Study of Adult Strabismus (SAS1)
Treatment and Outcomes in Subjects Enrolled with Divergence Insufficiency

Statistical Analysis Plan
Version 1.0

Statistical Analysis Plan Version: 1.0, 04Jun2020
Protocol Version: 2.0, 11Apr2016

VERSION HISTORY

The following table outlines changes for the analysis plan:

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	T. Dean	Z. Li	04Jun2020	The statistical analysis plan was started prior to the analysis of data but was completed after an initial draft of the manuscript was written.

Signature of author: _____

Signature of approver: _____

1.0 Overview

1.1 Study Synopsis

Adults diagnosed with divergence insufficiency (DI) were enrolled if eligibility criteria were met and one of the following treatments (subsequently referred to as treatment modalities) were prescribed at the enrollment visit: Botox, orthoptic exercises, prism, or surgery. The prescription of treatment for strabismus was at investigator discretion and was used to identify eligible participants. Treatment assignment was not part of the protocol.

1.2 Manuscript Objective

This study was designed to accomplish two study objectives:

- To describe clinical characteristics, symptoms, and prescribed treatments of adults diagnosed with DI at enrollment
- To characterize symptoms and clinical outcomes at 10 weeks and 12 months after the initiation of treatment

1.3 Primary Outcome: Treatment Success

The primary outcome is the proportion of participants who met success criteria. Success is evaluated at 10 weeks and at 12 months after treatment was initiated.

At each timepoint, participants were classified as successfully treated if **all** the following criteria were met:

- Participant indicated on the diplopia questionnaire (DQ) that diplopia in the distance was experienced "rarely" or "never" during the last week
- Additional treatment (defined in section 4.0) was NOT received prior to the office visit

2.0 Treatment at Enrollment

Participants were eligible for the study if one of four treatments was initiated at the enrollment visit:

1. Botox injection
2. Newly prescribed orthoptic exercises
3. Newly prescribed prism
4. Surgery

Newly Prescribed Prism

Participants who received newly prescribed prism were further categorized into the following subgroups, based on the amount (percent) of the underlying deviation that was corrected by the prism prescribed at enrollment:

- Low relieving prism (0 to <60% of underlying deviation corrected)
- High relieving prism (60 to <100% of underlying deviation corrected)
- Correcting prism (≥100% of underlying deviation corrected)

The percent of the deviation corrected by prism at enrollment is defined as $\frac{\textbf{\textit{total prism prescribed at enrollment}}}{\textbf{\textit{magnitude of distance deviation}}} \times \mathbf{100}$, where

- Total prism prescribed at enrollment is defined as the sum of the prism prescriptions in the left and right eyes at enrollment
- Magnitude of distance deviation is the size of the distance deviation measured by prism and alternate cover test (PACT)

Surgery

Participants who received surgery were further categorized into the following groups based on the type of surgery performed:

- Bilateral medial rectus recession
- Bilateral lateral rectus resection
- Other including:
    - Bilateral medial rectus muscle recession, superior rectus muscle nasal pole recession
    - Bilateral medial rectus muscle recession, superior rectus muscle recession
    - Bilateral lateral rectus muscle resection with superior transposition
    - Bilateral medial rectus muscle recession with superior transposition
    - Lateral rectus muscle tuck/plication, superior rectus muscle recession
    - Medial rectus muscle recession, lateral rectus muscle resection
    - Single medial rectus muscle recession
    - Single lateral rectus muscle tuck/plication

3.0 Re-enrollment

Participants enrolled into the prism and orthoptic exercises groups were given the option to re-enroll into the study if Botox or strabismus surgery was prescribed at the 10-week or 12-month office visit, and all other eligible criteria were met.

For participants who were re-enrolled following the prescription of strabismus surgery at the 10-week visit, the 10-week visit served as both the outcome visit for the initial treatment (prism or orthoptic exercises) and the enrollment visit for the second treatment (Botox or strabismus surgery). Similarly, for participants who were re-enrolled at the 12-month visit, the 12-month visit served as both the outcome visit for the initial treatment and the enrollment visit for second treatment.

