CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2a, Multicenter, Open-Label, Dose-Escalation Study to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA (DAXI) for Injection for the Treatment of Dynamic Forehead Lines (Frontalis) Following Glabellar Line Injections
Protocol Number:	1820202
Document Type:	Amended Protocol
Study Phase:	Phase 2a
Short Title:	Efficacy and Safety of DaxibotulinumtoxinA (DAXI) for Injection for Treatment of Forehead Lines (Frontalis)
Sponsor:	Revance Therapeutics, Inc. 7555 Gateway Boulevard Newark, CA 94560
Version:	Amendment 2; 04 March 2019

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

INVESTIGATOR'S AGREEMENT

I have carefully read the protocol entitled: "***A Phase 2a, Multicenter, Open-Label, Dose-Escalation Study to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA (DAXI) for Injection for the Treatment of Dynamic Forehead Lines (Frontalis) Following Glabellar Line Injections"*** 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	**Date**
Printed Name	
Institution Name	
Address	
City, State, Postal Code, Country	**Phone Number**

Table of Contents

[redacted]

LIST OF IN-TEXT TABLES AND FIGURES

[redacted]

[redacted]

LIST OF APPENDICES

[redacted]

[redacted]

LIST OF ABBREVIATIONS

AE	Adverse event
CI	Confidence interval
DAXI	DaxibotulinumtoxinA
DRC	Data Review Committee
eCRF	Electronic Case Report Form
FASE	Facial Age Self Evaluation
FHL	Forehead lines
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
GL	Glabellar lines
ICF	Informed consent form
IEC	Independent Ethics Committee
IGA-FWS	Investigator Global Assessment Frown Wrinkle Severity
IGA-FHWS	Investigator Global Assessment Forehead Wrinkle Severity
IM	Intramuscular
IRB	Institutional Review Board
kDa	Kilodalton
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NSAID	Nonsteroidal anti-inflammatory drug
PFWS	Patient Frown Wrinkle Severity
PFHWS	Patient Forehead 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

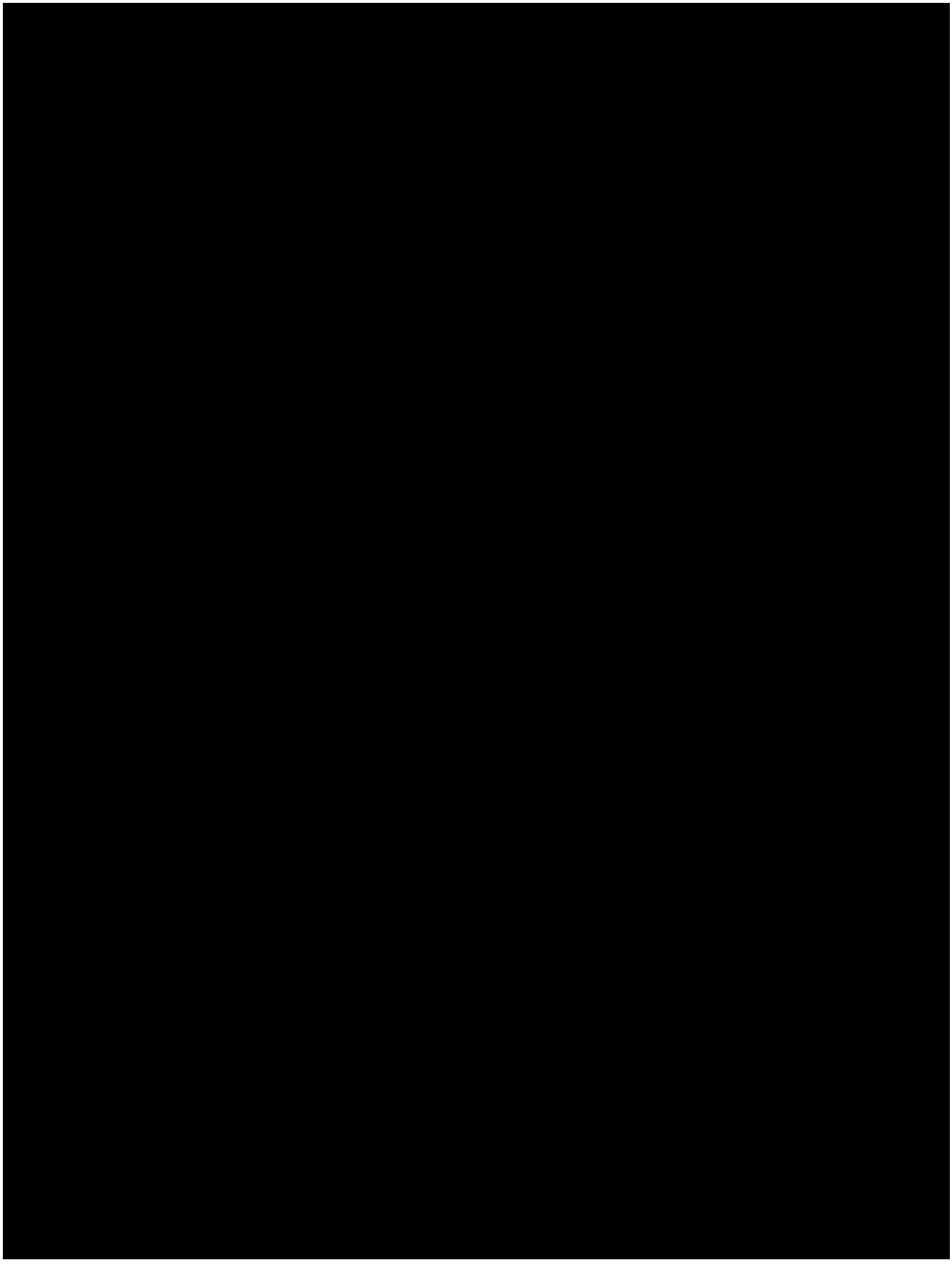
1. Protocol Summary

1.1. Synopsis

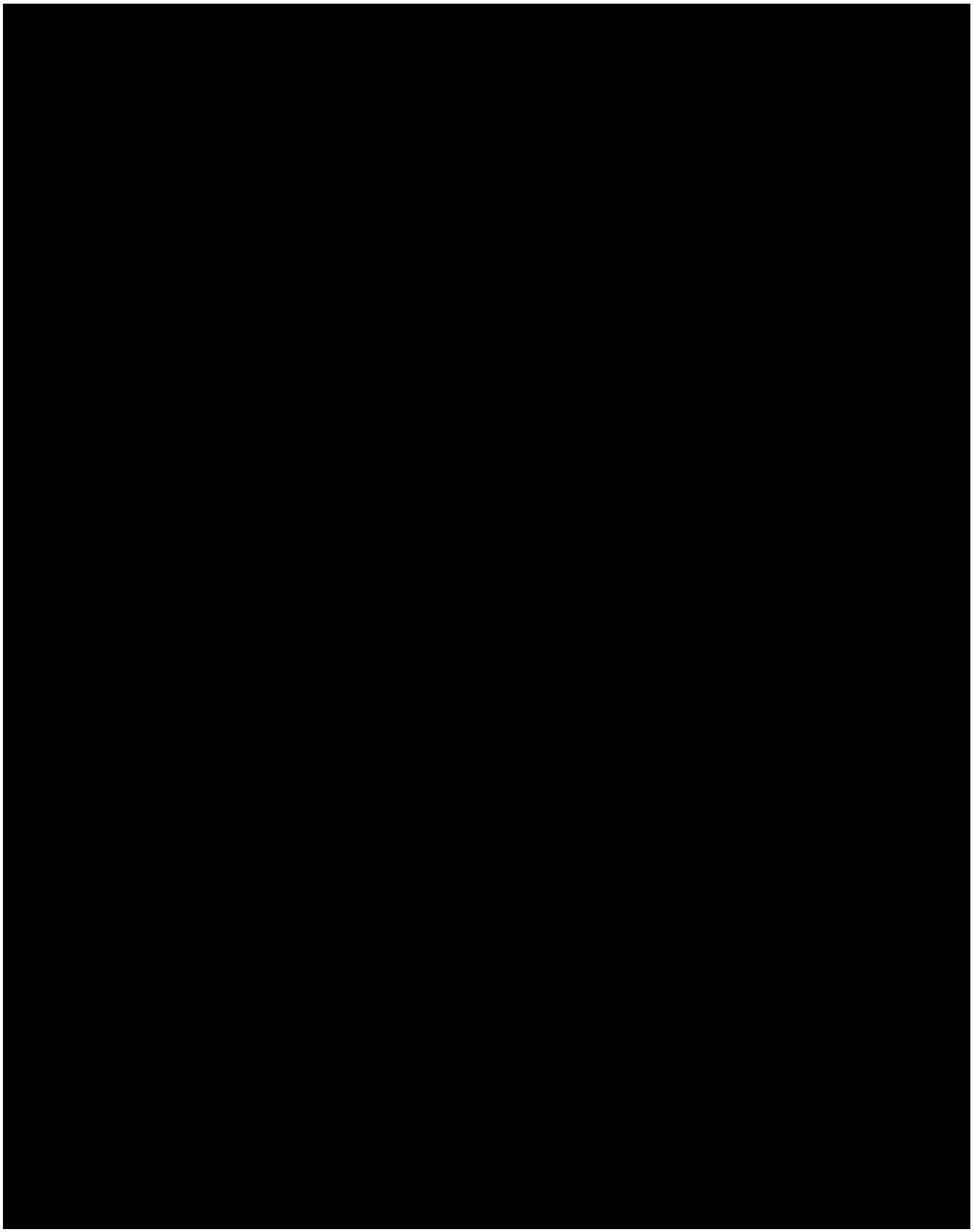
Name of Sponsor/Company:	Revance Therapeutics, Inc.
Name of Finished Product:	DaxibotulinumtoxinA for injection (DAXI for injection)
Name of Active Ingredient:	DaxibotulinumtoxinA
Protocol Title:	A Phase 2a, Multicenter, Open-Label, Dose-Escalation Study to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA (DAXI) for Injection for the Treatment of Dynamic Forehead Lines (Frontalis) Following Glabellar Line Injections
Short Title:	Efficacy and Safety of DaxibotulinumtoxinA (DAXI) for Injection for Treatment of Forehead Lines (Frontalis)
Rationale:	This phase 2a, multicenter, open-label, dose-escalation study will evaluate treatment of moderate or severe dynamic forehead lines (FHL) (frontalis) in conjunction with treatment of the glabellar complex. The proposed dosing regimen will consist of GL treatment on Day 1, followed by FHL treatment at Week 2. [redacted]

	[redacted]
Objectives	**Endpoints**
Primary	
• To evaluate the efficacy and safety of DAXI for injection in the treatment of dynamic FHL	• Proportion of subjects achieving a score of 0 or 1 (none or mild) in FHL severity at maximum eyebrow elevation at 4 weeks after FHL treatment (Week 6) on the Investigator Global Assessment Forehead Wrinkle Severity (IGA-FHWS) scale • Incidence, severity, and relationship to study drug of treatment-emergent AEs (TEAEs) and serious adverse events (SAEs) during the overall study duration.

