

Trial Protocol from ClinicalTrials.gov

Purpose

The purpose of this study is to compare the effectiveness of three commercially available botulinum toxin neuromodulators in the treatment of facial synkinesis using patient reported outcome measures.

Condition	Intervention	Phase
Facial Nerve Injuries Facial Paresis Associated With Facial Nerve Dysfunction Facial Asymmetry Synkinesis	Drug: OnabotulinumtoxinA Injectable Product Drug: AbobotulinumtoxinA Injectable Product Drug: Incobotulinumtoxin A Injectable Product	Phase 4

Study Type: Interventional

Study Design: Primary Purpose: Treatment
Study Phase: Phase 4
Interventional Study Model: Parallel Assignment
Masking: Participant
Allocation: Randomized

Official Title: Randomized, Single-blind Comparison of Three Commercially Available Botulinum Neuromodulators in the Management of Facial Synkinesis

Further study details as provided by Preston Ward, University of Utah:

Primary Outcome Measure:

- Change in Synkinesis Assessment Questionnaire (SAQ) Scores [Time Frame: Up to 4 weeks post-treatment. Recorded at pre-treatment, 1 week, 2 weeks, and at 4 weeks.]

The previously validated instrument, Synkinesis Assessment Questionnaire (SAQ), was administered in order to evaluate patient-perceived severity of synkinesis. This instrument was used for each of the three treatment arms and change in scores from baseline were compared at each time point between arms. SAQ scores are calculated as the sum of scores for 9 questions, which

each is scored from 1 to 5, divided by 45 and multiplied by 100. The total score therefore can range from 20 to 100. Lower SAQ scores represent less severe facial synkinesis, and higher scores more severe. We report here the mean total SAQ score each group. For additional information on the SAQ for facial synkinesis see Mehta et al. published in Laryngoscope in May 2007 (PMID: 17473697).

Secondary Outcome Measures:

- Adverse Events [Time Frame: Up to 4 weeks post-treatment. Recorded at pre-treatment, 1 week, 2 weeks, and at 4 weeks.]

We hypothesized that common minor events such as bruising and swelling at injection sites would occur equally for all treatment arms, but that no major adverse treatment effects would occur for any of the treatment arms. Major events are recorded here.

Enrollment: 71

Study Start Date: July 2012

Study Completion Date: March 2015

Primary Completion Date: March 2015

Arms	Assigned Interventions
<p>Active Comparator: OnabotulinumtoxinA Injectable Product onabotulinumtoxinA (Botox®, Allergan) administered for n=15 total treatments. Each patient in this arm was administered the Synkinesis Assessment Questionnaire (SAQ) to assess severity of synkinesis pre-treatment. SAQ was administered again at 1, 2, and 4 weeks post-treatment and improvements were compared to the other arms of the study.</p>	<p>Drug: OnabotulinumtoxinA Injectable Product Administered to treat facial synkinesis Other Names:</p> <ul style="list-style-type: none"> • Botox
<p>Active Comparator: AbobotulinumtoxinA Injectable Product abobotulinumtoxinA (Dysport®, Medicis) administered for n=13 total treatments. Each patient in this arm was administered the Synkinesis Assessment Questionnaire (SAQ) to assess severity of synkinesis pre-treatment. SAQ was administered again at 1, 2, and 4 weeks post-treatment and improvements were compared to the</p>	<p>Drug: AbobotulinumtoxinA Injectable Product Administered to treat facial synkinesis Other Names:</p>

other arms of the study.	<ul style="list-style-type: none"> • Dysport
Active Comparator: Incobotulinumtoxin A Injectable Product incobotulinumtoxinA (Xeomin®, Merz) administered for n=10 total treatments. Each patient in this arm was administered the Synkinesis Assessment Questionnaire (SAQ) to assess severity of synkinesis pre-treatment. SAQ was administered again at 1, 2, and 4 weeks post-treatment and improvements were compared to the other arms of the study.	Drug: Incobotulinumtoxin A Injectable Product Administered to treat facial synkinesis Other Names: <ul style="list-style-type: none"> • Xeomin

Quality assurance:

Data is entered in to a spreadsheet as it is extracted exactly from the electronic medical record. During review of the findings, the data is again checked against the medical record to ensure accuracy. Botulinum toxin types are also verified with scanned copies of the botulinum toxin injection sheet which is filled out and scanned in to the medical record at the time of treatment.

