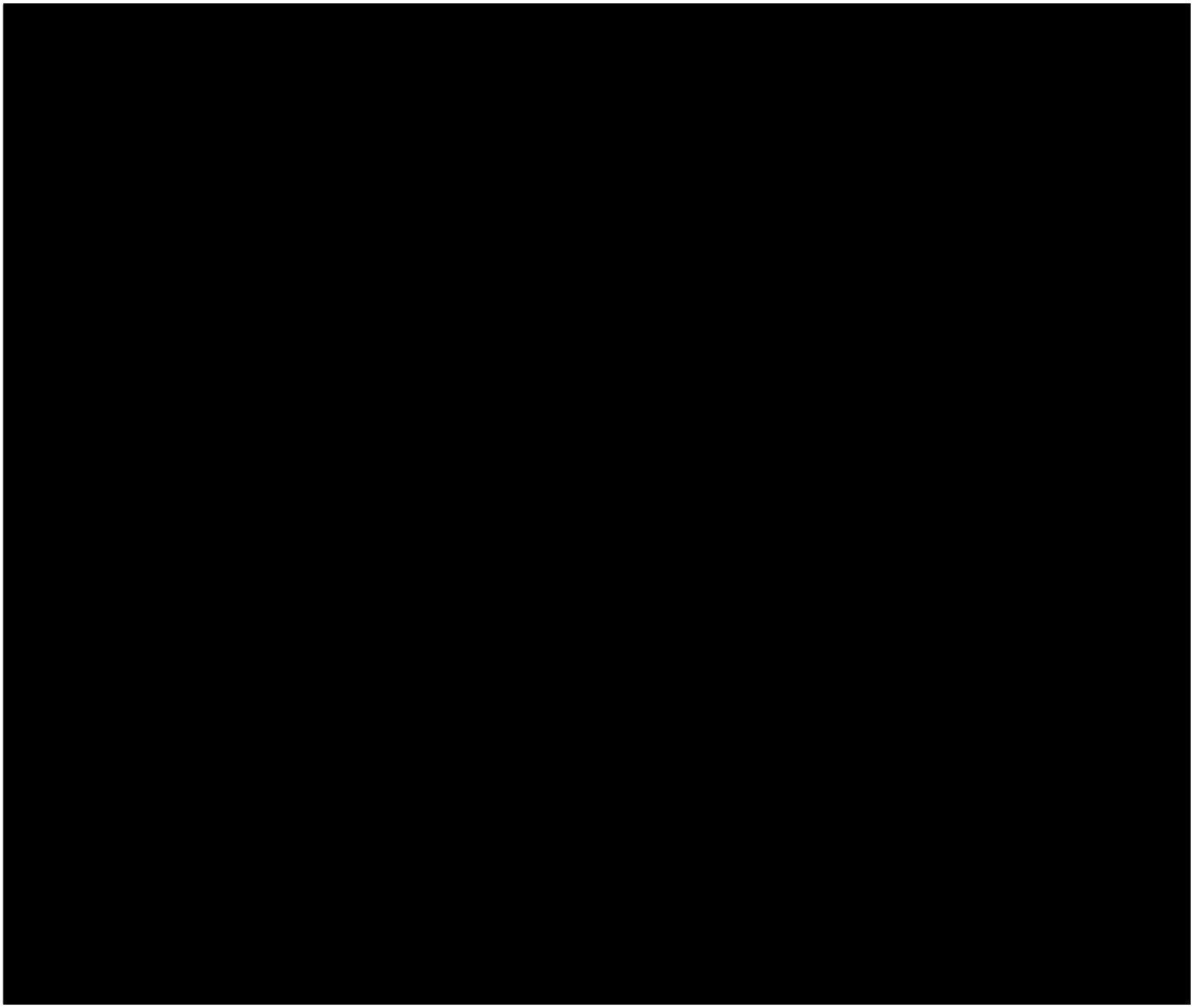
CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2a, Multicenter, Open-Label, Dose-Escalation Study to Evaluate the Efficacy, Safety, and Duration of Benefit of Increasing Doses of DaxibotulinumtoxinA for Injection (DAXI for injection) in the Treatment of Moderate or Severe Lateral Canthal Lines
Protocol Number:	1820205
Document Type:	Amended Protocol
Study Phase:	Phase 2a
Short Title:	Efficacy and Safety of Increasing Doses of DaxibotulinumtoxinA for Injection (DAXI for injection) in the Treatment of Moderate or Severe Lateral Canthal Lines
Sponsor:	Revance Therapeutics, Inc. 7555 Gateway Boulevard Newark, CA 94560
Version:	Amendment 2, 14 August 2019

The study 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).



Investigators Agreement

I have carefully read the protocol entitled: "***A Phase 2a, Multicenter, Open-Label, Dose-Escalation Study to Evaluate the Efficacy, Safety, and Duration of Benefit of Increasing Doses of DaxibotulinumtoxinA for Injection (DAXI for injection) in the Treatment of Moderate or Severe Lateral Canthal Lines***" and,

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

I agree to conduct this clinical study 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	**Date**
Printed Name	
Institution Name	
Address	
City, State, Postal Code, Country	**Phone Number**

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[redacted]

List of Abbreviations

[redacted]	[redacted]
AE	Adverse event
CI	Confidence interval
DAXI	DaxibotulinumtoxinA
DRC	Data Review Committee
eCRF	Electronic case report form
FASE	Facial Age Self Evaluation
FWS	Facial Wrinkle Severity
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
GL	Glabellar lines
ICF	Informed consent form
IEC	Independent Ethics Committee
IGA-LCWS	Investigator Global Assessment Lateral Canthal Wrinkle Severity
IM	Intramuscular
IRB	Institutional Review Board
kDa	Kilodalton
KM	Kaplan-Meier
LCL	Lateral canthal lines
MedDRA	Medical Dictionary for Drug Regulatory Affairs
[redacted]	[redacted]
NSAID	Nonsteroidal anti-inflammatory drug
PLCWS	Patient Lateral Canthal Wrinkle Severity
PHI	Protected health information
PI	Principal Investigator
SAE	Serious adverse event
SNAP-25	25 kDa synaptosome associated protein
SOA	Schedule of Assessments
TEAE	Treatment-emergent adverse event
UPT	Urine pregnancy test
WOCBP	Women of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company:	Revance Therapeutics, Inc.
Name of Finished Product:	DaxibotulinumtoxinA for injection (DAXI for injection)
Name of Active Ingredient:	DaxibotulinumtoxinA
Protocol Title:	A Phase 2a, Multicenter, Open-Label, Dose-Escalation Study to Evaluate the Efficacy, Safety, and Duration of Benefit of Increasing Doses of DaxibotulinumtoxinA (DAXI for injection) in the Treatment of Moderate or Severe Lateral Canthal Lines
Short Title:	Efficacy, Safety, and Duration of Benefit of Increasing Doses of DAXI for injection in the Treatment of Moderate or Severe Lateral Canthal Lines
Rationale:	This phase 2a, multicenter, open-label, dose-escalation study will evaluate treatment of moderate to severe lateral canthal lines (LCL). The proposed dosing regimen for LCL treatment in this study is 1 of 4 dose cohorts (approximately 16 subjects per cohort) [redacted]

	[redacted]
Objectives	**Endpoints**
Primary	
• To evaluate the efficacy and safety of DAXI for injection in the treatment of dynamic LCL	• Proportion of subjects achieving a score or 0 or 1 (none or mild) in LCL severity at maximum smile at Week 4 after LCL treatment on the Investigator Global Assessment Lateral Canthal Wrinkle Severity (IGA-LCWS) scale • Incidence, severity, and relationship to study drug of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) during the overall study duration.
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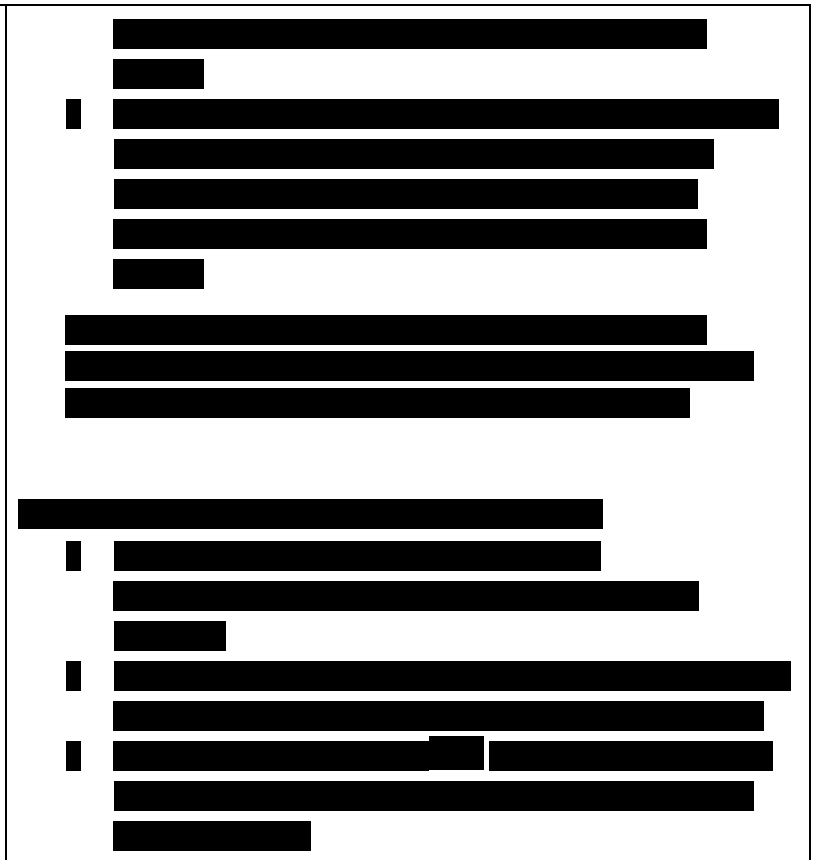
[redacted]	[redacted]



Study Population:

Approximately 64 male and female subjects, 18-65 years old, will be enrolled into the study. Subjects must meet all the inclusion criteria and none of the exclusion criteria to be eligible for this study.

