DaxibotulinumtoxinA Injection for Treatment of Adductor Spasmodic Dysphonia

Study Protocol and Statistical Analysis Plan

NCT05158166

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UCSF DEPARTMENT OF OTOLARYNGOLOGY

"DAXI" Clinical Research Protocol

A single-arm, open-label, dose-escalation clinical trial of DaxibotulinumtoxinA for treatment of adductor laryngeal dystonia

Protocol Number:	1.0
Version Date:	11.23.2022
Investigational Product:	DaxibotulinumtoxinA, "DAXI"
IND Number:	
Development Phase:	Phase 4
Sponsor:	Clark Rosen, MD UCSF Voice and Swallowing Center 2230 Post St #500 San Francisco, CA 94115
Funding Organization:	UCSF Department of Otolaryngology
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Coordinating Center:	N/A

Approval:

Clark Rosen, MD; Lewis Francis Morrison, MD Endowed Chair in Laryngology, Chief Division of Laryngology

11/23/2022

PI or Sponsor Signature (Name and Title) *Date*

The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT – single center

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study, enrolled under my supervision and providing with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 1.0

Protocol Title: A single-arm, open-label, dose-escalation clinical trial of DaxibotulinumtoxinA for treatment of adductor laryngeal dystonia

Protocol Date: 11.23.22

[redacted] 11/23/2022

Investigator Signature *Date*

Clark Rosen, MD; Lewis Francis Morrison, MD Endowed Chair in Laryngology, Chief Division of Laryngology

Print Name and Title

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Phone Number	(415) 885-7700

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LIST OF ABBREVIATIONS

AE	Adverse event
ADLD	Adductor laryngeal dystonia
Botox	OnabotulinumtoxinA
CAPE-V	Consensus Auditory-Perceptual Evaluation of Voice
CFR	Code of Federal Regulations
CPIB-10	Communicative Participation Item Bank-10
CRF	Case report form
DAXI	DaxibotulinumtoxinA
DMC	Data Monitoring Committee
EAT-10	Eating Assessment Tool-10
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LD	Laryngeal dystonia
OMNI-VES	OMNI Vocal Effort Scale
PI	Principal Investigator
PROMs	Patient Reported Outcome Measures
SAE	Serious adverse experience

VAS	Visual Analog Scale
VHI-10	Voice Handicap Index-10

PROTOCOL SYNOPSIS

TITLE	A single-arm, open-label, dose-escalation clinical trial of DaxibotulinumtoxinA for treatment of adductor laryngeal dystonia
SPONSOR	Clark Rosen M.D.
FUNDING ORGANIZATION	Departmental funding from the UCSF Department of Otolaryngology
NUMBER OF SITES	1
RATIONALE	Laryngeal dystonia (LD) is a neurologic condition causing aberrant contraction of the laryngeal musculature, leading to abnormal voicing during speech. The three types (adductor, abductor,and mixed) affect varying muscle groups which produce characteristic voice patterns. The vast majority of patients with SD have adductor type, which impacts the lateral cricoarytenoid and thyroarytenoid muscle complex. While many treatment modalities have been investigated, the most efficacious treatment is botulism toxin injection to these muscle groups, performed transcervically with or without electromyography (EMG) guidance. Patients undergoing this treatment typically require re-injection every three months. Due to its specialized nature, the laryngeal injections are not performed routinely outside of academic medical centers; thus, patients may come from a distance to receive this treatment. Both due to the significant impact on voice quality when the injections

	wear off and the sometimes challenging access to treatment, a longer acting agent is desire. Injectible daxibotulinumtoxinA (DAXI, Revance Therapeutics Inc., Newark, CA) is a FDA-approved botulinum toxin type A indicated for the treatment of glabellar lines. It has been shown in large clinical trials to provide safe, effective treatment for cervical dystonia and may offer longer-lasting results when compared with onabotulinumtoxinA. Thus, a study examining the effect of DAXI for patients with adductor laryngeal dystonia (ADLD) is proposed. This study aims to assess the efficacy of DAXI for transcervical laryngeal injection in patients with adductor laryngeal dystonia.
STUDY DESIGN	A single-arm, open-label, dose-escalation phase 4 study.
PRIMARY OBJECTIVE	Determine the efficacy of DAXI for treatment of ADLD.
SECONDARY OBJECTIVES	Compare duration of benefit between DAXI and BotoxA.
NUMBER OF SUBJECTS	20

