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GMA-US-NEU-0206

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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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

FORWARD Study

17JUL2017

Statistical Analysis Plan

Version *2.0*

Prepared by:

TABLE OF CONTENTS

List of Abbreviations

ACM-I	Assessment of Chronic Migraine – Impact
AE	adverse event
ANCOVA	analysis of covariance
BLOCF	baseline observation carried forward
BOTOX®	botulinum toxin Type A purified neurotoxin complex
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
HIT-6	Headache Impact Test
IM	Intramuscular
ITT	intent-to-treat
IWRS	interactive web response system
MedDRA	Medical Dictionary For Regulatory Activities
MIBS-4	Migraine Interictal Burden Scale
PHQ-9	Patient Health Questionnaire
PP	per protocol
PRO	Patient-Reported Outcomes
PT	preferred term
PTS	Patient Treatment Satisfaction
SAE	Serious Adverse Event
SOC	system organ class
ssITT	subset of the ITT Set
TEAE	treatment-emergent adverse event
U	Unit
WHO	World Health Organization
WOCF	worst observation carried forward
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire

1. Introduction

This document details the planned analyses for the FORWARD study, GMA-US-NEU-0206. This study was designed to evaluate the efficacy, safety, and tolerability of BOTOX® versus topiramate in adult patients with chronic migraine (CM) and consists of a 28-day run-in period within a 6-week screening window, followed by up to 36 weeks of study treatment, followed by up to 12 weeks of post-treatment follow-up.

A clinical study report will be prepared for the primary analysis when all patients have completed a Week 36 office visit (or exited the study prior to reaching the primary endpoint). There will be a database lock for the primary analysis after Week 36. A final clinical study report will be prepared after the final database lock and completion of the planned statistical analyses. This analysis plan will address both the primary analysis and the final analysis.

2. Objectives

The overall objective of this study is to compare the efficacy, safety, and tolerability of prophylactic treatment with BOTOX and topiramate in adults with CM.

3. Investigational Plan

3.1. Overall Study Design and Plan

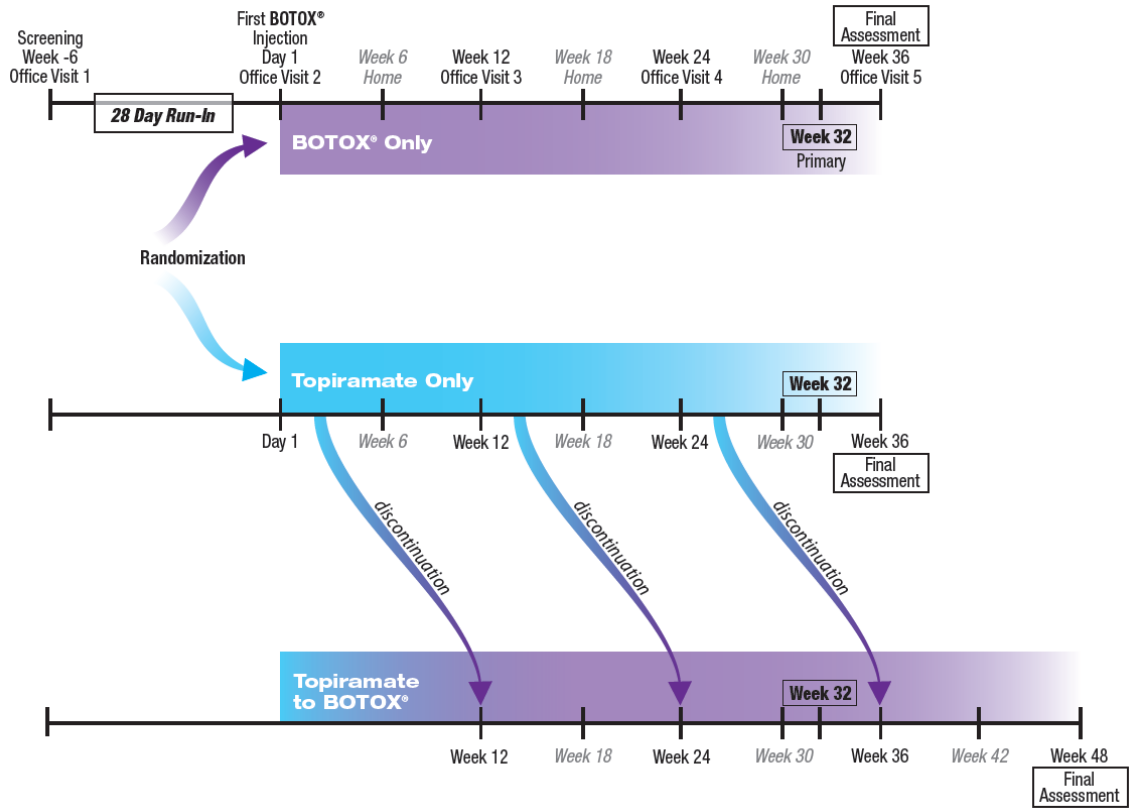
This is a prospective, multicenter, randomized, open-label, parallel-group, post-authorization study to evaluate the efficacy, safety, and tolerability of BOTOX versus topiramate in adult patients with CM. The study consists of a pretreatment period lasting 4 weeks, a treatment period with BOTOX or topiramate treatment lasting up to 36 weeks, and a post-treatment 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 switch over 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 (eDiary) during the entire study period (i.e., screening visit to exit visit).

