CLINICAL REVIEW

Application Type	BLA; 351 (a)
Application Number(s)	103000/5308
Priority or Standard	Standard
Submit Date(s)	November 13, 2017
Received Date(s)	November 13, 2017
PDUFA Goal Date	September 13, 2018
Division/Office	Division of Neurology Products/Office of New Drugs
Reviewer Name(s)	Suhail Kasim, M.D., M.P.H.
Review Completion Date	March 3, 2018
Established/Proper Name	BOTOX OnabotulinumtoxinA
(Proposed) Trade Name	BOTOX
Applicant	Allergan
Dosage Form(s)	Injection IM
Applicant Proposed Dosing Regimen(s)	None.
Applicant Proposed Indication(s)/Population(s)	Safety and effectiveness in patients below the age of 18 years have not been established for the indication chronic migraine prophylaxis.
Recommendation on Regulatory Action	No Action Indicated

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IM	Intramuscular
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

There are no FDA approved medications for pediatric chronic migraine headache prophylaxis. The supplemental BLA review includes review of the safety and efficacy of OnabotulinumtoxinA (BOTOX) in adolescent patients ages 12 to 17 years old for chronic migraine prophylaxis with information from study 191622-103 that was conducted to fulfill the required pediatric assessment (PMR#1/PMR 2469-1). See presubmission regulatory activity section 3.2.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Based on the information reviewed in the data submitted from study 191622-103 in response to PREA PMR#1/PMR 2469-1, safety and effectiveness in patients below the age of 18 years have not been established for the indication of chronic migraine prophylaxis. Study 191622-103 was a negative pediatric study, defined herein as a study that failed to demonstrate effectiveness in the pediatric population.

In addition, the submission and review of clinical study report for study 191622-103 fulfilled the required pediatric assessment (PMR#1/PMR 2469-1). Furthermore, it was previously determined (letter dated September 13, 2017) that the study requested under PREA postmarketing requirement PMR#2/PMR 2469-2 was no longer needed. See presubmission regulatory activity section 3.2.

1.3. Benefit-Risk Assessment

Not applicable.

2. Therapeutic Context

2.1. Analysis of Condition

Migraine is a common disabling primary headache disorder that affects an estimated 36 million

Americans[1], with a gender difference in prevalence. 18% women experience *episodic migraine* compared with 6% of men. Estimates of *chronic Migrain*e prevalence range from 1% to 3% (1.3% women compared with 0.5% of men). Based on an epidemiology study, the prevalence rate for chronic migraine in the US is 0.79% in adolescents (12-17 years); prevalence is highest in teens aged 16–17 years and higher in females than males (Table 1)[2]. The vast majority of adolescents in the referenced population-based study were Caucasian (97%). Many headache episodes occur during school hours, affecting school performance abilities and attendance, home and family activities, and socialization with friends. When headaches occur with sufficient frequency and severity to interfere with a child's life (e.g., missing school), preventive treatment is considered.

Table 1: Period Prevalence and Estimates of Chronic Migraine in Adolescents

Characteristic	Category	Chronic Migraine Prevalence
Age (years)	All, 12-17 years	0.79
	12-13 years	0.09
	14-15 years	0.22
	16-17 years	2.02
Gender	Female	0.15
	Male	1.39

Estimates were created by applying chronic migraine diagnostic criteria developed for adults to an adolescent population, because there were no established diagnostic criteria for chronic migraine in pediatric patients at the time of review of protocol 191622-103 that was issued a Special Protocol Assessment –Agreement Letter.
Source: Protocol 191622-103

Migraine is a complex neurovascular disorder involving central and peripheral events. Although the exact mechanism by which migraine is initiated is not clear, it is believed that brain dysfunction involving peripheral and central components of the trigeminovascular system are involved in the pathway leading to release of inflammatory mediators and subsequent propagation and perpetuation of pain in headache disorders, including migraine.

Adult Diagnosis Criteria

Migraines attacks are characterized as moderate to severe headache with associated hypersensitivity to environmental stimuli such as light and sound, as well as nausea. These headaches typically last from 4 to 72 hours if left untreated, are generally unilateral in nature, and frequently include throbbing or pulsating pain. Diagnosis of migraine is based on medical history and exclusion of secondary headache disorders by using a structured classification system using the International Classification of Headache Disorders – 3rd (beta version) (ICHD-3

[1] Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache*. 2015 Mar;55 Suppl 2:103-22.
[2] Lipton RB, et al. Prevalence and burden of chronic migraine in adolescents: results of the chronic daily headache in adolescents study (C-dAS). *Headache*. 2011 May;51(5):693-706.

beta). Episodic migraine (EM) by definition includes headaches that occur on fewer than 15 days per month, with usually between 4-14 days of migraine headache days. Chronic migraine (CM) is characterized by headaches on 15 or more days per month for at least 3 months; headaches must have the features of migraine on at least 8 days per month or respond to treatment specifically for migraine. Chronic migraine and episodic migraine are part of the spectrum of migraine disorders, but they are distinct clinical entities as classified by ICHD-3 beta guidelines for primary and secondary headache disorders[3].

Pediatric Diagnosis Criteria

Migraine headache in children and adolescents (aged less than 18 years) is more often bilateral than is the case in adults; unilateral pain usually emerges in late adolescence or early adult life. During the development program for BOTOX in adolescent chronic migraineurs although specific chronic migraine diagnostic criteria for adults were defined, there were no diagnostic criteria for chronic migraine in children or adolescents, and it was unknown at the time of protocol 191622-103 discussions whether the adult chronic migraine diagnostic criteria were optimal for pediatric chronic migraine. For example, clinical studies showed that the duration of the typical migraine episode was significantly shorter in younger children (12 years or younger) on average, than that of older adolescents (12 to 18 years) and adults. The ICHD-II 2004 criterion that was applied to study 191622-103 included the minimum duration criterion for the diagnosis of (episodic) migraine in children as 1 hour.