Inclusion Criteria:

To be eligible for participation, subjects must:

1. Provide written informed consent consistent with International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP) guidelines and local laws, including authorization to release health information, signed prior to any study procedures being performed
2. Be outpatient, male or female subjects, in good general health, 18-65 years old
3. Have a score of moderate (2) or severe (3) LCL at maximum smile effort as assessed by the IGA-LCWS (scores must be consistent bilaterally)
4. Have a score of moderate (2) or severe (3) LCL at maximum smile effort as assessed by the PLCWS (scores must be consistent bilaterally)
5. Have sufficient visual acuity without the use of eyeglasses (contact lens use is acceptable) to accurately assess their facial wrinkles
6. Be 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 areas (e.g., above the oral commissures) from screening through the end of the study

7. All women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT) result at the Screening Visit and must practice an effective method of contraception throughout the study (e.g., 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 (refer to Section 5.6 for additional information)
8. Able to understand the requirements of the study and be willing and able to follow all study procedures, attend all scheduled visits, and successfully complete the study.

Exclusion Criteria:

Subjects will not be eligible for study participation if they meet any of the following 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. Any history of facial nerve palsy (e.g., Bell's Palsy) or muscle weakness or paralysis in the treatment areas
3. Active skin disease, infections, or inflammation at the injection sites
4. History of or current significant facial asymmetry, eyelid ptosis or history of same, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or inability of investigator to completely or almost eliminate the LCL by physically spreading lateral canthal area apart while at rest
5. History of or current significant brow ptosis, significant brow asymmetry at rest or on brow elevation.
6. A score of 2 or higher in any category of the Regional House-Brackmann Facial Nerve Grading System at screening
7. Previous treatment with botulinum toxin type A in the face within 6 months prior to screening
8. Has had within the last 6 months prior to screening, or plans to receive, any botulinum toxin treatment (other than study treatment)
9. Has had within the last 6 months, or plans to receive, treatment with >200 U of any botulinum toxin anywhere in the body outside of the face within the last 6 months prior to screening through the end of the study

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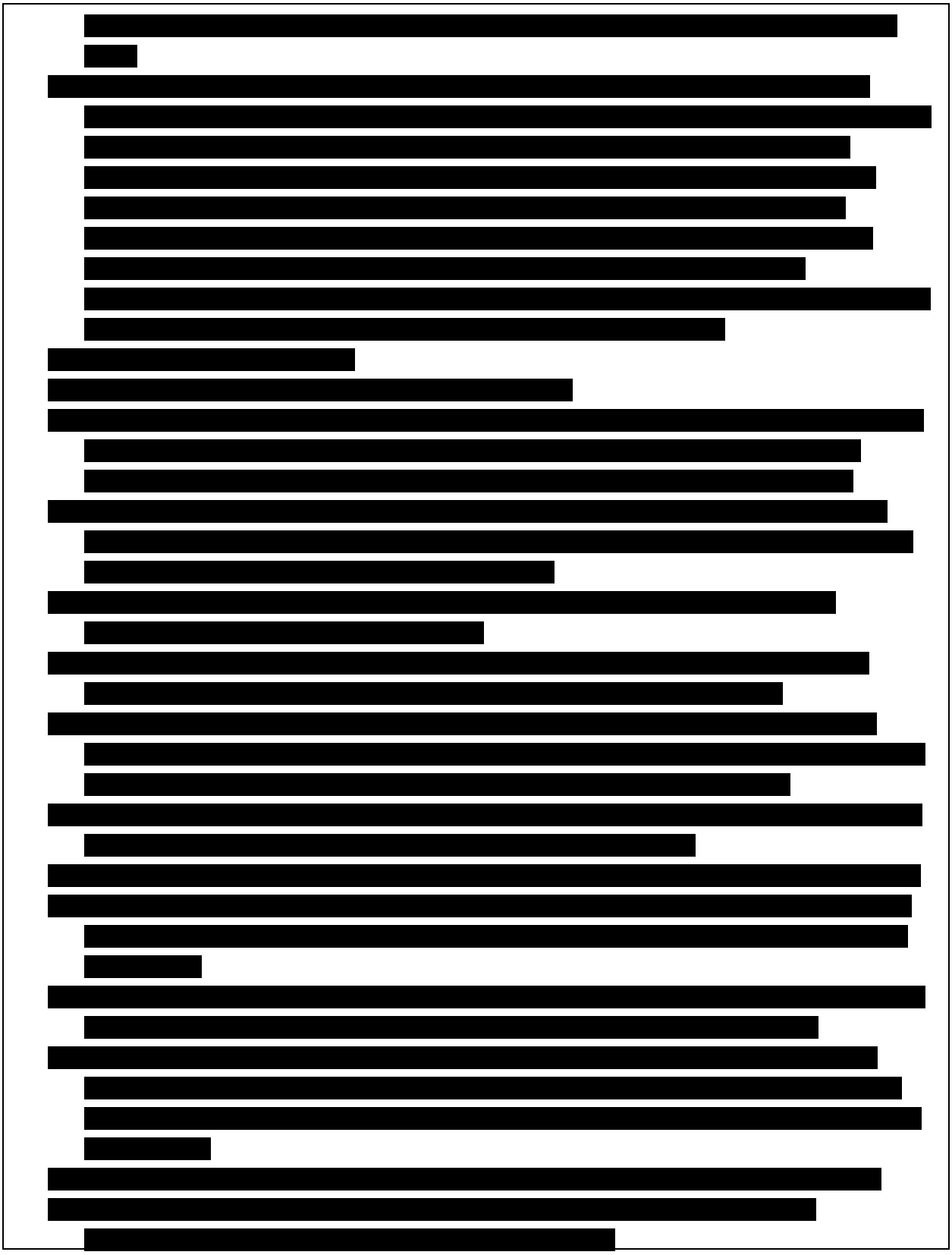


[redacted]

Overall Design:

This is a phase 2a, multicenter, open-label, dose-escalation study to evaluate the safety and efficacy of DAXI for injection for the treatment of subjects with moderate to severe LCL. This study will be conducted at 4 sites in the United States.

Approximately 64 subjects (18 to 65 years old) with moderate to severe LCL will be enrolled sequentially into 1 of 4 treatment cohorts (approximately 16 subjects per cohort) [redacted] Investigators will make all reasonable efforts to enroll equal proportions of subjects with moderate and severe LCL (based on baseline assessments) in each dosing cohort.

The total study duration will be up to 38 weeks, including up to 2 weeks for screening. Subjects will be followed for a minimum of 24 weeks from LCL treatment and up to 36 weeks or until scores on the maximal expression IGA-LCWS and PLCWS return to baseline, whichever occurs first. Subjects will then have a Final Evaluation Visit. Baseline, unless otherwise stated, refers to the last available assessment prior to LCL treatment (Day 1 Visit).

All treatments will be IM injections administered by the principal investigator (PI). [redacted]

[redacted]

[redacted] Revance has this right to stop or terminate the study at any time for any reason at their discretion or in consultation with the DRC.

Study Visits:

Study visits will occur at the Screening Visit (Day -14), Treatment Visit (Day 1), a safety follow-up phone call at Week 1, and follow-up visits at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36. Baseline for all efficacy assessments, unless otherwise noted, will be the last available assessment prior to LCL treatment (Day 1 Visit).

Efficacy Evaluations:

- IGA-LCWS
- PLCWS
- GAIS
- FASE
- FACE-Q™ Appraisal of Lines: Crow's Feet Lines

Baseline for all efficacy assessments associated with LCL severity, unless otherwise noted, refers to the last available assessment prior to LCL treatment (Day 1 Visit). Efficacy outcomes derived from the above list of assessments will be summarized descriptively by dose group and by timepoint. Count and proportion will be provided for responder endpoints (defined as proportion of subjects achieving certain status). Kaplan-Meier (KM) curves will be plotted by treatment group for each time-to-event endpoint to assess median duration of effect at maximum smile and at rest for selected endpoints. Dose-response will be explored using logistic regressions on the response rates (of key responder endpoints) and using log-rank test on the time-to-event endpoints. The effect of study center and baseline severity on the treatment outcome will also be explored.

Safety Evaluations:

- Clinical laboratory tests (hematology, serum chemistry, prothrombin time [PT], urinalysis)
- [redacted]
- [redacted]
- Injection site evaluation
- [redacted]
- Concomitant therapies/medications
- Collection of adverse events (AEs)
- [redacted]
- Vital signs
- Physical examination; [redacted]

All TEAEs occurring during the study will be recorded and classified according to Medical Dictionary for Drug Regulatory Affairs (MedDRA) terminology. All reported TEAEs will be summarized, in terms of the number of subjects reporting events, system organ class, preferred term, severity, relationship to study drug, and severity. For summarization of event causality and severity, subjects will be counted only once within a system organ class or preferred term for a given event using the event with the greatest relationship for causality and the highest severity. A summary of AEs leading to discontinuation will also be provided.

A by-subject listing of any SAEs will be provided and all SAEs will be summarized by severity and relationship to study treatment.

All AEs, including TEAEs, and SAEs will be summarized for the study overall and by dose group.

Clinical laboratory tests, including serum chemistry, hematology, PT (at the Screening Visit only), and urinalysis will be collected at the Screening Visit, Week 4, and Week 36 or Final Evaluation Visit, if applicable. [redacted]. A UPT for all WOCBP will be performed at the Screening Visit, Day 1, and Week 36 or the Final Evaluation Visit, if applicable.

