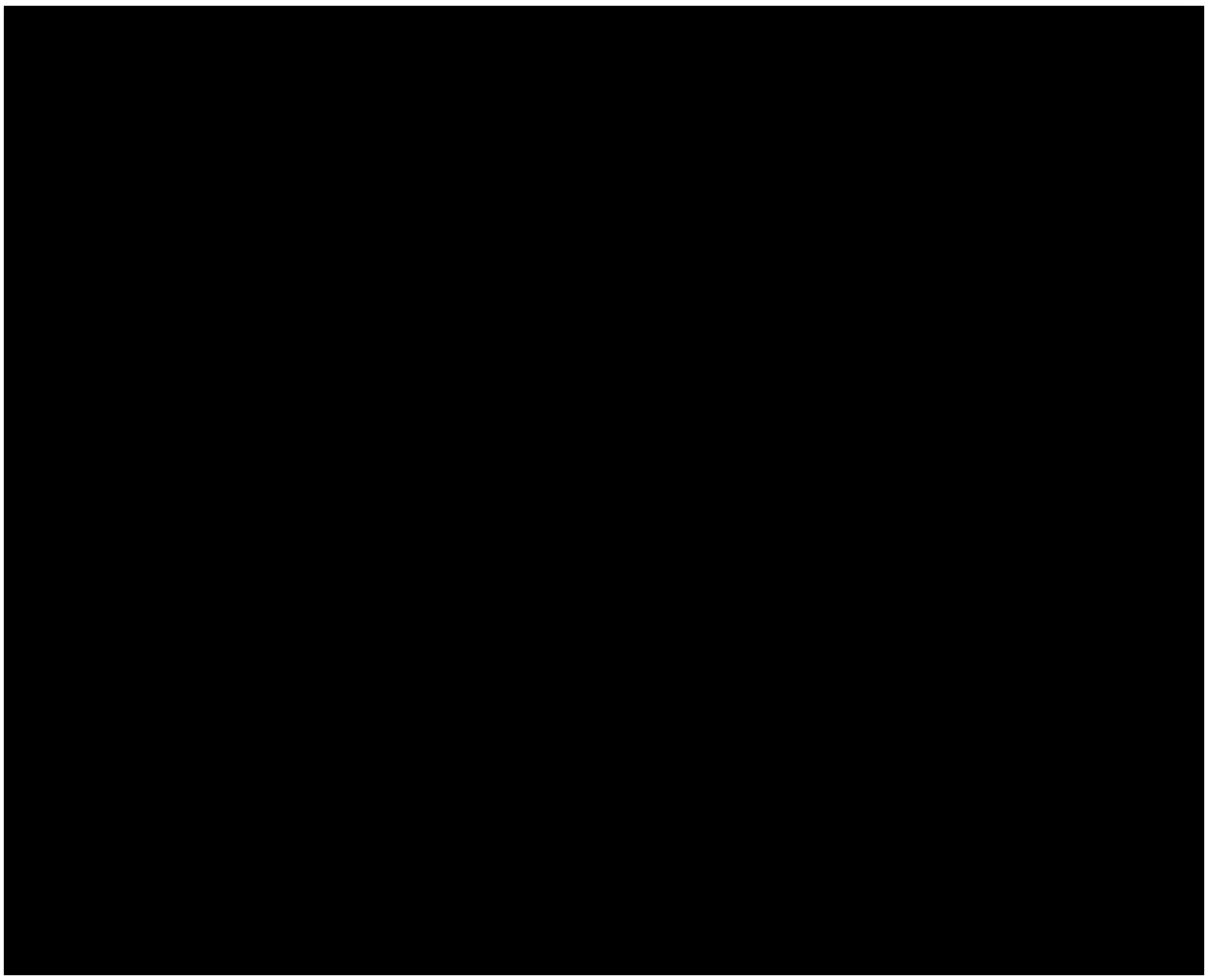
TITLE	A Phase 3, Randomized, Double-Blind, Placebo Controlled, Multi-Center Trial to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection to Treat Moderate to Severe Glabellar Lines (SAKURA-2)
PROTOCOL NUMBER	1620302
SPONSOR	Revance Therapeutics, Inc. 7555 Gateway Boulevard Newark, CA 94560 Tel.: 510.742.3400 Fax: 510.662.4903
DOCUMENT TYPE	Amended Protocol
VERSION	Amendment 1, 07 November 2016

The trial will be conducted in compliance with the obligations as detailed in this protocol, and all applicable regulations and guidelines (e.g., International Conference on Harmonisation [ICH] Good Clinical Practices [GCP] guidelines).

SIGNATURE PAGE



INVESTIGATOR'S AGREEMENT

I have carefully read the protocol entitled: "*A Phase 3, Randomized, Double-Blind, Placebo Controlled, Multi-Center Trial to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection to Treat Moderate to Severe Glabellar Lines*" and,

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the trial personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the trial protocol.

I agree to conduct this clinical trial according to the attached protocol, in compliance with all applicable laws and regulations, and in accordance with the ethical principles stipulated in the Declaration of Helsinki.

Investigator Signature

Printed Name | **Date**

Institution Name

Address

City, State Postal Code, Country | **Phone Number**

PROTOCOL SYNOPSIS

Name of Sponsor/Company:	Revance Therapeutics, Inc.
Name of Finished Product:	DaxibotulinumtoxinA for Injection
Name of Active Ingredient:	daxibotulinumtoxinA

Title of Trial:

A Phase 3, Randomized, Double-Blind, Placebo Controlled, Multi-Center Trial to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection to Treat Moderate to Severe Glabellar Lines (SAKURA-2)

Trial Center(s):	Up to 15 centers in the United States (US) and Canada
Number of Subjects Planned:	Approximately 300 subjects will be enrolled
Trial Period:	Up to 38 weeks, including 2 weeks for screening
Phase of Development:	3

Objective:

To evaluate the efficacy and safety of a single treatment of DaxibotulinumtoxinA for Injection for the treatment of moderate to severe glabellar lines compared to placebo.

Design and Methodology:

This is a Phase 3, randomized, double-blind, placebo-controlled, multi-center trial. Approximately 300 adult subjects with moderate to severe glabellar lines will be enrolled. Subjects will be randomly assigned in a 2:1 ratio to DaxibotulinumtoxinA for Injection 40 U or placebo.

All subjects will be followed for at least 24 weeks post-treatment for efficacy and safety assessments. If both Patient Frown Wrinkle Severity (PFWS) and Investigator Global Assessment Frown Wrinkle Severity (IGA-FWS) scores at maximum frown, return to baseline by the Week 24 visit or at a visit between Weeks 24 and 36, the visit at which that score is recorded will be the Final Evaluation Visit for the subject.

After the Final Evaluation Visit, all qualified subjects will have the option to enroll into an open-label, trial to evaluate the long-term safety of repeat use of DaxibotulinumtoxinA for Injection for the treatment of moderate to severe glabellar lines.