SUBJECT SELECTION CRITERIA	Inclusion Criteria: Age ≥18 Diagnosis of adductor laryngeal dystonia (ADLD) Previous successful treatment with BotoxA and stabilized dose for the last 3 treatments Acceptable form of birth control for females of childbearing potential. Women of childbearing age must have a negative pregnancy test Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the inclusion criteria listed in the subject selection section below. Exclusion Criteria: Age <18 Other neurologic conditions (ALS, Parkinson's disease, essential tremor, Meige syndrome, etc.) Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data. Naive from other types of Botox for 6 months including BotoxA
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Open-label dose of DAXI injected at either 0.625, 1.25, or 2.5 units. Dosage will be determined by subject's previous stabilized Botox dosage.

CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	N/A
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be in the study for up to 36 weeks. Total time for recruitment and completion of the study will be up to 2 years.
CONCOMMITANT MEDICATIONS	Allowed: all Prohibited: Other forms of Botox
EFFICACY EVALUATIONS	Validated laryngology PROMs, voice analysis via mobile app (voice recording sample), duration of effect
PRIMARY ENDPOINT	Efficacy, measured quantitively through VHI-10 questionnaires
SECONDARY ENDPOINTS	Duration of benefit, assessed qualitatively through phone call surveys
OTHER EVALUATIONS	Participant Questionnaires ○ CPIB-10 ○ OMNI-VES ○ EAT-10

	Clinician Scales ○ Unified spasmodic dysphonia rating scale (USDRS) ○ Phonalyze
SAFETY EVALUATIONS	Incidence of adverse events
PLANNED INTERIM ANALYSES	When approximately 50% of patients have completed the study's initial injection, an interim analysis for safety will be conducted.
STATISTICS **Primary Analysis Plan**	Safety profile including AE and SAEs will be reported. Simple descriptive statistics will be used to summarize toxicities in terms of type, severity and minimum or maximum values for laboratory measures, time of onset, duration, and reversibility or outcome. Tables will be created to summarize these toxicities and side effects. Safety Analyses will be performed on Safety Analysis Set.
Rationale for Number of Subjects	A sample size of 20 will provide 80% power to detect a difference of 6.6 at a significance threshold (alpha) of 0.05.

1 BACKGROUND

Approximately 50,000 people in North America have a diagnosis of adductor laryngeal dystonia (ADLD). Laryngeal dystonia (LD) is a neurologic condition causing aberrant contraction of the laryngeal musculature, leading to abnormal voicing during speech. The three types (adductor, abductor, and mixed) affect varying muscle groups which produce characteristic voice patterns. The vast majority of patients with SD have adductor type, which impacts the lateral cricoarytenoid and thyroarytenoid muscle complex. While many treatment modalities have been investigated, the most efficacious treatment is botulism toxin injection to these muscle groups, performed transcervically with or without electromyography (EMG) guidance. Patients undergoing this treatment typically require re-injection every three months. Due to its specialized nature, the laryngeal injections are not performed routinely outside of academic medical centers; thus, patients may come from a distance to receive this treatment. Both due to the significant impact on voice quality when the injections wear off and the sometimes challenging access to treatment, a longer acting agent is desire.

1.1 Overview of Non-Clinical Studies

An animal model has demonstrated reduced diffusion of the neurotoxin with this formulation which may account for its longer duration of effect. DAXI can be formulated without the use of human serum albumin ensuring its stability at room temperature before reconstitution.

1.2 Overview of Clinical Studies

Injectible daxibotulinumtoxinA (DAXI, Revance Therapeutics Inc., Newark, CA) has received FDA approval for treatment of glabellar lines and has been shown in large clinical trials to provide safe, effective treatment for cervical dystonia. DAXI may offer a longer-lasting result when compared with onabotulinumtoxin.

