator*

The patient should be supine for injection into the corrugators muscle. This muscle will be injected with 0.1 mL per site, bilaterally for a total of 2 injection sites (Figure 3). The corrugators muscle injection site is located approximately 1 finger's breadth (~1.5 cm) above the medial superior edge of the orbital ridge (bony landmark). Inject with the bevel of the needle pointing upward at a 45-degree angle away from the medial aspect of the muscle to avoid ptosis of the eyelid. Pinching the muscle may help adjust the depth of the needle insertion and reduce pain. Inject the needle halfway to the hub – stay superficial.

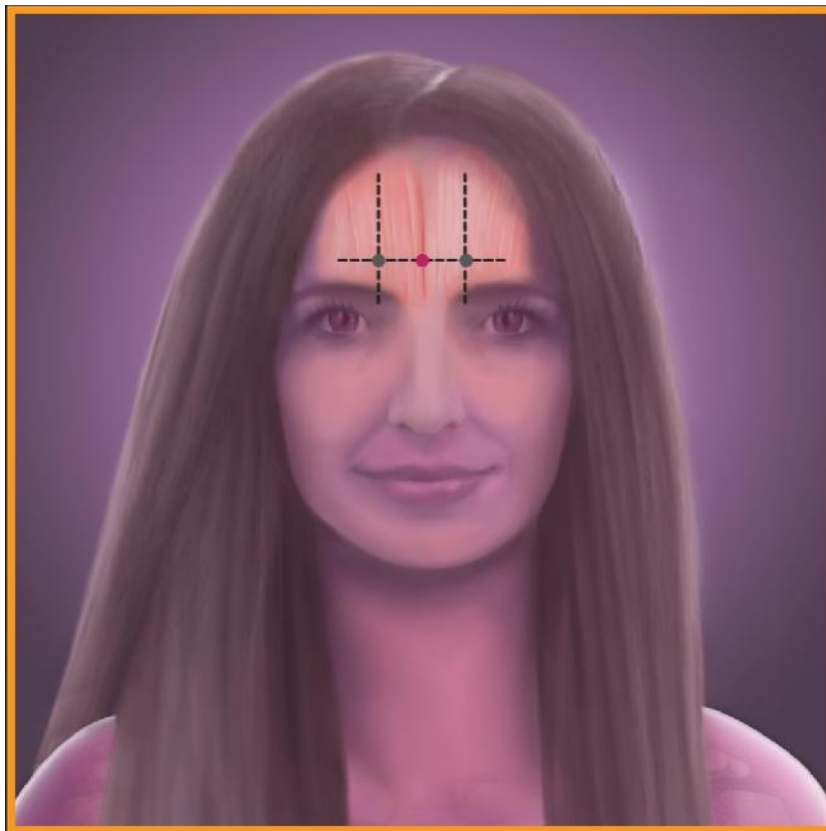
**Figure 3** Corrugator Muscle FSFD Injection Sites



*Procerus*

The patient should be supine for injection into the procerus muscle. This muscle will be injected with 0.1 mL for a total of 1 injection site located midline to the forehead (Figure 4). The insertion site for the procerus muscle injection is midline on the forehead, approximately 1 finger's breadth (~1.5 cm) above and midline to the medial superior aspect of the orbital ridge (bony landmark) of each eye. The injection site for this muscle should be approximately midway between the 2 corrugator injections (visualize a single straight line connecting all 3 of these injections). Inject with the bevel of the needle pointing directly upward. Inject the needle halfway to the hub – stay superficial.