2.2. Analysis of Current Treatment Options

During the approval of BOTOX in adults, there were no FDA approved medications, as headache prophylaxis specifically in pediatric chronic migraine. Topiramate was FDA approved for migraine prophylaxis in adolescents aged 12–17 years (in 2013), mid-way through the completion of study 191622-103 that was the required pediatric assessment (PMR#1/PMR 2469-1).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BOTOX is currently marketed in the U.S. for the following indications:

- Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant

[3] Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013 Jul;33(9):629-808.

of an anticholinergic medication
- Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication
- Prophylaxis of headaches in adult patients with chronic migraine (≥15days per month with headache lasting 4 hours a day or longer)
- Treatment of spasticity in adult patients
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients
- Treatment of blepharospasm associated with dystonia in patients ≥12 years of age
- Treatment of strabismus in patients ≥12 years of age

3.2. Summary of Presubmission/Submission Regulatory Activity

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), postmarketing pediatric studies were required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act when OnabotulinumtoxinA (BOTOX) efficacy supplement BLA 103000/S-5215 received approval for prophylaxis of headaches in adults with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer) on October 15, 2010. The postmarketing pediatric studies requested are referred to as PMR#1/PMR 2469-1 and PMR#2/PMR 2469-2, and shown below.

PMR#1/PMR 2469-1
Deferred pediatric Placebo-Controlled Efficacy and Safety Study under PREA #1 for prophylaxis of headaches in adolescents ages 12 to 17 with chronic migraine. The study must include a prospective baseline observation period of at least 4 weeks followed by a double-blind treatment phase of at least 12 weeks. The study must include an adequate evaluation of dose-response. The study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities and allow the use of appropriate rescue treatment. The protocol for this study must be submitted as a Special Protocol Assessment (SPA) and receive Division concurrence prior to the initiation of the study.

Final Protocol Submission: March 31, 2011
Study Completion: September 30, 2016
Final Report Submission: September 30, 2017

PMR#2/PMR 2469-2
Deferred pediatric 12-month Open-Label Safety Study under PREA for prophylaxis of headaches in adolescents ages 12 to 17 with chronic migraine. The study must include at least 300 patients

who received two BOTOX treatments at clinically relevant doses over a 6-month period (with at least 100 patients treated at the maximum recommended dose), and at least 100 patients who received four BOTOX treatments at clinically relevant doses over a 12-month period (with at least 60 patients treated at the maximum recommended dose). The study must assess local reactions, distant spread of toxin effects, BOTOX effects on blood glucose, and BOTOX effects on alkaline phosphatase (as a marker of bone metabolism). The safety study must include an adequate evaluation of immunogenicity.

Study Completion: December 30, 2021
Final Report Submission: December 30, 2022

Study protocol 191622-103 was previously issued a Special Protocol Assessment -Agreement Letter dated December 21, 2011 (under IND 07480) for the requested PREA PMR 2469-1 (study 191622-103; PMR#1/PMR 2469-1), which was completed by the expected date of September 30, 2016. The sponsor requested a deferral extension of PMR 2469-2, the 12 month open label safety study, while study 191622-103 issued under PMR#1/PMR 2469-1 was ongoing, and the Division granted this deferral extension with revised dates reflected above because the sponsor had demonstrated good faith efforts to complete study 191622-103 (letter dated January 8, 2015).

Following the completion of the adolescent efficacy study 191622-103 with OnabotulinumtoxinA in order to fulfill PMR 2469-1, the sponsor submitted a Type C meeting package to the Division on December 09, 2016, which included top-line efficacy findings from completed study 191622-103. The sponsor requested feedback from the Division regarding the need for conducting the long-term extension trial requested under PMR#2/PMR 2469-2. The Division determined (letter dated September 13, 2017) that the study requested under PREA postmarketing requirement PMR#2/PMR 2469-2 was no longer needed. Allergan was released from PMR#2/PMR 2469-2 requirement because the efficacy results for Study 191622-103, which was conducted to fulfill PMR#1/PMR 2469-1, did not support the efficacy for BOTOX for the prevention of chronic migraine in adolescents. A dose for use in a long-term safety study was not identified.

3.3. Foreign Regulatory Actions and Marketing History

See section 3.1.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Not applicable.

5.2. Review Strategy

I summarized the safety and efficacy information for the negative pediatric study 191622-103 that failed to demonstrate effectiveness in the pediatric population. The application was submitted to \\CDSESUB1\evsprod\BLA103000\103000.enx eCTD sequence 0338, and 0343 on November 13, 2017. OnabotulinumtoxinA and BOTOX refer to the study drug, and is one and the same marketed product.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 191622-103

6.1.1. Study Design

Overview and Objective

Title: Botulinum Toxin Type A Purified Neurotoxin Complex as Headache Prophylaxis in Adolescents (Children 12 to < 18 Years of Age) with Chronic Migraine.

