TITLE	An Open-Label, Multi-Center Trial to Assess the Safety of Single and Repeat Treatments of DaxibotulinumtoxinA for Injection for Treatment of Moderate to Severe Glabellar Lines (SAKURA OPEN-LABEL SAFETY)
PROTOCOL NUMBER	1620303
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, 20 March 2017

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: "*An Open-Label, Multi-Center Trial to Assess the Safety of Single and Repeat Treatments of DaxibotulinumtoxinA for Injection for Treatment of 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: An Open-Label, Multi-Center Trial to Assess the Safety of Single and Repeat Treatments of DaxibotulinumtoxinA for Injection for Treatment of Moderate to Severe Glabellar Lines (SAKURA-OLS)	
Trial Center(s):	Approximately 60 centers in the United States (US) and Canada
Number of Subjects Planned:	Approximately 1500 subjects will be enrolled for a single treatment in addition to approximately 600 roll over subjects from the phase 3 pivotal SAKURA-1 and -2 studies for a total of 2100 subjects.
Trial Period:	The duration of subject participation will vary depending on number of treatments and duration of follow-up. A subject may be on trial for a maximum of 86 weeks, inclusive of a two week screening period.
Phase of Development:	3
Objective: To evaluate the long term safety of DaxibotulinumtoxinA for Injection for the treatment of moderate to severe glabellar lines following single and repeat administration.	
Design and Methodology: This is a phase 3, open label, multi-center trial to assess the safety of single and repeat administration of DaxibotulinumtoxinA for Injection in subjects with moderate to severe glabellar lines. Approximately 1500 adult subjects will be enrolled for a single treatment; all subjects who have completed participation in either Revance protocol SAKURA-1 or SAKURA-2 will be rolled over for repeat treatments. Subjects will have the opportunity of receiving up to two repeat treatments in this trial. It is anticipated that approximately 400-500 subjects will be treated with three treatments at selected centers. All subjects will be followed for at least 12 weeks, and up to 36 weeks, after each treatment for 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 at the Week 12 visit, or at a visit between Weeks 12 and 36, the visit at which these two scores are recorded will be the Final Evaluation Visit, and for those subjects who receive multiple treatments (up to two), this visit will serve as a retreatment visit. Subjects with multiple treatments will have a Final Evaluation Visit at Week 12 following their final eligible treatment. All treatments will be intramuscular injections administered by a trained physician. Subjects will receive a total of 0.5mL of treatment, with of 0.1 mL administered per injection to five injection sites: two injections into each corrugator muscle and one injection in the procerus muscle. The duration of subject participation in this trial (SAKURA-OLS) will vary depending on the number of treatments and duration of follow-up. Subjects who completed participation in SAKURA-1 and SAKURA-2 trials may be eligible for treatment on their last visit as long as written informed consent for the SAKURA-OLS trial is obtained before any trial-related procedures (including any screening procedures) are performed and subjects meet eligibility criteria. Final Evaluation visit procedures of the controlled trials from which they are rolling over will serve as the baseline for this trial. A subject may be in SAKURA-OLS trial for a maximum of 86 weeks, inclusive of a two week screening period. The number of trial visits will vary per subject depending upon response to DaxibotulinumtoxinA for Injection. A subject may not be re-enrolled in the SAKURA-OLS trial after the Final Evaluation Visit (or after early discontinuation).	
Trial Visits:	

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

Screening (–Week 2), Treatment (Day 0), post the first treatment follow-up at Weeks 1, 2, 4, 8, and 12, then at Weeks 16, 20, 24, 28, 32, 36 or until the retreatment. Post the second treatment follow-up (for the subjects who are retreated) at Weeks 1, 2, 4, 8, and 12, then at Weeks 16, 20, 24, 28, 32, and 36 or until the retreatment. Post the third treatment follow-up (for the subjects who receive the third treatment) at Weeks 1, 2, 4, 8, and 12.

Safety Evaluations:

- Clinical laboratory tests (hematology, chemistry, prothrombin time [PT], urinalysis)
- [redacted]
- [redacted]
- Injection Site Evaluation
- [redacted]
- [redacted]
- Concomitant medications
- Collection of adverse events (AEs)
- [redacted]
- Vital Signs
- Physical Examination

Effectiveness Evaluations:

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

Other Evaluations:

- [redacted]

Diagnosis and Main Abbreviated Eligibility Criteria:

Outpatient, male or non-pregnant, non-nursing females, 18 years of age or older, 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

Statistical Analyses:

The trial subjects are eligible to receive up to three treatments. For analysis purposes, the corresponding summary period will be defined for each treatment. For the trial-overall summary, all available data observed during the trial will be included. For analyses associated with a specific treatment, the summary will include all data observed since the treatment until the next treatment, or until the last visit of the trial when there is no subsequent treatment. To account for varying subject follow-up duration, the total follow-up duration (i.e., patient-years) will be calculated for each summary period.

For the trial-overall summary, the baseline will be the last available value prior to the first treatment. For summaries associated with a specific treatment, the baseline will be the last available value prior to treatment (i.e., re-baselined).