[redacted]



[redacted]



[redacted]

Study Population:

Approximately 60 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:

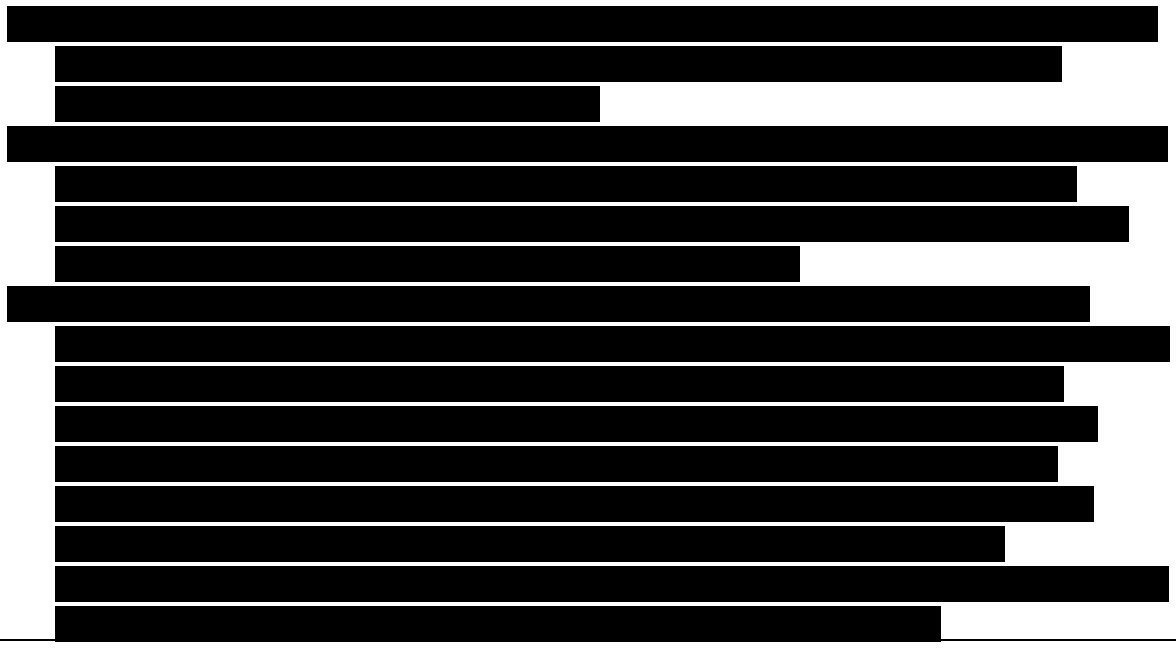
1. Provide written informed consent consistent with ICH-GCP guidelines and local laws, including authorization to release health information, signed prior to any study procedures being performed
2. Be outpatient, male or female subjects, in good general health, 18-65 years of age
3. Have a score of moderate (2) or severe (3) FHL during maximum contraction (eyebrow elevation) as assessed by the IGA-FHWS
4. Have a score of moderate (2) or severe (3) FHL during maximum contraction (eyebrow elevation) as assessed by the PFHWS
5. Have a score of moderate (2) or severe (3) GL during maximum frown based on the IGA-FWS scale
6. Have a score of moderate (2) or severe (3) on GL during maximum frown as assessed by the PFWS
7. Have sufficient visual acuity without the use of eyeglasses (contact lens use is acceptable) to accurately assess their facial wrinkles
8. 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 inferior orbital rim) from screening through the end of the study
9. 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)

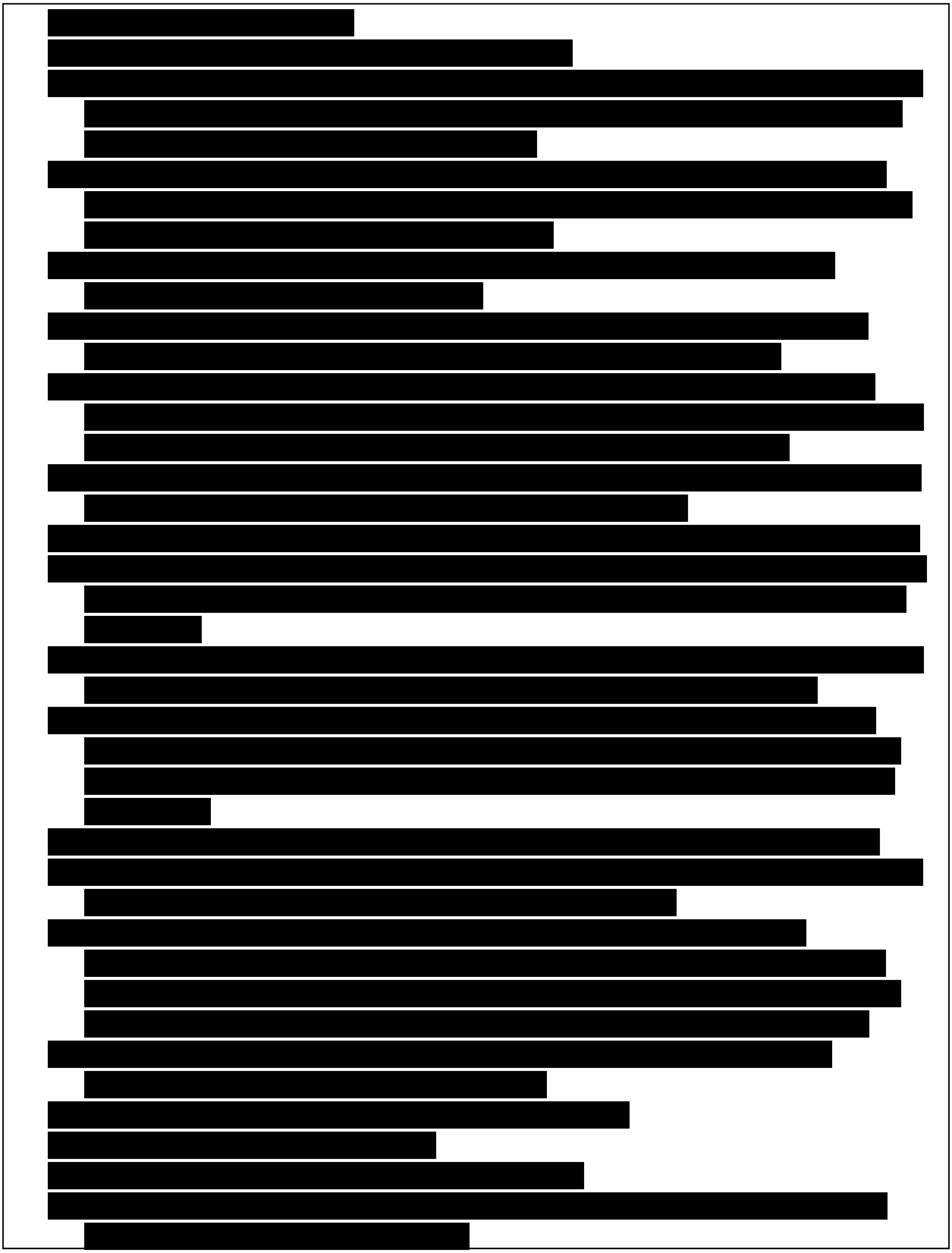
10. Able to understand the requirements of the study and be willing and able to follow all study procedures, attend all scheduled visits, and successfully complete the study.

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 the investigator to completely or almost eliminate GL or FHL by physically spreading medial brows apart or stretching the forehead skin while at rest
5. History of or current significant brow ptosis, significant brow or forehead line asymmetry at rest or on brow elevation. Evidence that frontalis activity is required to maintain eyelid position
6. Previous treatment with botulinum toxin type A in the face within 6 months prior to screening
7. Plans to receive botulinum toxin type A anywhere in the face (other than study treatment) from screening through the end of the study
8. Has not had within the last 6 months prior to screening, or plans to receive treatment through the end of the study with >200 U of any botulinum toxin anywhere else in the body outside of the face





[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 FHL in conjunction with treatment of the glabellar complex. This study will be conducted at 4 sites in the United States and Canada.

Approximately 60 subjects (18 years to 65 years of age) with moderate to severe FHL will be enrolled sequentially into 1 of 4 treatment cohorts (15 subjects per cohort) to receive DAXI for injection [redacted]. Investigators will make all reasonable efforts to enroll equal proportions of patients with moderate and severe FHL (based on baseline assessments) in each dosing cohort. Baseline for all cohorts will be defined as the Day 1 Visit prior to GL treatment. At the Day 1 study visit, subjects will receive a single 40 U dose of DAXI for injection for treatment of GL. At the Week 2 Visit, subjects will receive the assigned dose of DAXI for injection for the treatment of FHL. The total study duration will be up to 40 weeks including up to 2 weeks for screening. Subjects will be followed for a minimum of 24 weeks from GL treatment for safety or until all scores on the IGA-FWS and PFWS, as well as the IGA-FHWS and PFHWS return to baseline (Day 1 Visit prior to GL treatment) or until Week 38, whichever occurs first. Subjects will then have a Final Evaluation Visit. If the Data Review Committee (DRC) elects not to proceed with the FHL injection in a given dose cohort, subjects assigned to that cohort, who have already received GL treatment, will be followed for 14 weeks from the time of treatment (Day 1).

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

The decision to treat subsequent cohorts with the FHL dose will based upon review of the data by the DRC (refer to Section 9.4.1 for additional information). Revance has the right to stop or terminate the study at any time, for any reason, at their discretion or in consultation with the DRC.

FHL Treatment

Subjects may receive up to 2 treatments in this study (1 GL treatment and 1 FHL treatment) depending on the evaluation of the DRC. Dose escalation for FHL may be stopped at the discretion of the DRC. If the DRC elects not to proceed with FHL treatment in a given dose cohort, subjects assigned to that cohort who have already received GL treatment may receive only the GL treatment will be followed for 14 weeks from the time of treatment (Day 1).

The assessment for whether to proceed in a given dose cohort with FHL treatment will occur 2 weeks after GL treatment and the following criteria are met:

1. All WOCBP must have a negative UPT prior to treatment
2. No active skin disease or infections or inflammation at the injection sites
3. Subject has no condition or situation which, in the investigator's opinion, puts the subject at significant risk
4. No history or current evidence of ptosis
5. Presence of frontalis motion/movement ability
6. DRC approves administration of the intended dose.