[redacted]

[redacted]

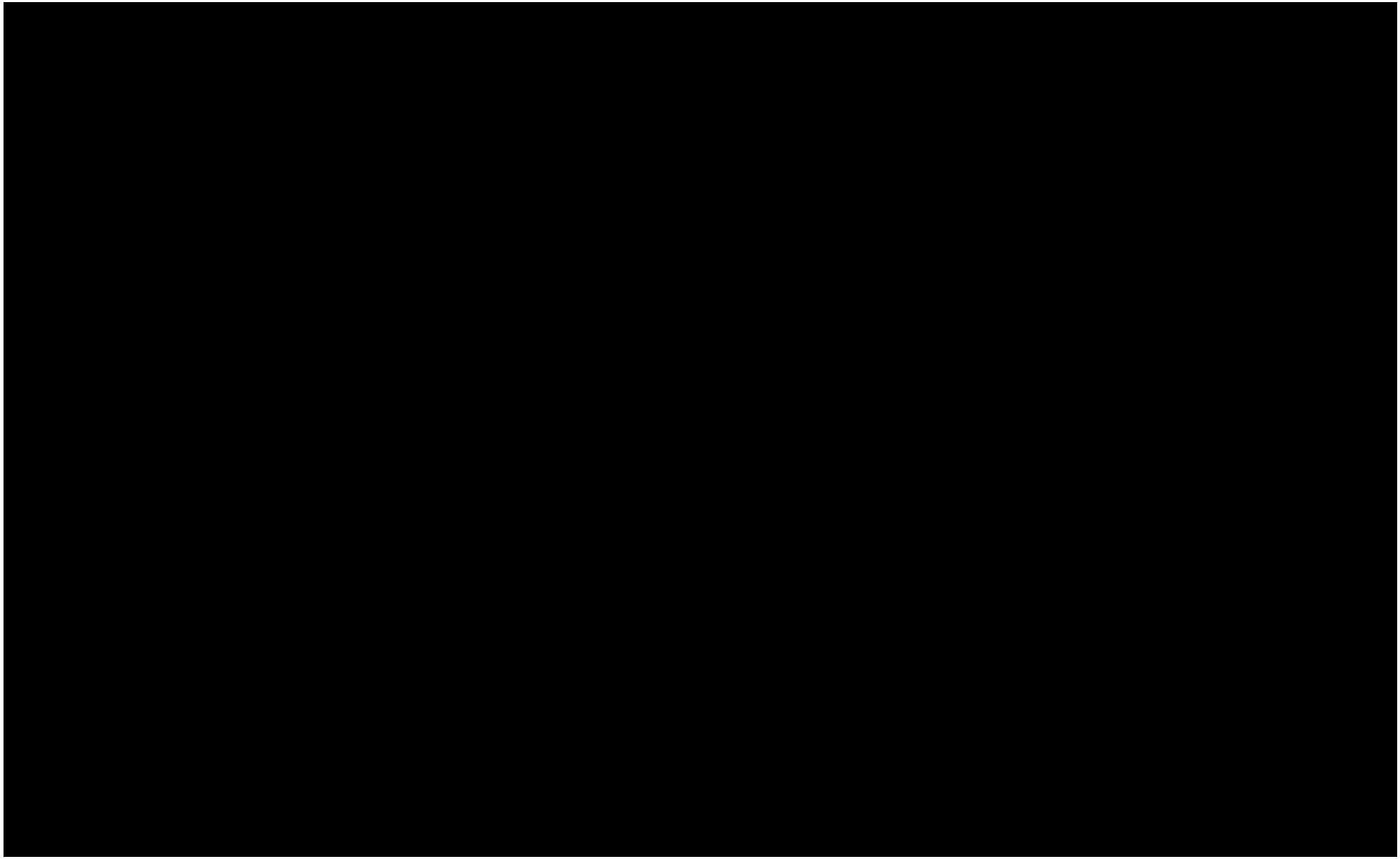
Other Evaluations:

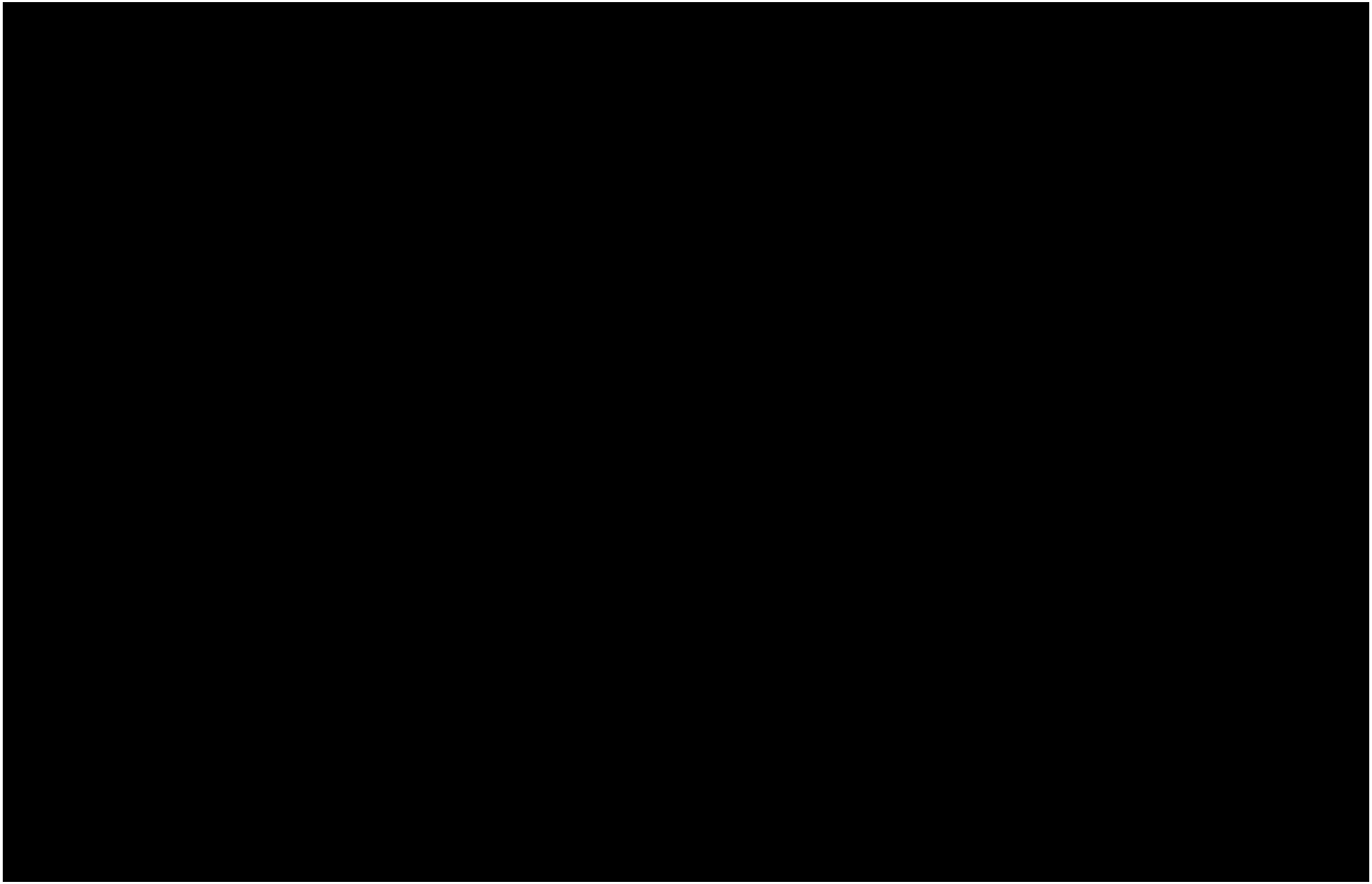
- [redacted]
- [redacted]
- [redacted]
- [redacted]

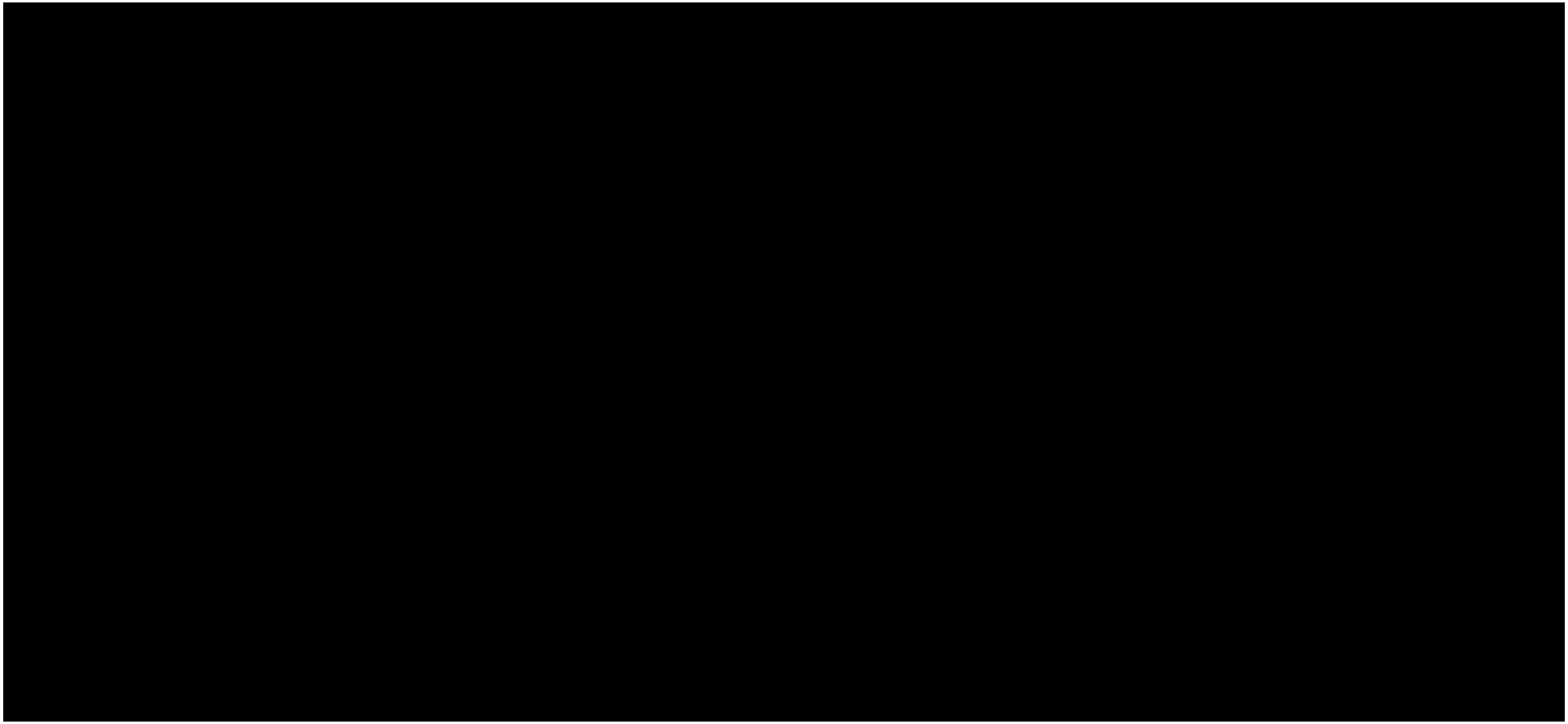
Number of Subjects:

Approximately 64 subjects are expected to participate in this study. Refer to Section 9.2 for additional information on sample size determination.

Disclosure Statement: This is an open-label, dose-escalation study with 4 treatment arms; neither subjects nor investigators/study staff will be blinded. All subjects will receive DAXI for injection for the treatment of moderate to severe LCL.







2. INTRODUCTION

The formation of wrinkles at the corners of the eyes, which are referred to as crow's feet lines or LCLs, are one of the primary signs of aging that can negatively impact the assessment of a person's age. These dynamic lines appear during facial muscle contractions, like smiling, and over time can become permanent or static, meaning that they are still visible when without muscle contraction (Kane, 2015).