The Investigator, trial center staff, subjects, and Sponsor will remain blinded to study treatment throughout the trial. Only the statistician responsible for the randomization codes will be unblinded to the treatment assignments.

Treatment Group	Test Article and Dose	No. of Subjects
Treatment 1	DaxibotulinumtoxinA for Injection 40 U	200
Treatment 2	Placebo	100

Trial Visits:

Screening (–Week 2), Treatment (Day 0), Follow-up at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36.

Safety Evaluations:

- Clinical laboratory tests (hematology, chemistry, prothrombin time [PT], urinalysis)

[redacted]

Name of Sponsor/Company:	Revance Therapeutics, Inc.
Name of Finished Product:	DaxibotulinumtoxinA for Injection
Name of Active Ingredient:	daxibotulinumtoxinA

- Injection Site Evaluation

[redacted]

- 12-lead ECG
- Concomitant medications
- Collection of AEs

[redacted]

- Vital Signs
- Physical Examination

Efficacy Evaluations:

- Investigator Global Assessment Frown Wrinkle Severity (IGA-FWS)
- Patient Frown Wrinkle Severity (PFWS)
- Investigator and Patient Global Aesthetic Improvement Scale (GAIS)

Other Evaluations:

- Photographs of treatment area
- Subject Global Satisfaction with Treatment Questionnaire
- Subject diary to capture subject severity ratings for the first 2 weeks following treatment

[redacted]

- Facial Age Self Evaluation (FASE)

Diagnosis and Main Abbreviated Eligibility Criteria:

Outpatient, male or non-pregnant, non-nursing females, 18–75 years of age, and in good general health with moderate (2) or severe (3) glabellar lines during maximum frown based on the IGA-FWS and PFWS. (Refer to Protocol Section 3.4 Eligibility Criteria).

Test Article, Dose and Mode of Administration:

DaxibotulinumtoxinA for Injection, 40 U, intramuscular injection, 0.5 mL

Control, Dose and Mode of Administration:

Placebo: DaxibotulinumtoxinA placebo, intramuscular injection, 0.5 mL

Statistical Analyses:

Primary Efficacy Endpoints

Primary clinical efficacy will be assessed by a blinded evaluator who will grade the severity of the subject's glabellar lines at maximum frown using the IGA-FWS. Also the subject will grade the severity of their glabellar lines at maximum frown using the PFWS. A responder will be defined as a subject who achieves a score of 0 or 1 (none or mild) and an improvement of at least two points from the baseline score, on both the IGA-FWS and PFWS scales concurrently at Week 4.

The Proportion of Responders will be compared between daxibotulinumtoxinA and placebo at Week 4 using the Cochran–Mantel–Haenszel (CMH) test stratified by trial center.

[redacted]

Name of Sponsor/Company:	Revance Therapeutics, Inc.
Name of Finished Product:	DaxibotulinumtoxinA for Injection
Name of Active Ingredient:	daxibotulinumtoxinA

[redacted]

Sample Size and Power Considerations

Estimates of treatment efficacy taken from trial RT002-CL002 show that a sample size of 200 and 100 for DaxibotulinumtoxinA 40 U for injection and placebo, respectively, [redacted].

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BoNTA	botulinum neurotoxin type A
BP	blood pressure
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
CRF	case report form
CRO	contract research organization
CS	clinically significant
ECG	Electrocardiogram
FASE	Facial Age Self Evaluation
FDA	Food and Drug Administration
[redacted]	[redacted]
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GLSS	Glabellar Line Severity Score
HHS	U.S. Department of Health and Human Services
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGA-FWS	Investigator Global Assessment Frown Wrinkle Severity
IRB	Institutional Review Board
ITT	intent to treat
kDa	Kilodalton
Kg	Kilogram
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MRC	Medical Research Council
NCS	not clinically significant
PFWS	Patient Frown Wrinkle Severity
PP	per protocol
PT	prothrombin time
Revance	Revance Therapeutics, Inc.

Abbreviation	Definition
RR	respiration rate
RT001	DaxibotulinumtoxinA Topical Gel
RT002	DaxibotulinumtoxinA for Injection
RTP004	Novel excipient, inactive ingredient
SAE	serious adverse event
SAS	Statistical Analysis System
SOP	standard operating procedure
TdP	Torsade de Pointe
U	units
UPT	urine pregnancy test
WHO	World Health Organization
WOCBP	woman of child bearing potential

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[redacted]

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1 BACKGROUND

The safety and effectiveness of botulinum toxin type A to act on the neuromuscular junction and relieve muscle spasm and its clinical effects such as strabismus, pain, and facial wrinkles has been well established for over 20 years (Scott, 1981; Carruthers, 1992; Spencer, 2002).

[redacted]

[redacted]

2 TRIAL OBJECTIVE

To evaluate the efficacy and safety of a single treatment of DaxibotulinumtoxinA for Injection for the treatment of moderate to severe glabellar lines compared to placebo.

3 TRIAL DESIGN

3.1 OVERALL TRIAL DESIGN

This phase 3, double blind, placebo-controlled, multi-center trial is designed to evaluate the efficacy and safety of a single intramuscular treatment of DaxibotulinumtoxinA for Injection for the temporary improvement in the appearance of glabellar lines in adults compared to a placebo. Approximately 300 adult subjects with moderate to severe glabellar lines will be enrolled.

3.1.1 DURATION OF TRIAL

The duration is up to 38 weeks on trial, including a screening period of up to two weeks followed by a single treatment and a follow-up period of up to 36 weeks post-treatment. All subjects will be followed for at least 24 weeks post-treatment.

3.1.2 CONTROL

Placebo to match DaxibotulinumtoxinA for Injection

3.1.3 DOSAGE/DOSE REGIMEN

Subjects will be randomized to receive one of the two treatments shown in Table 1.

Table 1: Description of Treatment Groups

Test Article and Dose	No. of Subjects
DaxibotulinumtoxinA for Injection 40 U	200
Placebo	100

All treatments will be intramuscular injections administered by a trained physician. Subjects will receive a single treatment of [redacted]. The Investigators, trial center staff, subjects, and Revance will remain blinded to the treatment group assignments. Only the statistician responsible for the randomization scheme will be unblinded to the treatment assignments.

3.1.4 VISIT SCHEDULE

A screening visit will be conducted up to two weeks prior to randomization, and subjects will be treated with investigational product on Day 0. Following treatment, subjects will complete a paper diary for the initial 2-week period to capture their assessment of the appearance of the lines. Post-treatment on-site follow-up visits will occur at Weeks 1, 2,

4, 8, 12, 16, 20, 24, 28, 32, and 36 or when the Patient and Investigator's Global Assessment Frown Wrinkle Severity (PFWS and IGA-FWS) scores return to baseline. All subjects should be followed up for a minimum of 24 weeks post treatment.

[redacted]

3.3 TRIAL POPULATION

Approximately 300 female or male subjects, 18–75 years of age, in good general health, with moderate or severe glabellar lines will be enrolled.