Study Visits:

Study visits will occur at the Screening Visit (Day -14), treatment days for GL and FHL (Day 1 and Week 2 Visits), a safety follow-up phone call at Weeks 1 and 3, and follow-up visits at Weeks 4, 6, 10, 14, 18, 22, 26, 30, 34, and 38.

Baseline for GL and FHL treatment will be the last assessment prior to GL treatment (Day 1 Visit).

Efficacy Evaluations:

- IGA-FWS
- IGA-FHWS
- PFWS
- PFHWS
- GAIS (assessed by the investigator and the subject for GL and FHL)
- FASE
- Responses to the FACE-Q™ Satisfaction with Forehead and Eyebrows and the FACE-Q™ Appraisal of Lines: Forehead Lines

Baseline for all efficacy assessments, unless otherwise noted, refers to the last assessment prior to GL 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 curves will be plotted by treatment group for each time-to-event endpoint to assess median duration of effect at maximum eyebrow elevation 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. Descriptive statistics will be provided for all efficacy variables at all timepoints.

Safety Evaluations:

- Clinical laboratory tests (hematology, serum chemistry, prothrombin time [PT], urinalysis)
- [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 on Day 1, Week 4, and Week 38 or Final Evaluation Visit. [redacted]

[redacted]

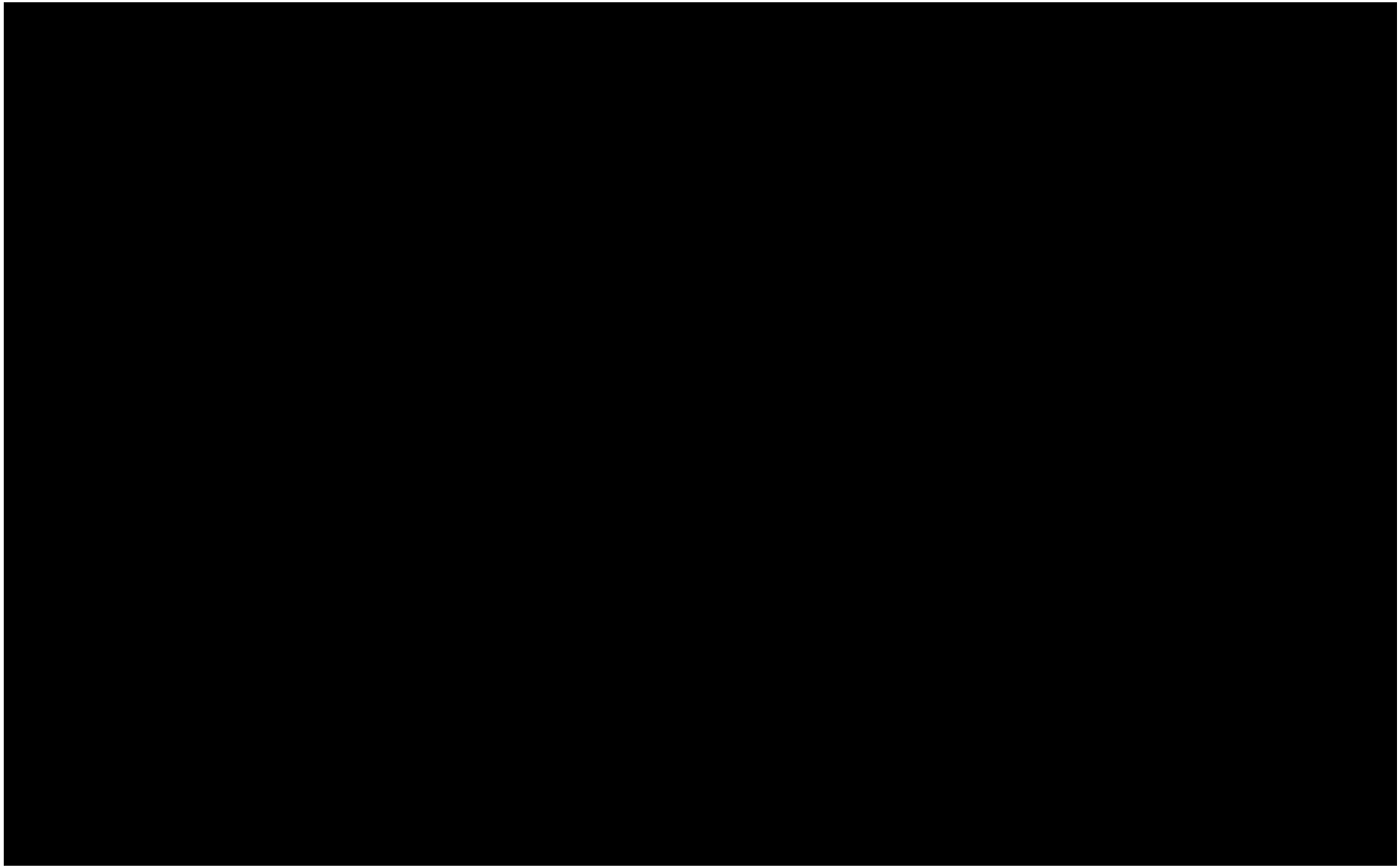
Other Evaluations:

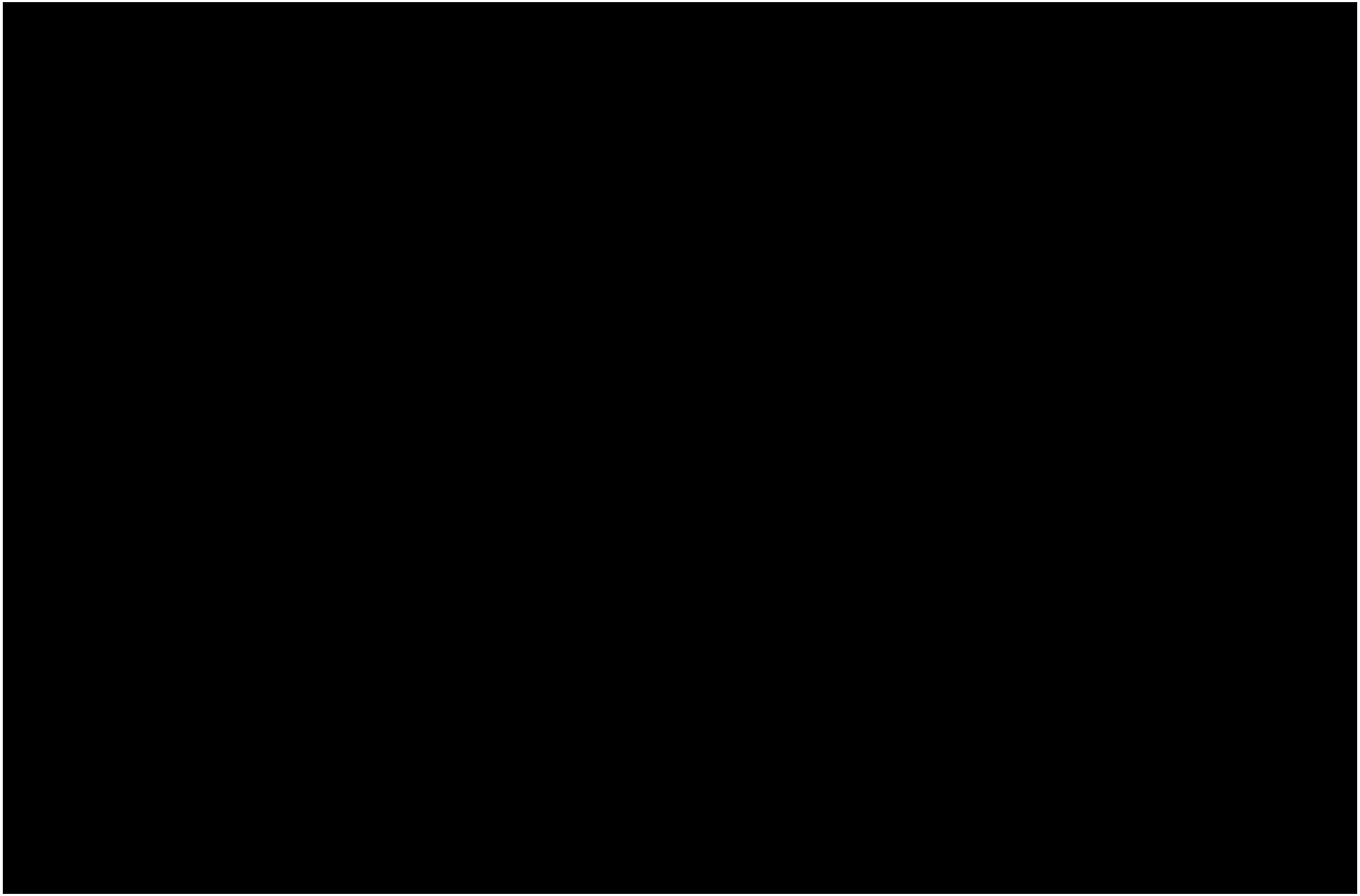
[redacted]