2 STUDY RATIONALE

This study aims to assess the efficacy of DAXI for transcervical laryngeal injection in patients with adductor laryngeal dystonia. Secondly, this study aims to assess whether DAXI provides longer clinical benefit than BotoxA for treatment of ADLD.

2.1 Risk / Benefit Assessment

Risks are mitigated through the use of fellowship-trained laryngologists who are experts at this type of injection.

Possible Risks: There are risks to taking part in any research study. Some of the most likely risks of participation in this study include:

- Having no effect on voice
- Requiring multiple injections
- Injection site pain or discomfort

There are also rare but serious risks of participation, like:

- *Difficulty swallowing, possibly requiring a temporary feeding tube*
- *Difficulty breathing, possibly requiring hospitalization*

Possible Benefits:

- Participants may benefit from participating in the study, but this cannot be guaranteed. When looking at previous trials with a different indication, DAXI provided a longer-lasting effect than traditional Botox.

The potential benefits may outweigh the risks as DAXI may ultimately decrease frequency of injection, while maintaining similar risk to Botox injection.

3 STUDY OBJECTIVES

3.1 Primary Objective

Evaluate efficacy of botulinum toxin A neurotoxin, daxibotulinumtoxinA (DAXI) among ADLD subject population

3.2 Secondary Objectives

Determine duration of clinical benefit to assess whether DAXI may provide longer clinical benefit than BotoxA for treatment of ADLD

4 STUDY DESIGN

4.1 Study Overview

This is a single-center, open-label, dose-escalation trial. 20 subjects are planned. Each subject will be administered a single dose of DAXI. If the subject does not achieve the desired self-reported voice improvement, at 1 week post injection an additional dose of DAXI will be administered.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

The following treatment regimens will be used:

- Injection of DAXI at the following doses: 0.625, 1.25, 2.5 units depending on subject's current standard dose of Botox.

Total duration of subject participation will be 36 weeks. Total duration of recruitment and completion of all procedures of the study is expected to be up to 2 years.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the difference in VHI-10 scores at 8 weeks after injection with DAXI. VHI-10 questionnaires will be given at baseline, day 14, then monthly.

5.2 Secondary Efficacy Endpoints

The secondary endpoint is duration of benefit, assessed by median time to baseline VHI-10 after treatment with DAXI and via phone call surveys. VHI-10 questionnaires will be given at baseline, day 14, then monthly until loss of benefit. Phone calls will be conducted at day 5, day 14, then monthly until loss of benefit.

5.3 Safety Evaluations

In the event of an adverse event, the study team will notify the medical monitor.

5.4 Other Evaluations

Participant Questionnaires

- CPIB-10
- OMNI-VES
- EAT-10

Clinician scales

- USDRS
- Phonalyze

SUBJECT SELECTION

5.5 Study Population

Participants with a diagnosis of adductor laryngeal dystonia who meet the inclusion and none of the exclusion criteria will be eligible for participation in this study. Participants will be recruited from the UCSF Voice and Swallowing Center and the National Spasmodic Dysphonia Association community.

5.6 Inclusion Criteria

- Age ≥18
- Diagnosis of adductor laryngeal dystonia
- Previous successful treatment with BotoxA and stabilized dose for the last 3 treatments
- Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
  - Has a negative pregnancy test at Visit 1, Day 0.
  - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 30 days prior to the injection (Day 1).
  - Has agreed to continue adequate contraception through 3 months following the injection (Day 90).
  - Is not currently breastfeeding.