3.4 ELIGIBILITY CRITERIA

3.4.1 INFORMED CONSENT AND AUTHORIZATION TO RELEASE HEALTH INFORMATION

Written informed consent will be obtained from all subjects before any study-related procedures (including any screening procedures) are performed. The Investigator may discuss the trial and the possibility for entry with a potential subject without first obtaining consent. However, a subject wishing to participate must give written informed consent prior to any study-related procedures being conducted, including those performed solely for the purpose of determining eligibility for study participation, and including withdrawal from current medication (if required prior to study entry). The Investigator has both the ethical and legal responsibility to ensure that each subject being considered for inclusion in this trial has been given a full explanation of the procedures and expectations for study participation.

The site-specific informed consent must be forwarded to Revance for approval prior to submission to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that is registered with the US Department of Health and Human Services (HHS) or applicable health authority. Each subject will sign the consent form that has been approved by the same IRB/IEC that was responsible for protocol approval. Each informed consent document must adhere to the ethical principles stated in the Declaration

of Helsinki and will include the elements required by FDA regulations in 21 CFR Part 50, as well as the elements required by the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline, and applicable federal and local regulatory requirements. The consent form must also include a statement that Revance, their designees, and auditing regulatory agencies will have direct access to the subject's records and medical history for study related purposes.

Once the appropriate essential information has been provided to the subject and fully explained by the Investigator (or a qualified designee) and it is felt that the subject understands the implications and risks of participating in the trial, the IRB/IEC approved consent document shall be signed and dated by both the subject and the person obtaining consent (Investigator or designee), and by any other parties required by the IRB/IEC or other regulatory authorities. The subject will be given a copy of the signed informed consent document with the original kept on file by the Investigator. All of the above activities must be completed before any study related procedures are conducted (including any screening study procedures).

3.4.2 INCLUSION CRITERIA

All subjects must meet the following inclusion criteria:

1. Provide written informed consent including authorization to release health information
2. Outpatient, male or non-pregnant, non-nursing females, 18–75 years of age, and in good general health
3. Moderate (2) or severe (3) glabellar lines during maximum frown based on the Investigator Global Assessment Frown Wrinkle Severity (IGA-FWS) scale
4. Moderate (2) or severe (3) glabellar lines during maximum frown based on the Patient Frown Wrinkle Severity (PFWS) scale
5. Willing to refrain from receiving facial fillers, laser treatments, use of any product that affects skin remodeling, or a product that may cause an active dermal response in the treatment area from screening through the end of the trial
6. Female subjects of childbearing potential must have a negative urine pregnancy test result at the Screening Visit and at the Treatment Visit, prior to investigational product administration, and practice an effective method of contraception throughout the trial (section 4.1.1)
7. Able to understand the requirements of the trial and sign informed consent including authorization to release health information
8. Willing and able to follow all trial procedures, attend all scheduled visits, and successfully complete the trial

3.4.3 EXCLUSION CRITERIA

Subjects will not be enrolled if they meet any of the following exclusion criteria:

1. Any neurological condition that may place the subject at increased risk with exposure to botulinum toxin type A, including peripheral motor neuropathic diseases such as amyotrophic lateral sclerosis and motor neuropathy, and neuromuscular junctional disorders such as Lambert-Eaton syndrome and myasthenia gravis
2. Muscle weakness or paralysis in the area receiving study treatment; or history of facial nerve palsy (e.g., Bell's Palsy)
3. Active skin disease, infections or inflammation at the injection sites
4. Significant facial asymmetry, eyelid ptosis or history of same, significant brow ptosis or history of same, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or inability of investigator to completely or almost completely eliminate glabellar lines by physically spreading medial brows apart while at rest
5. A score of 2 or higher in any category of the Regional House-Brackman Facial Nerve Grading System at screening
6. Previous treatment with botulinum toxin type A in the face within 6 months prior to screening
7. Plan to receive botulinum toxin type A anywhere in the face through the duration of the study
8. Treatment with greater than 200 U botulinum toxin type A anywhere else in the body outside of the face within the last 3 months prior to screening and through the end of trial

[redacted]

[redacted]

No additional exclusions may be applied by the investigator in order to ensure that the trial population will be representative of all eligible subjects.

Deviation from any entry criterion excludes a subject from enrollment into the trial.

4 TRIAL PROCEDURES

4.1 SUBJECT ENTRY PROCEDURES

Subject informed consent must be obtained prior to conducting screening procedures.

At the screening visit, procedures including vital signs, physical examination, collection of samples for hematology, chemistry, prothrombin time (PT), [redacted] urinalysis, urine pregnancy test (UPT) for WOCBP, collection of concomitant medication and medical history information, examination of the treatment area, PFWS, and IGA-FWS must be completed. Results from clinical laboratory tests and centrally-read ECG must be obtained and reviewed by the Investigator. Any WOCBP having a positive pregnancy test pre-treatment will not be treated.

After the required screening procedures are completed and study eligibility is confirmed as defined by the eligibility criteria in Sections 3.4.2 and 3.4.3, the subject will be randomized to treatment and the assigned blinded investigational product will be prepared by the blinded dose preparer and administered by the Investigator.

4.1.1 PREGNANCY

WOCBP must use an effective method of birth control during the course of the trial, such as the oral contraceptive pill, injection, implant, patch, vaginal ring, intrauterine coil, intrauterine device, tubal ligation, barrier method used WITH an additional form of contraception (e.g., sponge, spermicide or condom), abstinence, no heterosexual intercourse, or has a vasectomized partner. A female is considered to be of childbearing potential UNLESS she is post-menopausal (no menses for 12 consecutive months) or without a uterus and/or both ovaries.

Before enrolling WOCBP in this clinical trial, Investigators must review guidelines about study participation for WOCBP. The topics should generally include:

- Informed consent document
- Pregnancy prevention information
- Risks to unborn child(ren)
- Any drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during participation in this clinical trial and the potential risk factors for an

unintentional pregnancy. The subject must sign the informed consent document stating that the above-mentioned risk factors and the consequences were discussed with her.

During the trial, all WOCBP should be instructed to contact the Investigator immediately (within 24 hours) if they suspect they might be pregnant (e.g., missed or late menstrual cycle). The Investigator must immediately notify Revance or designated Contract Research Organization (CRO) of any female subject who becomes pregnant any time during study participation, record the information on the Pregnancy Notification Form and send the form to the CRO. The site will be asked to follow-up with the subject periodically during the pregnancy for ongoing health and safety information through term, as applicable. Subjects will remain on the trial.

4.2 SCHEDULE OF VISITS AND PROCEDURES

It is recommended that trial visits be scheduled at approximately the same time of day throughout the trial.

The IGA-FWS and Investigator GAIS should be performed by the same evaluator throughout the trial whenever possible. If it is not possible to use the same evaluator to follow the subject throughout the trial, two evaluators should examine the subject together and discuss findings for at least one prior visit. A schedule of study assessments is provided in Appendix J.