Minimally-invasive injectable treatments have become the most common aesthetic procedure worldwide (Baumann, 2016) with an increase in frequency over the last decade since the first approval of botulinum neurotoxin Type A (OnabotulinumtoxinA; BOTOX® Cosmetic; [package insert]. Allergan, Inc., 2017). This is largely the result of an exceptional safety profile, as well as the ability of botulinum neurotoxin Type A to rejuvenate and enhance the facial area when compared with more invasive cosmetic procedures.

Botulinum neurotoxin is produced by *Clostridium botulinum*, which is a gram-positive, spore-forming, anaerobic bacterium (Carruthers, 2015a). There are 7 distinct types (A-G), only types A and B have established clinical uses due to a longer duration of action compared to the other types (De Boulle, 2007). Botulinum neurotoxin Type A blocks acetylcholine release into the neuromuscular junction, which prevents muscle contractions in the injected area. The onset of muscle weakening typically begins within 48 hours after treatment and usually lasts between 4 and 5 months, although some patients have reported shorter or longer durations (Nestor, 2017; Carruthers, 2015; De Boulle, 2007).

The presence of facial lines at rest result from a combination of factors, including repeated facial muscle contractions, structural skin remodeling that occurs with aging, and damage from excessive sun exposure (Carruthers, 2016). Carruthers, et.al., identified 4 distinct patterns for lateral canthal lines: full-fan, lower-fan, central-fan, and upper-fan. The description of these lines emphasizes the orientation of the lines in the lateral canthal area and nearby facial regions. As the dynamic patterns for LCL are further elucidated, it has become possible for experienced practitioners to customize treatment of the lateral canthal region to match the pattern of a patient's lateral canthal lines.

The efficacy and safety of onabotulinumtoxinA for the treatment of LCL has been evaluated in a large-scale clinical development program consisting of 3 phase 3 studies (Carruthers, 2015b). Study 1 evaluated onabotulinumtoxinA for the treatment of LCL alone. A total of 445 subjects with moderate to severe LCL were randomized to receive either onabotulinumtoxinA 24 U (N=222) or placebo (N=223) (Baumann, 2016). At baseline, 60.5% of subjects had severe LCL. The primary efficacy endpoint was investigator-assessed response of LCL at maximum smile on the Facial Wrinkle Severity (FWS) scale at Day 30. Responder rates were significantly higher in the onabotulinumtoxinA-treated groups when compared with placebo. Composite investigator- and subject-assessed improvement of at least 2 grades from baseline scores on the FWS at Day 30 were higher for the onabotulinumtoxinA-treated group (26.1%) when compared with placebo (1.3%) (Carruthers, 2015b).

Study 2 was a 7-month, double-blind, randomized, placebo-controlled, parallel-group study with 2 treatment cycles of onabotulinumtoxinA or placebo. A total of 917 subjects were enrolled:

305 subjects received onabotulinumtoxinA 44U (24 U to LCL area and 20 U to GL area), 306 subjects received onabotulinumtoxinA 24 U (12 U to LCL Area and 0 U to GL area), and 306 subjects received placebo (Moers-Carpi, 2015). The primary efficacy outcome was based on investigator and subject assessments of LCL severity at maximum smile at Day 30 using an FWS. Responder rates were calculated based on the proportion of subjects achieving a composite investigator- and subject-assessed improvement of at least 2 grades from baseline scores on the FWS at Day 30. For this endpoint scores were significantly higher for the LCL-treated group (20.3%), and the LCL and GL treated group (21.3%) when compared with placebo (0%). The proportion of responders achieving a score of 0 (none) or 1 (mild) on the FWS for LCL was significantly higher (as rated by both the investigator and the subject) at Day 30 ($p < 0.001$) for the onabotulinumtoxinA group compared with the placebo group. Investigator-assessed responder rates were 59.0% and 54.9% in the onabotulinumtoxinA 44 U and 24 U groups, respectively. Subject responder rates at Day 30 were similar in the onabotulinumtoxinA-treated groups at 48.5% and 45.8%, respectively (Moers-Carpi, 2015). In general, when GL and LCL were treated simultaneously, responder rates were higher than those for LCL treatment alone.

The reported AEs for both Study 1 and Study 2 were mild or moderate in severity, with 58.1% of subjects reporting at least 1 AE. Most AEs were not considered to be treatment-related. The most frequently reported treatment-related AEs included injection site hematoma (including bruises), headache, and injection site hemorrhage, all of which occurred at a frequency of ≤3.1% in each of the 4 treatment cycles. Further, the incidence of treatment-related AEs tended to decline with repeated treatment. None of the subjects discontinued treatment due to an AE or SAE (Carruthers, 2015b).

Study 3 was a 5-month, double-blind, randomized, parallel-group, placebo-controlled extension study of the subjects who completed Study 2. Subjects who previously received onabotulinumtoxinA were eligible to receive the same dose in this study, while subjects who previously received placebo were randomized in a double-blind fashion to 1 of 2 treatment arms to receive either onabotulinumtoxinA 44 U or placebo. In this extension study, subjects were eligible to receive up to 2 additional treatment cycles. The endpoints were similar to Study 2 with the primary response being the proportion of subjects achieving a score of 0 or 1 on the FWS at Day 30. A total of 684 subjects were enrolled: 260 to the 44 U onabotulinumtoxinA group, 227 to the onabotulinumtoxinA 24 U, 101 subjects who previously received placebo and were randomized to the onabotulinumtoxinA 44 U group, and 96 subjects who previously received placebo and were randomized to the placebo group. Results were consistent with Study 2 with responder rates significantly higher in the onabotulinumtoxinA-treated groups at Day 30 and at all other timepoints in cycles 3 and 4 when compared with placebo. During the 1-year assessment period, 58.2% of subjects experienced at least 1 AE; however, most were mild in intensity. Notably, the incidence of treatment-related AEs appeared to decline with repeated treatments. Treatment-related AEs, all occurring in <3.1% of subjects in each treatment cycle, included site hematoma, headache, and injection site hemorrhage.

As minimally-invasive treatment becomes more widely used and accepted, and both men and women gain increased awareness of the recognition of facial aging and the aesthetic treatment options available, it is important to continue examining the potential benefits of such treatments in the context of unmet clinical need, improved self-satisfaction, and increased demand. Aesthetic products and procedures, while not medically necessary, can significantly improve

social and psychological functioning, as well as self-satisfaction, which can have a meaningful and significant impact on daily life and patient well-being (Fagien, 2008).

[redacted]

2.2. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of DAXI for injection may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy and safety of DAXI for injection in the treatment of dynamic LCL	• Proportion of subjects achieving a score or 0 or 1 (none or mild) in LCL severity at maximum smile at Week 4 after LCL treatment on the IGA-LCWS • Incidence, severity, and relationship to study drug of TEAEs and SAEs during the overall study duration.
[redacted]	
[redacted]	[redacted]
[redacted]	
	[redacted]

[redacted]	[redacted]

	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a phase 2a, multicenter, open-label, dose-escalation study to evaluate the safety and efficacy of DAXI for injection for the treatment of subjects with moderate or severe LCL. This study will be conducted at 4 sites in the United States.

[redacted] Subjects will be screened for eligibility and enrolled into the study after providing informed consent.

Approximately 64 subjects (18-65 years old) with moderate or severe LCL will be enrolled sequentially into 1 of 4 treatment cohorts (approximately 16 subjects per cohort)[redacted]. Investigators will make all reasonable efforts to enroll equal proportions of patients with moderate and severe LCL (based on baseline assessments) in each dosing cohort. The total study duration will be up to 38 weeks, including up to 2 weeks for screening. Subjects will be followed for a minimum of 24 weeks and up to 36 weeks or until scores on the maximal expression IGA-LCWS and PLCWS return to baseline (Day 1 Visit), or until Week 36, whichever occurs first. Subjects will then have the Final Evaluation Visit.

Cohorts 1 and 2 will be enrolled simultaneously. Subsequent cohorts (3 and 4) will be enrolled sequentially and gated by the decision from the Data Review Committee (DRC) upon reviewing available data (including safety, efficacy, and photographs/videos) of previous cohorts. The DRC will convene to review data 4 weeks after LCL treatment for the last subject in Cohorts 1 and 2. The DRC will reconvene again after the last subject in Cohort 3 reaches the Week 4 Visit. Revance reserves the right to terminate or stop the study at any time. Refer to Sections 1.2 and 9.5.1 for additional information.

[redacted]

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

[redacted]

All treatments will be IM injections administered by the PI. [redacted]

The area around the injection sites will be evaluated at the Screening Visit to assess for skin inflammation or active skin disease and at the Day 1, Week 2, and Week 4 Visits to determine if there is a cutaneous reaction to the investigational product. The assessment will be captured as a

global evaluation of the injection sites to assess for erythema, edema, burning or stinging sensation, itching, or bruising.

All subjects will be evaluated for improvement in LCL severity using the Revance-validated 4-point LCWS to assess LCL at rest and at maximum rest by both the investigator (IGA-LCWS) and the subject (PLCWS). An additional investigator- and subject-rated endpoint is the visual assessment of improvement from baseline in LCL severity on the GAIS at each post-treatment visit. Additional subject reported outcomes include responses to the FASE and FACE Q™: Appraisal of Lines: Crow's Feet Lines questionnaires, as well as the Subject Global Satisfaction with Treatment questionnaire.

[redacted]

4.4. Visit Schedule

A Screening Visit will be conducted up to 2 weeks prior to enrollment, and subjects will receive investigational product at baseline (Day 1). Following treatment, subjects will complete a paper diary for 2 weeks to capture their assessment of improvement in the appearance of LCL. A follow-up safety phone call will be conducted at Week 1. Post-treatment on-site follow-up visits

will occur at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36. The total study duration will be up to 38 weeks, including up to a 2-week screening period. Subjects will be followed for a minimum of 24 weeks post-treatment and up to 36 weeks or until scores return to baseline for the maximal expression IGA-LCWS and PLCWS or until the Week 36 Visit, whichever occurs first. Subjects will then have a Final Evaluation Visit.

Subjects will be evaluated for LCL severity using the Revance-validated 4-point IGA-LCWS and PLCWS at rest and at maximum smile effort.