- Adequate female contraception is defined as consistent and correct use of a Food and Drug Administration (FDA) approved contraceptive method in accordance with the product label. For example:
  - Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
  - Intrauterine device
  - Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
  - Sterilization of a female participant's monogamous male partner prior to entry into the study
  - Note: periodic abstinence (e.g. calendar, ovulation, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

5.7 Exclusion Criteria

- Age <18
- Other neurologic conditions (ALS, Parkinson's disease, essential tremor, Meige syndrome, etc.)
- Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.
- Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
- Naive from other types of Botox for 6 months including BotoxA

6 CONCURRENT MEDICATIONS

All currently prescribed medications are allowed

6.1 Allowed Medications and Treatments

Standard therapy for other conditions is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

6.2 Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

- Naive from other types of Botox for 6 months including BotoxA

7 STUDY TREATMENTS

7.1 Method of Assigning Subjects to Treatment Groups

N/A (open-label study).

7.2 Blinding

N/A (open-label study).

7.3 Formulation of Test and Control Products

7.3.1 Formulation of Test Product

Injectible daxibotulinumtoxinA (DAXI, Revance Therapeutics Inc., Newark, CA) is a FDA-approved botulinum toxin type A indicated for the treatment of glabellar lines. It has been shown in large clinical trials to provide safe, effective treatment for cervical dystonia and may offer longer-lasting results when compared with onabotulinumtoxinA. DAXI will be reconstituted using sterile saline into 1mL syringes at the desired dosage similar to clinical care for Botox.

7.3.2 Formulation of Control Product

N/A (open-label study).

7.3.3 Packaging and Labeling

Refer to DAXXIFY Package Insert.

7.4 Supply of Study Drug at the Site

7.4.1 Dosage/Dosage Regimen

Subject's Current* BotoxA Dose	**DAXI Dose 1**	**DAXI Dose 2**

0.625 units unilateral	0.625 unit	0.625 unit
1.25 units unilateral	1.25 units	1.25 units
2.5 units unilateral	2.5 units	2.5 units
0.625 units bilateral	0.625 unit	0.625 unit (contralateral)
1.25 units bilateral	1.25 units	1.25 units (contralateral)
2.5 units bilateral	2.5 units	2.5 units (contralateral)

*Current is defined as the average of subject's last 3 injections

7.4.2 Dispensing

DAXI will be received at the UCSF Voice and Swallowing Center. DAXI will be kept in a locked cabinet and refrigerator at the UCSF Voice and Swallowing Center with a log kept for usage.

7.4.3 Administration Instructions

DAXI will be reconstituted using sterile unpreserved saline into 1mL syringes within 2 hours of injection by a trained preparer. It will then be injected into the unilateral or bilateral thyroarytenoid/lateral cricoarytenoid (TA-LCA) complex using electromyographic (EMG) guidance.

Laterality of injection with DAXI will be dependent on the subject's usual injection pattern. If the patient has traditionally been injected on one side, DAXI will be injected on the same side. If the patient has traditionally been injected unilaterally but with alternating sides, DAXI injection will follow the alternating pattern. If the patient has traditionally received bilateral injections, DAXI will first be injected on the left side, and if a second dose is required, it will be injected on the right.

Laterality Rules

Traditionally unilateral	DAXI same side	
Traditionally unilateral/alternating	DAXI continues in sequence	
Traditionally bilateral	1st DAXI left	2nd DAXI right

7.5 Supply of Study Drug at the Site

The study drug is supplied by the research team.

7.5.1 Storage

Refer to DAXXIFY Package Insert.

7.6 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff.

7.7 Measures of Treatment Compliance

There is no treatment compliance because DAXI is an injectable medication. No DAXI goes home with participants.

8 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative.

8.1 Clinical Assessments

8.1.1 Concomitant Medications

No concomitant medications.

8.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

8.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

8.1.4 Physical Examination

A physical examination will be performed by either the investigator or a sub-investigator who is a physician at Visit # 1. New abnormal physical exam findings must be documented.

8.1.5 Vital Signs

N/A

8.1.6 Oximetry

N/A

8.1.7 Spirometry

N/A

8.1.8 Other Clinical Procedures

N/A

8.1.9 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

8.2 Clinical Laboratory Measurements

8.2.1 Hematology

N/A

8.2.2 Blood Chemistry Profile

N/A

8.2.3 Pregnancy Test

A urine pregnancy test will be obtained from female participants who are of childbearing age prior to their participation in the study at Visit 1.