4.2.1 SCREENING VISIT

The Screening Visit must take place within 14 days prior to investigational product administration at Day 0 (Treatment Visit). The following procedures must be performed and recorded at this visit:

1. Review trial procedures and information regarding the trial and obtain written informed consent
2. Review eligibility criteria
3. Obtain medical/surgical history, including prior toxin use, and demographic information, including Fitzpatrick skin type
4. Conduct patient education: Discuss the potential effect of DaxibotulinumtoxinA for Injection treatment, explain the PFWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for severity of their glabellar lines. Use the provided Patient Education Brochure
5. Measure and record vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure)
6. [redacted]
7. Obtain 12-lead ECG

8. Collect blood samples for clinical safety laboratory tests (hematology, chemistry, and PT)

[redacted]

The screening visit clinical laboratory test results, UPT and ECG report must be reviewed and signed by the Investigator; any abnormal results must be determined to be not clinically significant by the Investigator prior to randomization.

4.2.2 TREATMENT VISIT (DAY 0)

The Treatment Visit must be performed within 14 days of the Screening Visit. The following procedures must be performed and recorded:

Prior to Investigational Product Administration

1. Review eligibility criteria and confirm that all screening visit procedures have been completed, results reviewed, and recorded
2. Update medical/surgical history
3. Conduct patient education: Discuss the potential effect of DaxibotulinumtoxinA for Injection treatment, explain the PFWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for severity of their glabellar lines. Use the provided Patient Education Brochure

4. Measure and record vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure)

[redacted]

16. Once the Investigator has confirmed subject eligibility, enroll the subject

Investigational Product Preparation

The assigned, blinded investigational product will be prepared by the blinded, trained dose preparer according to trial-specific instructions. The prepared investigational product will be provided in a syringe to the Investigator for administration.

Investigational Product Administration

Investigational product will be administered by the Investigator to injection site in the designated treatment area (Appendix A) while the subject is in a sitting position.

1. Wear protective gloves for investigational product administration
2. Pull subject's hair away from the treatment area (forehead)
3. Wipe all injection sites with alcohol

4. Inject a dose of [redacted]

- [redacted]

After Investigational Product Administration

1. [redacted] obtain vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressures)

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

4.2.3 WEEK 1 FOLLOW-UP VISIT

At Week 1, following the first treatment, the subject will return to the office for a health status check, concomitant therapy/medication check, and a query about AEs that may have occurred.

The following procedures must be performed and recorded:

1. Query subject about concomitant therapy/medication
2. Query subject about any AEs

- [redacted]

[redacted]

7. Conduct patient education: discuss the potential effect of DaxibotulinumtoxinA for Injection treatment, explain the PFWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for severity of their glabellar lines. Use the provided Patient Education Brochure

[redacted]

4.2.4 FOLLOW-UP VISITS

At Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32 the following procedures must be performed and recorded:

[redacted]

2. Conduct patient education: discuss the potential effect of DaxibotulinumtoxinA for Injection treatment, explain the PFWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for severity of their glabellar lines. Use the provided Patient Education Brochure
3. At Week 2 only, measure and record vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure)

[redacted]

[redacted]

7. At Week 4 only, obtain 12-lead ECG

[redacted]

12. Provide [redacted] and Facial Age Self Evaluation (FASE) (Section 4.6.2.4) questionnaires to subject for completion

[redacted]

19. Assess AEs

[redacted]

4.2.5 FINAL EVALUATION VISIT OR EARLY DISCONTINUATION

The following procedures must be performed and recorded at the Final Evaluation Visit for each subject. Following treatment, subjects will be followed for safety until at least Week 24 and up to Week 36 with monthly visits until both IGA-FWS and PFWS scores have returned to baseline. The subject will then have a Final Evaluation Visit.

1. Conduct patient education: Discuss the potential effect of DaxibotulinumtoxinA for Injection treatment, explain the PFWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for severity of their glabellar lines. Use the provided Patient Education Brochure
2. Measure and record vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure)

[redacted]

10. Provide [redacted] and Facial Age Self Evaluation (FASE) (section 4.6.2.4) questionnaires to subject for completion

[redacted]

16. Assess AEs

[redacted]

[redacted]

If there are no safety concerns, the subject's participation in the trial is complete at this visit.

After the Final Evaluation Visit, all qualified subjects will have the option to enroll into an open-label, trial to evaluate the long-term safety of repeat use of DaxibotulinumtoxinA for Injection for the treatment of moderate to severe glabellar lines.

4.2.6 DISCONTINUATION/WITHDRAWAL PROCEDURES

A subject may voluntarily withdraw from study participation at any time. If the subject withdraws consent and discontinues from the trial, the Investigator will attempt to determine the reason for discontinuation and record the reason in the subject's trial records and on the case report form (CRF). If a subject withdraws consent because of an AE, that AE should be indicated as the reason for withdrawal. In the event of early discontinuation, (i.e., prior to the Final Evaluation) and whenever possible, the subject should be asked to return to the trial center to complete the assessments specified in the Final Evaluation Visit. Subjects who withdraw from the trial will not be replaced.

If at any time during the trial, the Investigator determines that it is not in the best interest of the subject to continue, the subject will be discontinued from participation. The Investigator can discontinue a subject from study participation at any time if medically necessary or if the subject has failed to follow trial procedures or to keep follow-up appointments. Appropriate documentation in the subject's trial record and CRF regarding the reason for discontinuation must be completed. Prior to discontinuing a subject from study participation, the Investigator will discuss his/her intentions with the Medical Monitor or designee.

All subjects who fail to return to the trial center for the required follow-up visits will be contacted by phone to determine the reason(s) why the subject failed to return for the necessary visit or elected to discontinue from the trial. If a subject is unreachable by telephone after a minimum of two documented attempts (one attempt on two different days), a registered letter will be sent requesting that contact be made with the Investigator.

Revance has the right to terminate or to stop the trial at any time. Should this be necessary, both Revance and the Investigator will ensure that proper study discontinuation procedures are completed.

4.3 VARIATION FROM SCHEDULED VISIT DAYS

To allow for scheduling flexibility, limited variation will be permitted from the specified time of each visit (Table 2).

Table 2: Allowed Variation from Scheduled Visit Days

Scheduled Visit	Allowed Variation
Week 1	+ 2 days
Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36	+/- 3 days

4.4 SCHEDULE OF VISITS AND PROCEDURES

A schedule of visits and procedures is provided in Appendix J.

4.5 SAFETY ASSESSMENTS

4.5.1 CLINICAL LABORATORY DATA

As outlined in Table 3, non-fasting samples for hematology, chemistry, PT and urinalysis will be collected at Screening, Week 4, and at the Final Evaluation Visit. [redacted] Blood and urine will be collected using applicable safety precautions and will be processed according to the central clinical laboratory's instructions. Urinalysis will be evaluated at the trial center using supplies provided by the sponsor.