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. Approximately 400 patients (200 patients per arm) will be enrolled at approximately 40 US sites. For data analysis purposes, the number of headache days during the first 28 calendar days of the screening period starting on the day of eDiary Touch device setup 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 intramuscular (IM) injections of either 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 BOTOX155 U (Day 1, Week 12 ± 7 days, and Week 24 ± 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).

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). The final/exit visit for patients who complete topiramate treatment will be at Week 36. Patients who discontinue topiramate treatment on or 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 patients who discontinue topiramate and subsequently receive BOTOX will be at Week 48 (or approximately 12 weeks after the last injection).

Figure 1 Study Design



3.2. Study Endpoints

Baseline for all eDiary efficacy endpoints is defined as the first 28 calendar days of the screening period starting on the day of eDiary Touch device setup and will be referred to as the baseline period. Baseline assessments for non-daily eDiary data (e.g., Headache Impact Test [HIT-6], Assessment of Chronic Migraine – Impact [ACM-I], and Controlled Oral Word Association Test [COWAT]) will be collected on the day of randomization and will be referred to as Day 1.

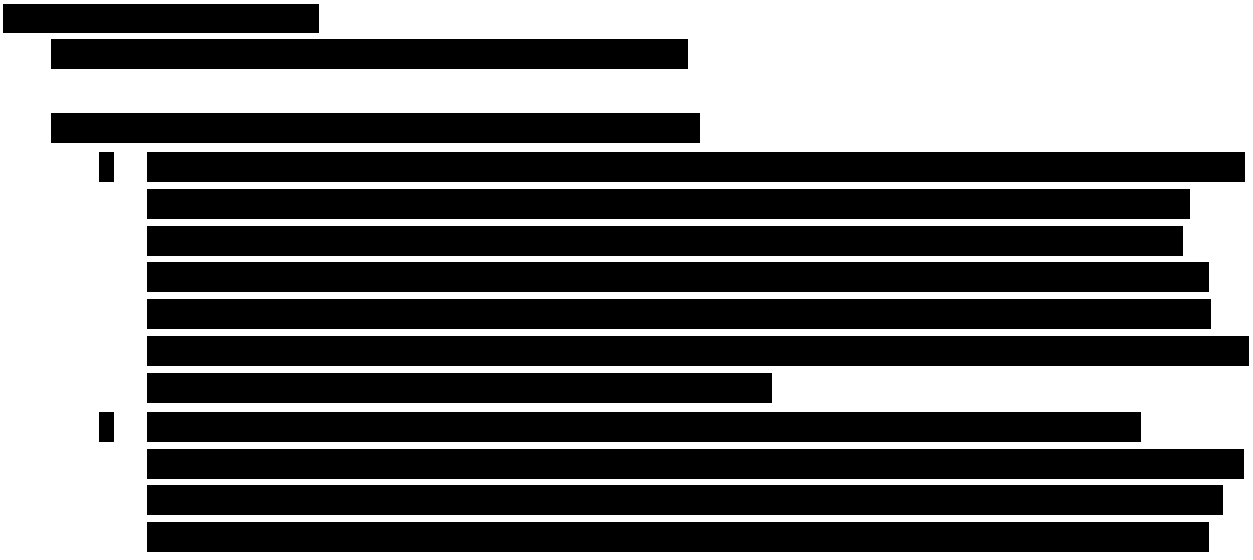
Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients with a ≥50% decrease from the baseline period 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).

Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

1. Change from the baseline period in the frequency of headache days per 28-day period ending with Week 32. This endpoint will be derived from the daily eDiary reports. It will be based on the count of headache days, defined as a calendar day (00:00 to 23:59), 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) (ie, ergot alkaloids, ergot combinations, opioids, serotonin receptor agonists ["triptans"], or combination analgesics [simple analgesics combined with opioids or barbituates with or without caffeine]).
2. Change from baseline Day 1 (randomization) in total HIT-6 score per 28-day period collected at Week 30.
3. Proportion of patients with a ≥70% decrease from the baseline period 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). This responder endpoint will be derived from the underlying primary variable of headache days.



[redacted]

3.3. Treatments

Patients randomized to receive BOTOX will receive 3 treatment sessions of BOTOX over the course of the treatment period, ie, at Day 1, Week 12 ± 7 days, and Week 24 ± 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, 2015).

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

3.4. Dose Adjustment/Modifications

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 (randomization), 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 (morning and evening dose). 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® 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 or discontinue from treatment, a dose taper period of up to 2 weeks is recommended.

Patients who discontinue topiramate at any time on or before Week 36 will receive treatment with BOTOX 155 U for the remainder of the study. The first BOTOX treatment will be administered during the 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. A patient who discontinues topiramate early will be considered a nonresponder even if they receive BOTOX treatment.

BOTOX treatment is administered by the physician per protocol and according to the BOTOX® US package insert, 2015, thus dose adjustment/modification will not be made. As with a topiramate patient who discontinues treatment, a patient who discontinues BOTOX early will be considered a nonresponder.