**Figure 4** Procerus Muscle FSFD Injection Sites

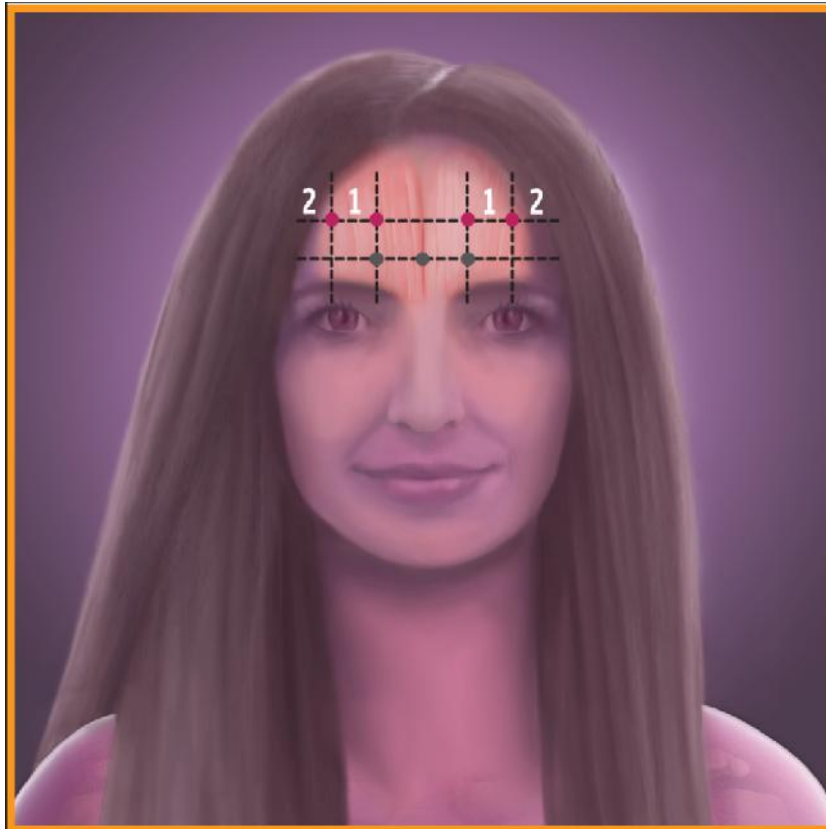




*Frontalis*

The patient should be supine for injection into the frontalis muscle. This muscle will be injected both medially and laterally with 0.1 mL per site, bilaterally for a total of 4 injection sites (Figure 5). For the medial injection sites, visually draw a line up from the medial edge of the orbital ridge. The injection site is approximately 1 finger's breadth (~1.5 cm) above the corrugators injection site. The lateral injection is parallel and approximately 1 finger's breadth (~1.5 cm) lateral to the first 2 injections. Make sure with these injections that the needle stays superficial to avoid the periosteum. A good rule of thumb is to inject superficially enough to raise a bleb. A common mistake is to inject the frontalis muscle too low, which can result in eyebrow ptosis. Go higher on the muscle than you may be first inclined to inject. The bevel of the needle should point upward for these injections.