Table 3: Clinical Laboratory Tests

Serum Chemistry	Hematology	Urinalysis	Additional Tests
Glucose Total bilirubin Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Blood urea nitrogen	Hemoglobin Hematocrit Leukocyte Count (total) Leukocyte Count (differential) Red Blood Cell Count Platelet Count	Specific gravity pH Glucose Protein Blood Bilirubin Ketones	Prothrombin time (PT) (Screening, Week 4 and Final Evaluation only) Urine Pregnancy (WOCBP only)* [redacted]

*If positive at timepoints after study treatment, confirm by serum pregnancy test

It is the Investigator's responsibility to review the results of all laboratory tests as they become available. For each laboratory test result outside the reference range, the Investigator must ascertain if the abnormal lab result is a clinically significant result for that individual subject. Likewise, if laboratory tests are taken at follow-up visits, the

Investigator must ascertain if this is an abnormal and clinically significant change pretreatment for that individual subject. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test. The Investigator must sign and date all written laboratory results (e.g., urinalysis, hematology, chemistry, PT, and pregnancy tests) and note Not Clinically Significant (NCS) or Clinically Significant (CS) for each out of range laboratory value. If a laboratory value is determined to be a clinically significant result for that subject, this may be considered an AE. Refer to Section 6.1.1 for further information.

[redacted]

4.5.2 PREGNANCY TESTING

All WOCBP will have a UPT at the Screening Visit, Treatment Visit pre-treatment, and Final Evaluation Visit or Early Discontinuation, if applicable. If any result is positive prior to treatment, the subject will not be allowed to participate. The results of the UPTs for WOCBP will be evaluated at the trial center. Refer to Section 4.1.1 for further information.

4.5.3 VITAL SIGNS

Vital signs (i.e., body temperature, respiration rate, sitting radial pulse rate, and sitting systolic and diastolic blood pressures) will be obtained at the Screening and Treatment Visit (pre- and post-treatment), Week 2, Final Evaluation or Early Discontinuation Visits and at any visit where signs or symptoms of botulinum toxicity is reported.

4.5.4 PHYSICAL EXAMINATION

A physical examination, in addition to vital signs, [redacted] general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, and extremities will be conducted at Screening, Week 2 and Final Evaluation or Early Discontinuation Visits. Significant physical examination findings that are present prior to investigational product administration are to be included on the Medical History page.

Significant physical examination findings which meet the definition of an adverse event will be recorded on the adverse event page post-treatment.

4.5.5 12-LEAD ECG

At Screening and Week 4, a single standard supine 12-Lead ECG will be obtained after a subject has rested quietly for at least 10 minutes using equipment provided from the central reader. The ECG data will be submitted to a central reader for measurement.

4.5.6 INJECTION SITE EVALUATION

Injection sites will be evaluated at the Screening Visit, Treatment Visit pre- and post-treatment (to determine if there is an immediate reaction to the investigational product), Follow-up Visits, and Final Evaluation Visit or Early Discontinuation Visit, if applicable. The assessment will be done as a global evaluation of the 5 injection sites (Table 4).

Table 4: Injection Site Evaluation

Assessment Descriptor	Present?	
	Yes	No
Erythema		
Edema		
Burning or Stinging (sensation as described by subject)		
Itching (sensation as described by subject)		
Bruising		

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
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4.5.10 ADVERSE EVENTS

Adverse Events (AEs) will be graded as mild, moderate, or severe as defined in Section 6.1.2 of this protocol.

AEs will be evaluated at the Treatment Visit post-treatment, Follow-up Visits, and Final Evaluation Visit or Early Discontinuation Visit, if applicable. Section 6 outlines the procedures for recording and reporting AEs.

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4.6 EFFICACY ASSESSMENTS

4.6.1 PRIMARY AND SECONDARY EFFICACY ASSESSMENTS

Efficacy assessments will include investigator assessment of glabellar line severity and glabellar line improvement, subject assessment of glabellar line severity and improvement. Efficacy assessments will be conducted with the subject in a sitting position. In order to have consistent eye positioning during the assessment, the investigator should ask the subject to focus on a fixed point in the examination room. The assessment should be conducted in a room with good overhead lighting or natural light from a window (but not direct sunlight).

4.6.1.1 Patient Frown Wrinkle Severity (PFWS)

At each clinic visit as designated in the Schedule of Trial Assessments (Appendix J), the subject will assess the visual appearance (at maximum frown and at rest after maximum frown) of the glabellar lines using the following 4 point scale for subject's assessment of Patient Frown Wrinkle Severity (Appendix B, Table 9). The assessment form will be provided directly to the subject to complete while reviewing the glabellar treatment area using a handheld mirror as outlined in Appendix B. Subjects with contact lenses should view their glabellar lines with contacts. Subjects wearing glasses should be advised to view their glabellar lines without glasses if possible. If glasses are needed for the subject to see their glabellar lines, then glasses can be worn for the assessment. The subject assessment must be completed before the Investigator completes the IGA-FWS assessment.

Table 9: Patient Frown Wrinkle Severity (PFWS)

Rating Score	Frown Wrinkle Severity	Description
0	None	No wrinkles
1	Mild	Very shallow wrinkles
2	Moderate	Moderate wrinkles
3	Severe	Deep wrinkles

[redacted]

[redacted]

4.6.1.2 Investigator Global Assessment Frown Wrinkle Severity

At each clinic visit as designated in the Schedule of Trial Assessments (Appendix J), the Investigator will assess the visual appearance (at maximum frown and at rest after maximum frown) of the glabellar lines using the IGA-FWS with the following 4 point scale (Table 10).

Table 10: Investigator Global Assessment Frown Wrinkle Severity (IGA-FWS)

Rating Score	Frown Wrinkle Severity	Description
0	None	No wrinkles
1	Mild	Very shallow wrinkles
2	Moderate	Moderate wrinkles
3	Severe	Deep and furrowed wrinkles

[redacted]

4.6.1.3 Global Aesthetic Improvement Scale

The Investigator and subject will assess the visual appearance (at maximum frown and at rest after maximum frown) of the glabellar line improvement from the baseline condition using the following 7 point severity Global Aesthetic Improvement Scale (GAIS, Table 11). Assessments will be made at the visits as designated in the Schedule of Trial Assessments (Appendix J).

The Patient GAIS assessment form (Appendix E) will be provided directly to the subject to complete while reviewing the glabellar treatment area (at maximum frown and at rest after maximum frown) using the supplied handheld mirror as outlined in Appendix E. Subjects with contact lenses should view their glabellar lines with contacts. Subjects wearing glasses should be advised to view their glabellar lines without glasses if possible.

If glasses are needed for the subject to see their glabellar lines, then glasses can be worn for the assessment. The subject assessment must be completed before the Investigator completes the IGA-FWS assessment.

Table 11: Global Aesthetic Improvement Scale

Rating Score	Wrinkle Improvement
-3	Very Much Worse
-2	Much Worse
-1	Worse
0	No Change
1	Improved
2	Much Improved
3	Very Much Improved

4.6.2 ADDITIONAL ASSESSMENTS

4.6.2.1 Subject Diary

At Day 0, subjects will be provided a paper diary Appendix D for the initial 2-week post treatment period to capture their assessment of the appearance of the lines at maximum frown using the 4 point severity scale. Subject's assessment of glabellar line severity is described above in Section 4.6.1.1, Table 9. Instructions on how to complete the diary will be provided with the diary to the subjects.