When data are analyzed, participants who were re-enrolled may contribute two outcomes to the analysis, one reflecting the results of prism treatment or orthoptic exercises, which was the initial prescribed treatment, and the other reflecting the results of strabismus surgery or Botox injection, which was received after the participant was re-enrolled. Even though some participants may contribute multiple outcomes to the analysis, there will be no adjustment for the potential correlation between these outcomes. Botox and strabismus surgery result in permanent changes to the ocular system and are not expected to be influenced by prior treatment with orthoptic exercises or prism. Therefore, it is safe to assume that outcomes collected for the initial treatment are independent of outcomes collected after re-enrollment.

4.0 Additional or Newly Initiated Treatment during Follow Up

Investigators were encouraged to observe enrolled participants for 12 months before initiating new treatment. However, given that this is an observational study, investigators were not limited in their ability to change existing treatment or to initiate new treatment. In a general sense, treatment prescribed after enrollment may be classified as "additional treatment" (also referred to as "newly initiated treatment"), but this definition depends on the treatment initiated at enrollment and the timing of the newly initiated treatment. Below are definitions of additional treatment.

Prism group

Participants enrolled following the prescription of prism were considered to have received additional treatment at 10 weeks if the treatment history form at 10 weeks indicated that Botox, orthoptic exercises, or surgery was received prior to the office visit. At 12 months, participants were considered to have received additional treatment if the treatment prescribed form at 10 weeks or the treatment prescribed form at 12 months indicated that Botox, orthoptic exercises, or surgery was prescribed or received.

When evaluating treatment success within prism subgroups (low-relieving prism, high-relieving prism, correcting prism), the prism prescription at follow-up was taken into consideration as well. In addition to the definition provided above, participants were considered to have received additional treatment if there was an increase in the prism prescription after enrollment. Participants were considered to have received additional treatment at 10 weeks if the treatment history form at 10 weeks indicated that the magnitude of the prism prescription had increased since enrollment. Participants were considered to have received additional treatment at 12 months if the treatment prescribed form at 10 weeks or the treatment history form at 12 months indicated that the magnitude of prism prescribed had increased since enrollment.

Surgery group

Participants who were prescribed surgery at enrollment were considered to have received additional treatment if the treatment history form at 10 weeks indicated that Botox or surgery was received prior to the office visit. Participants were considered to have received additional treatment at 12 months if the treatment prescribed form at 10 weeks or the treatment history form at 12 weeks indicated that Botox, orthoptic exercises, prism, or surgery was prescribed or received.

5.0 Primary Analysis

The following were tabulated by treatment prescribed at enrollment:

- The number and proportion of participants who met success criteria at distance (see Section 1.3) at 10 weeks
- The number and proportion of participants who met success criteria at distance (see Section 1.3) at 12 months

A 95% Clopper-Pearson confidence interval was calculated for each proportion.

Participants were included in analysis only if the DQ was completed at the visit. There was one exception to this rule, participants were considered a failure if additional treatment was received prior to the visit. If the 10-week treatment history form indicated that additional treatment was received prior to the 10-week visit, the participants was considered a failure both at 10 weeks and at 12 months. If the 12-month treatment history form or the 10-week treatment prescribed form indicated that additional treatment was received prior to the 12-month visit, then the participant was considered a failure at 12 months. When additional treatment was received prior to the visit, the participant was counted in the denominator but not the numerator when calculating the success proportion. It is acknowledged that this procedure is biased unless the 10-week and 12-month DQ data are not missing at random (NMAR), with those who missed that visit being in truth more likely to be failures than those who completed the visit. In that case, this procedure may be less biased. If the data are missing completely at random (MCAR), the resulting estimate of success is an underestimate.

6.0 Secondary Analyses

Data collected after additional treatment was received was no longer representative of the treatment initiated at enrollment. Consequently, data were excluded from analyses and tabulations if additional treatment was prescribed or received prior to the visit, unless otherwise specified.

6.1 Number and Proportion of Participants that Received Each Treatment

The number and proportion of participants that were prescribed each treatment at enrollment was tabulated. Participants who were re-enrolled will be counted twice: once for the initial treatment (orthoptic exercises or prism) prescribed at enrollment and again for the second treatment (Botox or surgery), prescribed at re-enrollment.