**Figure 5**                      **Frontalis Muscle FSFD Injection Sites**

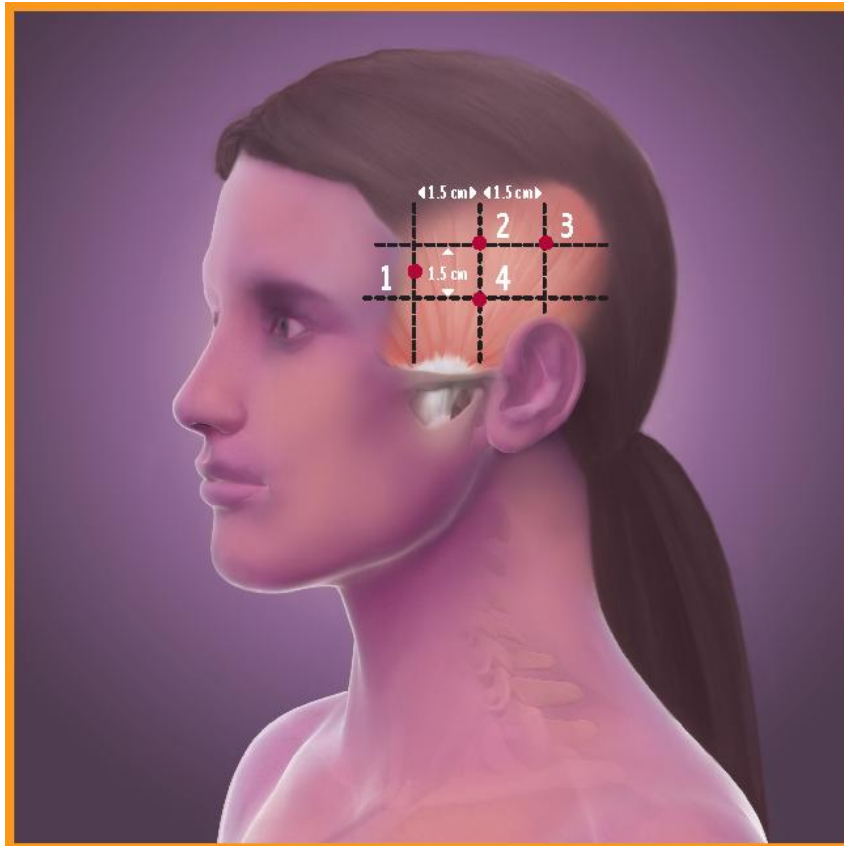


### *Temporalis*

The patient should be supine for injection into the temporalis muscle. This muscle will be injected in 4 sites with 0.1 mL per site, bilaterally for a total of 8 injection sites (Figure 6). Begin with the LEFT temporalis, then repeat the procedure symmetrically on the RIGHT side. Ask the patient to clench his or her teeth. Locate and palpate the anterior aspect of the temporalis muscle. Make the first injection approximately 2 finger's breadth (~3 cm) behind this point. Try to stay behind the hairline. Make the second injection ~0.5 cm superior and approximately 1 finger's breadth (~1.5 cm) posterior to the first injection in the medial aspect of the muscle. The third injection site will be parallel and ~1.5 cm posterior to the second injection. The fourth injection site should be ~1.5 cm below and perpendicular to the second injection into the medial aspect of the muscle.

**Figure 6**

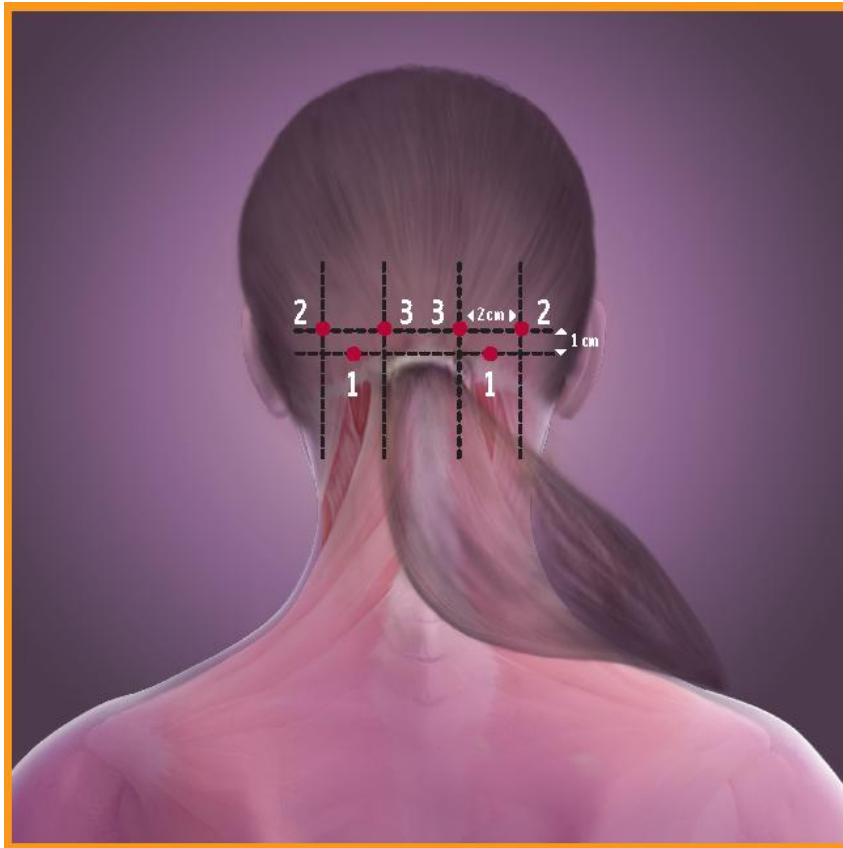
**Temporalis Muscle FSFD Injection Sites**



*Occipitalis*

The patient should be sitting for injection into the occipitalis muscle. This muscle will be injected in 3 sites with 0.1 mL per site, bilaterally for a total of 6 injection sites (Figure 7). To locate the occipitalis injection sites, palpate for the external occipital protuberance. Stay superior to the supranuchal ridge on either side of the occipital protuberance. Begin with the LEFT occipitalis muscle, then repeat the procedure symmetrically on the RIGHT side. Make the first injection just above the occipital protuberance along the supranuchal ridge and ~1 cm left of the external occipital protuberance. The second injection site is ~1 cm lateral to the first injection site and ~1 cm above it. The third injection site should be ~1 cm medial to the first injection site and ~1 cm above it.