4. General Statistical Considerations

[redacted]

Continuous data will be summarized using descriptive statistics (ie, n, mean, standard deviation [SD], median, minimum, and maximum). Categorical data will be summarized using the patient count and percentage in each category. Confidence intervals (CIs) will be 95% and 2-sided, unless otherwise stated. Data will be displayed in all listings sorted by treatment group and patient number. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999." Data will be displayed in all listings sorted by treatment group.

Patients will be identified in the listings by the patient identification number concatenated with the investigator number.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the nonzero counts. A row denoted "Missing" will be included in count tabulations specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of patients in that treatment group within the analysis set of interest, unless otherwise specified. Nonzero percentages will be rounded to one decimal place, except 100%, which will be displayed without any decimal places. Additional rounding rules are as follows:

- If the original value has 0 decimal places: mean, median, and CIs will have one decimal place and SD will have 2 decimal places
- If the original value has 1 decimal place: mean, median, and CIs will have 2 decimal places and SD will have 3 decimal places
- If the original value has 2 or more decimal places: mean, median, CIs, and SD will all have 3 decimal places

Minimum and maximum will always have the same decimal places as the original value, up to a maximum of 3 decimal places.

Visit labels will be assigned to each post-baseline record based on the windows or intervals for study day relative to the date of first dose (Table 1). A record with a study day closest to the target visit day will be chosen when multiple records fall in the same visit window. In case of a tie, the record with the earlier date will be chosen. Records that are not chosen will be treated as unscheduled assessments and will still be included in all analyses except 'by visit' analyses. If Day 1 is missing, the closest visit on or before the date of first dose will be used as baseline. Only nominal/scheduled visit data will be reported in the tables. All visits, including unscheduled visits, will be presented in the listings.

Table 1: Visit Windows

Visit	Range	Target Day
Screening	<Day 1	
Day 1	Day 1 to Day 7	Day 1
Week 6	Day 8 to Day 71	Day 43
Week 12	Day 72 to Day 99	Day 85
Week 18	Day 100 to Day 141	Day 127
Week 30	Day 142 to Day 255	Day 211
Week 24	Day 256 to Day 183	Day 169
Week 36	Day 184 to Day 267	Day 253
Week 42	Day 268 to Day 309	Day 295
Week 48	>Day 310	Day 337

For the e-diary data used to produce the headache endpoints, the intervals specified in Table 2 will be used. Baseline for the eDiary data is defined as the number of headache days during the 28 day run-in period. This run-in period will be the first 28 calendar days of the screening period starting on the day of eDiary Touch device setup.

Table 2: eDiary Analysis Endpoints

eDiary Week Ending	Trial Time
Baseline	The 28 days starting from the first eDiary entry
Weeks 1- 4	Days: 1-28
Weeks 5- 8	Days: 29-56
Weeks 9- 12	Days: 57-84
Weeks 13-16	Days: 85-112
Weeks 17-20	Days: 113-140
Weeks 21-24	Days: 141-168
Weeks 25-28	Days: 169-196
Weeks 29-32	Days: 197-224
Weeks 33-36	Days: 225-252
Weeks 37-40	Days:253-280
Weeks 41-44	Days: 281-308
Weeks 45-48	Days: 309-336

4.1. Sample Size

Approximately 400 patients (200 per arm) 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 ≥50% decrease from baseline in the frequency of headache days per 28-day period. The above calculations were based on a 2-sided test at alpha = 0.05, using the commercial software nQuery Advisor version 6.01, procedure PTT1 for a two-group continuity corrected Chi-squared test of equal proportions, with equal sample sizes.

The assumed responder rate for BOTOX was estimated from 2 Allergan Phase 3 double-blind, placebo-controlled studies which reported observed rates of 43.5% (113/260), 50.5% (141/279), and 47.1% (254/539) for Study 191622-079, Study 191622-080, and their 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. The corresponding rates for the Intent-To-Treat (ITT) analysis where patients who terminated from the study were treated as failures were reported as 41.3% (141/341), 46.4% (161/347), and 43.9% (302/688), respectively. Based on these 2 studies, the BOTOX responder rate for an ITT analysis at Week 32 ranged 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 + propranonol (n = 96) is described in Silberstein et al, 2012. The observed responder rates for ≥50% decrease in headache days from baseline reported at Week 24 were 28% (23/82) and 31% (26/84), respectively, for the 2 treatment groups. These rates correspond to 24% and 27%, respectively, for an ITT analysis where patients who terminate from the study are treated as failures. Rothrock et al, 2005 also describes an open-label study involving topiramate (n = 170), where a responder rate (≥50% reduction from baseline) of 38.8% (45/116) was reported. This rate corresponds to 29.4% for an ITT analysis where patients who terminate from the study are treated as failures. Thus, the ITT responder rate for topiramate ranged from 24% to 29.4%, and the value of 28% was deemed reasonable for sample size calculation purposes.

4.2. Randomization, Stratification, and Blinding

On Day 1, qualified patients will be randomly assigned at a 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.

Randomization is not stratified for this study.

At the screening visit, once informed consent is obtained, 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 eDiary, electronic case report form (eCRF), electronic clinical outcomes assessments (eCOA), 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 will log onto the IWRS at subsequent visits to log dispending of 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.

4.3. Analysis Sets

4.3.1. Intent-to-Treat

The ITT Set will include all randomized patients.

4.3.2. Subset of ITT

A subset of the ITT Set (ssITT) will exclude patients who discontinue treatment for any reason other than the following: AE, lost 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.

ssITT set analyses will be performed only as needed which will be determined when number of subjects in this population will be known.