5. STUDY POPULATION

Approximately 64 female or male subjects, 18-65 years old, with moderate to severe LCL will be enrolled. Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for the study

5.1. Inclusion Criteria

To be eligible for participation, subjects must:

1. Provide written informed consent consistent with International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP) guidelines and local laws, including authorization to release health information, signed prior to any study procedures being performed
2. Be outpatient, male or female subjects, in good general health, 18-65 years old
3. Have a score of moderate (2) or severe (3) LCL at maximum smile effort as assessed by the IGA-LCWS (scores must be consistent bilaterally)
4. Have a score of moderate (2) or severe (3) LCL at maximum smile effort as assessed by the PLCWS (scores must be consistent bilaterally)
5. Have sufficient visual acuity without the use of eyeglasses (contact lens use is acceptable) to accurately assess their facial wrinkles
6. Be 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 areas (e.g., above the oral commissures) from screening through the end of the study
7. All women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT) result at the Screening and Baseline Visits and must practice an effective method of contraception throughout the study (e.g., 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 (refer to Section 5.6 for additional information)
8. Able to understand the requirements of the study and be willing and able to follow all study procedures, attend all scheduled visits, and successfully complete the study.

5.2. Exclusion Criteria

Subjects will not be eligible for study participation if they meet any of the following 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. Any history of facial nerve palsy (e.g., Bell’s Palsy) or muscle weakness or paralysis in the treatment areas
3. Active skin disease, infections, or inflammation at the injection sites

4. History of or current significant facial asymmetry, eyelid ptosis or history of same, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or inability of investigator to completely or almost eliminate the LCL by physically spreading lateral canthal area apart while at rest
5. History of or current significant brow ptosis, significant brow asymmetry at rest or on brow elevation
6. A score of 2 or higher in any category of the Regional House-Brackmann Facial Nerve Grading System at screening
7. Previous treatment with botulinum toxin type A in the face within 6 months prior to screening through the end of the study
8. Plans to receive any botulinum toxin treatment (other than study treatment) from screening through the end of the study
9. Has had within the last 6 months, or plans to receive, treatment with >200 U of any botulinum toxin anywhere in the body outside of the face

[redacted]

5.3. 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 study 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, 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 study has been given a full explanation of the

procedures and expectations for study participation, as well as ample time to decide whether or not to participate and have all questions answered satisfactorily.

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 ICH GCP guideline, and applicable federal and local regulatory requirements. The consent form must also include a statement that Revance, their designees, auditing and 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 study, 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).

5.4. Lifestyle Considerations

While enrolled in this study, subjects must agree to refrain from receiving non-ablative laser or light treatments, microdermabrasion, or chemical peels (medium depth or deeper, for example TCA or phenol) in the treatment areas within 3 months before enrollment through the end of the study.

[redacted]

Refer to Section 6.4 for a complete list of prohibited medications during the study.

5.5. Protocol Deviations

This study will be conducted as described in this protocol, except for emergency situations 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). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact Revance or designee by telephone at the earliest possible time. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the investigator and Revance or designee.

5.6. Pregnancy

All WOCBP must use an effective method of birth control during the course of the study (e.g., 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 study, investigators must review guidelines with the subject about study participation for WOCBP with the subject. 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 study and the potential risk factors for an unintentional pregnancy. The subject must sign the informed consent document stating that the risk factors for unintentional pregnancy and the consequences were discussed with her.

During the study, all WOCBP should be instructed to contact the investigator immediately (within 24 hours) if pregnancy is suspected (e.g., missed or late menstrual cycle). The investigator, or qualified designee, must immediately notify Revance or designee of any female subject who becomes pregnant any time during study participation, record the information on Revance or designee Pregnancy Notification Form and send the form to Revance or designee. The investigator will be asked to follow-up with the subject periodically during the pregnancy for ongoing health and safety information through term, as applicable.

If an SAE occurs in conjunction with the pregnancy such as untoward outcome of the pregnancy or of the offspring (spontaneous abortion, or abnormality in the offspring) then the reporting time frame for an SAE must be met and SAE reporting procedures followed. In the event of a normal birth, follow-up with the subject will occur with a phone call until the first well visit, at which time, active follow-up to the pregnancy will cease.

6. STUDY INTERVENTION

The active pharmaceutical ingredient, daxibotulinumtoxinA, is a purified 150 kilodalton (kDa) botulinum neurotoxin type A, derived from the Hall strain *C. botulinum*. Produced by *C. botulinum* as a single inactive polypeptide chain of 150 kDa, daxibotulinumtoxinA undergoes proteolytic cleavage by proteases present in the fermentation culture to yield the active di-chain molecule comprised of a 100 kDa heavy chain and a 50 kDa light chain linked via both non-covalent interactions and a disulfide bond (Aoki, 2001). The heavy chain plays a role in binding, internalization, and translocation of daxibotulinumtoxinA into neuronal cells. The light chain acts as a site-specific metalloprotease causing selective cleavage and inactivation of the 25 kDa synaptosome associated protein (SNAP-25), which is a cell membrane localized component of the vesicular release machinery. This cleavage of SNAP-25 by the light chain of botulinum toxin type A blocks the synaptic vesicle exocytosis and subsequent release of acetylcholine, thus leading to a dose-dependent weakening of the target muscle.

6.1. Study Intervention(s) Administered

This is an open-label, nonrandomized study for the treatment of moderate or severe LCL. Subjects will be sequentially enrolled by cohort. All subjects will receive DAXI for injection on Day 1 according to their assigned cohort.

[redacted]

[redacted]

[redacted]

[redacted]

6.2.4. Investigational Product Administration

Investigational product will be administered by the PI to injection site in the designated treatment areas bilaterally while the subject is in a sitting position [redacted].

1. Wear protective gloves for investigational product administration
2. Pull subject's hair away from the treatment areas (lateral canthal region)
3. Wipe all injection sites with alcohol
4. [redacted]
5. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

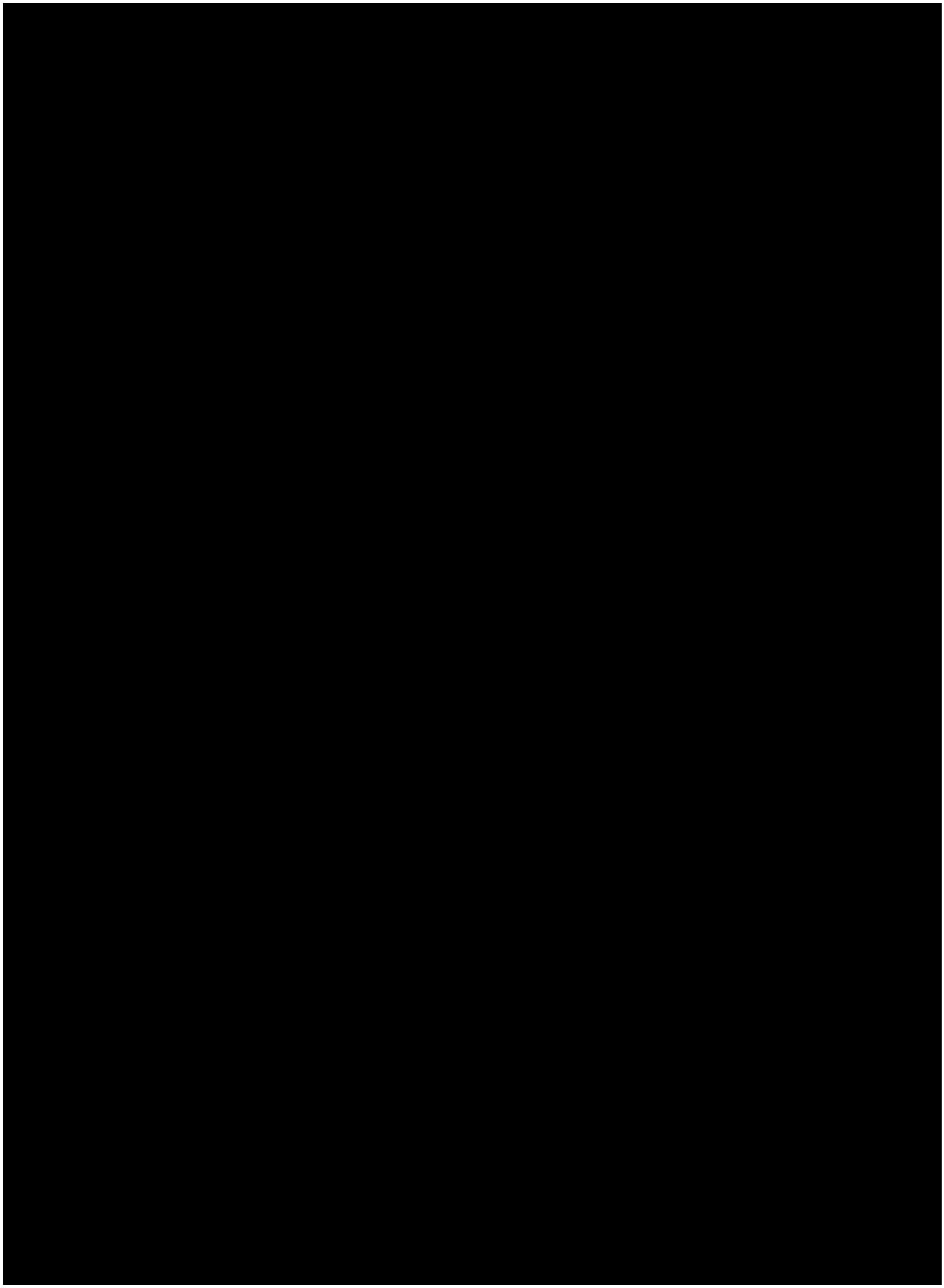
[redacted]