**Figure 7**                      **Occipitalis Muscle FSFD Injection Sites**

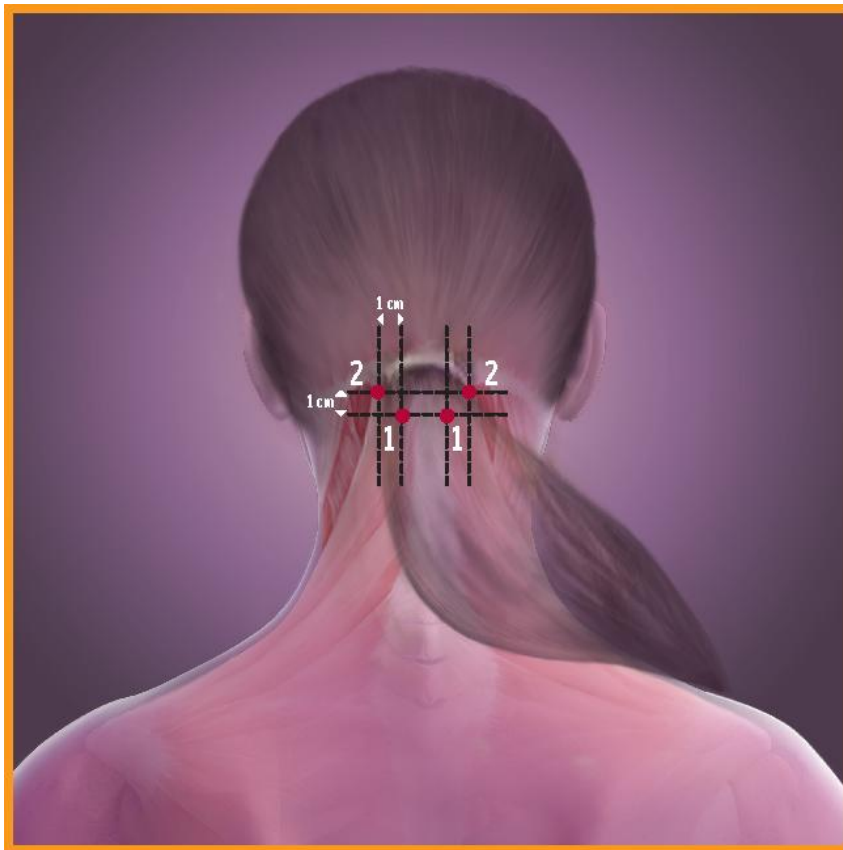


### *Cervical Paraspinal Muscle Group*

The patient should be sitting for injection into the cervical paraspinal muscle group. These muscles will be injected in 2 sites with 0.1 mL per site, bilaterally for a total of 4 injection sites (Figure 8). To locate the cervical paraspinal muscle group injection sites, palpate the cervical spine. Begin with the LEFT cervical paraspinal muscle group muscle, then repeat the procedure symmetrically on the RIGHT side. Make the first injection ~1 cm left of the midline of the cervical spine muscle and ~3 to 5 cm inferior to the occipital protuberance. The second injection site is ~1 cm superior diagonally toward the ear from the first injection.

