Cross-Discipline Team Leader Review

Date	August 31, 2018
From	Heather Fitter, M.D.
Subject	Cross-Discipline Team Leader Review
BLA # and Supplement#	100300/5308
Applicant	Allergan
Date of Submission	November 13, 2017
PDUFA Goal Date	September 13, 2018
Proprietary Name	BOTOX
Established or Proper Name	Onabotulinumtoxin A
Dosage Form(s)	Injection IM
Applicant Proposed Indication/Population	Description of negative pediatric migraine study results in labeling
Applicant Proposed Dosing Regimen	Description of negative pediatric migraine study results in labeling
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	N/A
Recommended Dosing Regimen	N/A

1. Benefit-Risk Assessment

OnabotulinumtoxinA received approval for an indication for the prophylaxis of headaches in adult patients with chronic migraine on October 15, 2010. A pediatric efficacy study, and a long-term safety study were required under PREA.

This application provides the results of the required pediatric studies, which were conducted in adolescents with chronic migraine. The efficacy study was clearly negative. The safety profile of Botox was similar to that seen in adult migraine patients. The applicant proposes that BOTOX should not be indicated for the prophylaxis of headaches in adolescent patients with chronic migraine, which is appropriate. The results of the failed study will be described in labeling.

The applicant has adequately addressed the postmarketing requirements for pediatric studies for the prophylaxis of headaches in patients with chronic migraine.

2. Background

Botox was approved for the prophylaxis of headaches in adult patients with chronic migraine on October 15, 2010, based on two efficacy trials and a long-term extension trial. The approval letter included the following two postmarketing requirements (PMRs):

PMR 2469-1
Deferred pediatric placebo-controlled efficacy and safety study under PREA 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.

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 191622-103 was conducted to address PMR 2469-1. The study was conducted under an agreed special protocol assessment (issued in a letter dated September 21, 2011).

Following completion of Study 191622-103, which had negative results, the applicant requested feedback from the FDA about whether they could be released from the requirement to do the long-term safety study (under PMR 2469-2). The Division met with the Pediatric Review Committee (PeRC), and it was decided that the applicant could be released from the requirement to conduct the long-term safety study, given the negative results of the adolescent efficacy study.

This memo will discuss the findings of the pediatric adolescent study and the recommended labeling changes based on this completed pediatric study.

3. Product Quality

No new product quality information was provided with this submission.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was provided with this submission.

5. Clinical Pharmacology

No new clinical pharmacology information was provided with this submission.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

Dr. Suhail Kasim conducted the efficacy review for this application and Dr. Jinnan Liu conducted the statistical review. Dr. Kun Jin was the Statistical Team Leader. Dr. Kasim reports that the applicant conducted one pivotal efficacy trial in pediatric patients age 12-17 years to satisfy PMR 2469-1, which was requested under PREA. This was a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of Botox administered intramuscularyly (IM) at two dose levels (74U and 155 U), as compared to placebo, in adolescents with chronic migraine. Adolescents with chronic migraine, defined as having at least 15 or more headache days per month with at least 8 of the monthly headaches being consistent with migraine for at least 6 months, were eligible for enrollment in the trial if they also reported at least 15 headache days during the 4-week baseline period. Patients with medication overuse headache and patients using concomitant prophylactic migraine medication were excluded. The study consisted of a 4-week baseline period and a 12-week treatment period. During the treatment period, patients received study drug injections at 31 sites across 7 specific head/neck muscles, as per the current FDA label for chronic migraine in adults. Patients were randomized 1:1:1 to receive Botox 155 U, Botox 74 U, or placebo. The primary endpoint and key secondary endpoints were measured after 12 weeks of treatment. The primary endpoint was the change from baseline in the frequency of headache days per 28-day period. A headache day consisted of a day with at least one hour of headache. The key secondary endpoints were as follows:

- 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
- 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