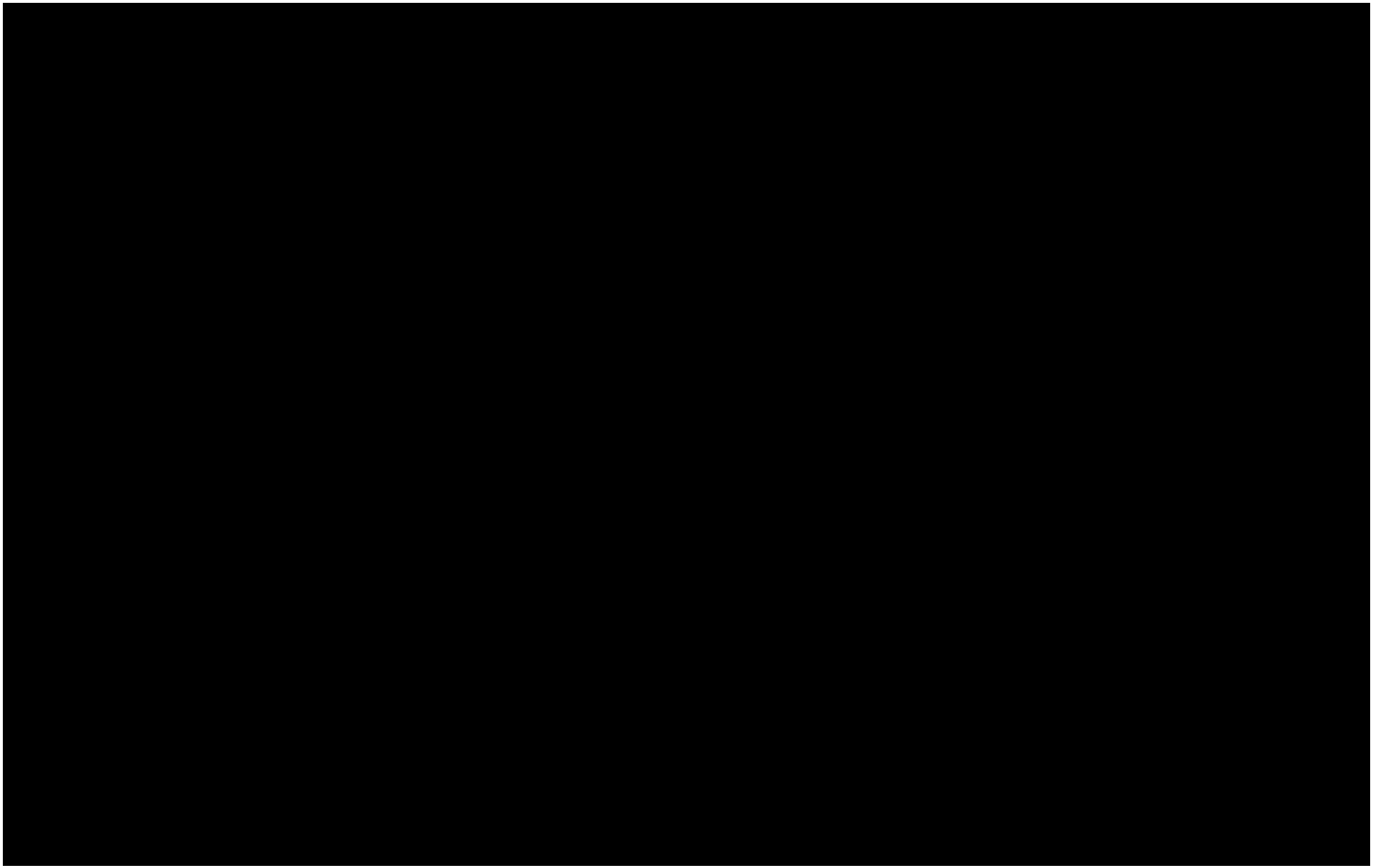
Number of Subjects:

Approximately 60 subjects are expected to participate in this study. Refer to Section 9.1 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 treatment of FHL and GL.







2. Introduction

Visible signs of facial aging include the formation of facial lines and folds, a decline in skin quality, an increase in skin pigmentation, and post-menopausal loss or redistribution of soft tissue volume and bone. Forehead lines are produced by the action of the frontalis muscle, a large, thin, vertically-oriented muscle which lifts the eyebrows (Hexsel, 2011; Klein, 2004). The frontalis muscle serves as an antagonist to the glabellar musculature, a natural depressor that is responsible for frowning and associated eyebrow movement. As the eyebrow is considered the aesthetic center of the upper face, forehead lines can significantly impact the aesthetic appearance of the face, contribute to increased signs of aging and convey unwanted social signals. However, both men and women have identified internal factors, such as wanting to look good for their age or having a more youthful appearance as very important and have prioritized forehead lines as bothersome areas for potential treatment regardless of age or available income (Jagdeo, 2016; Narurkar, 2015; Rossi, 2017).

In women, the first signs of aging can begin around the age of 35 and generally coincide with a decrease in self-rated attractiveness and self-confidence (Narurkar, 2015). Following menopause, additional changes to soft tissue distribution and bone also begin to appear.

Facial aging in men occurs earlier and differently. Men generally report the first signs of aging between 30 and 50 years of age, with static forehead lines being among one of the first features demonstrating the greatest visible change (Rossi, 2017).

Minimally-invasive injectable treatments have become the most common procedure worldwide (Carruthers, 2015) with an increase in frequency over the last decade since the first approval of botulinum neurotoxin Type A (Botox Cosmetic [onabotulinumtoxinA] UPSI, Allergan, Inc. 2013). This is largely the result of years of experience of patients and injectors, and a favorable risk-benefit profile.

Botulinum neurotoxin is produced by *Clostridium botulinum*, which is a gram-positive, spore-forming, anaerobic bacterium, which can both cause disease (e.g., botulism), as well as treat it (e.g., dystonia) (Simpson, 2004). 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 inhibits acetylcholine release at the neuromuscular junction, which prevents muscle contractions in injected muscles. 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 (Carruthers, 2015; De Boulle, 2007).

The efficacy and safety of botulinum toxin type A for the treatment of FHL has been evaluated in a number of studies. Solish et al. (2016) conducted the first large-scale, multicenter study of onabotulinumtoxinA with 40 U or 30 U total injected into both the frontalis and the glabellar complex. Complementary treatment of the glabellar complex in conjunction with the frontalis provides more satisfactory results and reduces the potential for eyebrow ptosis. At 4 weeks after the first injection, 94.4% of subjects at the 40 U dose and 84.2% of subjects at the 30 U dose were satisfied or very satisfied with the reduction in FHL severity. A longer duration of effect was noted in the 40 U dose group. There was no observed dose response noted in the incidence

of eyebrow- or eyelid-related AEs in either the 40 U and 30 U dose groups. The overall incidence of eyebrow ptosis across both doses (coded as facial paresis) was low at 2.3%.

Two multicenter, randomized, double-blind, placebo-controlled studies have evaluated onabotulinumtoxinA for the temporary improvement of moderate to severe FHL with simultaneous treatment of GL; one of the studies also assessed simultaneous treatment of lateral canthal lines. These studies enrolled 1178 subjects, of which 921 were randomized to receive onabotulinumtoxinA and 257 received placebo. A total of 165 and 197 subjects received 3 cycles of treatment over 1 year of 40 U and 64 U, respectively. The response rate for FHL was similar across all treatment cycles. In both studies, more than 75% of subjects were Very Satisfied or Mostly Satisfied with the treatment of facial lines, and the majority of subjects in both treatment groups achieved a ≥2-grade improvement from baseline in FHL severity (Botox Cosmetic [onabotulinumtoxinA] UPSI, Allergan, Inc. 2013) The overall incidence of reported AEs in these studies was low; headache (58 subjects [9%]) was the most frequently reported AE. The overall incidence of eyebrow- or eyelid-related AEs was very low. Brow ptosis and eyelid ptosis occurred in 13 subjects (2%) and 12 subjects (2%), respectively.

A large, 12-month, phase 3 study was conducted to examine simultaneous treatment of FHL, GL, and lateral canthal lines with onabotulinumtoxinA (De Boulle, 2018). This study enrolled 787 subjects, of which 313 subjects received onabotulinumtoxinA 64 U and 318 subjects received onabotulinumtoxinA 40 U (156 subjects received placebo). In subjects receiving 64 U and 40 U of onabotulinumtoxinA, a statistically significant improvement ($p<0.001$, respectively) in the appearance of FHL was observed at the 30-day timepoint and maintained, when compared with placebo, through Day 180. In subjects achieving a 2-point improvement in FHL severity from baseline, the investigator assessment of FHL improvement was statistically significant at all treatment timepoints through Day 180. Significantly more subjects who received 64 U onabotulinumtoxinA achieved a rating of none or mild, as assessed by the investigator, at Day 30 for FHL and GL severity ($p<0.001$). Additionally, eye-related TEAEs were very low; there were 2 cases each of eyelid and brow ptosis (0.6%) at the 64 U dose and 5 cases (1.6%) and 6 cases (1.9%), respectively, at the 40 U dose. The safety profile of onabotulinumtoxinA is well established and enhanced in this study by simultaneous treatment of FHL and GL, which has been shown to reduce the incidence of ptosis by stabilizing the elevator muscle.

As both men and women gain increased awareness of the recognition of aesthetic treatment options available to address the signs of facial aging, and as treatment becomes more widely used and accepted, 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]

[redacted]