4.3.3. Per Protocol

The Per Protocol (PP) Set will be a subset of patients in the ssITT Set who complete the study without major protocol deviations. Major protocol deviations include one or more of the following categories: major inclusion/exclusion criteria violations, poor study drug compliance, and other. The prespecified criteria for exclusion from the per protocol set are detailed in Section 115.1, and will be finalized prior to the database lock following the completion of the final post-treatment follow-up visit.

PP set analyses will be performed only as needed which will be determined when number of subjects in this population will be known.

4.3.4. Safety

The Safety Set will include all patients who received at least one dose of study drug.

5. Patient Disposition

Patient disposition will be summarized for all enrolled patients and will include the number and percentage of patients for the following categories: patients randomized, patients treated (Safety Set), patients in the ITT Set, patients in the ssITT Set, patients in the PP Set, patients completed (study treatment and study), patients who discontinued study treatment (including patients who discontinued from topiramate and switched to BOTOX), and patients who discontinued from the study. Denominators for percentages will be the total number of patients randomized into each treatment arm, and overall.

The reasons for study treatment discontinuation and study discontinuation will also be summarized in this table. The reasons for treatment discontinuation may include any of the following: AE, death, lost to follow-up, withdrawal of consent, patient became pregnant, includes non-compliant with study treatment regiment, treatment was ineffective, treatment was no longer needed, existed study due to C-SSRS or other. The reasons for discontinuation will be counted in the treatment arm for which the patient was receiving treatment at the time of discontinuation. These treatment arms will include BOTOX, topiramate, and topiramate + BOTOX.

All patient disposition data will be presented in a listing

5.1. Protocol Deviations

Protocol deviations will be documented by the clinical trial manager and reviewed monthly. They will be categorized as major and minor, and major deviations that would exclude patients from the PP analysis set will be identified and finalized prior to database lock in accordance with International Council for Harmonisation guideline -E9 (Statistical Principles for Clinical Trials). Major protocol deviations include but are not limited to:

- Violation of any inclusion/exclusion criteria
- Poor study drug compliance
- Other protocol deviations as defined by clinical review

Major protocol deviations will be summarized for the ITT Set. Patients will be counted in the treatment arm to which they were randomized. Counts and percentage of patients with each type of deviation will be provided. Denominators for percentages will be the total number of patients randomized into each treatment arm or overall.

All protocol deviations will be presented in a data listing.

5.2. Demographics and Baseline Characteristics

The demographic characteristics consist of age (years), age categories, sex, race, and ethnicity. The patient's age in years is recorded at screening. Age will be categorized as follows: 18 to <25, 25 to <35 years, 35 to <45 years, 45 to <55 years, and ≥55, and <40 years and, ≥40 years. Race categories will be reported as White, Black, Asian, Hispanic and Other. The baseline characteristics consist of baseline height, baseline weight, and baseline body mass index (BMI) (kg/m^2). Body mass index is calculated as body weight in kilograms/(height in meters)^2.

A summary of demographics and baseline information will be presented for the ITT, ssITT, and PP Sets. Patients will be counted in the treatment arm to which they were randomized. All continuous data will be summarized using descriptive statistics. Counts and percentage of patients for will be provided for all categorical data. Denominators for percentages will be the total number of patients randomized into each treatment arm or who received topiramate + BOTOX.

All patient demographics and baseline characteristics will be presented in a data listing.

5.3. General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The Safety Set will be used to summarize medical history overall (patients with any medical history) and for each system organ class (SOC) and preferred term (PT). Patients will be counted in the treatment arm to which they were randomized. Counts and percentage of patients

with each type of SOC and PT will be provided. Denominators for percentages will be the total number of patients randomized into each treatment arm, overall.

All patient medical history data including specific details will be presented in a listing.

5.4. Inclusion and Exclusion Criteria

The inclusion/exclusion criteria can be found in Section 4.3 and Section 4.4 of the protocol. A listing of patients not satisfying all inclusion/exclusion criteria will be presented in a listing. Inclusion/exclusion exemption along with the reason for the exception will also be presented in this listing.

6. Prior and Concomitant Treatments

A prior treatment is defined as any treatment that is started prior to the first dose of study drug. A concomitant treatment is defined as any treatment that has a start date and a stop date that is on or after the date of first dose of study drug. Treatments with start and stop dates that bracket the first dose date will be summarized as both a prior and concomitant treatment.

All treatments being taken by the patients upon entry into the study or at any time during the study (in addition to the investigational product) are regarded as concomitant treatments and must be documented on the appropriate section of the eCRF. Prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary. The total number of concomitant medications and procedures and the number and percentages of patients with at least one concomitant medication will be summarized by treatment arm. The number and percentages of all concomitant medications will be summarized by treatment arm and listed by drug class and preferred term and will be flagged as prophylactic or acute headache medications, if applicable. All summaries will be performed using the Safety Set. Patients will be counted in the arm in which they received treatment. Denominators for percentages will be the total number of patients treated in each treatment arm and overall.

All prior and concomitant medications as well as concomitant non-drug therapies, surgeries, and procedures will be presented in listings.