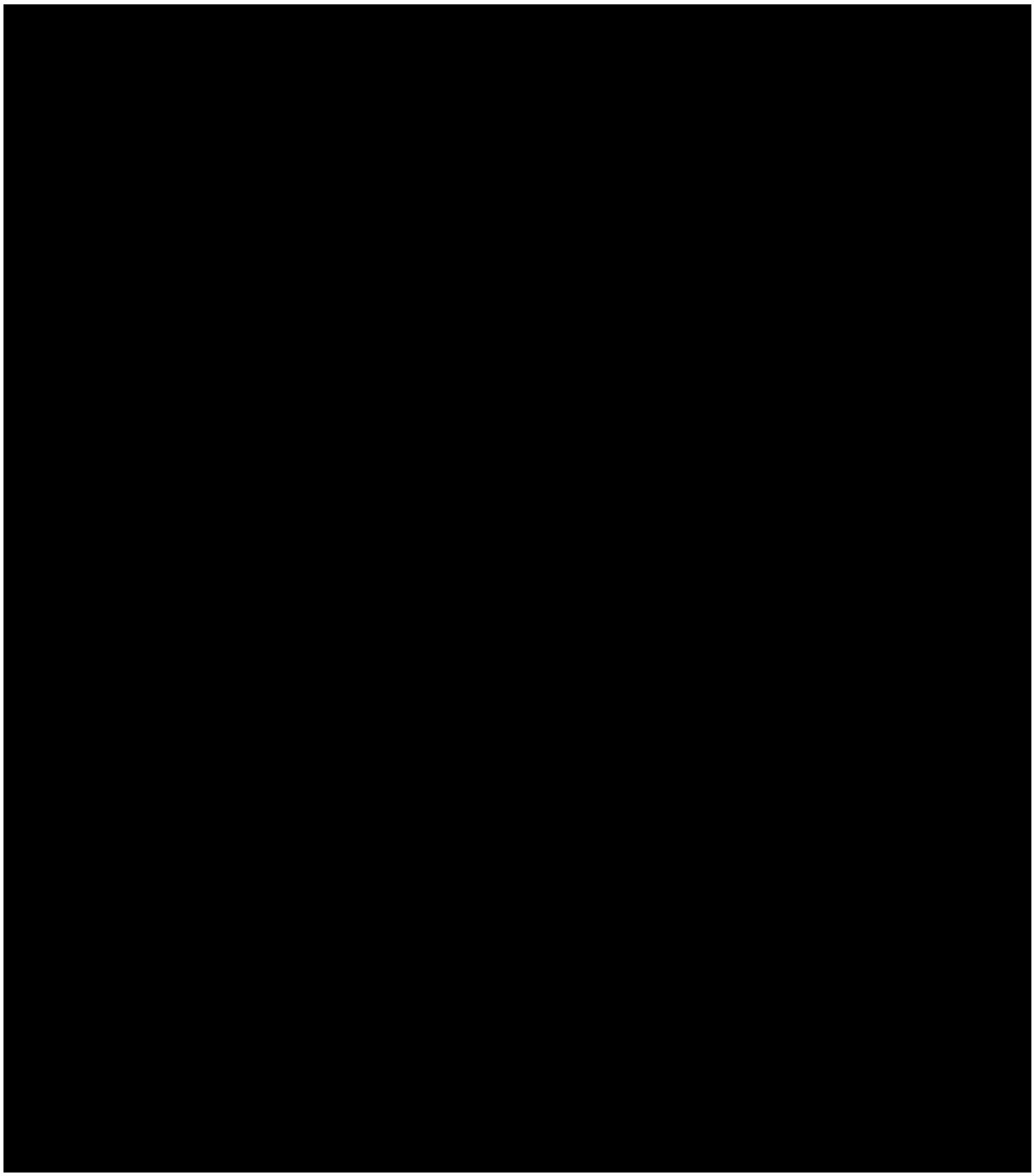
6.3. Concomitant Medications/Therapies

Concomitant medications are any prescription or over-the-counter preparations used by subjects during participation in the study. Use of concomitant medications will be recorded on the Concomitant Medications electronic case report form (eCRF) beginning at the Screening Visit (and anything taken during the previous 30 days) 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]





6.5. Dose Modification

Subjects will receive a single dose (consisting of 3 variable volume injections) according to assigned dose cohort in this study. The DRC will convene to review available data (including safety and photographs/videos) for Cohorts 1 and 2 prior to making a decision about the treatment of Cohort 3. The DRC will also convene to review applicable data (safety and photographs/video) prior to making a decision about the treatment of Cohort 4.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Subject Discontinuation/Withdrawal from the Study

A subject may voluntarily withdraw from study participation at any time. If the subject withdraws consent and discontinues from the study, the Investigator will attempt to determine the reason for discontinuation and record the reason in the subject's study records and on the eCRF. 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 consent is withdrawn, the subject should be asked to return to the study center to complete the assessments specified in the Final Evaluation Visit. Subjects who withdraw from the study will not be replaced. Subjects who withdraw from the study, but agree to continued follow-up, must be reconsented by the investigator for this limited participation in the study (unless this situation was adequately described in the original informed consent form [ICF]).

If at any time during the study, 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 study procedures or to keep follow-up appointments. Appropriate documentation in the subject's study record and eCRF 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 study 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 study. If a subject is unreachable by telephone after a minimum of 2 documented attempts (1 attempt on 2 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 study at any time. Should this be necessary, both Revance and the Investigator will ensure that proper study discontinuation procedures are completed.

7.2. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

Before a subject is deemed lost-to-follow-up, the study center should make every effort to contact the subject (refer to Section 7.1) and reschedule the missed visit as soon as possible. The subject should be counseled on the importance of visit compliance and should be questioned as to whether he or she wishes to continue in the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Subject Entry Procedures

Subject informed consent must be obtained prior to conducting screening procedures. Each signature must be personally dated by each signatory and the original retained by the PI as part of the study record. A signed copy must be provided to each subject (refer to Section 5.3).

8.2. Schedule of Visits and Procedures

It is recommended that study visits be scheduled at approximately the same time of day throughout the study. The IGA-LCWS and Investigator GAIS should be performed by the same evaluator throughout the study whenever possible. If it is not possible to use the same evaluator throughout the study, two evaluators should examine the subject together and discuss findings for at least 1 prior visit. The SOA is provided in Section 1.3.

8.2.1. Screening Visit

The Screening Visit must take place within 14 days prior to the LCL treatment visit (Day 1 Visit).

The following procedures must be performed and recorded at this visit:

1. Review study procedures and information regarding the study and obtain written informed consent and privacy authorization (as applicable)
2. Review eligibility criteria
3. Obtain medical/surgical history, including prior toxin use, and demographic information, including Fitzpatrick skin phototype
4. Once the investigator has confirmed eligibility, the subject will be enrolled
5. Conduct patient education: Discuss the potential effect of DAXI for injection treatment, explain the PLCWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for LCL severity. Use the provided Patient Education Brochure

[redacted]

[redacted]

8. Perform a physical examination,

[redacted]

10. Measure and record vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure); subjects must sit for at 5 minutes prior to having pulse and blood pressure measurements taken

[redacted]

12. Collect blood and urine samples for clinical safety laboratory tests (hematology, serum chemistry, PT, and urinalysis)

[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 enrollment.

8.2.2. Treatment Visit (Baseline/Day 1)

The LCL treatment visit at Baseline (Day 1 Visit) must be performed within 14 days of the Screening Visit. The LCL dose is administered at this visit. The following procedures must be performed and recorded for each visit:

Prior to Investigational Product Administration

1. Confirm that all screening procedures have been completed, results reviewed, and recorded
2. Review eligibility criteria
3. Update medical/surgical history

[redacted]

7. Conduct patient education: Discuss the potential effect of DAXI for injection treatment, explain the PLCWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for LCL severity. Use the provided Patient Education Brochure

[redacted]

[redacted]

11. Physical examination [redacted]

[redacted]

13. Measure and record vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure); subjects must sit for 5 minutes prior to having pulse and blood pressure measurements taken

[redacted]

16. Update concomitant therapy/medications since the Screening documenting the dose and dosing regimen of all prescription and non-prescription therapies and medications, including herbs, vitamins, or other nutritional supplements (Section 6.3).

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 (Refer to Appendix 2) while the subject is in a seated position.

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

[redacted]

After Investigational Product Administration

- [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]

8.2.3. Week 1 Follow-up Phone Call

At the Week 1 follow-up phone call, the subject will be contacted by the site staff 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:

- [redacted]
- [redacted]

3. Query subject about any new or ongoing AEs since the last visit

- [redacted]
- [redacted].

8.2.4. Follow-up Visits

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

[redacted]

3. Conduct patient education: discuss the potential effect of DAXI for injection treatment, explain the PLCWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for severity of their LCL. Use the provided Patient Education Brochure

[redacted]

13. Collect blood and urine samples for clinical safety laboratory tests (hematology, serum chemistry, and urinalysis) (Week 4 Visit only)

[redacted]

17. Assess any new or ongoing AEs since the last visit

[redacted]

8.2.5. Final Evaluation Visit (Week 36) 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 at a minimum of 24 weeks from LCL treatment and up to 36 weeks for safety or until maximal expression scores on the IGA-LCWS and PLCWS return to baseline or Week 36, whichever occurs first. Subjects will then have a Final Evaluation Visit at which time the following procedures must be performed and recorded:

[redacted]

2. Conduct patient education: Discuss the potential effect of DAXI for injection treatment, explain the PLCWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for severity of their LCL. Use the provided Patient Education Brochure

[redacted]

10. Perform a physical examination [redacted]

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

[redacted]

14. Collect blood and urine samples for clinical safety laboratory tests (hematology, serum chemistry, and urinalysis)

[redacted]

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

8.2.6. Variation from Scheduled Visit Days

To allow for scheduling flexibility, limited variation will be permitted from the specified time of each visit (Table 3).

Table 3: Allowed Variation from Scheduled Visit Days

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

8.3. Efficacy Assessments

Effectiveness assessments will include investigator assessment of LCL severity and improvement, as well as subject assessment of severity and improvement. Effectiveness assessments will be conducted with the subject in a sitting position. To ensure 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). Investigator assessments of improvement should be performed by the same evaluator throughout the study for a given subject. (Refer to Section 8.2.)

8.3.1. Investigator Global Assessment of Lateral Canthal Wrinkle Severity

At each clinic visit as designated in the SOA (Section 1.3), the investigator will assess the visual appearance (at rest and at maximum smile) of the LCL on each side of the face using the IGA-LCWS with the following 4-point scale (Table 4).

Table 4: Investigator Global Assessment Lateral Canthal Wrinkle Severity

Rating Score	Lateral Canthal Wrinkle Severity	Description
0	None	None to minimally visible line(s) lateral to the lateral canthus
1	Mild	Visible, shallow line(s) lateral to the lateral canthus
2	Moderate	Clearly visible, moderately deep line(s) lateral to the lateral canthus
3	Severe	Clearly visible, deep line(s) lateral to the lateral canthus with redundancy of skin

[redacted]

[redacted]

8.3.2. Patient Lateral Canthal Wrinkle Severity Scale

Subjects will complete the PLCWS scale at rest and at maximum smile, to assess the severity of the LCL on each side of the face at the Screening Visit, Day 1 Visit (Baseline), follow-up visits, and the Week 36 Visit or the Final Evaluation Visit, if applicable.

The subject assessment form will be provided directly to the subject to complete while reviewing his or her LCL using the supplied handheld mirror. Scores at screening and baseline must be consistent bilaterally.

Refer to Appendix 4 for additional information.