Data dictionary:

Not necessary as limited new terminology is used and all understood among the research group. Additional terminology is clearly described for the trial participants and described in the manuscript reporting the results of the study.

Recruitment:

Patients with facial synkinesis who were appropriate candidates for botulinum toxin chemodenervation therapy were offered voluntary participation in this trial. Patients who had returned to their baseline SAQ score after a minimum of 12 weeks since their previous treatment were permitted to re-enroll in the study for subsequent treatments.

Data collection:

At 1, 2, and 4 weeks post treatment, patients were again administered the SAQ. SAQ scores were calculated for each follow up time point. The average SAQ score in each treatment group (onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA) for each week was calculated, as well as the average improvement in SAQ scores.

Data management:

Data were initially recorded and stored in the secure, password protected, electronic medical record. Data were then extracted from the electronic medical record to a secure Excel spreadsheet stored on a password protected

computer. Only the principal investigator and those researchers involved in data analysis and interpretation were provided access to this data. Names and identifiable information were excluded from this spreadsheet so that the information could not be linked back to specific patients.

Data analysis:

Data were analyzed by first organizing the data in Excel, within the original spreadsheet used to record data, then exporting this data in to Prism 6 for Windows (GraphPad Software). Using Prism 6, characteristics of the data were assessed and statistical calculations were performed to determine significance of comparisons between groups. Details of these statistical tests are described below.

Reporting for adverse events:

Adverse events were recorded in the electronic medical record at each follow-up visit. These were then noted in the data spreadsheet as well to keep track of any events that had occurred over the study period. Minor adverse effects reported during the study included redness, bruising, swelling, and fullness at the injection sites which were not felt to be significant or noted to be qualitatively different between products. No major adverse treatment effects were reported during the course of the study.

Change management:

There were no significant changes to study protocol over the course of the study.

Sample size assessment to specify the number of participants or participant years necessary to demonstrate an effect:

<https://www.dssresearch.com/knowledgecenter/toolkitcalculators/statisticalpowercalculators.aspx> At an alpha level of 0.05, an estimated standard deviation of 10, an estimated average of SAQ 44 and comparison/test value of SAQ 55, a sample size was calculated of approximately 400. We were unable to obtain this sample size after nearly 3 years of enrolment from July 2012 to March 2015. However, despite not reaching this estimated sample size, we did identify a statistically significant finding at alpha level of 0.05 and with a standard deviation of approximately 10-15 per group.

Plan for missing data to address situations where variables are reported as missing, unavailable, "non-reported," uninterpretable, or considered missing because of data inconsistency or out-of-range results:

Patients without follow-up at the post-treatment time points of 1, 2, and 4 weeks were excluded and therefore no missing data was expected for SAQ values. The plan for any missing data in the study was to leave the data point

as missing without attempts to imputate the value or otherwise correct for missingness.

Statistical analysis plan describing the analytical principles and statistical techniques to be employed in order to address the primary and secondary objectives, as specified in the study protocol or plan:

The average SAQ score in each treatment group (onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA) for each week was calculated, as well as the average improvement in SAQ scores. Lower SAQ scores represented less severe patient reported disease. Percent improvement in SAQ score was calculated for each time point as the average post-treatment score divided by the average pre-treatment score for the treatment group, subtracted from 1. The SAQ scores for each time point and treatment groups were found to be normally distributed (passing both the D'Agostino & Pearson omnibus normality test as well as Shapiro-Wilk normality test) allowing for an assumption of Gaussian distribution in our following tests of statistical significance. Comparisons between treatments, and between time points within treatment groups were made with a one-way ANOVA followed by appropriate follow-up test for multiple comparisons. Comparisons within treatment groups between each follow-up time point, and the control pre-treatment time point were made using the Dunnett test (compares every mean to a control mean), whereas comparisons of different treatments at a given time point were made with the Tukey test (compares every mean to every other mean). A threshold of $p \leq 0.05$ was used for statistical significance.