8.2.4 Urinalysis

N/A

8.3 Pharmacokinetic Measurements

N/A

8.4 Research Laboratory Measurements

N/A

8.4.1 Cell Count and Differential

N/A

8.4.2 Sputum Cytokine Measurements

N/A

9 EVALUATIONS BY VISIT

9.1 Phone Screening (7 Days prior to injection)

1. Confirmation participants meet all inclusion criteria and no exclusion criteria review
2. If they have provided consent to contact, reach out and explain the study to them.
3. Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization via DocuSign.
4. Assign the subject a unique screening number.
5. Record demographics data.
6. Record medical history, including history of ADLD, diagnosis date, and prior Botox treatments.
7. Patient fills out baseline PROMs electronically through Qualtrics (VHI-10, CPIB-10, OMNI-VES, EAT-10)
8. Patient records their voice in Phonalyze for CPP and CAPE-V analysis

9.2 Visit 1 (Clinic Visit, Day 0)

1. Review of birth control history with female participants of childbearing potential.
2. For women of childbearing potential, counsel participants to use adequate birth control methods required during the trial to avoid pregnancy.
3. For women of childbearing potential, urine pregnancy test will be checked prior to injection.
4. Perform a complete physical examination.
5. Perform DAXI injection. Laterality of injection with DAXI will be dependent on the subject's usual injection pattern. If the patient has traditionally been injected on one side, DAXI will be injected on that same

side. If the patient has traditionally been injected unilaterally but with alternating sides, DAXI injection will follow the alternating pattern. If the patient has traditionally received bilateral injections, DAXI will first be injected on the LEFT side, and if a second dose is required, it will be injected on the right.

6. Record any Adverse Experiences during injection
7. Schedule participant for remote follow-up visit in 5 days.

9.3 Visit 2 (Phone Call, Day 5)

1. Phone call to assess clinical improvement
2. Ensure there is absence of dysphagia (using EAT-10 questionnaire), no injection site issue, or other adverse events using safety survey

9.4 Visit 3 (Optional Clinic Visit, Day 7-14)

1. Additional DAXI can be administered in office if the 1st injection does not have desired clinical effect
2. Injection occurs on same side if normally unilateral, or on opposite side if bilateral

9.5 Visit 4 (Phone call, Day 14*)

1. Phone call to assess clinical improvement
2. Ensure there is absence of dysphagia (using EAT-10 questionnaire), no injection site issue, or other adverse event

*Day 14 after most recent DAXI injection

9.6 Visits 5-10 (Remote Survey, every month starting 1 month after most recent injection)

1. Phone call to assess duration of benefit
2. Patient fills out PROMs electronically through Qualtrics to assess our primary (VHI-10) and secondary outcome measures

- VHI-10
- CPIB-10
- OMNI-VES
- EAT-10

3. Patient records their voice in Phonalyze for CPP and CAPE-V analysis
4. Patient will record whether DAXI still has desired effect

Data is collected monthly until loss of benefit.

For every instance when all PROMs and Phonalyze recordings are completed, patients will be paid $10, up to $150. After the completion of the study the number of entries will be tabulated and patient will be given a Visa gift card in the allotted amount. Patients who withdraw from the study will still be compensated for all instances when PROMs and Phonalyze recordings were completed.

9.7 Early Withdrawal Visit

N/A

10 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of drug product, whether or not related to that product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Package Insert or of greater severity or frequency than expected based on the information in the Package Insert.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events

will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

10.1.1 AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

10.1.2 AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

10.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

10.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF HRPP Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the UCSF Institutional Review Board (IRB), the site investigator will report SAEs immediately to the UCSF IRB and sponsor.