In addition to subjects who are directly enrolled, the trial also includes subjects rolling over from two pivotal phase 3 studies, SAKURA-1 and SAKURA-2. For the roll over subjects who are in the active treatment group in the prior trial, the first daxibotulinumtoxinA treatment in this open-label safety trial will in fact be their second daxibotulinumtoxinA treatment. Based on the subject’s prior exposure to DaxibotulinumtoxinA

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for Injection, the following two summary groups will be defined for the analysis: Group A and Group B. The former group will include all subjects who have received DaxibotulinumtoxinA for Injection in either protocol SAKURA-1 or SAKURA-2, and the latter group will include the remaining trial subjects.

Safety Analyses:

All treatment-emergent adverse events (AEs) occurring during the trial will be recorded and classified on the basis of MedDRA terminology. All reported treatment-emergent adverse events will be summarized, in terms of the number of subjects reporting events, system organ class, preferred term, severity, relationship to trial drug and seriousness. When summarizing events by causality and severity, each subject will be counted only once within a system organ class or a preferred term by using the event with the greatest relationship and highest severity within each classification. A list of AEs that lead to the subject's premature discontinuation of the trial will be provided.

Serious adverse events (SAEs) will be listed by subject. SAEs will be summarized by severity and relationship to trial treatment.

The summaries of AEs and SAEs will be performed for the trial overall, and for each of the three treatment periods. For SAEs and key AEs [redacted], rate-per-injection and rate-per-patient-year will be calculated. A 95% confidence interval will also be provided for the rate.

Effectiveness Analyses:

Effectiveness outcome measures, such as the Investigator Global Assessment Frown Wrinkle Severity (IGA-FWS), Patient Frown Wrinkle Severity (PFWS), Investigator and Patient Global Aesthetic Improvement Scale (GAIS), are evaluated at maximum frown and at rest after maximum frown over time during the trial. Response rates and duration of the response, defined based on various definitions (see Section 7.3 for details), are calculated.

Effectiveness data will be summarized as observed with no imputation for missing data. Descriptive statistics will be provided for all effectiveness variables at all timepoints for the summary group. 95% confidence intervals and/or p-values for comparing the difference between subgroups of interest (e.g., females vs. males, first treatment vs. second treatment, etc.) will be provided as appropriate. Kaplan-Meier curves will be plotted for the time-to-event endpoints.

When comparisons (e.g., females vs. males, first treatment vs. second treatment, etc.) are performed, the tests will be done at a significant level of 0.05 with no adjustment for multiplicity.

Sample Size Justification:

This is a safety trial with all subjects treated with the same investigational product. The sample size of approximately 2,100 is considered to be adequate in assessing safety based on several approaches. [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
CRF	case report form
CRO	contract research organization
CS	clinically significant
FDA	Food and Drug Administration
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
kDa	kilodalton
kg	kilogram
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.
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

Abbreviation	Definition
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]

[redacted]

2 TRIAL OBJECTIVE

To evaluate the long term safety of DaxibotulinumtoxinA for Injection for the treatment of moderate to severe glabellar lines following single and repeat administration.

3 TRIAL DESIGN

3.1 OVERALL TRIAL DESIGN

3.1.1 STRUCTURE

This is a phase 3, open label, multi-center trial to assess the safety of single and repeat administration of DaxibotulinumtoxinA for Injection in subjects with moderate to severe glabellar lines.

Approximately 1500 adult subjects will be enrolled for a single treatment; all consenting subjects who have completed participation in either Revance protocol SAKURA-1 or SAKURA-2 may be eligible to roll over for repeat treatments in this trial (SAKURA-OLS) on the last visit of the previous trial as long as written informed consent is obtained from all subjects before any trial-related procedures (including any screening procedures) are performed and subjects meet eligibility criteria. Subjects, will have the opportunity of receiving up to one or two repeat treatments in this trial. Of all subjects enrolled in SAKURA-1, SAKURA-2 and SAKURA-OLS, it is anticipated that approximately 400-500 total subjects will be treated for up to three treatments of DaxibotulinumtoxinA for Injection at select centers at the end of the trial; subjects from SAKURA-1 or SAKURA-2 will have received one treatment in the parent trial and up to two treatments in SAKURA-OLS, and subjects who did not participate in either SAKURA-1 or SAKURA-2 will have received between one and three treatments in the SAKURA-OLS.

3.1.2 DURATION

The duration of subject participation in this trial (SAKURA-OLS) will vary depending on the number of treatments and duration of follow-up. Subjects who completed participation in SAKURA-1 and SAKURA-2 trials may be eligible for participation in the SAKURA-OLS trial during their last visit as long as written informed consent for the SAKURA-OLS trial is obtained before any trial-related procedures (including any screening procedures) are performed and subjects meet eligibility criteria. Final Evaluation visit procedures of the controlled trials from which they are rolling over, end of trial PT, [redacted] will serve as the baseline for this trial. A subject may be in SAKURA-OLS trial for a maximum of 86 weeks, inclusive of a two week screening period. The number of trial visits will vary per subject depending upon response to DaxibotulinumtoxinA for Injection. A subject may not be re-enrolled in the SAKURA-OLS trial after the Final Evaluation Visit (or after early discontinuation).