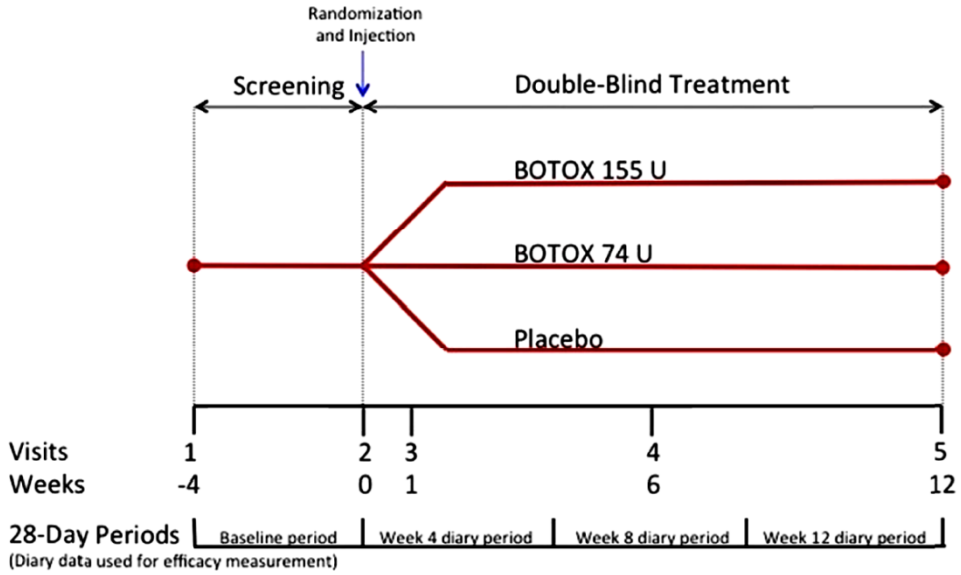
The objectives for this study are to evaluate the efficacy and safety of a single treatment session of 2 dosages of Intramuscular (IM) injected OnabotulinumtoxinA (74 U and 155 U) compared to placebo in adolescents (children 12 to < 18 years of age) with chronic migraine.

Trial Design

Study 191622-103 was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of a single treatment session with 2 dosages of Intramuscular OnabotulinumtoxinA (74 U and 155 U) compared with placebo in adolescents with chronic migraine who are 12 to <18 years of age on the day of randomization (Figure 1). Patients needed to have one or more hours of headache each day and with a history of chronic migraine

for at least 6 months prior to the Week -4 screening visit diagnosed according to the adult chronic migraine diagnostic criteria, *other than for minimum headache duration*, listed in the International Classification of Headache Disorders, 2nd edition (ICHD-II 2004). To qualify for the study, adolescents reported 15 or more headache days, *with each day consisting of a total of 1 or more hours of headache*, during the 4-week baseline period. Patients with headache medication overuse and other primary chronic headache disorders were excluded to ensure study results are not confounded. Concomitant headache prophylactic medication was not permitted, which may potential confound interpretation of efficacy and safety of OnabotulinumtoxinA.

Figure 1: 191622-103 Design Phase 3 Chronic Pediatric Migraine Study



Source: CSR 191622-103

Each treatment arm was expected to include at least 42 patients. The injection paradigm was standardized as 31 fixed-site fixed-dose (FSFD), intramuscular (IM) injections across 7 specific head/neck muscles as per the current FDA labeled injection paradigm for chronic migraine in adults (BOTOX US package insert, Table 2,

Figure 2). At each investigator site, patients were randomly assigned in a 1:1:1 ratio to receive BOTOX 155 U, BOTOX 74 U, or placebo. Patients maintained a daily electronic headache diary throughout the duration of the study. The total duration of study participation for each patient was 16 weeks, which included 5 office visits. There was a screening visit (week -4) followed by a 4-week, prospective baseline period to ensure patients met all inclusion/exclusion criteria. At the end of this baseline period, qualified patients were randomized and injected with the study treatment. Patients had in-office visits at week 1, week 6, and a final exit visit at week 12.

Treatment Administration

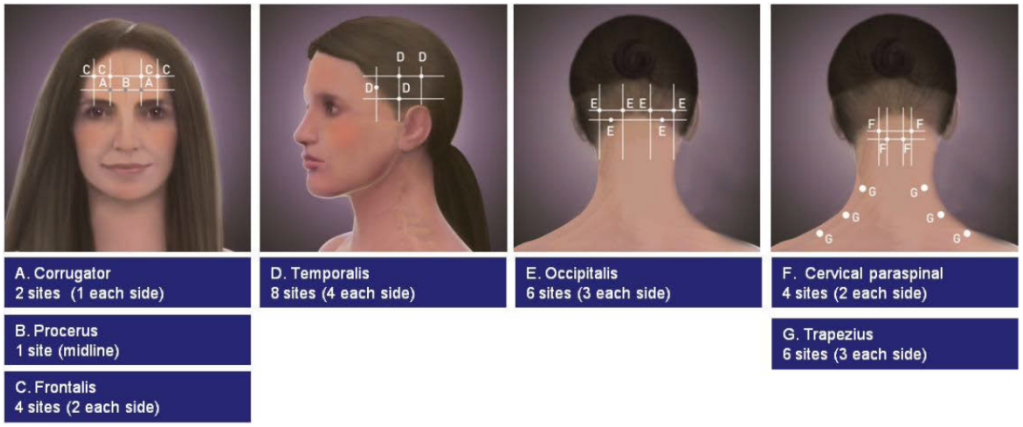
Patients received one treatment of either BOTOX 155 U, BOTOX 74 U or placebo administered IM to 31 injection sites (each as 0.1 mL injections) into 7 specific head/neck muscles using a Fixed Site Fixed Dose (FSFD) injection paradigm (Table 2) (

Figure 2).