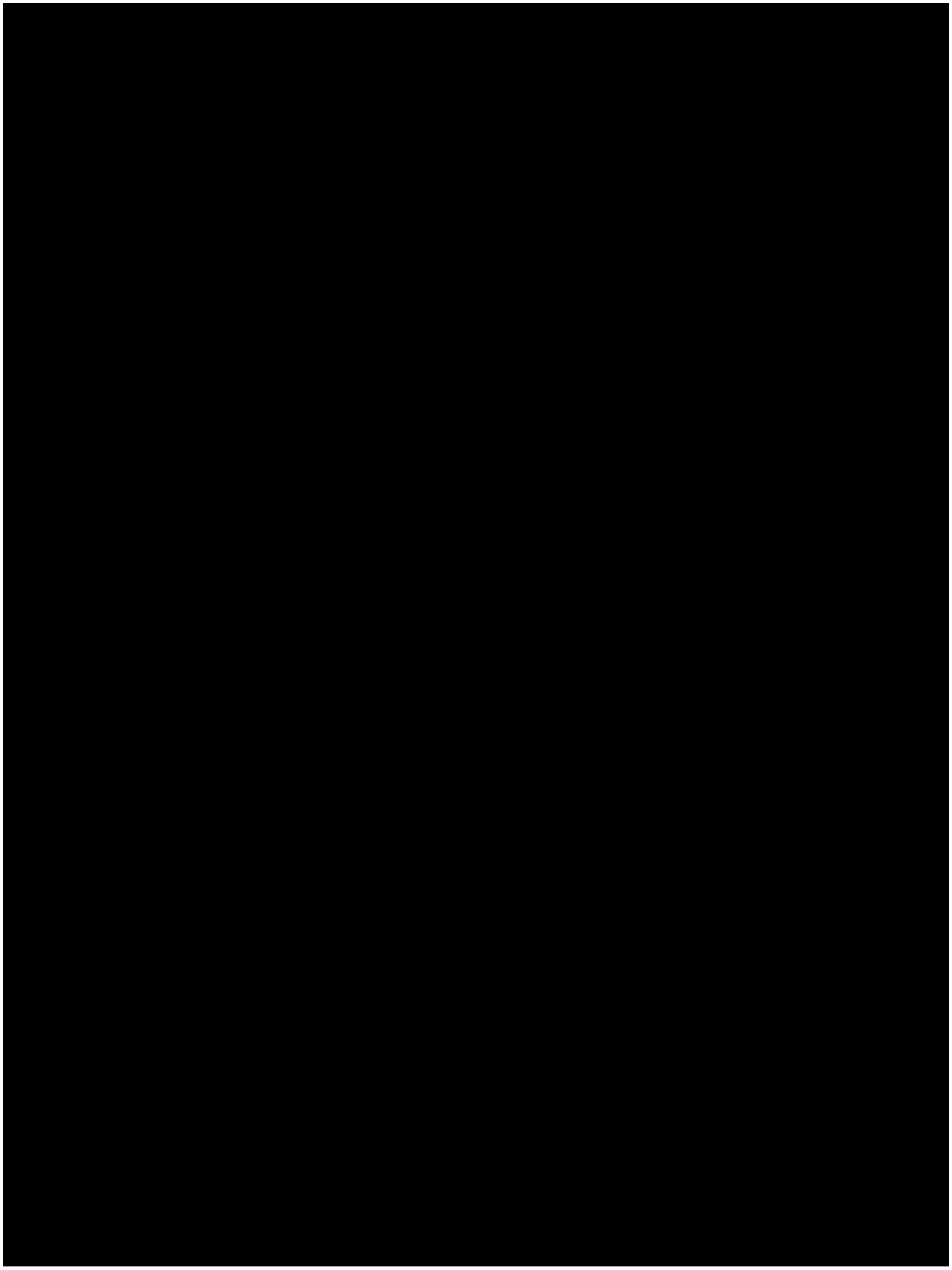
2.2. Benefit/Risk Assessment

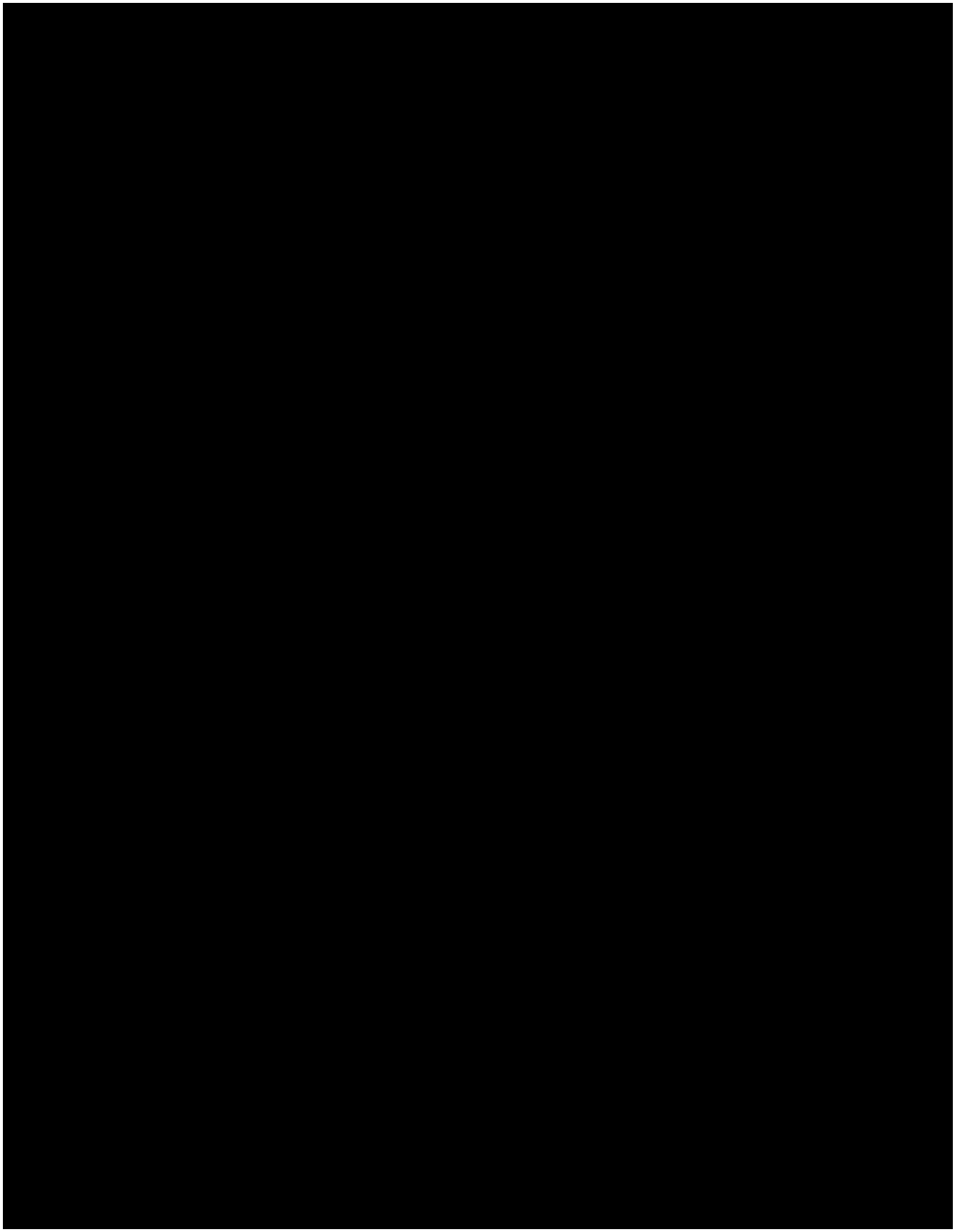
More detailed information about the known and expected benefits and risks and reasonably expected AEs of DAXI for injection may be found in the Investigator's Brochure.

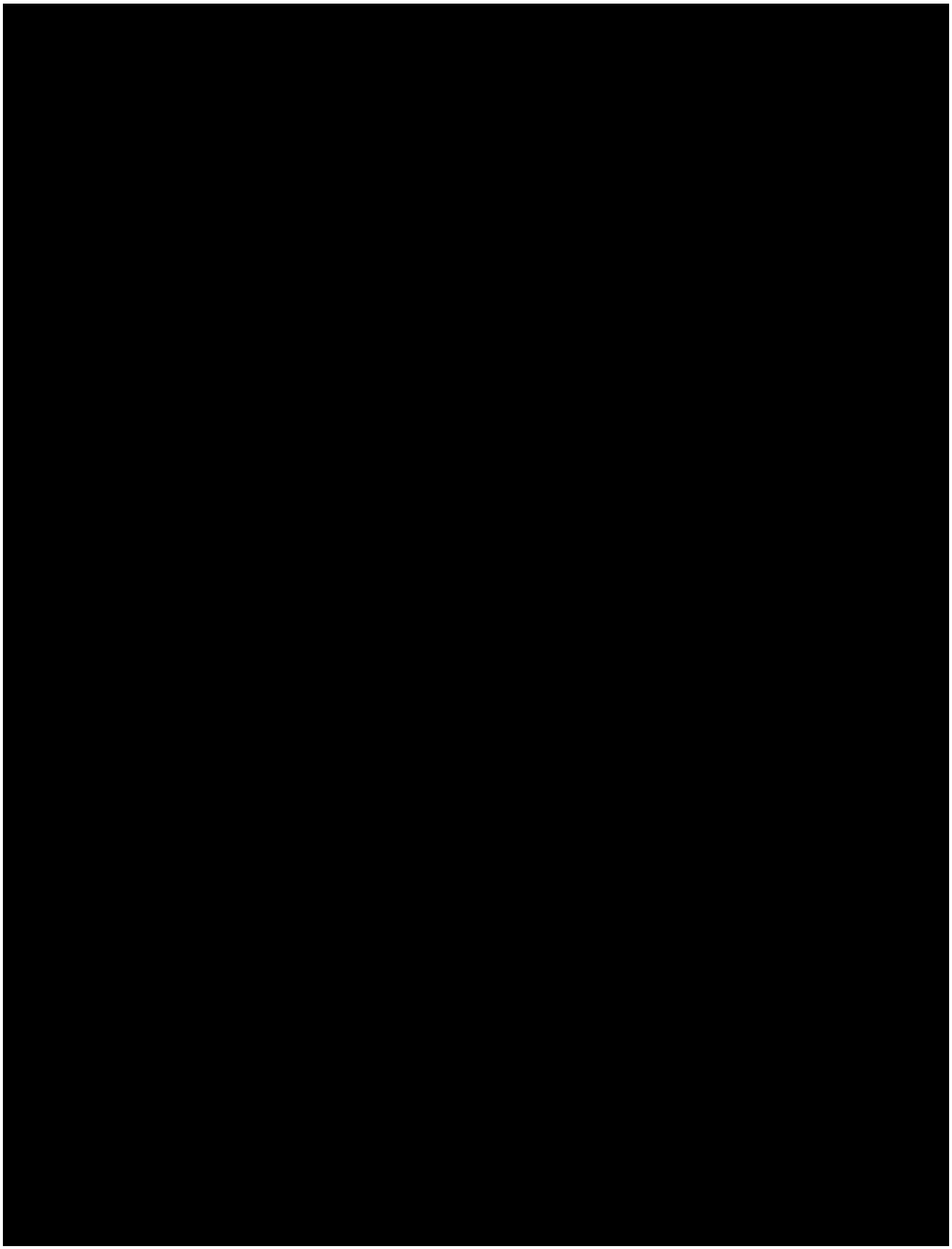
3. Objectives and Endpoints

All efficacy endpoints will be assessed using the last available assessment prior to GL treatment on Day 1 as baseline. All efficacy endpoints for FHL severity assessments, wherever applicable, will also be analyzed for GL severity assessments.

Objectives	Endpoints
Primary	
• To evaluate the efficacy and safety of DAXI for injection in the treatment of dynamic FHL	• Proportion of subjects achieving a score of 0 or 1 (none or mild) in FHL severity at maximum eyebrow elevation at 4 weeks after FHL treatment (Week 6) on the Investigator Global Assessment Forehead Wrinkle Severity (IGA-FHWS) scale • Incidence, severity, and relationship to study drug of treatment-emergent AEs (TEAEs) and serious adverse events (SAEs) during the overall study duration.







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 to severe FHL in conjunction with GL treatment. This study will be conducted at 4 sites in the United States and Canada.

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

Approximately 60 subjects (18-65 years of age) with moderate to severe FHL will be enrolled and sequentially assigned to 1 of 4 treatment cohorts (15 subjects per cohort) to receive DAXI for injection. Investigators will make all reasonable efforts to enroll equal proportions of patients with moderate and severe FHL (based on baseline assessments) in each dosing cohort. [redacted] The total study duration will be up to 40 weeks including up to 2 weeks for screening. Subjects will be followed for a minimum of 24 weeks from GL treatment for safety or until all scores on the IGA-FWS and PFWS, as well as the IGA-FHWS and PFHWS return to baseline (Day 1 Visit prior to GL treatment) or until Week 38, whichever occurs first. Subjects will then have a Final Evaluation Visit. If the DRC elects not to proceed with the FHL injection in a given dose cohort, subjects assigned to that cohort who have already received GL treatment will be followed for 14 weeks from the time of treatment (Day 1).

Sequential enrollment will occur for each cohort. The first cohort will be enrolled and treated. The DRC will convene to review available data (including safety, efficacy, and photographs/video) at Week 5 following GL treatment (3 weeks after FHL treatment) for each cohort before a decision is made to move forward with the next and subsequent doses. Revance reserves the right to terminate or stop the study at any time. Refer to Sections 1.2 and 9.4.1 for additional information.

All subjects will be evaluated for FHL severity using the Revance-validated 4-point IGA-FHWS and PFHWS at rest and at maximum eyebrow elevation, as assessed by both the investigator and the subject. In addition, to determine the efficacy response to the glabellar complex, subjects will be evaluated for improvement on the IGA-FWS and the PFWS at rest and at maximum frown.