4.6.2.2 Subject Global Satisfaction with Treatment Questionnaire

The subject will be asked to provide a rating of their satisfaction with the treatment results at the Week 4 visit. Following the subject's completion of the Patient GAIS, the subject will be given a questionnaire to rate their satisfaction with the treatment results. Subjects will be asked how satisfied or dissatisfied they are with how the treated area of the face looks (Appendix F).

[redacted]

4.6.2.4 Facial Age Self Evaluation (FASE)

At each clinic visit designated in the Schedule of Trial Assessments (Appendix J), the subject will be asked to rate their perceived age on a FASE questionnaire (Appendix H). Following the subject's completion of the Patient GAIS, the subject will be given a questionnaire to rate their perception of how old they think they look following the treatment. Subjects will be asked how old they think they look post treatment in order to evaluate the psychological impact.

[redacted]

4.7 SCREEN FAILURES

A screen failure subject will be a person from whom informed consent is obtained and is documented in writing (i.e., subject signs an informed consent form), but who does not meet the study eligibility requirements.

4.8 PROTOCOL DEVIATIONS

This trial will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the Investigator (or a responsible, appropriately trained professional designated by the Investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must contact Revance at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the trial. This decision will be documented by the Investigator and the Sponsor.

5 PROHIBITED THERAPIES AND MEDICATIONS

5.1 CONCOMITANT MEDICATIONS

Concomitant medications are any prescription or over-the-counter preparations used by subjects during participation in the trial. Use of concomitant medications will be recorded on the Concomitant Medications case report form (CRF) beginning at the Screening Visit until the Final Evaluation Visit. The dose and dosing regimen of all prescription and non-prescription therapies and medications, including herbs, vitamins, or other nutritional supplements administered will be documented.

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6 EVALUATION OF ADVERSE EVENTS

6.1 DEFINITIONS

For this protocol, an **adverse event (AE)** is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, clinically significant abnormal laboratory finding, injury or accident) that emerges or worsens following administration of investigational product and until the end of trial participation that may not necessarily have a causal relationship to the administration of the investigational product. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory result), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. A treatment-emergent AE is one that occurs after any period of exposure to treatment.

Pre-existing conditions, which increase in frequency or severity or a change in nature as a consequence of an investigational product use will also be considered an adverse event.

An unexpected AE is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Any clinically significant change in the study safety evaluations, (e.g., vital signs, injection site evaluation, [redacted] post-treatment must be reported as an AE.

A **serious adverse event (SAE)** is any untoward medical occurrence that results in any of the following outcomes:

- Death
- Life-threatening, (i.e., the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred. It does not apply to an AE that hypothetically might have caused death if it were more severe)
- Persistent or significant disability/incapacity or substantial disruption of the subject's ability to carry out normal life functions
- Requires in-patient hospitalization or prolongs hospitalization (i.e., a prolonged hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)
- Congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the molecule or investigational product before conception or during pregnancy)

- Does not meet any of the above serious criteria but based upon appropriate medical judgement may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above (i.e., is a significant or important medical event)

6.1.1 CLINICAL LABORATORY CHANGES

It is the Investigator's responsibility to review the results of all laboratory tests as they become available. For each laboratory test result outside the reference range, the Investigator must ascertain if the abnormal lab result is a clinically significant result for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed; the Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test. If this laboratory value is determined to be a clinically significant result for that subject, this may be considered an AE to be assessed according to severity.

The Investigator must sign and date all written laboratory reports (e.g., urinalysis, hematology, chemistry, PT, and pregnancy tests) and note Not Clinically Significant (NCS) or Clinically Significant (CS) for each out of range laboratory value.

6.1.2 INVESTIGATIONAL PRODUCT CAUSALITY AND SEVERITY

Relationship of an AE to investigational product will be assessed as follows:

- **Definite:** There is a clinically plausible time sequence between the onset of the AE and the administration of investigational product; when the event responds to withdrawal of investigational product and/or recurs with re-administration of investigational product
- **Probable:** There is a clinically plausible time sequence between the onset of the AE and the administration of investigational product; the AE is unlikely to be caused by the concurrent/underlying illness, other drugs or procedures
- **Possible:** There may or may not be a clinically plausible time sequence between the onset of the AE and the administration of investigational product and a cause cannot be ruled out
- **Unrelated:** There is not a temporal or causal relationship to investigational product administration

The Investigator is responsible for evaluating all AEs and determining the severity of the event. Severity will be categorized as mild, moderate or severe according to the following definitions:

- Mild : Event may be noticeable to subject; does not influence daily activities; usually does not require intervention

- Moderate : Event may be of sufficient severity to make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed
- Severe: Event may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the trial; treatment or other intervention usually needed

6.2 REPORTING ADVERSE EVENTS

The Investigator will assess subjects post-treatment and at each subsequent trial visit for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following non leading question: "How have you felt since your last visit?" All AEs (serious and non-serious) reported by the subject must be recorded on the source documents and CRFs.

In addition, an Investigator must report an SAE to Revance within 24 hours of their awareness of the event according to the procedure outlined below. All fatal or life-threatening SAEs should be telephoned to Revance or the authorized representative as soon as the investigator learns of the event.

6.3 SERIOUS ADVERSE EVENTS

An Investigator must report an SAE to Revance or the designated CRO's authorized representative within 24 hours of their awareness of the event:

1. Complete and return an SAE Form with all information known to date; including the investigator's assessment of causality.
2. If the event is fatal or life-threatening, telephone Revance or the authorized representative as soon as the investigator learns of the event.
3. Obtain and maintain all pertinent medical records (discharge summary, autopsy report, etc.) and medical judgments of medical personnel who assisted in subject's treatment and follow-up.
4. Provide follow-up information to Revance or the authorized representative.

Regulatory authorities, IRBs/IEC, and Investigators will be notified of SAEs in accordance with applicable regulations and requirements (e.g., GCPs, ICH Guidelines, national regulations and local requirements).

6.4 PROCEDURE FOR ACCESSING THE RANDOMIZATION CODE

All subjects will receive DaxibotulinumtoxinA for Injection or placebo. The investigators and trial center staff do not have access to the randomization code. Unblinding randomization codes are maintained by the unblinded statistician in a locked location.

In case of a serious adverse event where knowledge of the subject's treatment is required for the subject's clinical care and safety, the identity of the treatment administered may be requested. The Investigator must contact Revance by telephone with an explanation of the need for obtaining the subject's study treatment information. Documentation of accessing the randomization code should be recorded in the subject's medical record with the date and time the randomization code was accessed, and the names of the personnel involved.

6.5 FOLLOW-UP OF ADVERSE EVENTS

6.5.1 FOLLOW-UP OF NON-SERIOUS ADVERSE EVENTS

Non-serious AEs that are identified during the last scheduled trial visit (or early discontinuation, if applicable) must be recorded on the AE CRF as ongoing.