7. Study Treatment

7.1. Duration of Exposure

Duration of exposure is defined as the total number of days a patient is exposed to any study drug. For topiramate it will be presented as the total number of days from the first dose date (Day 1) to the last dose date (date of last dose minus the date of first dose + 1) as recorded on the End of Study/Early Withdrawal page on the eCRF. If the last dose date on the End of

Study/Early Withdrawal page is missing, or if a patient is lost to follow-up, but the eDiary confirms that the patient has taken study drug, the visit date following the last completed eDiary entry will be used. For BOTOX the duration of exposure will be defined as the total number of days from the first injection date (Day 1) to the last injection date plus 84 days (date of last dose + 84 days minus the date of first dose + 1) as recorded in the eCRF.

The duration of study drug exposure will be summarized for the Safety Set. Patients will be counted in the treatment arm for which they received treatment. Denominators for percentages will be the total number of patients treated in each arm.

7.2. Treatment Compliance and Modifications

Over the course of active treatment, each patient receiving topiramate will record the total daily dose taken in the eDiary 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 treatment 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). The overall topiramate compliance rate will be calculated by dividing the total mg of topiramate taken after Week 12 visit by the total mg of topiramate prescribed for all visits after Week 12 visit based upon the duration in the study and then multiplying by 100. The total mg of topiramate prescribed will be based on the maintenance dose set during the Week 12 visit.

The BOTOX compliance rate per visit will be calculated by choosing the minimum of the total units of BOTOX received at a visit divided by 155 U, the total number of injections sites divided by 31, 0.90 if a patient is +/- 8 to 10 days from the visit schedule or 0.80 if a patient is +/- 11 to 14 days from the visit schedule. This minimum value will then be multiplied by 100%. A patient that is 15 or more days from the visit schedule will result in a 0% for compliance (Table 3). The visit schedule is Day 1, Day 84 and Day 168. Overall BOTOX compliance will be the average of the total compliance from each visit.

Table 3: BOTOX Compliance Formula

Time to Next BOTOX Injection	BOTOX Compliance Formula
+/- 7 days from the visit schedule	$\text{Min}\left(\frac{\text{Units Injected}}{155\text{ U}}, \frac{\text{Sites Injected}}{31\text{ Sites}}\right) * 100\%$
+/- 8 to 10 days from the visit schedule	$\text{Min}\left(\frac{\text{Units Injected}}{155\text{ U}}, \frac{\text{Sites Injected}}{31\text{ Sites}}, 0.90\right) * 100\%$
+/- 11 to 14 days from the visit schedule	$\text{Min}\left(\frac{\text{Units Injected}}{155\text{ U}}, \frac{\text{Sites Injected}}{31\text{ Sites}}, 0.80\right) * 100\%$

+/- 15 or more days from the visit schedule	0%

For both the BOTOX and topiramate treatment arms, the number and percentage of patients in each compliance rate category (<80%, 80% – 100%, 100% – 120% and >120% as well as <80% and ≥80%) will be reported. If the treatment compliance is less than 80% or greater than 120% and treatment discontinuation is reported at the subsequent office visit, then date of last treatment taken/received from either the eCRF or the eDiary will be the reported as date of discontinuation. Percentages will be calculated from the number of patients who have received treatment in the study period.

If a patient discontinues topiramate treatment, the eCRF for treatment discontinuation must be completed to document the reason for discontinuation. The patient should not be exited from the study, because BOTOX must be administered at the next scheduled office visit (ie, Week 12, 24, or 36).

If a patient discontinues BOTOX treatment, the eCRF for treatment discontinuation must be completed to document the reason for discontinuation and the patient will be exited from the study.

Treatment compliance will be summarized for the Safety Set. Patients will be counted in the treatment arm in which treatment was received. The study drug compliance rate will be summarized using descriptive statistics. Counts and percentage of patients in each compliance rate category will be provided. Denominators for percentages will be the total number of patients who received treatment in each treatment arm and overall.

BOTOX treatment administration by visit, topiramate drug accountability, and topiramate drug accountability per eDiary will be presented in data listings.

8. Efficacy Analyses

All efficacy analyses will be conducted by grouping patients according to the treatment they were randomized to receive. The primary and secondary efficacy endpoints will be analyzed on the ITT Set. These analyses will be repeated for the ssITT and PP analysis sets. The primary indicator of efficacy for this study is the analyses on the ITT Set. The analyses for the ssITT and PP Sets will be considered supportive.

Family-wise error rate will be controlled using a hierarchical testing gatekeeping procedure. The testing will begin with the primary efficacy endpoint and continue 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 primary 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 be not be considered as an indicator of efficacy, but rather should be considered supportive, regardless of their nominal p-value.

For efficacy analyses, patients who discontinue topiramate and then receive BOTOX will be considered nonresponders and baseline data will be used for the remaining study days for the primary and secondary efficacy endpoints.

All efficacy data will be provided in data listings.

8.1. Primary Efficacy Endpoint

The primary efficacy measure is the proportion of patients with a ≥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, or combination analgesics [simple analgesics combined with opioids or barbiturate with or without caffeine]). This variable is derived from the eDiary 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).

8.1.1. Primary Analysis

Missing data

If there are at least 20 days for which the patient has reported headache data (for either headache days or headache-free days), but less than 28 days in a diary period, the data for counts will be prorated accordingly and rounded to the nearest whole number. The prorating will be based on the number of days with reported data in that period.

