Title Page

Protocol Title: A Phase 2b Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of AGN-151586 in Participants With Moderate to Severe Glabellar Lines

Protocol Number: 2034-201-008

Amendment Number: 1

Product: AGN-151586 (Botulinum Neurotoxin Serotype E, BoNT/E) for injection

Brief Protocol Title: AGN-151586 Dose-Ranging Study for Treatment of Glabellar Lines

Development Phase: 2b

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Refer to the final page of this protocol for electronic signature and date of approval.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	June 2020
Original Protocol	July 2019

Amendment 1 (June 2020)

Overall Rationale for the Amendment:

The primary purpose of this protocol amendment is to update study processes related to the analysis of immunogenicity samples for optional exploratory research and improve clarity of study processes as summarized below.

Section No. and Name	Description of Change	Brief Rationale
Title Page	Updated sponsor signatory's title	Update
8.2.5/Electrocardiograms	Added statement that exclusion alerts based on prespecified significant abnormal electrocardiogram findings are considered exclusionary for study eligibility (consistent with exclusion criteria in Section 5.2).	Improve clarity
8.8/Biomarkers and Other Assessments	Added statements that immunogenicity samples may be used for additional characterization of antibody response to other neurotoxin subtype(s) and described the informed consent process for this optional exploratory research.	Update
9.4.3.1/Immunogenicity Analyses	Added statement that additional immunogenicity exploratory analyses may be performed.	Update

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2b Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of AGN-151586 in Participants With Moderate to Severe Glabellar Lines

Protocol Number: 2034-201-008

Amendment Number: 1

Brief Title: AGN-151586 Dose-Ranging Study for Treatment of Glabellar Lines

Study Phase: 2b

Study Rationale:

The purpose of this Phase 2b study is to evaluate the safety and efficacy of AGN-151586 over a range of doses for the treatment of moderate to severe glabellar lines (GL).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Efficacy: To compare the efficacy between placebo and a range of doses of AGN-151586 for the treatment of GL in participants with moderate to severe GL • Safety: To compare the safety between placebo and a range of doses of AGN-151586 for the treatment of GL in participants with moderate to severe GL	• Achievement of a ≥ 2-grade improvement from baseline on the Facial Wrinkle Scale With Photonumeric Guide (FWS) according to investigator assessments of GL severity at maximum frown at any postintervention timepoint through Day 7. • Incidence of adverse events; change from baseline in hematology/chemistry/urinalysis laboratory, vital sign, and electrocardiogram (ECG) parameters; and presence of antidrug antibodies

Overall Study Design:

- This is a multicenter, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the safety and efficacy of a single study intervention cycle of AGN-151586 in participants with moderate to severe GL.
- Participants are adults 18 to 65 years old, with moderate to severe GL at maximum frown (as assessed by the investigator using the FWS).
- Up to 5 doses of AGN-151586 will be evaluated and compared with placebo in a sequential cohort design, starting with the lowest dose.
- Each cohort will enroll a balanced distribution of participants with moderate or severe GL severity at maximum frown per investigator assessment (at least 40% and no more than 60% of either).

- The primary efficacy measure is the investigator's assessments of GL at maximum frown using the FWS.
- Participants will undergo a Screening Visit up to 30 days before randomization on Day 1. All screening data must be available to the investigator prior to randomization on Day 1.
- On Day 1, participants will be randomly assigned in a 3:1 ratio to receive AGN-151586 or placebo. Enrollment stratification will be by baseline GL severity at maximum frown, assessed by the clinician (principal investigator or physician subinvestigator) using the FWS.
- Study intervention on Day 1 will be administered as 5 injections in the glabellar complex (1 in the procerus and 2 in each corrugator).
- Participants will remain in the clinic for the first 12 hours after administration of study intervention for serial assessments at Hours 4, 8 and 12. Thereafter, participants return to the clinic on Day 2 (Hour 24 and Hour 36), Day 3 (Hour 48 and Hour 60), Day 7, Day 14, Day 21, Day 28, Day 35, and Day 42.
- For each dose group, an internal data monitoring committee (DMC), independent from the study team, will review select safety and efficacy data from a subset of participants ($n \geq 16$) with data through 14 days postintervention (in addition to cumulative data from the prior cohort[s]).
- The DMC may recommend proceeding with the nominal dose for the next cohort, request additional data (eg, data from additional participants in the cohort, data from visits after Day 14), request to repeat the current dose or a lower dose, request an intermediate dose be evaluated (between the dose of the current cohort and the nominal dose for the next cohort), or request dose escalation be terminated.

Number of Participants:

Approximately 200 participants will be enrolled. Accounting for a dropout rate of 10%, it is anticipated that approximately 180 participants will complete the study. A total of up to 5 dose cohorts are planned with a randomization allocation of 3:1 for AGN-151586 (n = 30) and placebo (n = 10) for each cohort.