Any clinically significant abnormal test results, e.g., laboratory findings, at the final assessment should be followed to resolution or until determined by the Investigator to be stabilized. Repeat tests may be indicated to establish this.

If a subject has any clinically significant, trial-related abnormalities at the end of the trial, the Medical Monitor should be notified and every effort made by the Investigator to arrange follow up evaluations at appropriate intervals to document the course of the abnormalities.

6.5.2 FOLLOW-UP OF POST TRIAL SERIOUS ADVERSE EVENTS

SAEs that are identified on the last scheduled contact (or early discontinuation, if applicable) must be recorded on the AE CRF page and reported to the CRO and Revance according to the reporting procedures outlined in Section 6.3. This may include unresolved previously reported SAEs, or new SAEs. The Investigator should follow these SAEs until the events are resolved, or the subject is lost to follow-up. The Investigator should continue to report any significant follow-up information to the Medical Monitor, Revance and the IRB/IEC up to the point the event has been resolved. Resolution means the subject has returned to the baseline state of health, or the Investigator does not expect any further improvement or worsening of the subject's condition.

Any new SAEs reported by the subject to the Investigator that occur after the last scheduled contact and are determined by the Investigator to be reasonably associated with the administration of investigational product should be reported to Revance and the IRB/IEC.

7 STATISTICAL ANALYSIS

7.1 GENERAL CONSIDERATIONS

The analysis of data from the trial will be performed when all subjects have completed the trial or discontinued prematurely, and all data are in the database and have been cleaned and verified. All statistical programming will be performed using statistical analysis system (SAS) version 9.4 or higher.

A Statistical Analysis Plan, describing all statistical analyses, will be provided as a separate document prior to database lock and unblinding of the study treatments.

7.2 ANALYSIS POPULATIONS

All subjects who are randomized and receive treatment will be included in the Intent-to-Treat (ITT) population. The summaries will be by treatment as randomized.

All subjects who are randomized, receive treatment, and have provided at least one post-treatment safety assessment will be included in the safety population. The summaries will be by treatment actually received.

The Per-Protocol (PP) population will include subjects from the ITT population who complete the 4-week evaluation without a major protocol violation. [redacted]

[redacted]

7.3 TRIAL ENDPOINTS

Unless specified otherwise, all endpoints associated with IGA-FWS, PFWS, GAIS, or Subject's Diary, henceforth will be based on assessments at maximum frown.

Primary Efficacy Endpoint:

The primary efficacy endpoint of the trial is the proportion of responders with the response defined as

- Achieving a score of 0 or 1 (none or mild) and an improvement of at least two points from baseline on both IGA-FWS and PFWS scales concurrently at Week 4

Henceforth in the document, the response defined above in the primary efficacy endpoint will be abbreviated as "2-point composite response." The subjects who achieve the 2-point composite response will be abbreviated as "2-point composite responders."

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Safety Endpoints:

- Frequency, severity and relationship to study drug of treatment-emergent adverse events during the first four weeks post treatment and the overall study duration
- Frequency, severity and relationship to study drug of treatment-emergent serious adverse events during the first four weeks post treatment and the overall study duration

7.4 SUMMARIES OF TRIAL CONDUCT AND TREATMENT GROUP COMPARABILITY

The number of subjects randomized will be tabulated by trial center and treatment group. Subject disposition (the number of subjects randomized, treated, and completing each key trial visits) will be tabulated by treatment group. Premature study discontinuation and reasons for discontinuation will be summarized. Eligibility criteria deviations and other major protocol violations will be summarized.

Demographic and baseline characteristics will be summarized for all randomized subjects by treatment groups.

7.5 EFFICACY ANALYSES

Unless specified otherwise, the main method of handling missing efficacy data will be

[redacted]

[redacted]. See Section 7.5.5 for details on methods of handling missing data.

[redacted].

Descriptive statistics will be provided for all efficacy variables at all timepoints by treatment group. The point estimate of the treatment difference and 95% confidence interval (CI) of the difference (or 90% CI when the comparisons are 1-sided) will be generated.

[redacted]

7.5.1 PRIMARY EFFICACY ENDPOINT

Primary clinical efficacy will be assessed by the blinded evaluator who will grade the severity of the subject's glabellar lines at maximum frown using the IGA-FWS and the subject who will grade the severity of their glabellar lines at maximum frown using the PFWS. A response is defined as achieving a score of 0 or 1 (none or mild) and an improvement of at least two points from the baseline, on both the IGA-FWS and PFWS scales concurrently at the time point of evaluation. With both IGA-FWS and PFWS using a 4-point scale and the target population having a score of 2 or 3 (moderate or severe) at baseline, achieving an improvement of at least two points is inclusive in the status of achieving a score of 0 or 1 (none or mild). Henceforth, the response defined here will be abbreviated as "2-point composite response."

The proportion of subjects who have a 2-point composite response at Week 4 will be compared between daxibotulinumtoxinA and placebo using the Cochran–Mantel–Haenszel (CMH) test stratified by trial center using a two-sided test with a Type I error rate of 0.05.

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7.5.5 HANDLING MISSING DATA AND OTHER CONSIDERATIONS

Missing Data

[redacted] For endpoints that are a composite and/or derived from study assessments, imputation of missing data will be performed on the original assessments first.

No imputations will be utilized for the PP analyses.

As needed, a model-based multiple imputation approach may be explored to assess the impact of different imputation methods on the trial outcomes.

Pooling Data

Most of the efficacy endpoints are analyzed with trial center as a stratification factor. The trial is intended to be conducted in a manner such that a minimum of 5 ITT subjects in each treatment group will be enrolled at each trial center/site. In the event that there are too few subjects in a treatment arm at a single site, this site will be combined with another to achieve the desired minimum sample size per arm.

7.5.6 SENSITIVITY AND SUBGROUP ANALYSES

The robustness of main analysis results for the primary and secondary endpoints will be evaluated via sensitivity analyses on the per-protocol population and on data with missing values imputed using different approaches, such as no imputation (observed data only) or when necessary, multiple imputation.

Statistical tests will be conducted to identify if there are extreme trial centers that could affect the interpretation of common statistical and clinical conclusions. A CMH test of the primary efficacy endpoint will be conducted with factors of treatment group stratified by trial center. [redacted]

[redacted]

7.6 SAFETY ANALYSES

7.6.1 ADVERSE EVENTS

Safety summaries and analyses will be performed on the safety population. Descriptive statistics will be presented to summarize the safety data.

All AEs will be recorded and classified on the basis of MedDRA terminology. Treatment-emergent AEs are those AEs with an onset on or after the date and time of study treatment. All treatment-emergent AEs will be summarized by treatment group, system organ class, preferred term, severity, relationship, and seriousness.

Comparisons between treatment groups will be made by tabulating the frequency of subjects with one or more treatment-emergent AEs (classified into MedDRA terms) from baseline (post-treatment) to Week 4 as well as from baseline (post-treatment) through the duration of the trial.