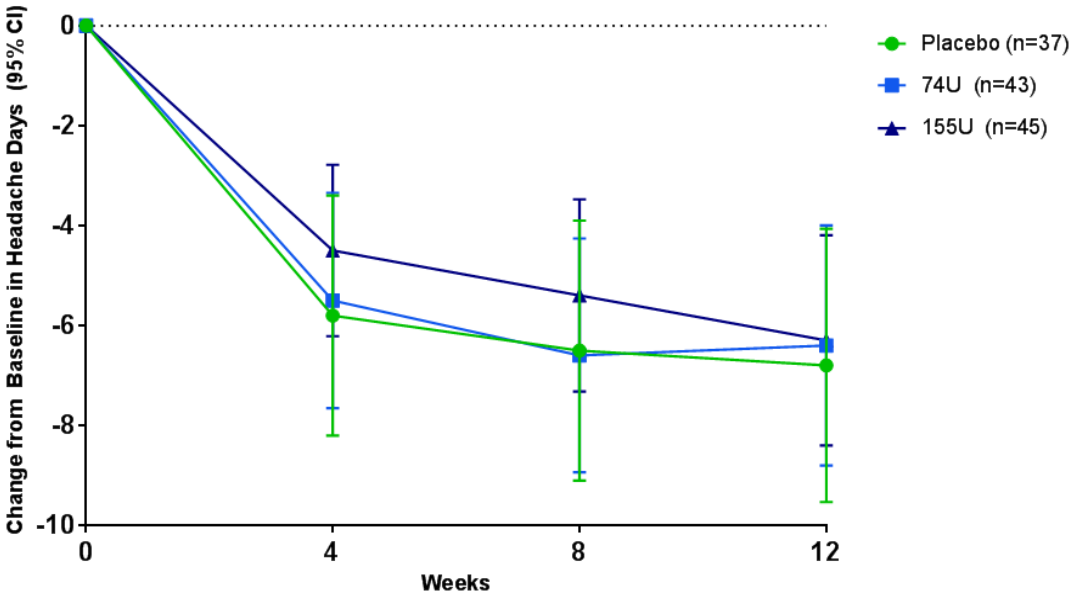
The primary comparison between treatment groups was done by the covariate analysis of variance (ANCOVA) of the change from baseline, with baseline frequency of headache days as a covariate, with investigator center as a stratifying cofactor, and with treatment group as main effect. To control the type-1 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 the p-value from that primary comparison was 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.

Results

One hundred and twenty five patients were randomized into the study across 28 sites in the United States. Ninety two percent of the patients completed the study. There were no significant differences between treatment groups with respect to demographic characteristics. The mean age was 15.1 years, there were 78% females patients, and 81% of patients were Caucasian. It is important to note that 63-70% of patients were 15 years of age or older. The reported baseline number of headache days of any severity was 23-25.

There was no statistically significant or even numerical superiority of Botox over placebo for either dose level of Botox. At Week 12, there was a reduction of 6.3 and 6.4 days in the frequency of monthly headache days in the Botox 155 U and Botox 74 U treatment groups, respectively, compared with a reduction of 6.8 days in the placebo group (see Figure 1).

Figure 1: Mean Change from Baseline in Frequency of Headache Days: Study 191622-103 (source: applicant submission)



Dr. Liu reports that since the comparison between the high dose and the placebo group was negative, the testing to compare the low dose to placebo or the testing of the secondary endpoints was not carried out.

Efficacy conclusions

The applicant conducted a well-controlled and adequate study to evaluate the efficacy of Botox at two dose levels, compared with placebo, for the prophylaxis of headaches in adolescent patients with chronic migraine. The study was clearly negative. The negative study results will be described in Section 8 under "Use in Specific Populations".

8. Safety

Dr. Suhail Kasim conducted the safety review for this application. Dr. Kasim reports that 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. The overall incidence of adverse events was similar between adolescents and adult patients treated with Botox 155 U (23% vs. 26%). The incidence of adverse events in patients on placebo was also similar between adolescents and adult patients (11% vs. 9%). Dr. Kasim reports that 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, but none of the SAEs appeared treatment-related. Dr. Kasim reports that there were no new safety signals identified in the adolescent safety population, as compared to the adult database.

A 16-year-old female experienced facial paresis 2 days after receiving Botox 155 U. The facial paresis reportedly resolved after 49 days, without any sequelae. This event is consistent with the possible distant spread of toxin, which is described in labeling.

Safety conclusions

No new safety signals were identified in the adolescent safety database, as compared to the adult safety database. The most commonly reported (≥ 3% overall incidence) adverse events were neck pain, upper respiratory tract infection, nasopharyngitis, migraine, dizziness, and musculoskeletal pain. Most of these events were reported as mild to moderate. There were three serious adverse events reported, although none appeared treatment-related.

9. Pediatrics

The Division met with Pediatric Review Committee (PeRC) on July 25, 2018. PeRC agreed that the results of the adolescent study do not support efficacy, and that this information should be described in the label.

10. Labeling

Agreement was reached with the applicant on labeling. The following information will be added to Section 8.4 in labeling under the heading "Pediatric Use":

(b) (4)

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/

HEATHER D FITTER
09/06/2018

ERIC P BASTINGS
09/06/2018