6.2 Participant characteristics at Enrollment and Medical History

The following characteristics reported at enrollment were tabulated according to the treatment initiated at enrollment:

- Sex
- Race/Ethnicity (White versus non-White)
- Age (18-24, 25-34, 35-44, …, 75-84, 85-91)
- Whether or not refractive correction (spectacles or contact lenses) was worn at the office visit
- Prior treatment for strabismus (orthoptic exercises, prism, none)
- Coexisting neurological conditions (Parkinson’s, progressive supranuclear palsy, basal ganglia disease, stroke, intracranial tumor)
- Other conditions (epiretinal membrane; age-related macular degeneration; macular pathology; heart disease; diabetes; autoimmune disease; significant head trauma; hypertension; cancer of bladder, breast, or prostate)

The mean, standard deviation, median, and interquartile range (IQR) will be calculated for age at enrollment.

6.3 Clinical Characteristics at Enrollment

The following clinical characteristics measured at enrollment were tabulated according to the treatment initiated at enrollment:

- Frequency of diplopia at distance during the last week
- Frequency of diplopia in reading position during the last week
- Horizontal deviation at distance (measured using PACT)
- Horizontal deviation at near (measured using PACT)
- Whether or not prism was needed to fuse in free space at distance

The mean, standard deviation, median, and IQR were tabulated for the following:

- Horizontal deviation at distance (measured using PACT)
- Horizontal deviation at near (measured using PACT)
- DQ score
- Adult-Strabismus (AS-20) general function score
- AS-20 reading function score
- AS-20 self-perception score
- AS-20 interaction score

6.4 Secondary Definition of Success: Successful Treatment at Both Distance and Near

Successful treatment at both distance and near is defined as diplopia reported "rarely" or "never" both in the reading position and in the distance, and no additional treatment prescribed.

The following were tabulated by treatment prescribed at enrollment:

- The number and proportion of participants who met success criteria at both distance and near at 10 weeks
- The number and proportion of participants who met success criteria at both distance and near at 12 months

A 95% Clopper-Pearson confidence interval was calculated for each proportion.

Participants were included in analysis only if the DQ was completed at the visit. There was one exception to this rule. If the treatment history form or the treatment prescribed form at the 10-week visit indicated that additional treatment was received, then the participant will be considered a failure at 12 months. It is acknowledged this procedure may be biased (see Section 4.0).

6.5 Successful Treatment within Prism and Surgery Subgroups

The following were tabulated within prism and surgery treatment subgroups:

- The number and proportion of participants that met success criteria at distance at 10 weeks
- The number and proportion of participants that met success criteria at both distance and near at 10 weeks

- The number and proportion of participants that met success criteria at distance at 12 months
- The number and proportion of participants that met success criteria at both distance and near at 12 months

A 95% Clopper-Pearson confidence interval was calculated for each proportion.

Participants were included in analysis only if the DQ was completed at the visit. There was one exception to this rule: participants were considered a failure if additional treatment was received prior to the visit. It is acknowledged this procedure may be biased (see Section 5.0).

6.6 Secondary Clinical Outcomes

The following statistics will be calculated to describe the DQ score and each AS-20 subscale score at each visit, according to the treatment initiated at enrollment:

- Mean score at visit and standard deviation
- Mean change in score from enrollment and the corresponding 95% confidence interval

These statistics were also calculated according to treatment subgroups.

6.7 Treatment Success for Participants Enrolled into the Surgery Group by Whether Prism was Prescribed Prior to Enrollment or No Prior Treatment was Reported

The following were tabulated for participants who were prescribed surgery at enrollment according to whether prism was prescribed prior to enrollment or no treatment was prescribed prior to enrollment:

- The number and proportion of participants that met success criteria at distance at 10 weeks
- The number and proportion of participants that met success criteria at both distance and near at 10 weeks
- The number and proportion of participants that met success criteria at distance at 12 months
- The number and proportion of participants that met success criteria at both distance and near at 12 months

A 95% Clopper-Pearson confidence interval was calculated for each proportion.

Participants were included in analysis only if the DQ was completed at the visit. There was one exception to this rule: participants were considered a failure if additional treatment was received prior to the visit. It is acknowledged this procedure may be biased (see Section 5.0).