Injection sites will be evaluated at screening for signs of skin inflammation or active disease. The GL treatment areas will be evaluated at Day 1 (pre- and post-treatment) and at Weeks 2 and 4. The FHL treatment areas will be evaluated at Week 2 (pre- and post-treatment) and at Weeks 4 and 6. 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. The glabellar complex will be injected in a 5-point injection pattern and the frontalis muscle will be injected in a 3-point injection pattern. The same assessment will be used to evaluate all 8 injection sites.

4.1.1. FHL Treatment

Subjects may receive up to 2 treatments in this study (1 GL treatment and 1 FHL treatment) depending on the evaluation of the DRC. Dose escalation for FHL may be stopped at the discretion of the DRC. If the DRC elects not to proceed with FHL treatment in a given dose cohort, subjects assigned to that cohort who have already received GL treatment will be followed for 14 weeks from the time of treatment (Day 1).

The assessment for whether to proceed in a given dose cohort with FHL treatment will occur 2 weeks after GL treatment and the following criteria are met:

1. All WOCBP must have a negative UPT prior to treatment.
2. No active skin disease or infections or inflammation at the injection sites.
3. Subject has no condition or situation which, in the investigator's opinion, puts the subject at significant risk.
4. No history or current evidence of ptosis.
5. Presence of frontalis motion/movement ability.
6. DRC approves administration of the intended dose.

4.4. Visit Schedule

A Screening Visit will be conducted up to 2 weeks prior to enrollment, and subjects will be treated with investigational product at the Day 1 Visit for GL and at the Week 2 visit for FHL. Following each treatment, subjects will complete a paper diary for 2 weeks to capture their assessment of improvement or satisfaction with the appearance of GL and FHL. Follow-up safety phone calls will be conducted at Weeks 1 and 3. Post-treatment on-site follow-up visits will occur at Weeks 2, 4, 6, 10, 14, 18, 22, 26, 30, 34, and 38. The total study duration will be up to 40 weeks, including up to 2 weeks for screening. Subjects will be followed for a minimum of 24 weeks from GL treatment for safety or until all scores on the IGA-FWS and PFWS, as well as the IGA-FHWS and PFHWS, return to baseline (Day 1 Visit prior to GL treatment) or until Week 38, whichever occurs first. Subjects will then have a Final Evaluation Visit. If the DRC elects not to proceed with the FHL injection in a given dose cohort, subjects assigned to that cohort who have already received GL treatment will be followed for 14 weeks from the time of treatment (Day 1).

Subjects will be evaluated for FHL severity using the Revance-validated 4-point IGA-FHWS and PFHWS at rest and at maximum eyebrow elevation. In addition, to determine the efficacy

response to GL subjects will be evaluated for improvement to a score of 0 or 1 (none or mild) on the IGA-FWS and the PFWS at rest and at maximum frown.

5. Study Population

Approximately 60 female or male subjects, 18 to 65 years of age, with moderate to severe GL and FHL will be enrolled. Investigators will make all reasonable efforts to enroll equal proportions of patients with moderate and severe FHL (based on baseline assessments) in each dosing cohort. 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 ICH-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 to 65 years of age
3. Have a score of moderate (2) or severe (3) FHL during maximum contraction (eyebrow elevation) as assessed by the IGA-FHWS
4. Have a score of moderate (2) or severe (3) FHL during maximum contraction (eyebrow elevation) as assessed by the PFHWS
5. Have a score of moderate (2) or severe (3) GL during maximum frown based on the IGA-FWS scale
6. Have a score of moderate (2) or severe (3) on GL during maximum frown as assessed by the PFWS
7. Have sufficient visual acuity without the use of eyeglasses (contact lens use is acceptable) to accurately assess their facial wrinkles
8. 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 inferior orbital rim) from screening through the end of the study
9. 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)
10. 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 the investigator to completely or almost eliminate GL or FHL by physically spreading medial brows apart or stretching the forehead skin while at rest
5. History of or current significant brow ptosis, significant brow or forehead line asymmetry at rest or on brow elevation. Evidence that frontalis activity is required to maintain eyelid position
6. Previous treatment with botulinum toxin type A in the face within 6 months prior to screening
7. Plans to receive botulinum toxin type A anywhere in the face (other than study treatment) from screening through the end of the study
8. Has not had within the last 6 months prior to screening, or plans to receive treatment through the end of the study with >200 U of any botulinum toxin anywhere else in the body outside of the face

[redacted]

[redacted]

[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 trial and the possibility for entry with a potential subject without first obtaining consent. However, a subject wishing to participate must give written informed consent prior to any study-related procedures being conducted, including those performed solely for the purpose of determining eligibility for study participation, and including withdrawal from current medication (if required prior to study entry). The investigator has both the ethical and legal responsibility to ensure that each subject being considered for inclusion in this trial has been given a full explanation of the procedures and expectations for study participation, as well as ample time to decide whether or not to participate and have all questions answered satisfactorily.

The site-specific informed consent must be forwarded to Revance or designee for approval prior to submission to an Investigational Review Board (IRB)/Independent Ethics Committee (IEC) that is registered with the US Department of Health and Human Services 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 ICH GCP guideline, and applicable federal and local regulatory requirements. The consent form must also include a statement that Revance, their designees, and auditing regulatory agencies will have direct access to the subject's records and medical history for study related purposes.

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

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. Subjects must not have brow tattoos or microblading within 3 months of enrollment or plan to have these procedures through the end of the study. Subject must also avoid upper facial hair removal in the treatment areas above the orbital rim (e.g., waxing, plucking, or threading)

for a total of 6 weeks during the study (2 weeks before GL treatment and 4 weeks after FHL treatment).

[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 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. A female is 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 about study participation for WOCBP with the subject. The topics should generally include:

- Informed consent form content
- 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 above-mentioned 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 the Pregnancy Notification Form and send the form to Revance or designee. Subjects will remain enrolled in the study but will not be treated. The investigator will be asked to follow-up with a phone call with the subject periodically throughout the pregnancy and post-delivery as applicable for ongoing health and safety information, as applicable.

If a serious adverse event (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 baby visit to ensure no SAEs are identified in the neonate, 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 cell binding, internalization, and translocation of daxibotulinumtoxinA into nerve 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, non-randomized study. Subjects will be sequentially enrolled by cohort. All subjects will receive DAXI for injection according to assigned cohort. Subjects will receive a 40 U dose of DAXI for injection at the Day 1 Visit) for the treatment of GL and one additional dose of DAXI for injection at the Week 2 Visit for the treatment of FHL according to assigned cohort.

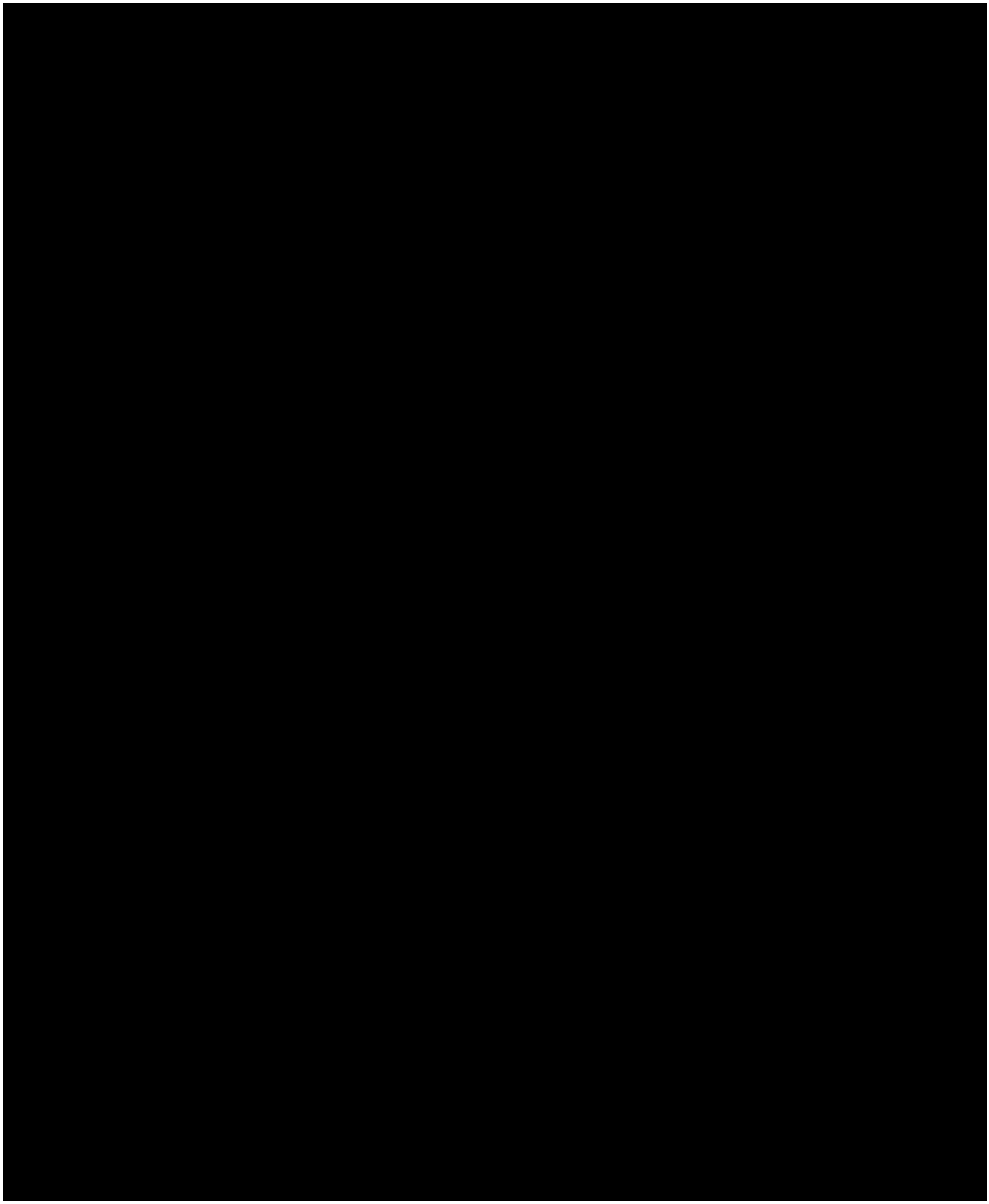
[redacted]

6.2.4. Investigational Product Administration

Investigational product will be administered by the PI to injection site in the designated treatment area. [redacted]

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

[redacted]