Table 2: Number of Injection Sites per Muscle Area for the Fixed-Site, Fixed-Dose Injection Paradigm

Head/Neck Area	Left Side	Right Side	Total
Corrugator	1	1	2
Procerus	0	0	1 (midline)
Frontalis	2	2	4
Temporalis	4	4	8
Occipitalis	3	3	6
Cervical Paraspinal Muscle Group	2	2	4
Trapezius	3	3	6
Total	15	15	31
Source: CSR 191622-103			

Figure 2: Study 191622-103 FSFD Injection Site Locations



Source: CSR 191622-103

Patients were masked to the study medication and dose received. To maintain the blinding of the study medication and dose, the investigator, person performing the injection, or site personnel who are involved in evaluating the patient were not involved preparing the study medication. An independent person assigned to prepare the study medication added preservative-free 0.9% saline to each 100 U study vial according to the instructions provided in the "Independent Reconstitutor's Guide." Patients were injected with 30-gauge, 0.5 inch

injection needles that have been securely fastened to the injection syringes. The protocol detailed injection techniques with a specific order for injection and recommended measures to reduce pain and discomfort.

Study Endpoints

Primary Efficacy Endpoint

- The primary efficacy measure was the change from baseline in the frequency of headache days per 28-day period. The primary timepoint was week 12, defined as the 28-day period ending with week 12.

A headache day was defined as a calendar day (00:00 to 23:59) with 1 or more hours of headache per the patient diary.

Secondary Efficacy Endpoints

- Change from baseline in frequency of severe headache days per 28-day period
- Change from baseline in total cumulative hours of headache on headache days per 28-day period. *This variable is derived from the headache diary. It is the sum of total headache duration for days with headaches of at least 1 hour total duration.*
- The proportion of patients with ≥ 50% decrease from baseline in the frequency of headache days per 28-day period
- The proportion of patients who are prescribed oral rescue migraine prophylactic treatment

Statistical Analysis Plan

All efficacy analyses were performed using the intent-to-treat (ITT) population, consisting of all randomized patients. For efficacy data analyses, patients were analyzed according to randomization assignment, regardless of actual treatment received. The diaries data were summarized for the first 28 days of the baseline period (approximately day -28 to day -1) preceding randomization on study day 1. After the injection on day 1, headache data will be summarized for each of the subsequent 28 day (4 week) intervals (1-28, 29-56 and 57-84 days after treatment).

Missing data Imputation Rule: If a patient reported any diary data for less than 20 days of a 28 day period, the patient's scores (such as headache day count) for that period was set to missing for tables of observed data. If any posttreatment 28 day period had less than 20 days of diary data, the patient's headache count for that particular 28 day period was set to missing. In order to have complete data for ITT analyses, these missing values were estimated using a modified last observation carried forward within treatment (mLOCFw) approach and rounded

to the nearest whole number.

Primary Efficacy Analysis
The primary efficacy analysis was on the change from baseline in the frequency of headache days per 28-day period and the primary timepoint was the 28 days ending with week 12.

The primary comparison between treatment groups was done by the covariate analysis of variance (ANCOVA) of the change from baseline, with baseline frequency of headache days as a covariate, with investigator center as a stratifying cofactor, and with treatment group as main effect. Investigator centers with fewer than 6 patients were pooled into one small-center group for statistical modeling. Except for investigator centers, subgroups were pooled for the primary analysis.

To control the type-1 error rate for multiple pairwise comparisons of doses, a gatekeeping approach was used. The higher dose (155 U) was compared to placebo first, at the alpha=0.05 level. If and only if the p-value from that primary comparison is 0.05 or less, the lower dose (74 U) was compared to placebo, also at the 0.05 level. If each dose was significantly better than placebo, the higher dose was compared with the lower dose, also at the 0.05 level.

The definitions were altered for two sensitivity analyses (to a calendar day with any headache and, separately, with 4 or more total hours of headache).

Secondary Efficacy Analysis
There was no pre-specified analysis plan to account for secondary efficacy variables. Analysis of the variables was performed at the nominal significance level, without adjusting for multiplicity.

No changes were made to the planned analyses following database lock.

Protocol Amendments

Allergan submitted protocol amendments to previous agreed upon SPA protocol 191622-103. The amendments submitted included an updated protocol incorporating the statistical recommendations following issue of the SPA Agreement Letter, with minor clarifications to the exclusion criterion and the questionnaire instructions, and assessments of suicidal ideation and behavior using the C-SSRS as a standard safety measure required by the Division of Neurology Products for all ongoing or planned clinical studies. These amendments had no impact on the clinical study design, the populations including the originally agreed upon statistical analysis plan.

6.1.2. Study Results

Compliance with Good Clinical Practices

Allergan provided attestation that the study was conducted in accordance with good clinical practice (GCP).

Patient Disposition

Post-Randomization
125 patients were randomized into the study (45 BOTOX 155 U, 43 BOTOX 74 U, and 37 placebo), across 28 study sites in the US and 92.0% (115/125) completed the study. Two patients in the BOTOX 155 U were randomized but were determined to be ineligible for the study before receiving drug. 10 patients (8.0%) discontinued the study early. The most common reason leading to discontinuation was lack of efficacy (4 patients [3.2%]). There were no significant protocol deviations.

Baseline Demographic and Disease Characteristics

There were no significant differences between the treatment groups with respect to their baseline demographic characteristics being representative of the chronic migraine patient population. The mean age for patients in this study was 15.1 years, and most patients were female (78.4%; 98/125) and Caucasian (80.8%; 101/125). 60-70% patients were older than 15 years old, and on average patients experienced at baseline 23-25 headache days of any severity.