Table 5: Patient Lateral Canthal Wrinkle Severity

Rating Score	Lateral Canthal Wrinkle Severity	Description
0	None	No line(s) lateral to the lateral canthus
1	Mild	Barely visible, shallow line(s) lateral to the lateral canthus
2	Moderate	Clearly visible, moderately deep line(s) lateral to the lateral canthus
3	Severe	Clearly visible deep line(s) lateral to the lateral canthus with redundancy of skin

8.3.3. Global Aesthetic Improvement Scale (GAIS)

The investigator and subject will assess the visual appearance (at maximum smile) of the LCL improvement from the baseline condition on each side of the face using the following 7-point severity GAIS (Table 6). Subjects will use the baseline assessment photograph for comparison when reviewing the visual appearance for LCL to assess improvement following treatment. Assessments will be made as designated in the SOA (Section 1.3).

The Patient GAIS Assessment Form (Appendix 4) will be provided directly to the subject to complete while reviewing the lateral canthal treatment areas (at maximum smile) using the supplied handheld mirror as outlined in Appendix 5. Subjects with contact lenses should view

their treatment areas while wearing their contact lenses. Subjects who wear glasses must have sufficient visual acuity to be able to view their treatment areas without the use of glasses. The subject assessment must be completed before the investigator completes the IGA-LCWS assessment.

Table 6: 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

8.3.4. Facial Age Self Evaluation (FASE)

At each clinic visit designated in the SOA (Section 1.3), the subject will be asked to rate their perceived age on a FASE questionnaire (Appendix 7). Following the subject's completion of the Patient GAIS, the subject will be given the FASE questionnaire to rate their perception of how old they think they look following treatment.

8.3.5. FACE-Q™ Appraisal of Lines: Crow's Feet Lines

At each follow-up visit designated in the SOA (Section 1.3), the subject will be asked to rate their perception of themselves on the FACE-Q Appraisal of Lines: Crow's Feet Lines (Appendix 9). This questionnaire asks subjects to rate how bothered they are by their LCL using 7 questions about general appearance using a rating scale of 1 to 4 with 1 representing Not Bothered and 4 representing Extremely Bothered. Refer to Appendix 9 for additional information.

[redacted]

[redacted]

8.3.6.1.2. Subject Global Satisfaction with Treatment Questionnaire

The subject will be asked to provide a rating of their satisfaction with the treatment results at the at all timepoints after treatment using the Subject Global Satisfaction with Treatment Questionnaire. Following the subject's completion of the Patient GAIS, the subject will be given the 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 8).

8.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the SOA (Section 1.3).

8.4.1. Physical Examination

A targeted physical examination, [redacted], will be conducted at the Screening Visit, Day 1 Visit, and Week 36 Visit or the Final Evaluation Visit, if applicable. Significant physical examination findings that are present prior to investigational product administration are to be included on the Medical History eCRF.

Significant physical examination findings after investigational product administration, which meet the definition of an AE, will be recorded on the AE eCRF post-treatment.

8.4.2. 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 Visit, Day 1 Visit, and Week 2 and Week 36 or the Final Evaluation Visit, if applicable. Subjects must sit for 5 minutes prior to having pulse and blood pressure measurements taken. Any new abnormal findings or worsening from baseline at subsequent assessments, if judged clinically significant, should be recorded as an AE on the AE eCRF page.

[redacted]

8.4.3. Pregnancy Testing

A UPT is required for all WOCBP at screening, baseline (pre-treatment) and Week 36 or Final Evaluation Visit. A positive result prior to treatment will exclude the subject from study participation. The results of the UPT will be evaluated at each study center. If any subject has a positive UPT, a serum pregnancy test is required for confirmation.

If a female subject becomes pregnant while participating in the study, the investigator or site designee must complete the Pregnancy Report Notification Form provided by Revance or designee as soon as the pregnancy is confirmed (see Section 5.6).

8.4.4. Injection Site Evaluation

Injection sites will be evaluated at the Screening Visit to assess for skin inflammation or active skin disease and at the Day 1, Week 2, and Week 4 Visits to determine if there is an immediate reaction to the investigational product. The assessment will be done as a global evaluation of the 3 injection sites for LCL on each side of the face (Table 7). Refer to Appendix 2 for additional information.

Table 7: 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		

If the subject answers yes to any of these items, it should be captured and recorded as an AE in the eCRF.

8.4.5. Clinical Safety Laboratory Assessments

As outlined in Table 8, non-fasting samples for hematology, chemistry, PT (screening only) and urinalysis will be collected at the Screening Visit and the Week 4 and 36 Visits, or Final Evaluation Visit if applicable. [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 study center using supplies provided by Revance or designee.

Table 8: 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) UPT (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 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 or Clinically Significant 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.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

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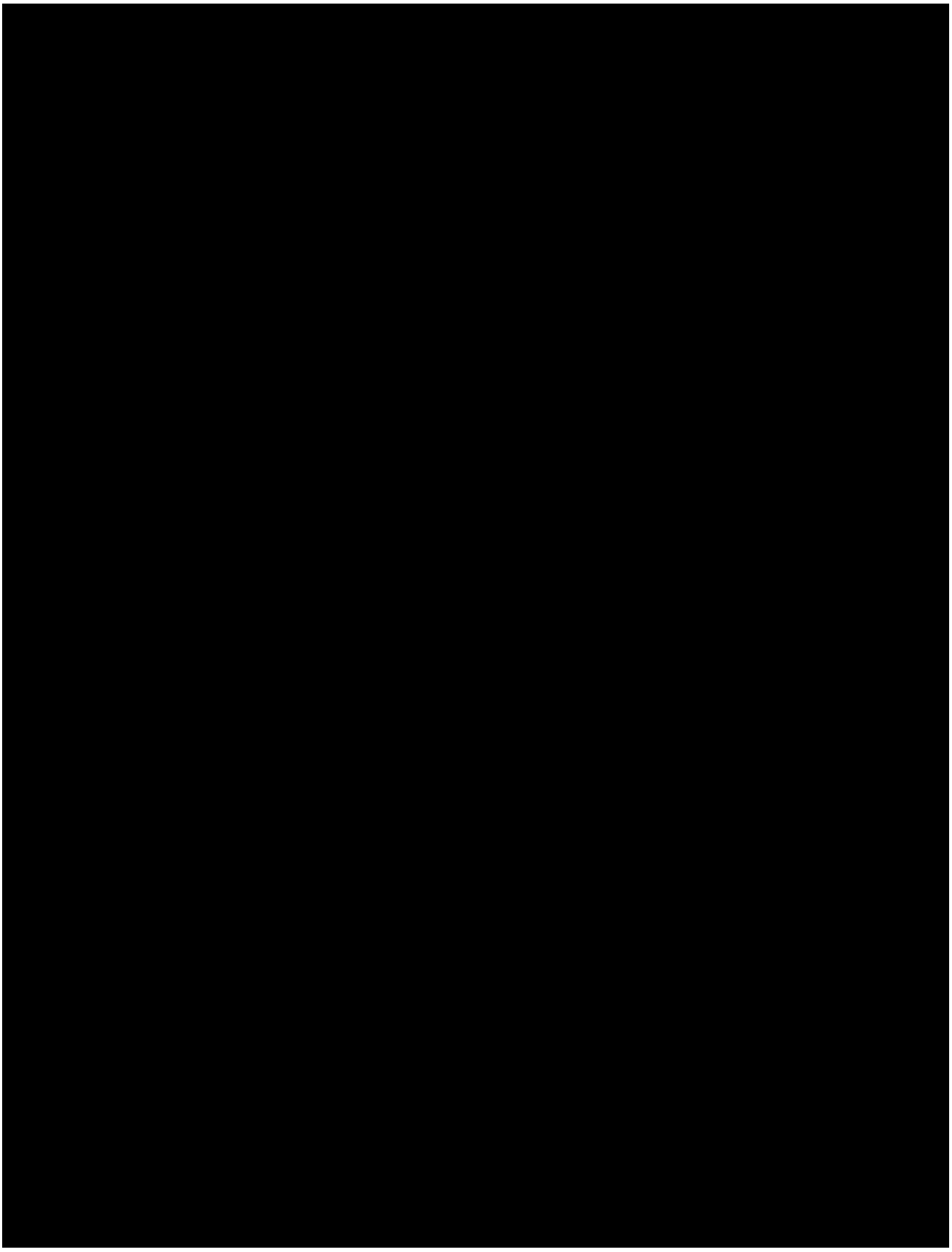


8.5. Adverse Events and Serious Adverse Events

8.5.1. Evaluation of Adverse Events and Serious Adverse Events

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 study 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 change in the study safety evaluations, (e.g., vital signs, injection site evaluation, [redacted]) post-treatment determined to be clinically significant by the investigator 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)

8.5.2. Assessment and Reporting Requirements

The investigator will assess each subject post-treatment and at each subsequent study 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) will be collected from the signing of the ICF until the Final Evaluation Visit. Any AE reported by the subject must be recorded on the source documents and eCRFs.

All AEs will be collected from Day 1 until Week 36 or the Final Evaluation Visit at all timepoints as specified in the SOA (Section 1.3). Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as well.