3.1.3 CONTROL

Not applicable. All subjects will be treated with DaxibotulinumtoxinA for Injection.

3.1.4 DOSAGE/DOSE REGIMEN

All treatments will be intramuscular injections administered by a trained physician. Injections must be performed only by the principal investigator contracted at the center.

[redacted]

3.1.5 VISIT SCHEDULE

A screening visit will be conducted up to two weeks prior to the first treatment.

Following the first treatment at Day 0, subjects will have on-site post-treatment visits at Week 1, 2, 4, 8 and 12, then thereafter, monthly up to Week 36 or until both Patient Frown Wrinkle Severity (PFWS) and Investigator Global Assessment Frown Wrinkle Severity (IGA-FWS) scores at maximum frown return to baseline (or until the second treatment for the subjects who will receive multiple treatments). Following the second treatment (if received), subjects will have on-site post-treatment visits at Week 1, 2, 4, 8 and 12, then thereafter monthly up to Week 36 or until the third treatment. Following the third treatment (if received), subjects will have on-site post-treatment visits at Week 1, 2, 4, 8 and 12. Subjects who receive multiple treatments will have a Final Evaluation Visit twelve weeks after the final treatment.

Starting at the Week 12 visit following the first (or the second) treatment, and evaluated thereafter monthly up to Week 36, subjects at selected centers may be retreated if retreatment criteria (see Section 3.4.4) are met. Subjects at the selected centers will receive up to a total of up to three treatments (up to two treatments for roll over subjects) during SAKURA-OLS.

[redacted]

3.3 POPULATION

Approximately 2,100 female or male subjects, 18 years of age or older, in good general health, with moderate or severe glabellar lines will be enrolled. Subjects who completed participation in SAKURA-1 or SAKURA-2 may be eligible for participation in the SAKURA-OLS trial on the last visit of the previous trial as long as written informed consent is obtained from all subjects before any trial-related procedures (including any screening procedures) are performed and subjects meet eligibility criteria. Final Evaluation visit procedures of the previous trial, end of trial PT, [redacted] will serve as the baseline for this trial.

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 trial-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 trial-related procedures being conducted, including those performed solely for the purpose of determining eligibility for trial participation, and including withdrawal from current medication (if required prior to trial 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 trial 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 trial 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 trial related procedures are conducted (including any screening trial 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 years of age or older, 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 (refer to 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
9. In the opinion of the investigator, roll over subjects demonstrated compliance with the study procedures and visit requirements during SAKURA-1 or SAKURA-2 and are capable of complying with the study procedures and visit requirements in SAKURA-OLS

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 trial 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 24 weeks prior to screening
7. Plan to receive botulinum toxin type A anywhere in the face through the duration of the trial
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 the 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.

3.4.4 ELIGIBILITY CRITERIA FOR RETREATMENT

Subjects will have the opportunity of receiving up to two repeat treatments in this trial. It is anticipated that approximately 400-500 subjects will be treated with three treatments at selected centers. Assessment for retreatment will occur after subjects have completed at least 12 weeks of safety follow-up and when the following criteria are met:

1. Return of IGA-FWS and PFWS severity scores to baseline
2. Women of child-bearing potential (WOCBP) must have a negative urine pregnancy test (UPT) prior to treatment
3. No active skin disease or infections or inflammation at the injection sites
4. Subject has no condition or situation which, in the Investigator's opinion, puts the subject at significant risk

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 must be obtained and reviewed by the Investigator. Any WOCBP having a positive pregnancy test pre-treatment will not be treated. The corresponding Final Evaluation Visit assessments may be used to determine eligibility for subjects rolling-over from Protocol SAKURA-1 or SAKURA 2. The [redacted] end of trial PT collected during studies SAKURA-1 or SAKURA-2, will serve as the baseline assessment for subjects rolling-over from these two studies.

After the required screening procedures are completed and trial eligibility is confirmed as defined by the eligibility criteria in Sections 3.4.2 and 3.4.3, the subject will be enrolled in the trial and the investigational product will be prepared by the 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 trial 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 trial 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 trial participation, record the information on the Pregnancy Notification Form, and send the form to the CRO. The trial center 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 until the end of the trial's follow-up period. Pregnant subjects will not be eligible for retreatment.

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 trial assessments is provided in Appendix F.

The progression of a subject through the trial will be dependent upon the duration of the effect (response).

4.2.1 SCREENING VISIT

The Screening Visit may take place within 14 days prior to investigational product administration at Day 0 (Treatment Visit). Subjects who completed participation in SAKURA-1 or SAKURA-2 may be eligible for participation in the SAKURA-OLS trial on the last visit of the previous trial as long as written informed consent is obtained from all subjects before any trial-related procedures (including any screening procedures) are performed and subjects meet eligibility criteria. Final Evaluation visit procedures of the previous trial, end of trial PT, [redacted] will serve as the baseline for this trial.