For example, if there are 24 days with reported data in a 28-day diary window, the headache day count will be multiplied by 28/24 and rounded to a whole number. If the patient reported total daily headache durations that indicated 16 headache days and 8 headache-free days, the patient's standardized counts after prorating by 28/24 would be 19 headache days and 9 headache-free days.

If a patient reports eDiary data for less than 20 days in a 28-day period, the patient's entries for this time period will be set to missing.

A baseline observation carried forward (BLOCF) method will be utilized to impute missing values for the primary analysis. This type of imputation replaces the missing value with the baseline value; thus, if a patient has a missing entry for any reason (eg, discontinuation due to AE, lost to follow-up, lack of efficacy), the baseline value data will be utilized and the patient will be considered a nonresponder. Patients who discontinue BOTOX and patient randomized to topiramate who discontinue treatment and subsequently receive BOTOX will be considered nonresponders for the primary and secondary analyses and thus baseline value data will be utilized.

BLOCF will also be used to impute missing values for the PRO analyses.

Analysis method

The primary null hypothesis is that BOTOX and topiramate are equally effective, as measured by the proportion of patients with a ≥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 arms will be performed using a logistic regression model, adjusted by the baseline number of headache days as a covariate. The treatment effect will be summarized using an adjusted odds ratio and 95% Wald confidence limits. The p-value from the Wald Chi-square test will also be reported. A 2-sided test with a p-value less than or equal to 0.05 will be considered as statistically significant. All centers will be pooled for this analysis.

The primary analysis will be repeated for the PP and ssITT Sets, if appropriate.

8.1.2. Sensitivity Analysis

Sensitivity analyses of the primary variable will be performed for the ITT Set in the following ways:

1. Repeating the primary analysis using Fisher's exact test.
2. The same logistic regression methods but applying the Worst Observation Carried Forward (WOCF) imputation method for missing values when there are less than 20 days of reported data in the eDiary. Specifically, this will use a patient's worst-case observation within the 28-day period to populate the missing values within that time period.
3. The same logistic regression methods will be re-calculated on "observed data" (ie, without imputation for missing counts when there are less than 20 days of reported data).

A sensitivity analysis will also be performed for the PRO variables to determine if there is a difference in the imputed data versus the observed data. Continuous data will be analyzed with a t-test and Fisher's exact test will be used for the categorical data.

8.2. Secondary Efficacy Endpoints

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. 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.

1. **Change from baseline in the frequency of headache days per 28-day period.**
   This variable will be derived from the daily eDiary reports. It will be based on the count of headache 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) (ie, ergot alkaloids, ergot combinations, opioids, serotonin receptor agonists ["triptans"], or combination analgesics [simple analgesics combined with opioids or barbituates with or without caffeine]) days per 28-day period at Week 32.

   The change from baseline in frequency of headache days will be compared between BOTOX and topiramate arms via analysis of covariance (ANCOVA) with baseline headache day count as the covariate. The estimated mean change from baseline and 95% CIs will be summarized for each treatment along with the 2-sided p-value. If the p-value is less than or equal to 0.05 then it will be considered as statistically significant and testing will continue to the next secondary efficacy analysis. The rules for data handling and missing value imputation will be the same as used for the primary endpoint.

2. **HIT-6 Score change from baseline**
   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 continuous total score will be used in this analysis. The categorical HIT-6 scores will be summarized in a separate table.

   The total HIT-6 score from the 28-day period collected at Week 30 will be compared between treatment arms using a nonparametric rank analysis of covariance (rank ANCOVA) (Stokes et al, 2000), with treatment as a factor and adjusting for the baseline value. If the p-value is less than or equal to 0.05, then it will be considered statistically significant and testing will continue to the final secondary efficacy analysis. The BLOCF method will be used for missing values for this endpoint.

3. **The proportion of patients with a ≥70% decrease from baseline in the frequency of headache days.**
   The ≥70% responder rate will be analyzed using the same methods used to analyze the primary endpoint; a logistic regression model adjusted by the baseline frequency of headache days. Exact conditional logistic regression analysis will be performed if there are convergence issues with the default unconditional analysis. The rules for data handling and missing value imputation will be the same as used for the primary endpoint.

All secondary analyses will be repeated for the PP and ssITT Sets, if appropriate.

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eDiary. The sum of the total scores will be divided by the number of MIBS-4 questionnaires taken over each 28-day period. The average continuous score will be used for this analysis.

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9. Safety Analyses

All analyses of safety will be conducted using the Safety Set. All patients will be summarized according to the treatment they actually received, but the subgroup of topiramate patients who initially received topiramate and then switched to BOTOX will be summarized as follows:

- All safety assessments occurring prior to the date of the first dose of BOTOX will be summarized for the topiramate treatment arm.
- All safety assessments except AEs occurring on or after the date of the first dose of BOTOX will be summarized separately for the topiramate + BOTOX subgroup.
  For all AEs, the total number of patients (N) in each treatment arm will represent the number of patients that received that treatment. A patient may be counted in both treatment arms. The overall total will be the number of patients that received any treatment. The topiramate + BOTOX treatment arm will be a subset of the BOTOX treatment arm and will include patients that received both treatments. Denominators for percentages will be the total number of patients in each treatment arm or overall.
  Treatment-emergent AEs (TEAEs) include all AEs that start on or after the first dose of study medication up to the final visit, or are present prior to the first dose but increase in severity after the first dose of study medication up to the final visit. For patients who switch from topiramate to BOTOX, TEAEs starting on or after the date of the first BOTOX injection will be counted in the treatment arm that they are related to, as determined by a physician. If the TEAE is related to both treatments or if the relationship is unknown, it will be counted in both treatment arms but only once in the total. The topiramate + BOTOX subset will summarize all TEAEs that occurred after a patient has switched from topiramate to BOTOX.