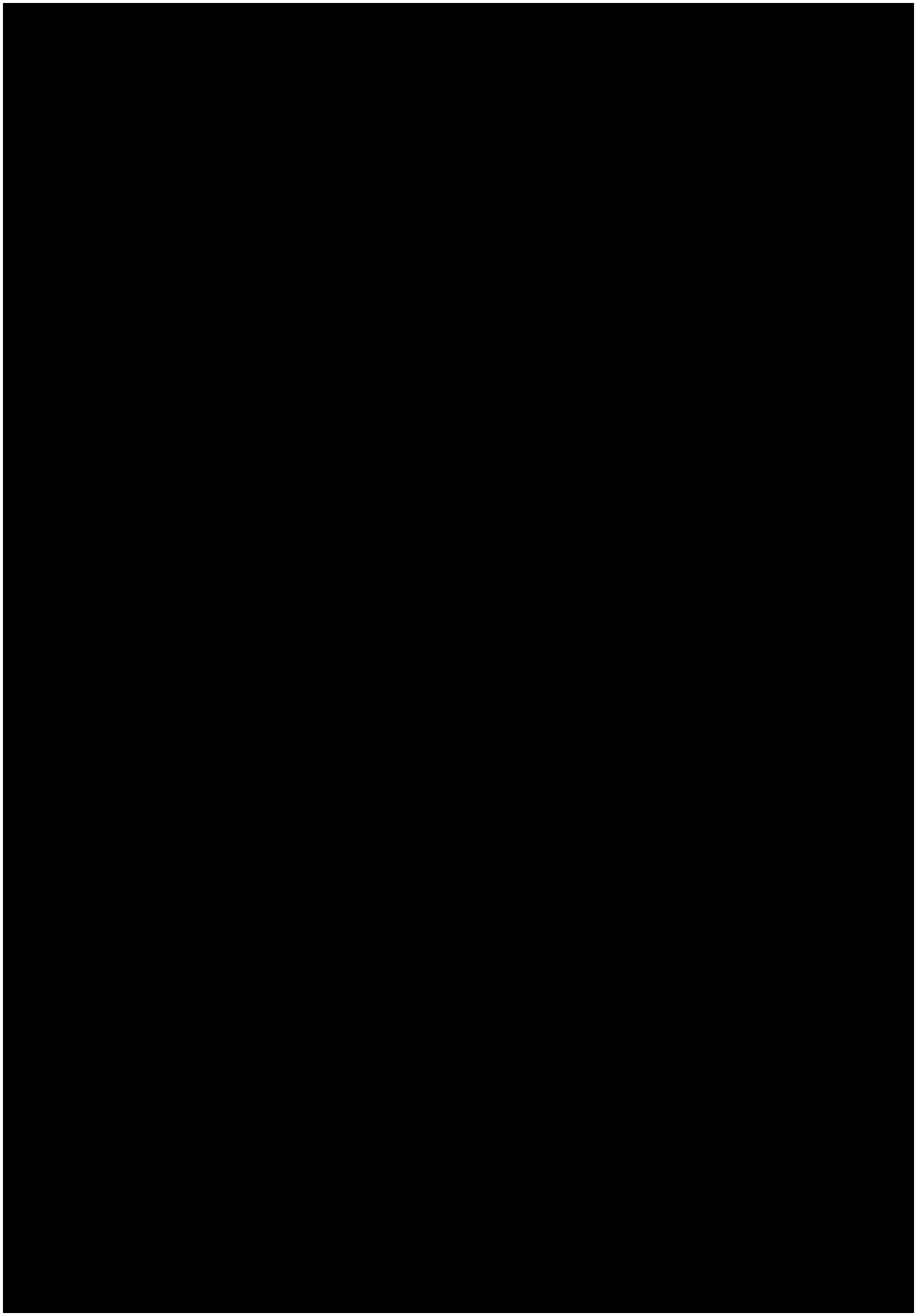
[redacted]

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 including 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 may receive up to 2 treatments in this study (1 GL treatment and 1 FHL treatment) depending on the evaluation of the DRC. The DRC may elect not to proceed with FHL treatment in a given dose cohort. Therefore, subjects may receive the GL treatment and not the FHL treatment in a dose cohort.

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) where consent was not 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 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 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 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 (see 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 trial. The IGA-FHWS, IGA-FWS, and Investigator GAIS should be performed by the same evaluator throughout the study. 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 GL treatment visit (Day 1 Visit).

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

1. Review study procedures and information regarding the trial 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 criteria, the subject will be enrolled

[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 should sit for 5 minutes prior to taking pulse and blood pressure

[redacted]

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

[redacted]

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

[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 Visits (Day 1 and Week 2)

The GL Treatment Visit (Day 1 Visit) must be performed within 14 days of the Screening Visit. The FHL Treatment Visit will occur at the Week 2 Visit. The following procedures must be performed and recorded for each visit:

Prior to Investigational Product Administration

1. Confirm that all screening visit procedures have been completed, results reviewed, and recorded (Day 1 Visit only)
2. Review eligibility criteria
3. Update medical/surgical history (Day 1 Visit only)
4. Once the investigator has confirmed subject eligibility, enroll the subject (Day 1 Visit only)

[redacted]

[redacted]

15. Physical examination [redacted]

[redacted]

17. Measure and record vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure); subjects should sit for 5 minutes prior to taking pulse and blood pressure

[redacted]

20. Conduct patient education for GL and FHL evaluation: Discuss the potential effect of DAXI for injection treatment, explain the PFWS and PFHWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for GL and FHL severity. Use the provided Patient Education Brochure

[redacted]

23. Record concomitant therapy/medications at the Screening Visit (and in the 30 days prior to 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 Section 6.2.4) 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.
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]

8.2.3. Week 1 and 3 Follow-Up Phone Call

At the Week 1 and 3 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]

2. Query subject about any new or ongoing AEs since the last visit
3. Query subject about concomitant therapy/medication

[redacted]

8.2.4. Follow-up Visits

At Weeks 4, 6, 10, 14, 18, 22, 26, 30, and 34 the following procedures must be performed and recorded:

[redacted]

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

[redacted]

12. Conduct patient education for GL and FHL evaluation: discuss the potential effect of DAXI for injection treatment, explain the PFWS and PFHWS measurement and the categories of the severity assessment scales, and instruct the subjects to consider depth of lines for severity of their GL and FHL. Use the provided Patient Education Brochure

[redacted]

[redacted]

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

[redacted]

8.2.5. Final Evaluation Visit (Week 38)

The following procedures must be performed and recorded at the Final Evaluation Visit for each subject. Following treatment, subjects will be followed for at least 24 weeks from GL treatment for safety or until all scores on the IGA-FWS and PFWS, as well as the IGA-FHWS and PFHWS return to baseline (Day 1 Visit) or until Week 38, whichever occurs first. Subjects will then have a Final Evaluation Visit at which time the following procedures must be performed and recorded:

[redacted]

8. Perform a physical examination [redacted]

[redacted] (hematology, serum chemistry, and urinalysis)

13. Conduct patient education for GL and FHL evaluation: Discuss the potential effect of DAXI 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]

16. Assess for any new or ongoing AEs since the last visit

[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
Weeks 1, 2, and 3	+ 2 days
Weeks 4, 6, 10, 14, 18, 22, 26, 30, 34, and 38	+/- 4 days

8.3. Efficacy Assessments

Effectiveness assessments will include investigator assessment of GL and FHL severity and improvement on the IGA-FWS and IGA-FHWS, as well as subject assessment of severity and improvement on the PFWS and PFHWS. 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 Frown 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 frown) of the GL using the IGA-FWS with the following 4-point scale (Table 4).

Table 4: Investigator Global Assessment Facial 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]

8.3.2. Investigator Global Assessment Forehead 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 eyebrow elevation) of the FHL using the IGA-FHWS with the following 4-point scale (Table 5).

Table 5: Investigator Global Assessment Forehead Wrinkle Severity (IGA-FHWS)

Rating Score	Forehead Wrinkle Severity	Description	
		At Rest	At Maximum Eyebrow Elevation
0	None	No horizontal forehead lines	None to minimally visible horizontal forehead line(s)
1	Mild	Barely visible, shallow horizontal forehead line(s)	Visible, shallow horizontal forehead line(s)
2	Moderate	Clearly visible, moderate depth horizontal forehead line(s)	Clearly visible, moderate depth horizontal forehead line(s)
3	Severe	Clearly visible, deep horizontal forehead line(s) with redundancy of skin	Clearly visible, deep horizontal forehead line(s) with redundancy of skin

[redacted]

8.3.3. Patient Frown Wrinkle Severity (PFWS)

Subjects will complete the Patient Frown Wrinkle Severity (PFWS) assessment (at rest and at maximum frown) to assess the severity of the GL at the Screening Visit, Treatment Visit pre-treatment, Follow-up Visits, and Final Evaluation Visit.

The subject assessment form will be provided directly to the subject to complete while reviewing their GL treated area using the supplied handheld mirror. Refer to Appendix 6 for additional information.

Table 6: 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

8.3.4. Patient Forehead Wrinkle Severity (PFHWS)

At each clinic visit as designated in the SOA (Section 1.3), the subject will assess the visual appearance of FHL using the PFHWS (at rest and at maximum eyebrow elevation). The assessment form will be provided directly to the subject to complete while reviewing the treatment areas using the supplied handheld mirror. Subjects who wear contact lenses should view the treatment areas while wearing their contact lenses. Subjects who wear glasses must have sufficient visual acuity to view the treatment areas without glasses. The subject assessment must be completed before the investigator completes the IGA-FHWS assessment. Refer to Appendix 7 for additional information.

Table 7: Patient Forehead Wrinkle Severity (PFHWS)

Rating Score	Forehead Wrinkle Severity	Description	
		At Rest	At Maximum Eyebrow Elevation
0	None	No horizontal forehead lines	None to minimally visible horizontal forehead line(s)
1	Mild	Barely visible, shallow horizontal forehead line(s)	Visible, shallow horizontal forehead line(s)
2	Moderate	Clearly visible, moderate depth horizontal forehead line(s)	Clearly visible, moderate depth horizontal forehead line(s)
3	Severe	Clearly visible, deep horizontal forehead line(s) with redundancy of skin	Clearly visible, deep horizontal forehead line(s) with redundancy of skin

The assessment will represent wrinkle severity at each given time point and will not be based on a comparison to the pre-treatment defect level. It is recommended that visit assessments be completed by the subject as close to the same time of day as possible.

8.3.5. Global Aesthetic Improvement Scale (GAIS)

The investigator and subject will assess the visual appearance (at maximum eyebrow elevation) of the improvement from the baseline condition in FHL and in visual appearance in the improvement of GL during maximum frown using the following 7-point severity GAIS (Table 8). Subjects will use the baseline assessment photograph for comparison when reviewing the visual appearance for GL and FHL to assess improvement following treatment. Assessments will be made as designated in the SOA (Section 1.3).