Table 3: Study 191622-103 Adolescent Chronic Migraine Baseline Characteristics

Demographic Parameters	Placebo (N=37) n (%)	BOTOX 155 U (N=45) n (%)	BOTOX 74 U (N=43) n (%)
Sex			
Male	8 (21.6)	8 (17.8)	11 (25.6)
Female	29 (78.4)	37 (82.2)	32 (74.4)
Age			
Mean years (SD)	15.2 (1.5)	15.1 (1.4)	15.0 (1.5)
Min, max (years)	12, 17	12, 17	12, 17
Age Group			
≥ 12 - < 15 years	11 (29.7)	14 (31.1)	16 (37.2)
≥ 15 - < 18 years	26 (70.3)	31 (68.9)	27 (62.8)
Race			

White	26 (70.3)	38 (84.4)	37 (86.0)
Black or African American	4 (10.8)	1 (2.2)	0
Hispanic or Latino	6 (16.2)	5 (11.1)	4 (9.3)
BMI (mean)	23.2 (3.86)	22.5 (3.77)	22.0 (3.95)
Number Headache days, any severity			
Mean (95% CI)	25.3 (23.97, 26.57)	23.2 (21.92, 24.57)	23.4 (21.89, 24.85)
< 26 days (n)	12	28	22
mean	20.8	20.4	19.4
≥ 26 days (n)	25	17	21
mean	27.4	28.0	27.5
Number Headache days Severe			
Mean (95% CI)	9.1 (6.35, 11.86)	7.0 (5.49, 8.47)	7.84 (5.91, 9.72)

Efficacy Results – Primary Endpoint

There was no statistically significant or numerically superior mean between-group difference for the primary efficacy endpoint, mean change from baseline in the frequency of headache days during the 28-day period ending with week 12. At week 12 there were -6.3 and -6.4 days in the BOTOX 155 U and BOTOX 74 U groups, respectively, compared with -6.8 days in the placebo group (Table 4).

The results are suggestive that study 191622-103 as designed was a negative pediatric study, defined herein as a study that failed to demonstrate effectiveness in the adolescent chronic migraine population. Study protocol 191622-103 was previously issued a Special Protocol Assessment -Agreement Letter dated December 21, 2011 (under IND 07480) for the requested PREA PMR#1/PMR 2469-1.

Reviewer Comment
Please note that the headache duration criterion for an attack in pediatric patients was revised to at least 2 hours in the ICHD-3 beta (2013 publication) from 1 hour duration specified in the ICHD-II 2004 criterion that was originally used while finalizing the study design for the Special Protocol Assessment pediatric study protocol 191622-103. The ICHD-3 beta criterion was revised likely to increase the sensitivity for migraine diagnosis and make distinctions from other headaches that may be experienced. The ICHD-3 beta has the disclaimer that the evidence for untreated durations of less than 2 hours in children has not been substantiated. In a post-hoc analysis conducted by the sponsor using data for headache duration of at least 4 hours at baseline or for patients with severe headaches or any other post-hoc clinically meaningful measures for efficacy did not show any numerical differences from placebo, showing similar

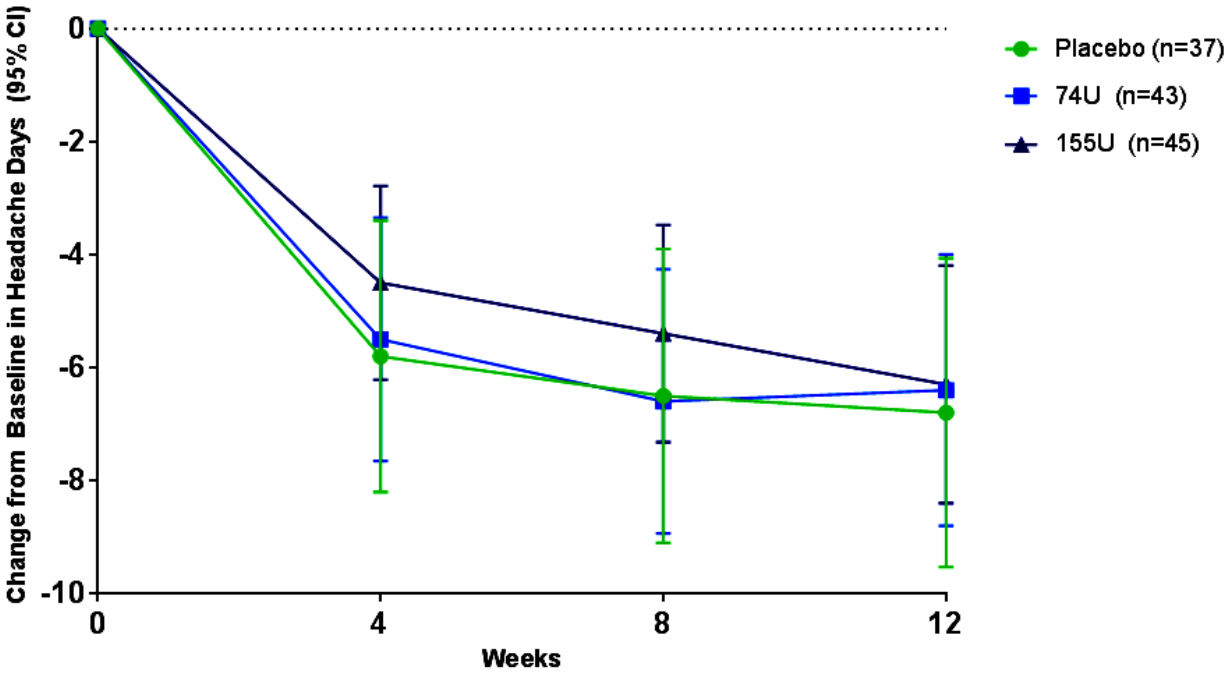
trends observed with the primary endpoint.