Statistical hypothesis testing will not be performed on any safety results

9.1. Adverse Events

An AE is defined as 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 AE can therefore be any unfavorable or 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, AEs will be assessed regardless of the administration of a pharmaceutical product.

Adverse events will be assessed, documented, and recorded in the eCRF and will be classified by SOC and PT according to MedDRA version 16.0 or higher throughout the study (ie, after informed consent has been obtained). All AEs collected from the time of informed consent that are prior to study treatment will be defined as pretreatment AEs and will be presented in the listings.

A TEAE is defined as an AE that meets any of the following conditions:

- Begins on or after the first dose of study drug and before the final scheduled office visit at Week 36;
- Begins before the first dose of study drug and worsens in severity on or after the first dose of study drug and before the final scheduled office visit at Week 36;
- Is completely missing an onset date and the end date is on or after the first dose of study drug

If a patient receives BOTOX after receiving topiramate, the physician will be asked to determine if the AE is due to BOTOX or topiramate or unknown.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as follows:

Missing onset dates (where “UK” and “UKN” indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume the onset date is 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the onset date is the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the onset date is the date of the first dose of study drug. If the year is the same as the first dose of study drug, and the end date (after any

imputation) is prior to the first dose of study drug, then assume the end date for the onset date.

Missing end dates (where "UK" and "UKN" indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the end date is the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume the end date is 31-DEC-YYYY.

9.1.1. Incidence of Adverse Events

All AEs will be summarized for the Safety Set in the manner described in Section 9. Counts and percentage of patients with each type of AE will be provided. Denominators for percentages will be the total number of patients treated in each arm or overall. At each level of patient summarization, a patient is counted once if the patient reported one or more events.

An overview summary of the number and percentage of patients with any TEAE, serious TEAE, study drug-related TEAE, study drug-related serious TEAE, TEAE leading to treatment discontinuation, TEAE leading to study discontinuation, and AE leading to death will be provided by treatment arm.

Treatment-emergent AEs will also be summarized separately for each injection cycle for BOTOX treated patients.

The following summary tables will be repeated for any TEAE, serious TEAE, study drug-related TEAE, study drug-related serious TEAE, TEAE leading to treatment discontinuation, TEAE leading to study termination, and AE leading to death.

Summaries of the total number of TEAEs and the number and percentage of patients with at least one TEAE will be provided by treatment group. The number and percentage of patients and the number of events will also be presented by SOC and PT in descending order from the SOC with the highest total incidence (that is, summed across all treatment groups) to the SOC with the lowest total incidence. If the total incidence for any 2 or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in alphabetical order. At each level of patient summarization, a patient is counted once if the patient reported one or more events.

All AEs, will be presented in a by-patient listing.

9.1.2. Relationship of Adverse Events to Study Drug

A summary of TEAEs by relationship to study drug will be presented in a table by incidence of occurrence. The relationships will be collected as the possibility that study drug caused the event

and will be reported as “Related” or “Not Related”. In the TEAE relationship table, if a patient reports multiple occurrences of the same AE, only the most closely related occurrence will be presented. Treatment-emergent AEs that are missing a relationship will be presented in the summary table as “Related”, but will be presented in the data listing with a missing relationship. Percentages will be calculated by the number of patients in the Safety Set. Denominators for percentages will be the total number of patients treated in each arm or overall.

The TEAE data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 9.1.1.

9.1.3. Severity of Adverse Event

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the eCRF page. In the TEAE severity table, if a patient reported multiple occurrences of the same TEAE, only the most severe will be presented. Treatment-emergent AEs that are missing severity will be presented in tables as “Severe” but will be presented in the data listing with a missing severity. Counts and percentage of patients within each category will be provided using the Safety Set. Denominators for percentages will be the total number of patients treated in each arm or overall.

A clinical determination will be made of the intensity of an AE. 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.

The AE data will be categorized and presented by SOC, PT, and severity in a manner similar to that described in Section 9.1.1.

9.1.4. Serious Adverse Events

The seriousness of an AE should be assessed by the Investigator independently from the severity of the AE. A serious AE (SAE) is defined as any untoward medical occurrence that, at any dose, results in death, is life-threatening, is a congenital anomaly/birth defect, requires inpatient hospitalization or prolongation of existing hospitalization, or results in a persistent or significant disability/incapacity.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

The serious TEAE data will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1.

A by-patient listing of SAEs will be presented.

9.1.5. Adverse Events Leading to Treatment Discontinuation

A summary of TEAEs with a study drug action taken of either "Drug Withdrawn" or "Switched to BOTOX" will be presented in a table. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Counts and percentage of patients within each category will be provided. Denominators for percentages will be the total number of patients treated in each arm or overall.

Treatment-emergent AEs leading to treatment discontinuation will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1.