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)

[redacted]

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

[redacted]

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

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]

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

Investigational Product Preparation

The assigned investigational product will be prepared by the 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]

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]

4.2.3 WEEK 1 FOLLOW-UP VISIT

At Week 1, following 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]

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 Week 2 following treatment, and Weeks 4, 8, 12, and monthly until subject qualifies for retreatment or Final Evaluation Visit, the following procedures must be performed and recorded:

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. At Week 2 only, measure and record vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure)

[redacted]

6. At Week 4 only, collect blood samples for clinical safety laboratory tests (hematology and chemistry)

[redacted]

15. Assess AEs

[redacted]

[redacted]

4.2.5 RETREATMENT PROCEDURES

At select centers, subjects may be eligible for retreatment up to two times. In addition to the procedures performed during the follow-up visit, the following retreatment procedures should also be performed:

Prior to Investigational Product Administration

[redacted]

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

[redacted]

7. Once the Investigator has confirmed subject eligibility for retreatment, the subject will be treated. The trained dose preparer will prepare the assigned investigational product according to trial-specific instructions

After Investigational Product Administration

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

[redacted]

3. Assess for AEs

[redacted]

4.2.6 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 12 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. If a subject has received multiple treatments, the Final Evaluation Visit will occur at Week 12 following the final treatment.

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]

[redacted]

15. Assess AEs

[redacted]

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

4.2.7 UNSCHEDULED VISITS

If an AE occurs that in the Investigator's opinion requires a clinical examination for further assessment, the subject should be brought in for an unscheduled visit. If signs of suspected ptosis are reported or observed, obtain photographs of subject in primary gaze with brow relaxed, and in primary gaze with brow elevated.

4.2.8 DISCONTINUATION/WITHDRAWAL PROCEDURES

A subject may voluntarily withdraw from trial 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 trial 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 trial 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 trial 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 1).

Table 1: Allowed Variation from Scheduled Visit Days

Scheduled Visit (Post Each Treatment)	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 F.

4.5 SAFETY ASSESSMENTS

4.5.1 CLINICAL LABORATORY DATA

As outlined in Table 2, non-fasting samples for hematology, chemistry, PT (Screening only) and urinalysis will be collected at Screening, Week 4 visits, prior to Retreatment (as applicable), and at the Final Evaluation Visit. [redacted]. Blood and urine specimens 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 2: 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 only) Urine Pregnancy (WOCBP only)* [redacted]

*If positive at timepoints after trial 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 from 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]

[redacted]

4.5.2 PREGNANCY TESTING

All WOCBP will have a UPT at the Screening Visit, prior to any 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, Treatment Visit (pre- and post-treatment), Week 2, Final Evaluation or Early Discontinuation Visits, [redacted].

4.5.4 PHYSICAL EXAM

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 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 five injection sites (Table 3).

Table 3: 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]

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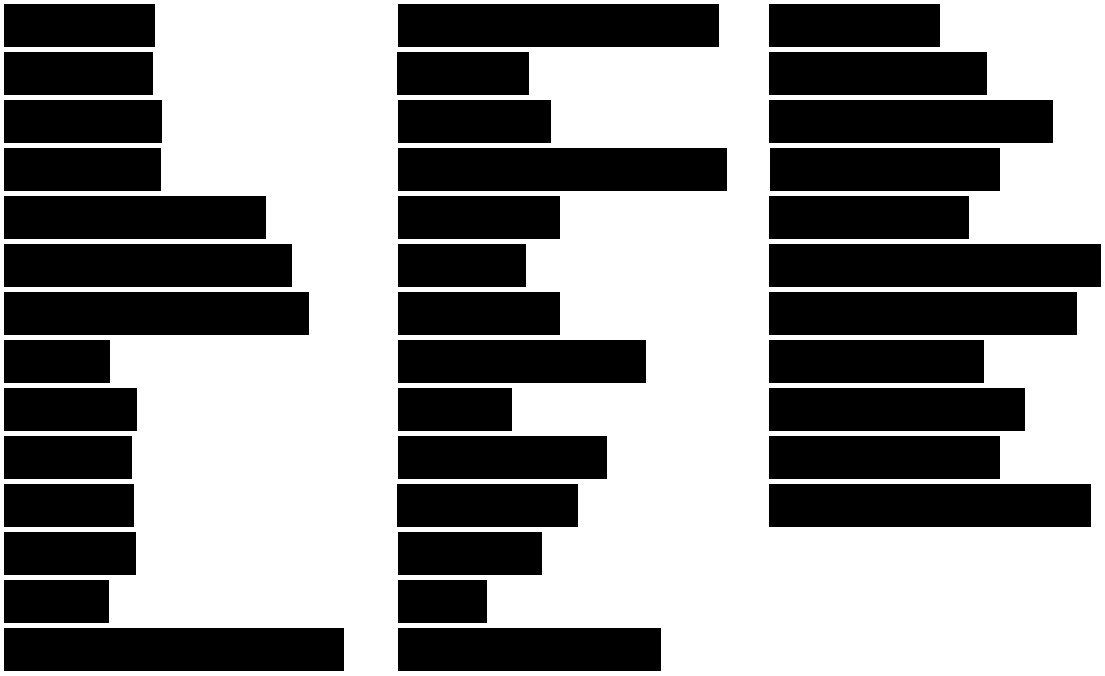
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4.5.9 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.