**Figure 8**

**Cervical Paraspinal Muscle Group FSFD Injection Sites**

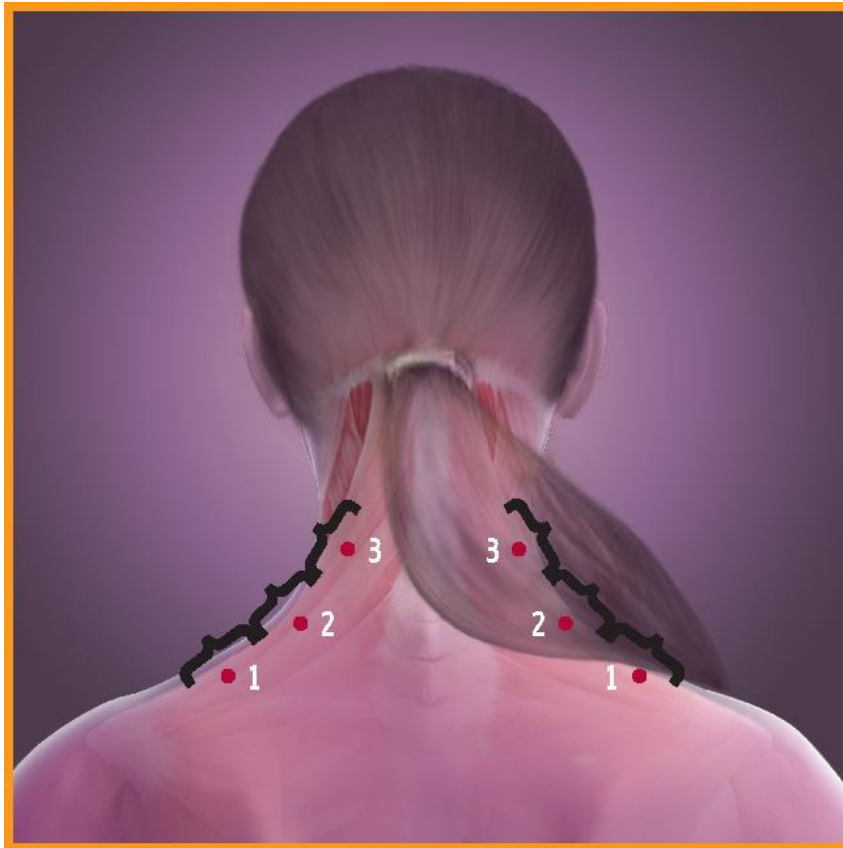


### *Trapezius*

The patient should be sitting for injection into the trapezius muscle. This muscle will be injected in 3 sites with 0.1 mL per site, bilaterally for a total of 6 injection sites (Figure 9). The trapezius muscle is a triangular-shaped, superficial muscle that fans from the neck into the shoulder. Visually divide the upper portion of the muscle (from the neck to the shoulder) into 3 sections per side. Injections will be in the middle of each of these sections. Begin with the LEFT trapezius muscle, then repeat the procedure symmetrically on the RIGHT side. Make the first injection to the lateral, inferior section of the muscle (closest to the shoulder). Move medially to the middle section of the trapezius muscle for the second injection. Then, move sideways and upward to the superior section of the muscle for the third injection.

**Figure 9**

**Trapezius Muscle FSFD Injection Sites**



## 12.2 Glossary of Abbreviations

<b>Term/Abbreviation</b>	<b>Definition</b>
ACM-I	Assessment of Chronic Migraine – Impact
AE	adverse event
ANCOVA	analysis of covariance
BOTOX <sup>®</sup>	Botulinum Toxin Type A Purified Neurotoxin Complex (US Adopted Name is onabotulinumtoxinA)
C	Celsius
CM	chronic migraine
COWAT	Controlled Oral Word Association Test
C-SSRS	Columbia-Suicide Severity Rating Scale
CTS	Clinician Treatment Satisfaction
eCOA	electronic clinical outcomes assessment
eCRF	electronic case report form
FDA	Food and Drug Administration
GCIA	Global Cognitive Impairment Assessment
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
HIT-6 <sup>™</sup>	Headache Impact Test
ICH	International Conference on Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd edition
IM	intramuscular
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MIBS-4	Migraine Interictal Burden Scale
OTC	over-the-counter
PHQ-9	Patient Health Questionnaire
PP	per protocol
PRO	patient-reported outcomes
PTS	Patient Treatment Satisfaction
SAP	statistical analysis plan
SOC	system organ class
ssITT	subset of the ITT population

TENS	transcutaneous electrical stimulation
triptans	serotonin receptor agonists
U	unit
WCI	worst case imputation
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire - Specific Health Problem