10.3 Protocol Defined Important Medical Findings Requiring Real Time Reporting

N/A

10.4 Medical Monitoring

Dr. Clark Rosen should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (415) 885-7700

11 DISCONTINUATION AND REPLACEMENT OF PARTICIPANTS

11.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation (falsifying eligibility criteria) requiring discontinuation of study treatment
- Lost to follow-up
- Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All participants who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

11.2 Withdrawal of Participants from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

11.3 Replacement of Participants

N/A

12 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Failure to report an AE

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Investigator will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

13 DATA SAFETY MONITORING

A Data Monitoring Committee (DMC) to review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study, according the UCSF IRB. The DMC will be made up of the investigator team (PI, other study clinicians, and research assistants) will be meeting at least every 2 weeks to review preliminary data. At this time, the following will be reviewed:

- Enrollment (number of participants)

- Adverse events
- Any unexpected voice/swallow/breathing problems based on the survey data collected
- Any phone calls by participants to the Voice and Swallowing Center
- Breaches of confidentiality
- Unanticipated problems

This information will be shared with the UCSF IRB every 6 weeks. If there are any adverse events or unanticipated problems, this will be communicated immediately. An interim analysis will be conducted and reported three months after the study start date, or after the 10th subject is recruited, whichever comes first. Any participants whose confidentiality has been breached will be notified as soon as possible.

A study subject's participation in the trial will be withdrawn immediately for any the following criteria:

- The patient wishes to end participation
- The patient undergoes an additional laryngeal Botox injection (at UCSF or elsewhere)
    - Unrelated medical event/condition which impacts voice/swallowing
- The trial will be halted immediately for any of the following events:
    - If a pattern of poor clinical outcomes is seen
    - For multiple adverse events
    - At UCSF IRB discretion

Based on UCSF IRB guidelines, this trial does not meet criteria for a Data Safety Monitoring Board, although one would be assembled if requested by the UCSF IRB. The study has none of the following features:

- There is a significant likelihood of a serious adverse event to participants
- The study is conducted at multiple sites and the level of risk is greater than minimal
- The study generates data that are blinded or randomized
- The study involves a large number of patients randomized to one of two or more interventions

- A study for which the performance of an interim analysis is crucial for the protection of the participants
- First use in humans
- First use in children
- The study involves gene therapy, stem cell therapy, or other novel interventions for which long-term outcome data are not known or available

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below. Discuss with statistician

14.1 Data Sets Analyzed

All eligible patients who are in study and receive at least one dose of DAXI will be included in the safety analysis.

14.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: race, gender, age, duration of ADLD.

14.3 Analysis of Primary Endpoint

Our primary outcome is the difference in VHI-10 score at 8 weeks after injection with DAXI. This will be determined using a paired t-test with subjects pre-treatment VHI-10 scores as a control. Our second primary outcome measure is the duration of effect of DAXI, assessed qualitatively through phone calls, compared to patients' prior Botox treatment. We will produce a Kaplan-Meier curve to illustrate the duration of clinical benefit after treatment with DAXI.

14.4 Analysis of Secondary Endpoints

A secondary outcome will be comparing the duration of effect of DAXI with patients' prior Botox treatment. Specifically, we will determine the median time to baseline VHI-10 after treatment with DAXI and produce a Kaplan-Meier curve to illustrate the duration of clinical benefit.

14.5 Interim Analysis

Every 6 weeks:

- Information will be shared with the UCSF IRB.

Every 3 months:

- An interim analysis will be conducted and reported or after the 10th subject is recruited

14.6 Sample Size and Randomization

One primary outcome is the difference in VHI-10 score at 6 weeks after injection with DAXI. The normative values of the VHI-10 have been established, with a normal value of 2.83 and standard deviation of 3.93. One prospective study for Botox in SD determined a pretreatment VHI-10 score of 22.58 +/- 7.09 and 6-week post-treatment 20.86 +/- 7.24. The difference had a standard deviation of approximately 10. A sample size of 20 will provide 80% power to detect a difference of 6.6 at a significance threshold (alpha) of 0.05.