[redacted]



4.6 EFFECTIVENESS ASSESSMENTS

Effectiveness assessments will include Investigator assessment of glabellar line severity and glabellar line improvement, subject assessment of glabellar line severity and improvement. Effectiveness 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 PATIENT FROWN WRINKLE SEVERITY (PFWS)

At each clinic visit as designated in the Schedule of Trial Assessments (Appendix F), 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 8). The assessment form will be provided directly to the subject to complete while reviewing the glabellar treatment area using the supplied 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 8: 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]

4.6.2 INVESTIGATOR GLOBAL ASSESSMENT FROWN WRINKLE SEVERITY

At each clinic visit as designated in the Schedule of Trial Assessments (Appendix F), 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 9).

Table 9: 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]

4.6.3 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 10). Assessments will be made as designated in the Schedule of Trial Assessments (Appendix F).

The Patient GAIS assessment form (Appendix D) 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 D. 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 10: 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

4.6.4 ADDITIONAL ASSESSMENTS

[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 trial 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.

[redacted]

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 trial 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

Not Applicable: open label trial.

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.

The trial has up to three treatments. Depending on the analysis purpose, the corresponding summary period will be defined for each treatment. For the trial-overall summary, all available data observed during the trial will be included. For analyses associated with a specific treatment, the summary will include all data observed since the treatment until the next treatment, or until the last visit of the trial when there is no subsequent treatment. To account for varying subject follow-up duration, the total follow-up duration (i.e., patient-years) will be calculated for each summary period.

For the trial-overall summary, the baseline will be the last available value prior to the first treatment. For summaries associated with a specific treatment, the baseline will be the last available value prior to treatment (i.e., re-baselined).

7.2 ANALYSIS POPULATIONS

The Safety-Evaluable population will include all subjects who are exposed to the investigational product and who provide any post-treatment safety information.

Analyses specifically associated with each of the three treatment periods will be performed on a subset of the safety-evaluable population, including only those subjects who receive trial treatment and have post-treatment safety information for the specific treatment. These safety-evaluable sub-populations will be respectively identified as Treatment-1-Evaluable, Treatment-2-Evaluable, or Treatment-3-Evaluable.

In addition to subjects who are directly enrolled, the trial also includes subjects rolling over from two pivotal phase 3 studies, SAKURA-1 and SAKURA-2. For the roll over subjects who are in the active treatment group in the prior trial, the first daxibotulinumtoxinA treatment in this open-label safety trial will in fact be their second daxibotulinumtoxinA treatment. Based on the subject's prior exposure to DaxibotulinumtoxinA, the following two summary groups will be defined for the analysis:

- **Group A**: all subjects who have received DaxibotulinumtoxinA for injection in SAKURA-1 or SAKURA-2
- **Group B**: all subjects in the trial who are not in Group A

7.3 TRIAL ENDPOINTS

Safety Endpoints:

- Incidence, severity and relationship to trial drug of treatment-emergent adverse events during each treatment and the trial overall
- Incidence, severity and relationship to trial drug of treatment-emergent serious adverse events during each treatment and the trial overall

Effectiveness Endpoints:

Unless specified otherwise, all endpoints associated with IGA-FWS, PFWS or GAIS henceforth will be based on assessments at maximum frown. When applicable, similar endpoints based on assessments at rest after maximum frown will also be summarized.

For the endpoints that are derived from a comparison with the baseline, two derivation rules using different reference timepoints as the baseline (i.e., trial baseline or treatment baseline) will be applied separately.

- Time to retreatment since the first trial treatment (on Treatment-1-Evaluable only)
- Time to retreatment since the second trial treatment (on Treatment-2-Evaluable only)
- Time to return to, or worse than, baseline on both IGA-FWS and PFWS
- Time to return to 2 or 3 (moderate or severe) on both IGA-FWS and PFWS
- Proportion of subjects with a ≥2 point improvement from baseline on both IGA-FWS and PFWS at each visit over time
- Proportion of subjects with a score of 0 or 1 (none or mild) on IGA-FWS at each visit over time
- Proportion of subjects with a score of 0 or 1 (none or mild) on PFWS at each visit over time
- Proportion of subjects with a ≥1 point improvement from baseline on both IGA-FWS and PFWS at each visit over time