Table 4: Baseline and Change From Baseline in Frequency of Headache Days During the 28-Day Period Ending With Week 12 With mLOCFw: Intent-to-Treat Population (as Randomized)

Time Period	Statistics	BOTOX 155U (N=45)	BOTOX 74U (N=43)	PLACEBO (N=37)	P-value[a] BOTOX 155U vs PLACEBO	P-value[a] BOTOX 74U vs PLACEBO
Baseline	N	45	43	37	0.059	0.062
	Mean	23.2	23.4	25.3		
	SD	4.4	4.8	3.9		
	Median	23.0	25.0	27.0		
	Min, Max	15 , 28	15 , 28	9 , 28		
	95% CI	21.92, 24.57	21.89, 24.85	23.97, 26.57		
Week 4	N	45	43	37	0.237	0.579
	Mean	-4.5	-5.5	-5.8		
	SD	5.7	7.0	7.2		
	Median	-3.0	-6.0	-4.0		
	Min, Max	-22 , 4	-23 , 7	-23 , 3		
	95% CI	-6.23, -2.79	-7.70, -3.37	-8.15, -3.36		
Week 8	N	45	43	37	0.325	0.690
	Mean	-5.4	-6.6	-6.5		
	SD	6.4	7.6	7.8		
	Median	-4.0	-6.0	-5.0		
	Min, Max	-23 , 3	-27 , 7	-23 , 7		
	95% CI	-7.35, -3.53	-8.88, -4.23	-9.15, -3.93		
Week 12	N	45	43	37	0.474	0.482
	Mean	-6.3	-6.4	-6.8		
	SD	7.0	7.8	8.2		
	Median	-5.0	-5.0	-2.0		
	Min, Max	-27 , 3	-23 , 7	-26 , 6		
	95% CI	-8.45, -4.22	-8.83, -4.01	-9.56, -4.06		

Source: CSR 191622-103, Table 14.2-1
mLOCFw = modified last observation carried forward. Using the mLOCFw method, missing values were imputed by substitution of the previous 28-day period score multiplied by the ratio of the within-treatment mean for the missing-data 28-day period divided by the within-treatment mean for that previous 28-day period. *A headache day was defined as a calendar day with 1 or more total hours of headache as recorded by the patient in the electronic diary*.
[a] P-values for comparisons between treatment groups are based on the analysis of covariance model with baseline frequency of headache days as a covariate, investigator center as a stratifying cofactor, and treatment as main effect, using Type III sum of squares. Type I error for multiple pair-wise comparisons is controlled by gate-keeping approach. For baseline, comparisons are based on the analysis of variance model with investigator center as a stratifying cofactor, and treatment as main effect, using Type III sum of squares.

Figure 3: 191622-103 Mean Change from Baseline in Frequency of Headache days



Source: IND 07480, Type C Meeting Package December 2016 (Study 191622-103, Figure 1).

Efficacy Results – Secondary and other relevant endpoints

Secondary endpoints were not analyzed for study 191622-103 that was not positive for the primary endpoint.

Dose/Dose Response

There was no numerical trend suggestive of any dose response for study 191622-103 that was not positive for the primary endpoint.

Doses Evaluated and the Injection Schema

The FDA approved BOTOX chronic migraine adult dose regimen is 155 U that includes 31 injections administered using a fixed-site, fixed dose (FSFD) injection paradigm divided across 7 specific head and neck muscles with a recommended retreatment schedule every 12 weeks (see section 6.1.1, Table 2, Figure 2). Allergan evaluated labeled recommended dose (in adults) of BOTOX 155 U using the FSFD injection paradigm and an additional lower dose that is approximately 50% less than the currently labeled dose (i.e., 74 U), which appeared acceptable for evaluation.

Reviewer Comment
This dosing schema and dose groups was acceptable for evaluation. The 155 U dose was demonstrated to be safe to use during adult studies, and although adult migraineurs were exposed to higher doses efficacy was not demonstrated with these doses. With regards to concerns regarding possible distant spread of toxin effects (PDSOT) effects relative to the current proposed doses, children with upper limb spasticity are treated with up to BOTOX 300 U.

There were no controlled clinical studies evaluating the efficacy of BOTOX in pediatric chronic migraine, and with limited information in published literature at the time of review of study 191622-103. Approximately 50 adolescents (14-18 years) received one or more BOTOX open-label treatments. The doses ranged from 60 U to 112 U per treatment session (reference: Chan et al, 2009). In addition, a single abstract reported limited data from a retrospective chart review of 42 adolescents, aged 16.02 ± 3.25 (9.5% male) who received one or more BOTOX open-label treatments with average doses of 88.29 ± 24.2 (approximate range from 64 U to 112 U) per treatment session (reference: Kabbouche et al, 2005). Allergan provided additional justification for the proposed dose from adult studies using analyses of the safety data from the adult phase 3 studies. Subgroup analyses of younger adults (aged 18-24 years) and older adults (≥ 25 years), and for adults who were small in stature and weight (i.e., BMI < 20) for the dose level groups in study 191622-103 did not reveal a consistently higher adverse event rate with higher dose exposure when analyzing by BMI (surrogate for "size" of patient).