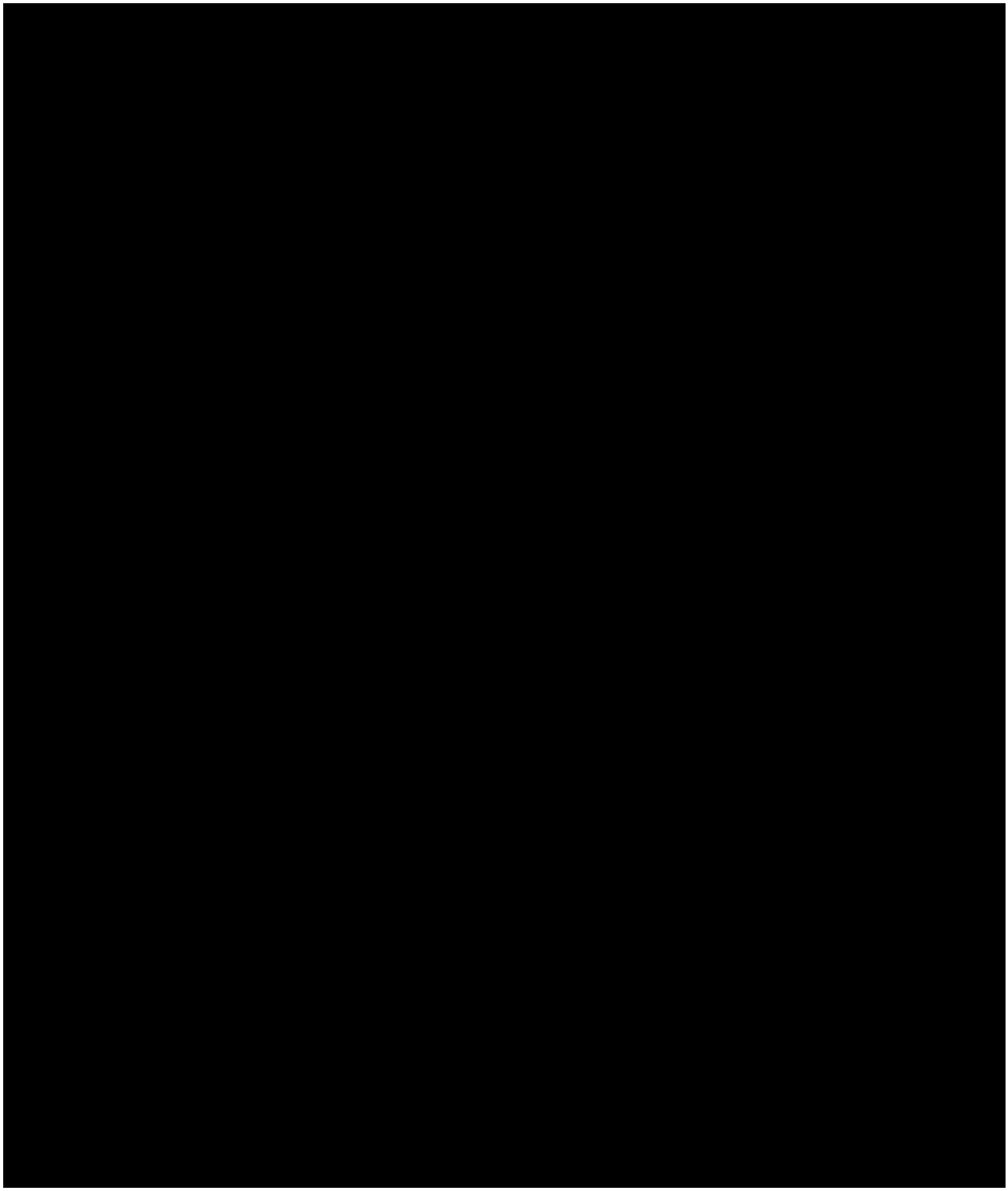
All SAEs will be recorded and reported to Revance or designee immediately within 24 hours of their awareness of the event. All fatal or life-threatening SAEs should be telephoned to Revance or the designee's authorized representative as soon as the investigator learns of the event.

8.5.3. Serious Adverse Events

The investigator must report an SAE to Revance or the designee'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. Contact Revance or the authorized representative for a fatal or life-threatening event as soon as the investigator or study staff are aware of the event
3. Obtain and maintain all pertinent medical records (e.g., discharge summary, autopsy report) and medical judgments of medical personnel who assisted in subject's treatment and follow-up
4. Provide follow-up information to Revance or designee within 24 hours of awareness

Regulatory Authorities, IRBs/ IECs, and investigators will be notified of SAEs in accordance with applicable regulations and requirements (e.g., ICH-GCP, national regulations and local requirements).



8.5.5. Follow-up of Non-Serious Adverse Events

All AEs that are identified during the last scheduled study visit (or the Final Evaluation Visit, if applicable) must be recorded on the AE eCRF 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, study-related abnormalities at the end of the study, 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 unless the Medical Monitor determines that follow-up is sufficient.

8.5.6. Follow-up of Post-Study Serious Adverse Events

Any SAEs that are identified on the last scheduled contact (or at early discontinuation, if applicable) must be recorded on the AE eCRF and reported to Revance or designee according to the reporting procedures outlined in Section 8.5.2. 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 or designee 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 or designee and the IRB/IEC.

8.5.7. 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 study; treatment or other intervention usually needed

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The data from the study running sequentially in cohorts with dose-escalation can be used to assess the maximal tolerable dose level in treating the LCL. It can also be used to assess the effective doses and the potential dose-response. When assessing the dose-response on a responder endpoint, the null hypothesis will be that each dose group has the same rate of response and the alternative hypothesis will be that not all doses groups have the same response rate. That is,

H_0: $r_1 = r_2 = r_3 = r_4 = r_5$ versus

Ha: $r_i \neq r_j$ for at least a pair of dose groups (i, j), i=1, 2, 3 or 4 and j=i+1 to 5,

Where r_i is the response rate for dose group i.

9.2. Sample Size Determination

The sample size is not determined by the power of formal hypothesis tests. [redacted]

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined and the summary groups for analysis will be based on the actual dose for LCL received (which is expected to be consistent with the enrollment cohorts):

Population	Description
Enrolled	All subjects who receive the LCL treatment
LCL-Evaluable	All enrolled subjects who have any post-LCL treatment assessment of IGA-LCWS at maximum smile
Safety	All enrolled subjects

9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the detailed methods of analysis, the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

In general, descriptive summaries will include means, standard deviations, and range for continuous variables, and counts and proportions for categorical measures. Unless otherwise

stated otherwise, a 95% confidence interval will be provided for means and proportions. No formal hypothesis tests are planned, but group comparisons may be performed as exploratory analyses. No multiplicity adjustments or imputation of missing data are planned.

9.4.1. Efficacy Analyses

Unless otherwise noted, baseline for all efficacy assessments refers to the last available assessment prior to LCL treatment. Efficacy outcomes will be summarized. Descriptive statistics will be provided for all efficacy variables at all timepoints.

The primary efficacy endpoint will be the proportion of subjects achieving a score or 0 or 1 (none or mild) in LCL severity assessed by IGA-LCWS at maximum smile. The LCLs will be evaluated on both sides of the face and both scores will be recorded. If different ratings are obtained from the left and the right sides of the face, subjects will be scored using the higher (i.e., more severe) rating. The dose response in the proportion of responders at Week 4 will be explored using the logistic regression stratified by baseline LCWS severity and study center. Additional measures to assess the effectiveness outcomes will include the investigator GAIS evaluated at maximum smile at each visit. Various responder endpoints associated with the LCWS, such as achieving certain status or certain magnitude of improvement from baseline, will be derived from these effectiveness outcomes for each visit. These responder endpoints will be analyzed by statistical models similar to that for the primary endpoint.

Duration of response will be evaluated by various time-to-event endpoints. Kaplan-Meier (KM) curves will be plotted by dose group for each time-to-event endpoint.

Responder and time-event endpoints defined based on subject assessments for LCL wrinkle severity (such as PLCWS and the subject GAIS for LCL) will be summarized in the same way as those by investigator assessments. Similarly, the endpoints defined based on scores assessed at rest will be summarized in the same way as those on scores assessed at maximum smile.

9.4.2. Safety Analyses

All AEs occurring during the study will be recorded and classified according to MedDRA terminology. Those occurring during or after treatment are considered as treatment-emergent. All reported TEAEs will be summarized, in terms of the number of subjects reporting events, system organ class, preferred term, severity, relationship to study drug, and seriousness. For summarization of event causality and seriousness, subjects will be counted only once within a system organ class or preferred term using the event with the event with the greatest relationship for causality and the event with the highest severity. A summary of TEAEs leading to discontinuation will also be provided.

A by-subject listing of any SAEs will be provided and all SAEs will be summarized by severity and relationship to study treatment.

Clinical laboratory test results will be summarized by visit and if applicable a shift table will be used to evaluate the shift in status from baseline at each visit.

9.5. Interim Analyses

A formal interim analysis of the data will be performed 8 weeks after the last LCL treatment.

9.5.1. Data Review Committee (DRC)

Cohorts 1 and 2 will be enrolled simultaneously. Safety data and subject photographs will be evaluated by the DRC at 4 weeks after LCL treatment in Cohorts 1 and 2 before a decision is made to move forwarded with the next and subsequent doses. The DRC will reconvene again after the last subject in Cohort 3 reaches the Week 4 Visit. Safety data will be monitored throughout the study by the DRC at regular intervals.

Dose escalation for LCL may be stopped at the discretion of the DRC as outlined in the DRC Charter.

The full details for the roles and responsibilities of the DRC will be detailed in the study-specific DRC charter.

10. Records Management

10.1. Data Collection

For this study, all protocol-specified data will be recorded in the source documents, and data will be entered on the eCRFs from the source documents. In addition to signature confirmation that a subject meets the study eligibility criteria, upon each subject's completion of the study, 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 study data be verifiable with the source data which 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 study 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 any screening procedures.

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 study center. Site personnel will be responsible for providing resolutions to the data queries and for correcting the eCRFs, as appropriate. All unused Revance or designee study materials and binders must be returned to Revance or designee upon completion of the study.

The investigator must keep written or electronic source documents for every subject participating in the clinical study. 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, study number, and the date of the evaluation.

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

Subjects will authorize the use of their protected health information (PHI) during the informed consent process in accordance with the applicable privacy requirements. Subjects who deny permission to use and disclose PHI will not be eligible to participate in the study. The investigator will ensure that the study documents forwarded to Revance or their designee, and any other documents, contain no subject names or other PHI, such as medical record number or date of birth.

Any amendments and corrections necessary will be undertaken in both the source documents and eCRFs (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 eCRF should be cancelled out to avoid unnecessary follow-up inquiries.

Regulatory authorities, the IRB/IEC and/or Revance's Quality Assurance department (or designee) may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. The investigator must guarantee direct access to these documents. eCRFs will be kept by Revance or 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 or designee after descriptive and statistical analyses and reports have been generated and are complete.

10.2. File Management at the Study Center

It is the responsibility of the investigator to ensure that the study center maintains all source and essential documents in accordance with ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, Section 8 – Essential Documents for the Conduct of a Clinical Study.

10.3. Records Retention at the Study 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 2 years after Revance notifies the investigator that the data will not be submitted for review by any Regulatory Authority

Regardless of applicable retention period, the investigator must not dispose of any records or essential documents relevant to this study 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 study. Such documentation is subject to inspection by Revance or designee and relevant regulatory agencies. If the investigator withdraws from the study (e.g., relocation, retirement) all study-related records should be transferred to a mutually agreed upon designee. Notice of such transfer will be provided to Revance in writing.

[redacted]

12. ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the protocol, the ICH Guidance for Industry E6 (R2) 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 ICF) to Revance or designee before investigational product will be shipped to the study center.

[redacted]

[redacted]

[redacted]

[redacted]