- Proportion of subjects with a ≥1 point improvement (i.e., improved, much improved, or very much improved) on GAIS at each visit over time (with investigator's assessment and subject's self-assessment summarized separately)
- Proportion of subjects with a ≥2 point improvement (i.e., much improved, or very much improved) on GAIS at each visit over time (with investigator's assessment and subject's self-assessment summarized separately)
- Proportion of subjects with a ≥3 point improvement (i.e., very much improved) on GAIS at each visit over time (with investigator's assessment and subject's self-assessment summarized separately)
- Mean GAIS score at each visit over time (with investigator's assessment and subject's self-assessment summarized separately)

7.4 SAFETY ANALYSES

Safety data collected for the overall trial period will be summarized for the Safety-Evaluable population. Summaries associated with each of the three treatment periods will be performed on the corresponding sub-population (i.e., Treatment-1-Evaluable, Treatment-2-Evaluable or Treatment-3-Evaluable). To account for varying subject follow-up duration, the total follow-up duration (i.e., patient-years) will be calculated for each summary period.

Descriptive statistics will be presented to summarize the safety data.

7.4.1 ADVERSE EVENTS

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 trial treatment. All treatment-emergent AEs will be summarized by system organ class, preferred term, severity, relationship, and seriousness. When summarizing events by causality and severity, each subject will be counted only once within a system organ class or a preferred term by using the event with the greatest relationship and highest severity within each classification.

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 trial drug, corrective treatment, outcome, and drug relatedness. The event onset relative (in number of days) to the date of first trial treatment administration, as well as to the date of last trial treatment

administration prior to the event, will be provided. In addition, a list of adverse events that lead to the subject's premature discontinuation of the trial will also be provided.

Serious adverse events (SAEs) will be listed by subject. SAEs will be summarized by severity and relationship to trial 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.

The summaries of AEs and SAEs will be performed for the trial overall, and for each of the three treatment periods. For SAEs and key AEs [redacted], rate-per-injection and rate-per-patient-year will be calculated. A 95% confidence interval will also be provided for the rate.

7.4.2 LABORATORY TESTS

Laboratory test results will be summarized with descriptive statistics by visit. Change from Screening to Final Evaluation Visit 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 and presented in the data listings.

7.4.3 VITAL SIGNS AND PHYSICAL EXAMINATION

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

7.4.4 INJECTION SITE EVALUATION

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

[redacted]

7.4.7 CONCOMITANT THERAPIES/MEDICATIONS

Concomitant therapies/medications used at Screening and during the trial 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-Evaluable population.

[redacted]

7.4.9 EFFECTIVENESS ANALYSIS

Effectiveness data will be summarized as observed with no imputation for missing data. Descriptive statistics will be provided for all effectiveness variables at all timepoints by the summary group. 95% confidence intervals and/or p-values for comparing the difference between subgroups of interest (e.g., females vs males) will be provided as appropriate. Kaplan-Meier curves will be plotted for the time-to-event endpoints defined in Section 7.3.

When comparisons (e.g., females vs males, Treatment 1 vs Treatment 2, etc.) are performed, the tests will be done at a significant level of 0.05 with no adjustment for multiplicity.

7.4.10 SAMPLE SIZE AND POWER CONSIDERATIONS

This is a safety trial with all subjects treated with the same investigational product. The sample size of approximately 2,100 is considered to be adequate in assessing the safety based on several approaches. [redacted]

[redacted]

[redacted]

[redacted]

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 trial 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 Trial Coordinator. Data queries will be sent to the trial center. Trial center 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 trial 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
- Trial 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 trial 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.

[redacted]