A secondary outcome will be comparing the duration of effect of DAXI with patients' prior Botox treatment. Specifically, we will determine the median time to baseline VHI-10 after treatment with DAXI and produce a Kaplan-Meier curve to illustrate the duration of clinical benefit. A large retrospective study from Blitzer et al from described the average duration of benefit to be about 15.1 weeks with a standard deviation of 12.3 weeks [10]. Unpublished data from our institution revealed an average duration of 18.9 weeks with a standard deviation of 7.2 weeks. Using the data from our institution, a sample size of 20 will provide 80% power to detect a difference in average duration of 2.4 weeks. (This calculation assumed a with-subject correlation coefficient of 0.875.)

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) into a REDCap database when the information corresponding to that visit is available. Participants will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by subject number and initials.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail.

The Investigator is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

15.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the REDCap and Qualtrics system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent & HIPAA Authorization Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

15.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor-Investigator according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.7 Subject Confidentiality

In order to maintain subject confidentiality, only subject number and subject initials will identify all study participants on CRFs and other documentation

submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the Investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Package Insert, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written

unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be

given ample opportunity to inquire about details of the study. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.

8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. STUDY VISITS

	SCREENING	VISIT 1 (CLINIC VISIT, DAY 0)[a]	VISIT 2 (PHONE CALL, DAY 5)[a]	VISIT 3 (OPTIONAL CLINIC VISIT, DAY 7-14)[a]	VISIT 4 (PHONE CALL, DAY 14)[a]	VISIT 5-10 (STARTING 1 MONTH AFTER LAST DAXI INJECTION, MONTHLY UNTIL LOSS OF BENEFIT)
Informed Consent	X					
Medical History	X					
Urine pregnancy test (if applicable)		X				
Physical Exam		X				
DAXI Injection		X		X		
USDRS		X		X		
Phone call to assess duration of benefit			X		X	X
EAT-10	X		X		X	
VHI-10	X				X	X
OMNI-VES	X				X	X
CPIB-10	X				X	X
Phonalyze recording	X				X	X

[a] ±2 days

APPENDIX 2. INVESTIGATORS

Clark Rosen, MD

VyVy Young, MD

Yue Ma, MD

Aviva Fliker, MD

Sarah Schneider, MS, CCC-SLP

APPENDIX 3. FINANCIAL CONSIDERATIONS

Participants will be compensated for participation in the study. For every completed survey and VoiceEvalu8 entry, they will be paid $10, up to $150. At the completion of the study, the number of entries will be tabulated and the patient will be given a Visa gift card in the allotted amount.

APPENDIX 4. SAFETY SURVEY

- Pain, swelling or bruising at the injection site
- Headache
- Flu-like symptoms
- Trouble speaking or swallowing
- Breathing problems
- Cough
- Hoarseness

APPENDIX 5. REFERENCES

1. Carruthers, J., et al., *Injectable DaxibotulinumtoxinA for the Treatment of Glabellar Lines: A Phase 2, Randomized, Dose-Ranging, Double-Blind, Multicenter Comparison With OnabotulinumtoxinA and Placebo.* Dermatol Surg, 2017. **43**(11): p. 1321-1331.
2. Jankovic, J., et al., *Injectable DaxibotulinumtoxinA in Cervical Dystonia: A Phase 2 Dose- Escalation Multicenter Study.* Mov Disord Clin Pract, 2018. **5**(3): p. 273-282.

3. Carruthers, J.D., et al., *DaxibotulinumtoxinA for Injection for the Treatment of Glabellar Lines: Results from Each of Two Multicenter, Randomized, Double-Blind, Placebo- Controlled, Phase 3 Studies (SAKURA 1 and SAKURA 2).* Plast Reconstr Surg, 2020. **145**(1): p. 45-58.
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5. Rumbach, A., P. Aiken, and D. Novakovic, *Outcome Measurement in the Treatment of Laryngeal dystonia: A Systematic Review of the Literature.* J Voice, 2019. **33**(5): p. 810 e13-810 e39.
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8. Belafsky, P.C., et al., *Validity and reliability of the Eating Assessment Tool (EAT-10).* Ann Otol Rhinol Laryngol, 2008. **117**(12): p. 919-24.
9. Arffa, R.E., et al., *Normative values for the Voice Handicap Index-10.* J Voice, 2012. **26**(4): p. 462-5.
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