7. Integrated Review of Effectiveness

See information discussed in section 6.1.2 for clinical study 191622-103.

8. Review of Safety

This supplement to BLA 103000/5308 for onabotulinumtoxinA (BOTOX) included a controlled clinical study requested under PREA PMR#1/PMR 2469-1 for the indication, prophylaxis of headaches in adolescents with chronic migraine. As reviewed above in section 6.1.2, the controlled clinical study 191622-103 was not positive for the primary endpoint or any other clinically meaningful measures for efficacy, and therefore failed to identify a dose for further recommendation for use.

Allergan adequately addressed monitoring for adverse events including possible distant spread of toxin effects (PDSOT) in the pediatric study 191622-103. The majority of adverse events in the adolescent study were mild or moderate in severity. The most commonly reported (≥ 3%

overall incidence) adverse events were neck pain, upper respiratory tract infection, nasopharyngitis, migraine, dizziness, and musculoskeletal pain (Table 5).

Table 5: Study 191622-103 Number (%) of Patients Reporting the Most Common (≥ 1% Total Overall) Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class[a] Preferred Term	BOTOX 155U (N=43)	BOTOX 74U (N=43)	Placebo (N=37)	Total (N=123)
Overall	21 (48.8)	23 (53.5)	14 (37.8)	58 (47.2)
Gastrointestinal disorders	2 (4.7)	1 (2.3)	0	3 (2.4)
Vomiting	1 (2.3)	1 (2.3)	0	2 (1.6)
General disorders and administration site conditions	2 (4.7)	3 (7.0)	2 (5.4)	7 (5.7)
Injection site pain	1 (2.3)	1 (2.3)	0	2 (1.6)
Infections and infestations	6 (14.0)	8 (18.6)	10 (27.0)	24 (19.5)
Nasopharyngitis	2 (4.7)	2 (4.7)	1 (2.7)	5 (4.1)
Bronchitis	1 (2.3)	0	2 (5.4)	3 (2.4)
Sinusitis	1 (2.3)	0	1 (2.7)	2 (1.6)
Upper respiratory tract infection	0	3 (7.0)	4 (10.8)	7 (5.7)
Pharyngitis streptococcal	0	2 (4.7)	0	2 (1.6)
Influenza	0	1 (2.3)	1 (2.7)	2 (1.6)
Injury, poisoning and procedural complications	0	2 (4.7)	3 (8.1)	5 (4.1)
Contusion	0	1 (2.3)	1 (2.7)	2 (1.6)
Head injury	0	1 (2.3)	1 (2.7)	2 (1.6)
Musculoskeletal and connective tissue disorders	6 (14.0)	6 (14.0)	1 (2.7)	13 (10.6)
Neck pain	3 (7.0)	5 (11.6)	0	8 (6.5)
Musculoskeletal discomfort	2 (4.7)	0	0	2 (1.6)
Musculoskeletal pain	1 (2.3)	3 (7.0)	0	4 (3.3)
Musculoskeletal stiffness	1 (2.3)	1 (2.3)	0	2 (1.6)
Nervous system disorders	7 (16.3)	5 (11.6)	4 (10.8)	16 (13.0)
Dizziness	3 (7.0)	0	1 (2.7)	4 (3.3)
Migraine	1 (2.3)	3 (7.0)	1 (2.7)	5 (4.1)
Headache	1 (2.3)	2 (4.7)	0	3 (2.4)
Hyperaesthesia	0	1 (2.3)	1 (2.7)	2 (1.6)
Psychiatric disorders	3 (7.0)	1 (2.3)	2 (5.4)	6 (4.9)
Anxiety	1 (2.3)	1 (2.3)	0	2 (1.6)
Insomnia	1 (2.3)	0	1 (2.7)	2 (1.6)
Respiratory, thoracic and mediastinal disorders	1 (2.3)	1 (2.3)	2 (5.4)	4 (3.3)
Oropharyngeal pain	0	0	2 (5.4)	2 (1.6)

Source: CSR 191622-103, Table 12-2

The overall incidence of adverse events were similar for adolescents and adults in both the BOTOX 155 U group (10 [23.3%] vs. 177 [25.8%], respectively) and the placebo groups (4 [10.8%] vs. 63 [9.1%], respectively). See Table 6.

Table 6: Number (%) of Patients Reporting the Most Common (≥ 1% Total Overall) Adverse Events in Adolescent (Study 191622-103) and the Adult Chronic Migraine Studies (Label)