Number of Sites:

Approximately 10 US investigational sites

Intervention Groups and Study Duration:

The total duration of study participation for each participant is up to approximately 72 days. Participants will attend the following visits:

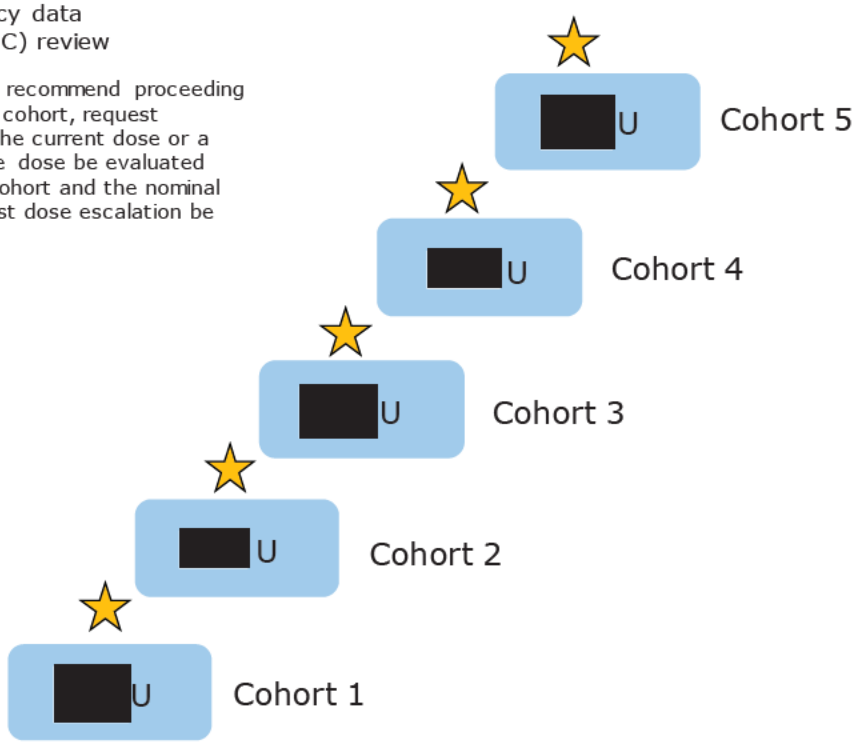
- Screening (up to 30 days before randomization)
- Day 1
    - Hour 0 (randomization and administration of study intervention)
    - Hour 4
    - Hour 8
    - Hour 12
- Follow-up visits:
    - Day 2, Hour 24
    - Day 2, Hour 36
    - Day 3, Hour 48
    - Day 3, Hour 60
    - Weekly (Days 7, 14, 21, 28, and 35)
- Exit (Day 42)

Data Monitoring Committee: Yes

1.2. Schema

= 14-day safety and efficacy data monitoring committee (DMC) review

At each DMC review, the DMC may recommend proceeding with the nominal dose for the next cohort, request additional data, request to repeat the current dose or a lower dose, request an intermediate dose be evaluated (between the dose of the current cohort and the nominal dose for the next cohort), or request dose escalation be terminated.



n = 40 per cohort at 3:1 randomization (AGN-151586:placebo)

1.3. Schedule of Activities (SoA)

Visit Number	1	2				3	4	5	6	7	8	9	10	11	12
Study Period	Screening (Days −30 to −1)	Randomization and Study Intervention (Day 1)[a]	Day 1[b]			Follow-up: Day 2		Day 3		Day 7	Day 14	Day 21	Day 28	Day 35	End of Study (Day 42 or Early Exit)
Time after administration of study intervention	--	--	4 h	8 h	12 h	24 h	36 h	48 h	60 h						
Visit windows	--	--	± 1 h	± 1 h	± 1 h	± 2 h	± 2 h	± 2 h	± 2 h	± 1 day	± 1 day	± 1 day	± 1 day	± 1 day	± 1 day
Consent/ authorization	X														
Demographics	X														
Height and weight	X														
Inclusion/ exclusion criteria	X	X													
Medical/surgical history	X														
[redacted]		X		X		X		X		X	X	X	X	X	X
[redacted]		X													
[redacted]				X		X		X		X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit Number	1	2			3	4	5	6	7	8	9	10	11	12
Study Period	Screening (Days −30 to −1)	Randomization and Study Intervention (Day 1)[a]	Day 1[b]			Follow-up: Day 2		Follow-up: Day 3		Follow-up: Day 7	Follow-up: Day 14	Follow-up: Day 21	Follow-up: Day 28	Follow-up: Day 35	End of Study (Day 42 or Early Exit)
Time after administration of study intervention	--	--	4 h	8 h	12 h	24 h	36 h	48 h	60 h						
Visit windows	--	--	± 1 h	± 1 h	± 1 h	± 2 h	± 2 h	± 2 h	± 2 h	± 1 day	± 1 day	± 1 day	± 1 day	± 1 day	± 1 day
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standardized facial photography		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[d]	X	X	X			X		X		X	X	X	X	X	X
Vital sign measurements[e]	X	X	X			X		X		X	X	X	X	X	X
Neurologic assessments[f]	X	X	X			X		X		X	X	X	X	X	X
Urine pregnancy test (WOCBP)[g]	X	X													X
12-lead ECG[h]	X					X		X		X					X
Collection of blood and urine samples for hematology, chemistry, and urinalysis laboratory testing[i]	X							X		X					X

