U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	BLA 103000 / Serial Number 0338
Drug Name:	BOTOX (botulinum toxin type A)
Indication(s):	Chronic Migraine in Adolescents
Applicant:	Allergan
Date(s):	November 13, 2017 (date received by CDER)
Review Priority:	Standard Review/Memo
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1 EXECUTIVE SUMMARY

This supplemental BLA submission is to fulfill the required pediatric assessment for BOTOX in the treatment and prevention of chronic migraine in adolescent patients. The study doses are 74 U and 155 U via a standardized injection paradigm.

The efficacy evidence is from one study 191622-103.

1.1 Conclusions and Recommendations

The pivotal study in adolescent patients with CM did not present statistical evidence that BOTOX, at dose of 74 U, or 155 U, is efficacious for the treatment of CM based on reduction in monthly headache days. The two dose levels show similar efficacy result as the placebo.

1.2 Brief Overview of Clinical Study 191622-103.

The Phase 3 pediatric study 191622-103 is a multi-center, randomized, double-blinded, parallel group and placebo controlled 16-week (4-week baseline and 12-week double blind period) study for CM with a single treatment session of two dose levels 74 U, and 155 U.

This study is completed and the study report is included in the current submission. No study data nor SAS codes is submitted due to the negative result.

1.3 Statistical Issues and Findings

No major statistical issues were found. Related IND number is 007480.

2 INTRODUCTION

One negative pediatric study 191622-103 is included in this statistical review for efficacy evaluation.

2.1 Overview

BOTOX® (botulinum toxin type A) is a purified neurotoxin complex (US Adopted Name is onabotulinumtoxinA).

BOTOX® received FDA approval in Oct 2010 for the prophylaxis of headaches in adults with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer). As a part of Allergan's post marketing commitments required under PREA, Allergan agreed to conduct an initial multicenter double-blind placebo controlled study (191622-103) in North America to evaluate two BOTOX® doses (155U, 74U) vs. Placebo in adolescents (ages 12-17 years).

Table 1 List of All Studies included in Review

Study Number	Phase and Design	Treatment Period	Dose Levels	# of Subjects per Arm	Study Population
191622-103	Phase 3	12 weeks	155 U, 74 U, placebo	45, 43, 37	CM, Adolescents

This study is multi-center, randomized, double-blinded, parallel group and placebo controlled.

2.2 Data Sources

All documents reviewed for this supplement NDA submission are in electronic form. Please note that there are no data files and programming code files in this submission due to the negative study result.

At the time of review the following is the link to the EDR Location:
\\CDSESUB1\evsprod\BLA103000\0338

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy Study - 191622-103

3.1.1 Description of the Study

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

This study had its first subject enrolled on 26 December 2012, last subject completed on 02 August 2016, and the study report was created on the date of 10 May 2017. The database was locked on 15 September 2016.

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. At each investigator site, patients were randomly assigned in a 1:1:1 ratio to receive BOTOX 155 U, BOTOX 74 U, or placebo. The injection paradigm was standardized as 31 fixed-site, fixed-dose (FSFD), IM injections across 7 specific head/neck muscles as per the current US labeled injection paradigm. Each treatment arm was to include approximately 42 patients.

The total duration of study participation for each patient was 16 weeks. Patients kept a daily electronic headache diary throughout the study, and completed 5 office visits. A screening visit at Week -4 was followed by a 4-week prospective baseline period to ensure that patients met all inclusion and exclusion criteria. On Day 1, qualified patients were randomized and injected with the study treatment, and then returned for office visits at Weeks 1, 6, and 12. Patients who indicated that they wanted to drop out of the study before the Week 12 exit visit were asked if they would be willing to continue providing diary data and/or return for the Week 12 visit.

Eligible patients are 12 to 18 years of age, with medical history of CM for at least 6 months, with 15 or more headache days during the 4-week baseline period with each day having a total of 1 or more hours of headache.

3.1.2 Efficacy Variables

3.1.2.1 Primary Endpoint

The primary endpoint for this study was the change in monthly headache days from baseline to the last 4 weeks of the 12-week double-blind treatment phase.