	Adolescent CM[1] 1 Cycle (12 weeks)				PREEMPT Adult CM[2] 1 Cycle			
Treatment-Related Adverse Event System Organ Class (Preferred Term)	**BOTOX 155U (N = 43)**		**Placebo (N = 37)**		**BOTOX 155U (N = 687)**		**Placebo (N = 692)**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
OVERALL	**10**	**23.3%**	**4**	**10.8%**	**177**	**25.8%**	**63**	**9.1%**
Eye Disorders								
Eyelid ptosis	0	0.0%	0	0.0%	21	3.1%	2	0.3%
Lacrimation increased	1	2.3%	0	0.0%	0	0.0%	0	0.0%
General disorders and administration site conditions								
Injection site pain	1	2.3%	0	0.0%	16	2.3%	11	1.6%
Injection site bruising	0	0.0%	1	2.7%	1	0.1%	3	0.4%
Facial pain	0	0.0%	1	2.7%	0	0.0%	1	0.1%
Musculoskeletal and connective tissue disorders								
Neck pain	2	4.7%	0	0.0%	37	5.4%	12	1.7%
Muscular weakness	0	0.0%	0	0.0%	20	2.9%	1	0.1%
Myalgia	0	0.0%	0	0.0%	16	2.3%	2	0.3%
Musculoskeletal stiffness	1	2.3%	0	0.0%	13	1.9%	3	0.4%
Musculoskeletal pain	1	2.3%	0	0.0%	10	1.5%	3	0.4%
Musculoskeletal chest pain	1	2.3%	0	0.0%	0	0.0%	0	0.0%
Musculoskeletal discomfort	1	2.3%	0	0.0%	0	0.0%	0	0.0%
Nervous system disorders								
Headache	1	2.3%	0	0.0%	17	2.5%	9	1.3%
Facial paresis	1	2.3%	0	0.0%	14	2.0%	0	0.0%
Migraine	1	2.3%	1	2.7%	7	1.0%	4	0.6%
Dizziness	1	2.3%	1	2.7%	1	0.1%	4	0.6%
Paraesthesia	1	2.3%	0	0.0%	1	0.1%	0	0.0%
Syncope	0	0.0%	1	2.7%	1	0.1%	1	0.1%

Source: IND 07480, Type C Meeting Package December 2016 (Study 191622-103, Figure 1).
[1] Allergan Protocol 191622-103, Table 14.6-1, All Treatment-Related Treatment-Emergent AEs, by Preferred Term within Primary SOC, Safety Population (as Treated)
[2] Allergan PREEMPT Phase 3 Adult Trials in labeling, Integrated Summary of Safety, Table 3-6.1, Treatment-Related Adverse Events, by Preferred Term within Primary SOC by Treatment Cycle

No patient died or discontinued from the study due to an adverse event. Serious adverse events (SAE) were reported by 2.4% (3/123) of patients overall, and all required hospitalization, although none of the SAEs appear treatment-related.

- Patient (b) (6) (BOTOX 155 U group), 13 year old Caucasian male, experienced severe cellulitis of the left foot. The infection to the foot occurred on Day 40 after BOTOX injection administration to the head and neck. He was hospitalized for antibiotics, and the cellulitis resolved after 15 days without sequelae.
- Patient (b) (6) (BOTOX 74 U group) 13 year old Caucasian female, experienced severe appendicitis on Day 30, which lasted 3 days and resolved without sequelae after an appendectomy and medication.
- Patient (b) (6) BOTOX 74 U group) 16 year old Caucasian female, experienced continuing acute migraine attacks beginning 10 days since the administration of BOTOX 74 U. On Days 22 and 32, she was hospitalized for intractable chronic migraine without aura and without status migrainous of moderate severity. During both times, she was managed with various combinations of parenteral and oral medications, and discharged with prophylactic propranolol. 8-weeks after the last hospitalization the migraines resolved without sequelae.

Possible Distant Spread of Toxin Adverse Events (PDSOT)
Patient (b) (6) 16 year old Caucasian female experienced 2 days after the administration of BOTOX 155 U (2.3%, 1/43) a PDSOT adverse event of facial paresis (verbatim investigator term: unable to raise eyebrows). It was reported as inability to raise eyebrows of mild intensity. Examination showed decreased ability to raise eyebrows, but otherwise normal examination of the cranial nerves. There was no treatment reported for the non serious event. The facial paresis resolved without sequelae 49 days later. The event of facial paresis is consistent with the local pharmacological effects of BOTOX described in labeling.

There were no significant differences in the vital signs or physical exam findings for the groups. No patient reported suicidal ideation or behavior at any point during study 191622-103 based on the C-SSRS evaluations. The results from laboratory evaluations did not reveal any trends indicating that BOTOX 155 U or 74 U had an impact on hematology or blood chemistry in this patient population. The majority of patients were negative for binding antibody at baseline and study exit. At Week 12, 2 patients in each of the BOTOX 155 U and 74 U groups were positive for binding antibodies. None of these patients was positive for neutralizing antibodies.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The following information is recommended for labeling. Safety and effectiveness in patients below the age of 18 years have not been established.

In a 12-week, multicenter, double-blind, placebo-controlled clinical trial, 123 adolescent patients (ages 12 to 17 years) with chronic migraine were randomized to receive treatment with BOTOX 74 Units, BOTOX 155 Units, or Placebo. This trial did not establish efficacy of BOTOX treatment compared with placebo for the prophylaxis of headaches in adolescents with chronic migraine. Adverse reactions observed in this clinical trial in adolescents were similar to those reported in clinical trials in adults.

11. Risk Evaluation and Mitigation Strategies (REMS)

None considered for the efficacy supplement.

12. Postmarketing Requirements and Commitments

Waiver - Ages 0 to 11 years 11 months inclusive

It was previously agreed upon to waive studies in patients less than 11 years old for migraine prophylaxis during original BLA approval for chronic migraine prophylaxis in adults (2010). Studies are impossible or highly impractical because the number of pediatric patients is so small or is geographically dispersed. There is currently no accepted definition of chronic migraine in the pediatric population. The International Headache Society classification of chronic migraine exists only for adults. Chronic migraine is rare in children under 12 years of age (as it develops typically after several years of intermittent migraine, that is already relatively infrequent below age 12), and therefore it does not appear possible to study chronic migraine in children younger than 12.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUHAIL KASIM
07/31/2018

HEATHER D FITTER
08/01/2018