Serious adverse events (SAEs) will be listed by subject. SAEs will be summarized by treatment group, severity, and relationship to study treatment. Each subject will be counted only once within a system organ class or a preferred term using the event with the greatest relationship and greatest severity.

All information pertaining to AEs noted during the trial will be listed by subject, detailing the verbatim description given by the Investigator, preferred term, system organ class, start date, stop date, severity, action taken regarding study drug, corrective treatment, outcome, and drug relatedness. The event onset will also be shown relative (in number of days) to the date of first study treatment administration. In addition, a list of subjects who prematurely discontinue from the trial due to adverse events will also be provided.

7.6.2 LABORATORY TESTS

Laboratory test results will be summarized with descriptive statistics for each treatment group at Screening and Final Evaluation Visit. Change from Screening to Final Evaluation Visit also will be summarized for continuous test results.

Shift tables will be presented to summarize laboratory test results at Screening and Final Evaluation Visit. Normal ranges established by the central laboratory will be used to

determine shifts. A listing of all out-of-range laboratory test results at any evaluation will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by each investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

[redacted]

UPTs will be summarized for all treated subjects in the category of WOCBP by treatment group and presented in the data listings.

7.6.3 VITAL SIGNS AND PHYSICAL EXAMINATION

Vital signs and abnormal findings from the physical examination will be summarized with descriptive statistics for each treatment group by visit.

7.6.4 INJECTION SITE EVALUATION

Outcomes of the injection site evaluations will be tabulated by visit.

[redacted]

7.6.8 CONCOMITANT THERAPIES/MEDICATIONS

Concomitant therapies/medications used at Screening and at each trial visit will be coded using the World Health Organization (WHO) drug dictionary and summarized by treatment group, Anatomical Therapeutic Chemical (ATC) second level term, and preferred name for the Safety population.

7.6.9 ECG

The results of the ECG data will be tabulated by visit.

7.7 SAMPLE SIZE AND POWER CONSIDERATIONS

Estimates of treatment efficacy taken from trial RT002-CL002 show that a sample size of 200 and 100 for DaxibotulinumtoxinA 40 U for injection and placebo, respectively, [redacted]

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9 RECORDS MANAGEMENT

9.1 DATA COLLECTION

For this trial, all protocol-specified data will be recorded in the source documents, and data will be entered on the CRFs from the source documents. In addition to signature confirmation that a subject meets the study eligibility criteria, upon each subject's completion of the trial, the Investigator will sign a statement indicating that all pages of the subject's case report have been reviewed. Signature stamps and "per signatures" are not acceptable.

It is Revance's policy that the trial data be verifiable with the source data that necessitates access to all original recordings, laboratory reports, and other records for each subject. The Investigator must therefore agree to allow access to subjects' records, and source data must be made available for all trial data. Subjects (or their legal representatives) must also allow access to their medical records. Subjects will be informed of the importance of increased record access and permission granted by signature on the informed consent document prior to Screening.

Checks will be performed to ensure the quality, consistency, and completeness of the data. Instances of missing or un-interpretable data will be resolved with the Investigator or Study Coordinator. Data queries will be sent to the trial center. Site personnel will be responsible for providing resolutions to the data queries and for correcting the CRFs, as appropriate. All unused Revance source documents and binders must be returned to Revance upon completion of the trial.

The Investigator must keep written or electronic source documents for every subject participating in the clinical trial. The subject file that identifies the study in which the subject is participating must include the subject's available demographic and medical information including:

- Name
- Contact information
- Date of birth
- Sex
- Medical history
- Concomitant diseases
- Concomitant therapies/medication
- Study visit dates
- Performed examinations, evaluations, and clinical findings

- Investigational product administration
- AEs, SAEs, or pregnancy (as applicable)

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment must be included in the subject's source document (e.g., laboratory value listings). All these documents must have at least the subject's initials, trial number, and the date of the evaluation.

The data recorded during the course of the trial will be documented in the CRF and/or the trial-specific forms. Before or at study termination, all data must be forwarded to Revance. The data will then be recorded, evaluated, and stored in anonymous form in accordance with data-protection regulations.

Subjects will authorize the use of their protected health information during the informed consent process in accordance with the applicable privacy requirements. Subjects who deny permission to use and disclose protected health information will not be eligible to participate in the trial. The Investigator will ensure that the trial documents forwarded to Revance, and any other documents, contain no mention of subject names.

Any amendments and corrections necessary will be undertaken in both the source documents and CRFs (as appropriate) and countersigned by the Investigator, or documented designee, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids. The Investigator must state his/her reason for the correction of any data. In the case of missing data/remarks, the entry spaces provided in the CRF should be cancelled out so as to avoid unnecessary follow-up inquiries.

Regulatory authorities, the IRB/IEC and/or the Revance's Quality Assurance group (or designee) may request access to all source documents, CRFs, and other trial documentation for on-site audit or inspection. The Investigator must guarantee direct access to these documents. CRFs will be kept by Revance or an authorized designee in a secured area. Clinical data will be recorded in a computer format for subsequent statistical analyses. Data files will be stored on electronic media with a final master data file kept by Revance after descriptive and statistical analyses and reports have been generated and are complete.

9.2 FILE MANAGEMENT AT THE TRIAL CENTER

It is the responsibility of the Investigator to ensure that the trial center file is maintained in accordance with ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, Section 8 – Essential Documents for the Conduct of a Clinical Trial.

9.3 RECORDS RETENTION AT THE TRIAL CENTER

It is a Revance requirement that all Investigators participating in clinical studies maintain detailed clinical data for one of the following periods:

- Country-specific requirements, or
- A period of at least 2 years following the last approval of a marketing application approved by a Regulatory Authority in an ICH region or until there are no pending or contemplated marketing applications in an ICH region, or,
- A period of two years after Revance notifies the Investigator that the data will not be submitted for review by any Regulatory Authority

The Investigator must not dispose of any records or essential documents relevant to this trial without either (1) written permission from Revance, or (2) providing an opportunity for Revance to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial. Such documentation is subject to inspection by Revance and relevant regulatory agencies. If the Investigator withdraws from the trial (e.g., relocation, retirement) all trial-related records should be transferred to a mutually agreed upon designee. Notice of such transfer will be provided to Revance in writing.

10 MONITORING, COMPLIANCE, AND QUALITY

All aspects of the trial will be monitored by Revance or authorized representatives of Revance according to Good Clinical Practices (GCP) and Standard Operating Procedures (SOPs) for compliance with applicable government regulations, (i.e., Informed Consent Regulations and Institutional Review Board regulations).

[redacted]

11 ETHICS AND RESPONSIBILITY

This trial must be conducted in compliance with the protocol, the ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance and the applicable regulatory requirements. Investigators must submit all essential regulatory documentation, as required by local and national regulations (including IRB/IEC approval of the protocol and informed consent form) to Revance before investigational product will be shipped to the trial center.

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