The Patient GAIS assessment form (Appendix 5) will be provided directly to the subject to complete while reviewing the glabellar treatment area (at maximum eyebrow elevation and maximum frown) using the supplied handheld mirror as outlined in Appendix 5. Subjects who wear contact lenses should view their treatment area while wearing their contact lenses. Subjects who wear glasses must have sufficient visual acuity to view their treatment area without glasses. The subject assessment must be completed before the investigator completes the IGA-FWS and IGA-FHWS assessment.

Table 8: 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

8.3.6. 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 9). Following the subject's completion of the Patient GAIS, the subject will be given a questionnaire to rate their perception of how old they think they look following the treatment.

8.3.7. FACE-Q™

At each clinic visit designated in the SOA (Section 1.3), the subject will be asked to complete the FACE-Q™ Satisfaction with Forehead and Eyebrows and the FACE-Q™ Appraisal of Lines: Forehead questionnaires (Appendix 11). The questionnaires ask subjects to rate how bothered they are by their FHL using 7 questions about general appearance with a rating scale of 1 to 4 with 1 representing Not Bothered and 4 representing Extremely Bothered. Refer to Appendix 11 for additional information.

[redacted]

8.3.9.1.2. Subject Global Satisfaction with Treatment Questionnaire

At each clinic visit designated in the SOA (Section 1.3), the subject will be asked to provide a rating of their satisfaction with the treatment results. Following the subject's completion of the Patient GAIS, the subject will be given the Subject Global Satisfaction with Treatment 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 10).

8.4. Safety Assessments

Planned time points 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 and at the Day 1, Week 2 and Final Evaluation Visits. 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.

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 and at the Day 1 and Week 2 and 38 Visits, or Final Evaluation Visit, [redacted]. New abnormal findings or worsening from baseline (Day 1 prior to GL treatment) at subsequent assessments, if judged clinically significant, should be recorded as an AE.

8.4.3. Pregnancy Testing

A UPT is required for all WOCBP at screening and a UPT is required at the Screening Visit and at the Day 1 (pre-treatment), Week 2 and 38 Visits 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 a 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 screening for signs of skin inflammation or active disease. The GL treatment areas will be evaluated at the Day 1 Visit (pre- and post-treatment) and at the Week 2 and 4 Visits. The FHL treatment areas will be evaluated at the Week 2 Visit (pre- and post-treatment) and at the Week 4 and 6 Visits. The assessment will be done as a global evaluation of the 5 injection sites for GL and 3 injection sites for FHL (Table 9). (Refer to Appendix 12 for additional information.)

Table 9: 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 10, non-fasting samples for hematology, chemistry, PT (screening only) and urinalysis will be collected at screening, Week 4 Visit, and Week 38 or 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 study center using supplies provided by Revance or designee.

Table 10: 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]

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, if 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 [redacted]) after GL and FHL 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;
  NOTE: 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 subjects after GL and FHL treatment and at each subsequent study visit for the occurrence of AEs. 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 signing of the ICF until the Final Evaluation Visit at each 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 38 or Final Evaluation Visit at the time points 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 on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

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.

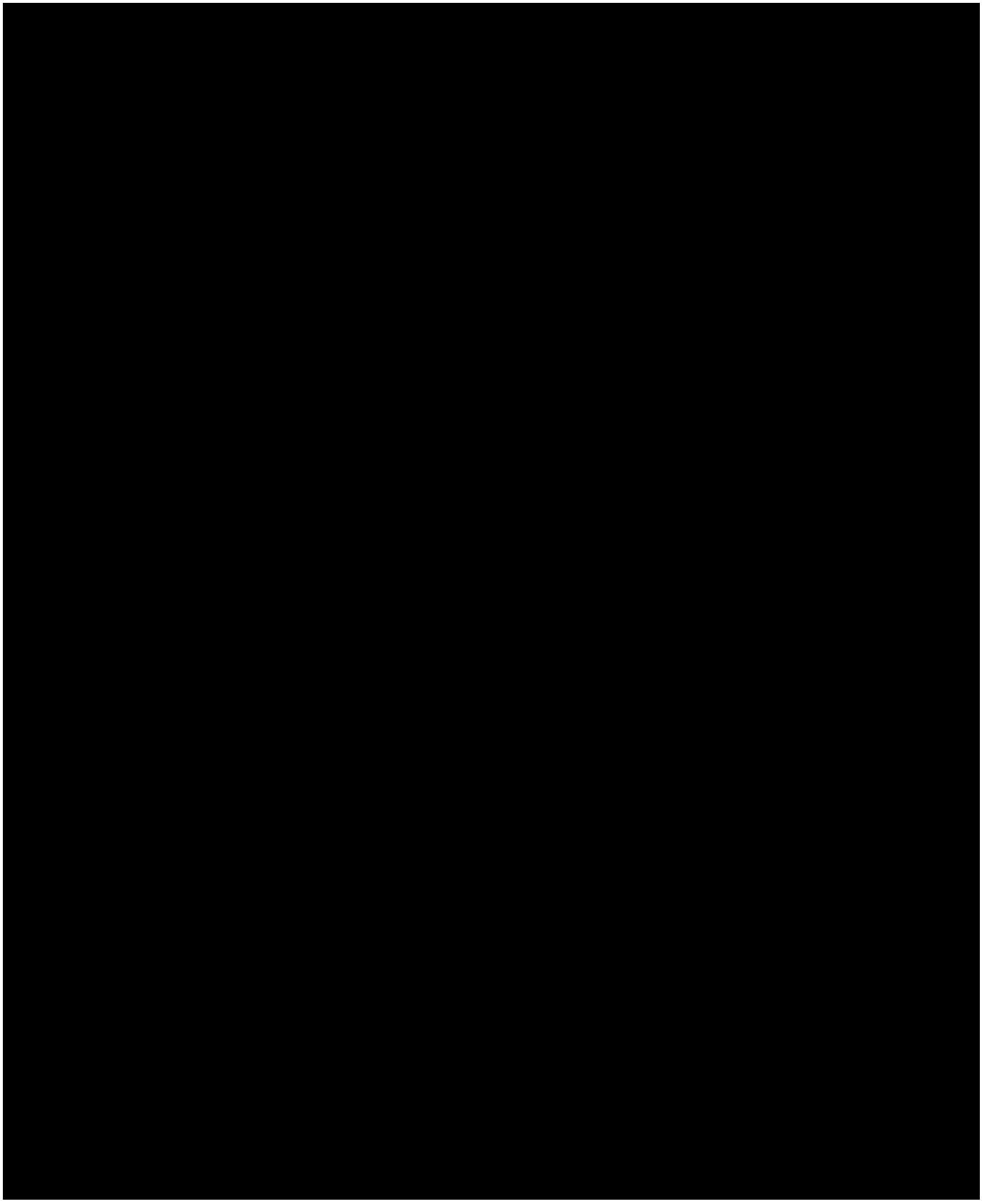
8.5.3. Serious Adverse Events

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 the 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 (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 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 Guidelines, national regulations and local requirements).

[redacted]



8.5.5. Follow-up of Non-Serious Adverse Events

Any AEs that are identified from Day 1 through the last scheduled study visit (or Final Evaluation Visit) 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 AEs 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 until the medical monitor determines that follow-up is sufficient.

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

SAEs that are identified on the last scheduled contact (or Final Evaluation Visit) 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, follow-up is sufficient, 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 to 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. Sample Size Determination

The sample size is not determined by the power of any hypothesis testing. [redacted]

9.2. 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 FHL received (which is expected to be consistent with the enrollment cohorts):

Population	Description
Enrolled	All subjects who receive the GL treatment
GL-Evaluable	All enrolled subjects who have any post-GL treatment assessment of IGA-FWS at maximum frown
FHL-Evaluable	All enrolled subjects who receive the FHL treatment and have any post-FHL treatment assessment of IGA-FHWS at maximum eyebrow elevation
Safety	All enrolled subjects
Safety-FHL	All enrolled subjects who receive the FHL treatment

9.3. 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 ranges for continuous variables; and counts and proportions for categorical measures. Unless otherwise stated, a 95% CI will be provided for means and proportions. No formal hypothesis tests are planned, but may be performed as exploratory analyses. No multiplicity adjustments or imputation of missing data are planned.

9.3.1. Efficacy Analyses

Unless otherwise noted, baseline for all efficacy assessments for GL refers to the last available assessment prior to GL treatment for those associated with GL severity and for FHL refers to the last available assessment prior to FHL treatment for those associated with FHL severity.

The primary efficacy endpoint will be the proportion of subjects achieving a score of 0 or 1 (none or mild) on the FHWS as assessed by IGA-FHWS at maximum eyebrow elevation at Week 6. The dose response in the proportion of responders at 4 weeks after the FHL treatment (Week 6) will be explored using the logistic regression stratified by baseline FHWS severity (last assessment prior to GL treatment at Day 1 Visit) and study center to assess the dose-response. Additional measures to assess the effectiveness outcomes will include the IGA-FHWS, PFHWS, GAIS evaluated at maximum contraction (eyebrow elevation) and at rest at each visit. Various responder endpoints associated with the FHWS, 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 curves will be plotted by dose group for each time-to-event endpoint and median duration with associated 95% CIs will be provided.

Similar responder and time-event endpoints associated with the GL wrinkle severity defined based on the assessments for GL wrinkle severity such as IGA-FWS, PFWS or GAIS on GL, will be summarized similarly to those endpoints associated with FHWS. Efficacy outcomes will be summarized. Descriptive statistics will be provided for all efficacy variables at all timepoints. Note that exploratory analyses of the change in FHL severity from Day 1 (post-GL treatment) to Week 2 and from pre-FHL treatment (Week 2 pre-treatment) to post treatment will also be performed.

9.3.2. Safety Analyses

Adverse events (AEs) occurring during the study will be recorded and classified according to MedDRA terminology. Those occurred one 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.

9.4. Interim Analyses

Due to the nature of the study design, data will be evaluated after each dosing cohort achieves a pre-specified milestone (e.g., 5 weeks after last subject's enrollment) before a decision is made to move forward with the next dosing cohort. In addition, a formal interim analysis of the data will be performed when all subjects finish 8 weeks after receiving the FHL treatment or have withdrawn from the study earlier.

9.4.1. Data Review Committee

Due to the dose-escalation nature of the study design, safety data and subject photographs/videos will be evaluated by the DRC at Week 5 following GL treatment (3 weeks after FHL treatment) for each cohort before a decision is made to move forward with the next and subsequent doses. If the DRC elects not to proceed with the FHL injection in a given dose cohort, subjects will be followed for 14 weeks from the time of treatment (Day 1).

Dose escalation for FHL 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 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 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. The 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 (R2) 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 informed consent form) to Revance or designee before investigational product will be shipped to the study center.

[redacted]

[redacted]

[redacted]

[redacted]