9.1.6. Death

All deaths occurring any time from the time of informed consent to study conclusion will be summarized by reason and presented in a table. A supportive listing will be generated to provide patient-specific details including the reason for death for all patients in the ITT Set.

9.2. Serum Chemistry

Blood samples will be collected for clinical laboratory testing at screening for all patients. Blood samples will additionally be collected for patients who discontinue topiramate and switch to BOTOX prior to their first administration of BOTOX.

The following serum chemistry laboratory tests will be included: blood urea nitrogen (BUN) (mg/dL), calcium (mg/dL), creatinine (mg/dL), sodium (mEq/mL), potassium (mEq/mL), chloride (mEq/mL), carbon dioxide (mEq/mL), and alkaline phosphatase (U/L). All chemistry data will be presented in a by-patient listing.

Laboratory assessments will be performed by a central laboratory. All summaries will be based on the units provided by the central laboratory; no conversion will be done.

9.3. Vital Sign Measurements

Vital signs will be measured at screening, Day 1, and each subsequent office visit.

Systolic and diastolic blood pressure and pulse rate over 30 seconds should be taken after patients have been at rest (seated) for at least 2 minutes. Blood pressure should be recorded in mmHg. Pulse rate should be measured in beats per minutes. Oral, axillary, or tympanic body temperature should be taken. The same route should be used throughout the study. If oral temperature is taken, the patient should not have any oral intake for at least 5 minutes prior to the measurement. Temperature as Fahrenheit (°F) or Celsius (°C) should be specified on the source document and the eCRF.

Summary tables will be presented for vital sign data by treatment group for patients in the Safety Set. Observed results at each visit will be presented.

All vital sign data will be presented in a by-patient listing.

9.4. Physical Examination

At screening and study exit, the investigator will examine the patient for any detectable abnormalities of the following body systems: general appearance; neck (including thyroid); head, eyes, ears, nose, and throat; lungs; heart/cardiovascular; abdomen; neurologic; extremities; back; musculoskeletal; lymphatic; skin; and other. The neurologic examination should be conducted to detect the presence of any significant sensory/motor abnormalities.

Height and weight should be measured at screening, Day 1, and each subsequent office visit using the same scale and ruler for all patients at a given investigator site when possible.

A table will summarize physical examination results by treatment group and overall for the Safety Set. Each visit captures the status of a body system and any finding associated with the body system as normal, abnormal, or not done. The summary will include the number and percentage of patients with each physical examination outcome for the following body systems: skin; head, eyes, ears, nose, and throat (respiratory; cardiovascular; gastrointestinal; endocrine/metabolic; genitourinary; neurological; blood/lymphatic; musculoskeletal; and other. Patients will be counted in the arm in which they were treated. Denominators for percentages will be the total number of patients treated in each arm.

Physical examination results for all patients will be presented in a listing.

9.5. Pregnancy Test

Urine pregnancy testing will be conducted at screening, on day 1, and each subsequent office visit to confirm continued non-pregnant status prior to study drug administration or study completion.

A listing will be presented for pregnancy test status.

9.6. Urine Drugs of Abuse

Illicit drug urine testing will be conducted at screening and day 1, prior to study treatment administration, and will be performed at the investigator site.

A listing will be presented for urine drugs of abuse at screening.

9.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be conducted at the screening visit and each subsequent office visit. At screening, patients will be asked about the 12 months prior to the screening visit along with a separate assessment for lifetime prior to the screening visit. For visits after the screening visit, the assessment will be for the time period since the previous visit. The assessments will be summarized for each treatment group using the Safety Set.

Among the questions for each assessment time period (lifetime, prior 12 months, since previous visit) are a set of 10 questions intended to elicit a yes or no response from the patient (as deduced by the investigator site's interview of the patient) and a question (post-screening only) regarding completed suicide. Among those questions are 5 regarding suicidal ideation, arranged in order of increasing severity (1= wish to be dead, 2= non-specific suicidal thoughts, 3= method without intent to act, 4= some intent but without plan and 5= intent and plan). Also included are 6 questions in the suicidal behavior section of the C-SSRS (non-suicidal self-injurious behavior, preparatory behavior, aborted attempt, interrupted attempt, actual attempt, and completed suicide).

C-SSRS data will be summarized separately for the following sets of responses: (1) year prior to screening, (2) baseline as reported under "since screening" at the randomization visit and (3) by visit reported as "since last visit." Overall ideation and behavior responses for the treatment period will be done by taking the most severe response (eg, a yes response at any time point for a specific ideation or behavior question).

Counts and percentage of patients with each answer on the questionnaire will be provided. Summary statistics will include the count and percentage of patients for each of the 11 ideation and behavior categories separately and also overall for any ideation, for any behavior and for any ideation or behavior. Denominators for percentages will be the total number of patients treated in each arm.

10. Interim Analysis

There is no interim analysis planned for this study.

11. Deviation from Protocol-Specified Analyses

The subset of ITT and Per-protocol population analyses will not be performed since subjects who would discontinued due to reasons specified and subjects with major protocol deviations, respectively, is expected to be few; hence difference on number of subjects in each of the two populations and the ITT population is minimal.

12. References

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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

17JUL2017

Statistical Analysis Plan Version 2.0

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Issued by: [redacted] Date: ___/___/___

Reviewed by: Date: ___/___/___

Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

DocuSigned by:

Reviewed by: [redacted]

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