Patients who had returned to their baseline SAQ score after a minimum of 12 weeks since their previous treatment were permitted to re-enroll in the study for subsequent treatments. Twenty-eight patients were studied, and 6 of these 28 were enrolled multiple times accounting for 11 of the 38 treatments studied. To ensure the baseline SAQ scores of these patients receiving repeat treatments did not differ from patients receiving a single treatment, the average pre-treatment SAQ score for patients undergoing repeat treatments was compared to the average pre-treatment SAQ score of single treatment patients for each type of botulinum toxin neuromodulator. These groups were evaluated for normality of distribution by the same method as described above, with single treatment patients passing tests of normality; normality for the repeat patients could not be determined due to the small number of treatments for each of these patients. Statistical comparisons were then made between the pre-treatment SAQ scores for repeat treatment patients and the respective (same type of botulinum toxin) single treatment patients. In order to preference type I error and identify any possible difference between these groups, we made an assumption of normality and used a one-way ANOVA

followed by a Holm-Sidak multiple comparison test. The Holm-Sidak method was chosen as it has more power to identify significant differences than other possible methods such as that of Bonferroni.

► **Eligibility**

Ages Eligible for Study: 18 Years and older

Sexes Eligible for Study: All

Inclusion Criteria:

- Facial synkinesis

Exclusion Criteria:

- Previous complication from botulinum toxin neuromodulator injection
- Inability to understand or complete the SAQ survey
- Inability to participate in follow-up
- Pregnancy

► **Contacts and Locations**

Investigators

Principal Investigator: Preston D Ward, MD University of Utah

► **More Information**

Publications:

[Choi KH, Rho SH, Lee JM, Jeon JH, Park SY, Kim J. Botulinum toxin injection of both sides of the face to treat post-paralytic facial synkinesis. J Plast Reconstr Aesthet Surg. 2013 Aug;66\(8\):1058-63. doi: 10.1016/j.bjps.2013.04.012. Epub 2013 May 15.](#)

[Nettar KD, Yu KC, Bapna S, Boscardin J, Maas CS. An internally controlled, double-blind comparison of the efficacy of onabotulinumtoxinA and abobotulinumtoxinA. Arch Facial Plast Surg. 2011 Nov-Dec;13\(6\):380-6. doi: 10.1001/archfacial.2011.37. Epub 2011 Jun 20. Erratum in: Arch Facial Plast Surg. 2012 Mar;14\(2\):140.](#)

[Saad J, Gourdeau A. A direct comparison of onabotulinumtoxinA \(Botox\) and IncobotulinumtoxinA \(Xeomin\) in the treatment of benign essential blepharospasm: a split-face technique. J Neuroophthalmol. 2014 Sep;34\(3\):233-6. doi: 10.1097/WNO.0000000000000110.](#)

[Mehta RP, WernickRobinson M, Hadlock TA. Validation of the Synkinesis Assessment Questionnaire. Laryngoscope. 2007 May;117\(5\):923-6.](#)

[Filipo R, Spahiu I, Covelli E, Nicastrri M, Bertoli GA. Botulinum toxin in the treatment of facial synkinesis and hyperkinesis. Laryngoscope. 2012 Feb;122\(2\):266-70. doi: 10.1002/lary.22404. Epub 2012 Jan 17.](#)

[Armstrong MW, Mountain RE, Murray JA. Treatment of facial synkinesis and facial asymmetry with botulinum toxin type A following facial nerve palsy. Clin Otolaryngol Allied Sci. 1996 Feb;21\(1\):15-20.](#)

[Naumann M, Albanese A, Heinen F, Molenaers G, Relja M. Safety and efficacy of botulinum toxin type A following long-term use. Eur J Neurol. 2006 Dec;13 Suppl 4:35-40. Review.](#)

Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD: Yes

Plan Description: IPD is to be shared among the first author of the study and the principal investigator for purposes of data acquisition and analysis. This data will be limited to that necessary to addressing the research question, specifically, the type of botulinum toxin used for treatment, the dates of treatment, and the SAQ scores at the pre-treatment, and post-treatment follow-up visits. Any adverse events related to treatment will also be available.

Supporting Materials:

Time Frame:

Access Criteria:

ClinicalTrials.gov Identifier: NCT03048383

Responsible Party: Preston Ward, M.D., University of Utah

Other Study ID Numbers: 56158

Human Subjects Protection Review Board Status: Approved