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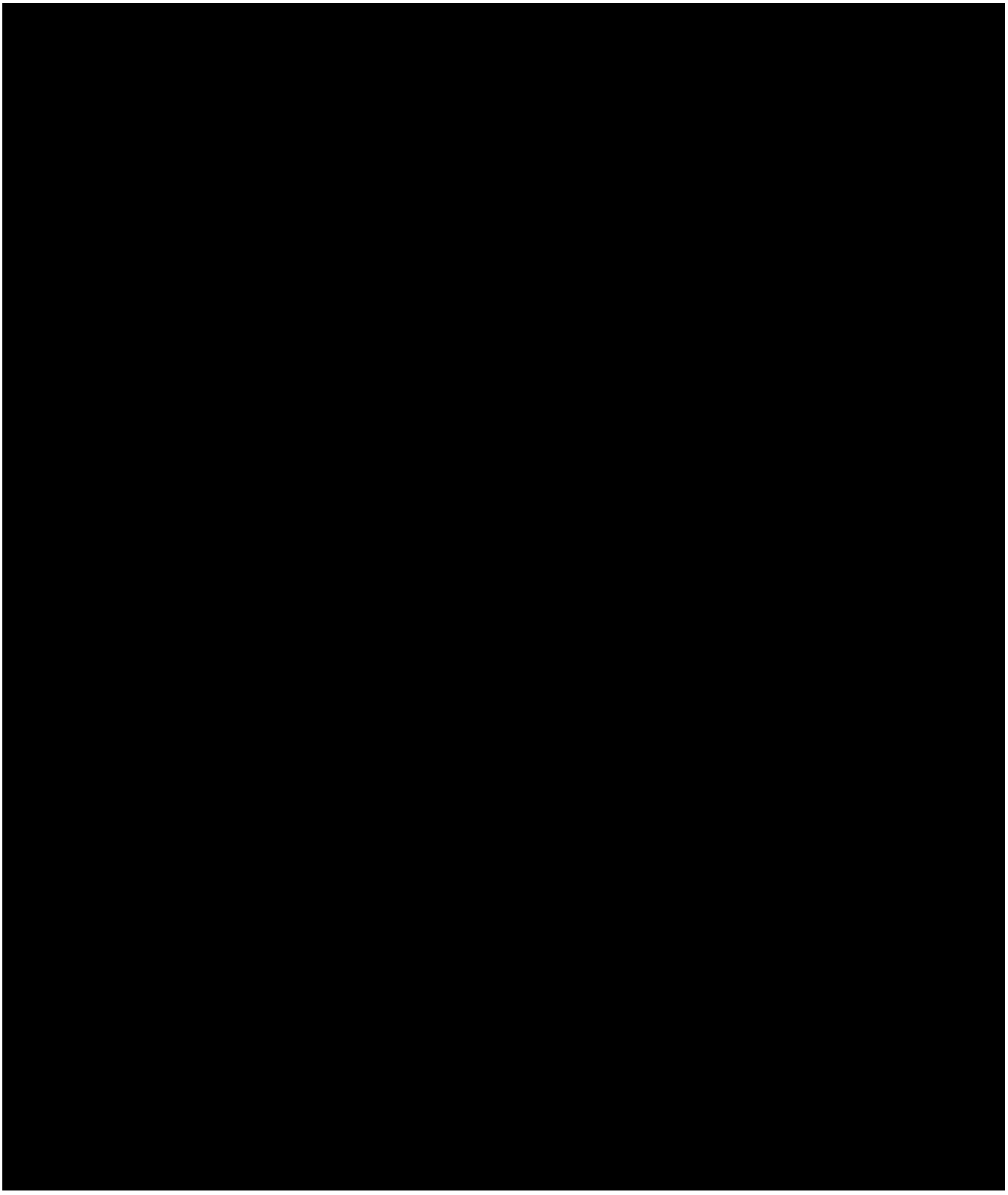