3.1.3 Statistical Analysis Methods

Efficacy analyses were based on the ITT population. Subjects were grouped based on the assigned treatment.

3.1.3.1 Analysis of the Primary Endpoint

The primary endpoints were analyzed using an analysis of variance model including treatment group, baseline value, stratification factor(center) with treatment as the main effect.

3.1.3.2 Multiplicity Adjustment

The multiplicity adjustment method was pre-specified and deemed adequate.

3.1.4 Patient Results

3.1.4.1 Patient Disposition

A total 125 patients were randomized into the study (45 BOTOX 155 U, 43 BOTOX 74 U, and 37 placebo), and 123 patients received at least 1 dose of study medication (43 BOTOX 155 U, 43 BOTOX 74 U, and 37 placebo). Two patients in the BOTOX 155 U were randomized but were determined to be ineligible for the study before receiving drug. Of the 125 patients who were randomized into the study, 92.0% (115/125) completed the study. A total of 10 patients (8.0%) discontinued the study early. The most common reason leading to discontinuation was lack of efficacy (4 patients [3.2%]).

The ITT population consisting of all randomized patients was used for efficacy data analyses.

3.1.4.2 Patient Baseline Demographic Characteristics

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).

3.1.4.3 Patient Baseline Disease Characteristics

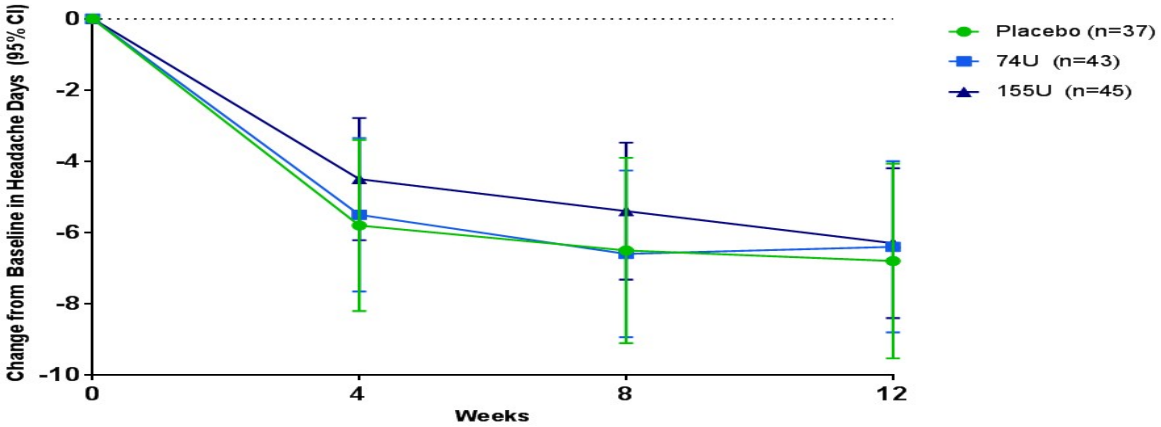
Baseline disease characteristics were consistent with a CM adolescent patient population and were balanced across the treatment groups.

The mean age at onset of chronic baseline was 10.5 years and the mean time since diagnosis was 4.3 years. The majority (66.4%; 83/125) of patients did not have allodynia at baseline.

3.1.5 Efficacy Results

3.1.5.1 Efficacy Results of the Primary Endpoint

Figure 1 Mean Change from Baseline in Frequency of Headache Days



Since the comparison between the high dose and the placebo group as showed in the above figure did not have any difference, the statistical test for comparing the lower dose and the placebo group does not need to be carried out, nor does any of the secondary endpoint analysis.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

The study did not provide evidence of efficacy of BOTOX for the treatment of chronic migraine in adolescent patients. No major statistical issues were identified.

4.2 Conclusions and Recommendations

The efficacy results obtained from the statistical analyses of the study did not support the conclusion that BOTOX is effective in treating adolescent patients with chronic migraine at either of the evaluated doses.

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/

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08/06/2018

KUN JIN
08/06/2018
I concur with the review.

HSIEN MING J HUNG
08/07/2018