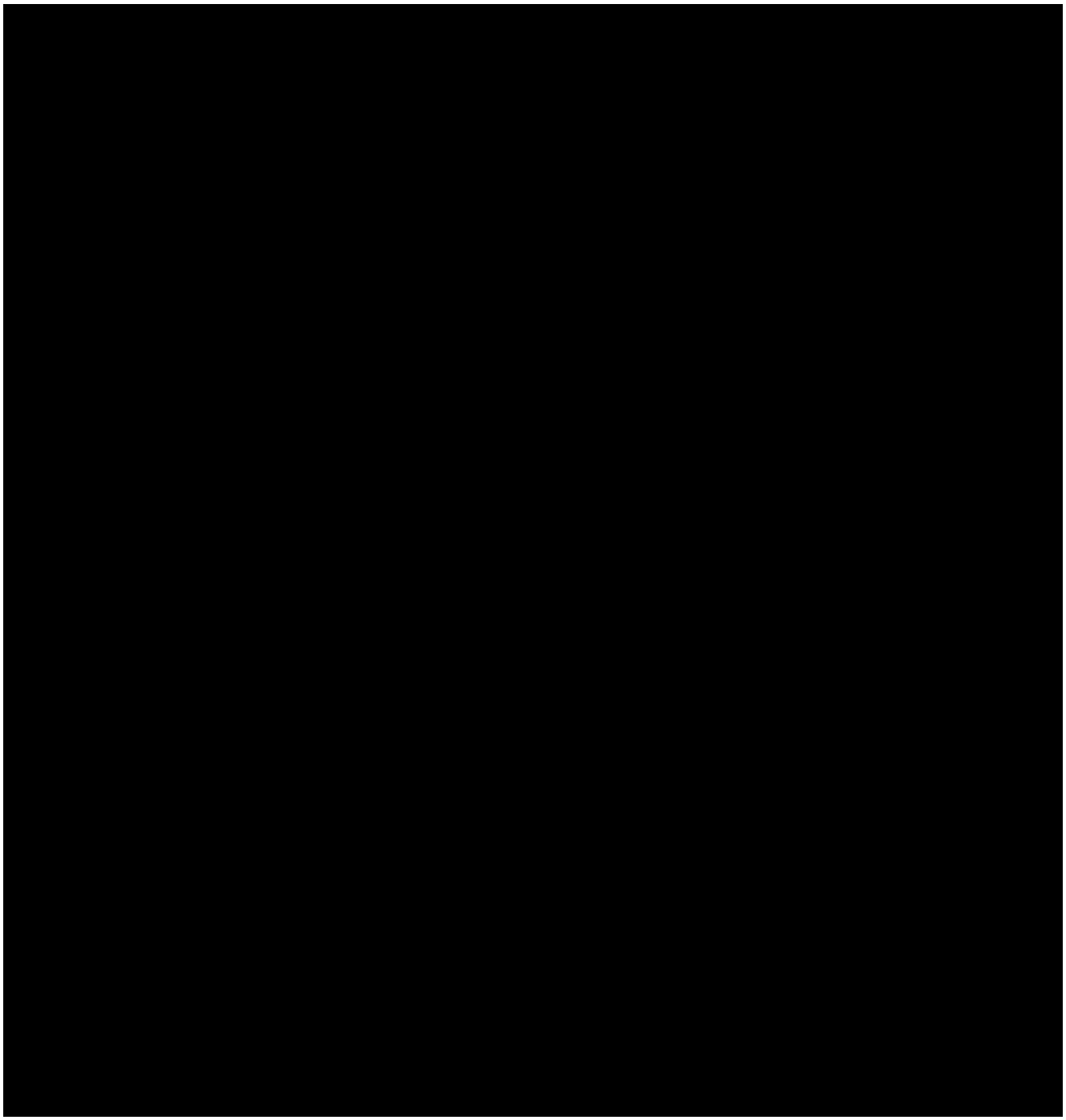

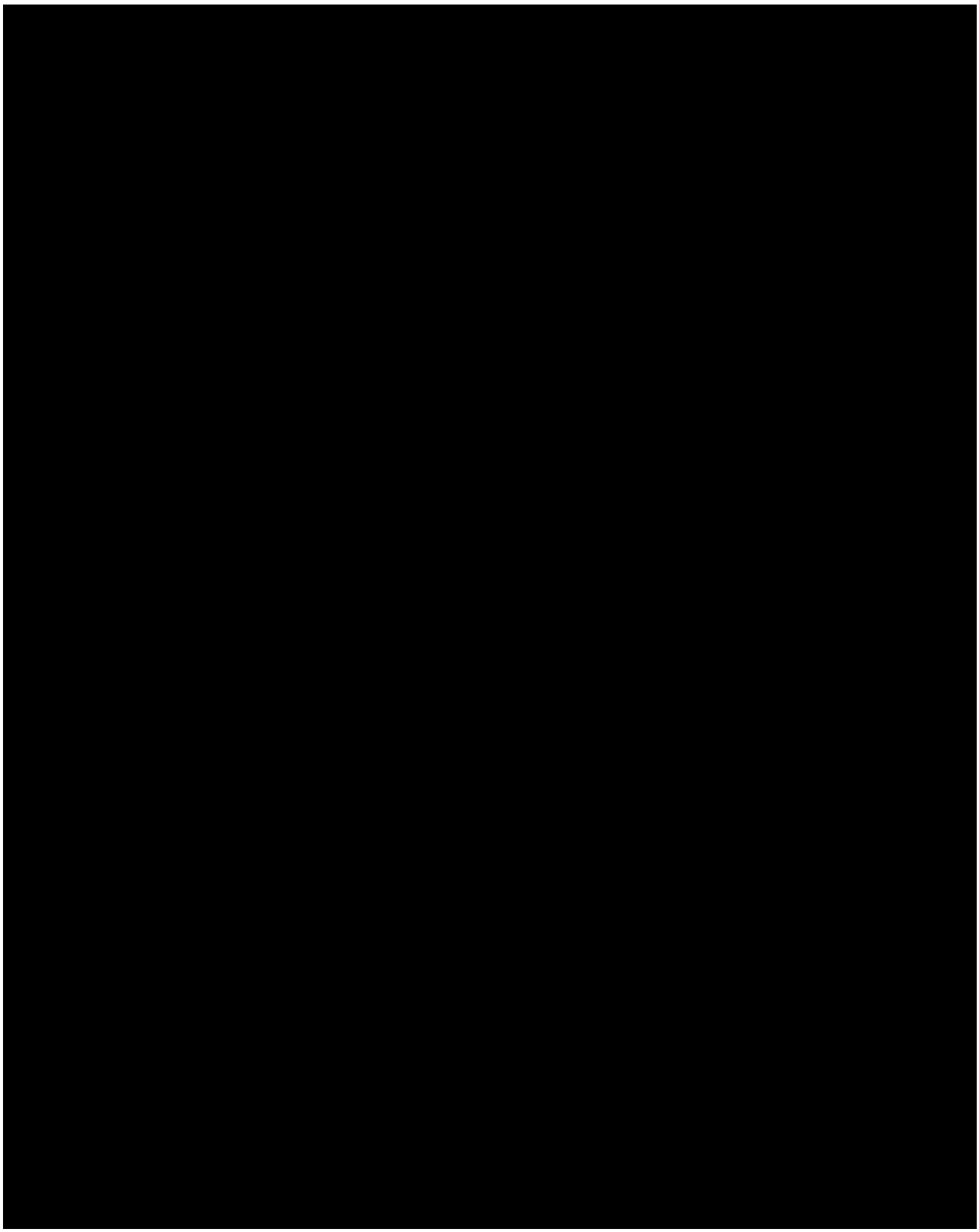

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