Visit Number	**1**	**2**			**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study Period	**Screening (Days −30 to −1)**	**Randomization and Study Intervention (Day 1)[a]**	**Day 1[b]**			**Follow-up**								**End of Study (Day 42 or Early Exit)**
						Day 2		**Day 3**		**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	
Time after administration of study intervention	**--**	**--**	**4 h**	**8 h**	**12 h**	**24 h**	**36 h**	**48 h**	**60 h**						
Visit windows	**--**	**--**	**± 1 h**	**± 1 h**	**± 1 h**	**± 2 h**	**± 2 h**	**± 2 h**	**± 2 h**	**± 1 day**	**± 1 day**	**± 1 day**	**± 1 day**	**± 1 day**	**± 1 day**
Collection of blood samples for immunogenicity testing	X									X			X		X
Adverse events	X	X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study intervention administration		X (0 h)													

ECG = electrocardiogram; [redacted]; GL = glabellar lines; WOCBP = women of childbearing potential

[a] All makeup must be removed and hair not obscuring the upper face prior to completing any assessment. All assessments must be completed before administration of study intervention at Hour 0.

[b] Participants must remain at the investigational site on Day 1 (ie, from baseline procedures through Hour 12 assessment).

[c] The investigator and participant must grade the severity of GL using the FWS at the same time, first at rest, then at maximum frown. The investigator and participant must not discuss their results with each other.

[d] A complete physical examination is to be done at the Screening Visit and EOS/Early Exit Visit. An *abbreviated physical examination* is to be done at other visits. The *abbreviated physical examination* is limited to an examination of general appearance, heart, lungs, and abdomen.

[e] Vital sign measurements includes pulse rate, respiration rate, blood pressure, and body temperature. Participants are to be seated for at least 2 minutes before measurements are collected.

[f] The neurologic assessment includes the Focused Symptom Questionnaire and Focused Neurologic Examination.

[g] Women of childbearing potential (WOCBP) must have a negative pregnancy test at the Screening Visit and on Day 1 prior to randomization. The investigator may ask the participant to perform a urine pregnancy test at any time, which must be conducted at the investigational site. At each visit, site personnel must discuss with WOCBP and males with partners who are WOCBP compliance with contraceptive use.

[h] A 12-lead ECG will be taken with the participant in a semirecumbent position for ≥ 10 minutes before starting the tracing.

[i] Nonfasting

[j] Participant must be observed for at least 30 minutes after study intervention for adverse events.

2. Introduction

2.1. Study Rationale

The purpose of this Phase 2b study is to evaluate the safety and efficacy of AGN-151586 over a range of doses for the treatment of moderate to severe GL.

2.2. Background

Botulinum Neurotoxin Serotype E

The bacterium *clostridium botulinum* produces several distinct serotypes of botulinum neurotoxins designated A through G (Barash 2014; Keller 2006). These neurotoxins are some of the most potent molecules in nature, and all have the capability to block skeletal muscle contraction by blocking presynaptic acetylcholine release at the neuromuscular nerve junction. Even though they have similar modes of action, each serotype has distinct properties that differentiate them from each other.

Botulinum Neurotoxin Serotype E has been shown to inhibit muscle contraction by preventing the acetylcholine release at the neuromuscular junction. This effect has been shown in animals as well as humans (Adler 2001; Eleopra 1998). Epidemiologic studies in humans who have contracted botulism caused by BoNT/E have shown classic signs of systemic disease characterized by flaccid paralysis with earlier onset than classic botulism with BoNT/A (McLaughlin 2004).

In the published literature, BoNT/E has a distinct profile with a faster onset and shorter duration of effect compared with BoNT/A. Nonclinical studies have shown BoNT/E to have faster translocation in neurons (Keller 2004) and faster inhibition on neuromuscular transmission (Wang 2008), suggesting its potential effect of faster onset of action in comparison with BoNT/A. A clinical trial in humans showed that participants recovered faster from paralysis after BoNT/E was injected into extensor digitorum brevis muscles, suggesting its duration of conferring paralytic effect might be shorter than BoNT/A (Eleopra 1998).

Indication

Glabellar lines are deep furrows or *frown lines* in the glabellar area of the face and result from the repetitive functional action of the underlying mimetic facial musculature during animation (Blitzer 1993). The development of facial lines (such as GL) is an age-related change of the face that occurs because of the repetitive muscle contractions that are associated with common facial expressions. Thus, these facial lines can be observed with contraction (dynamic rhytides) or in more severe cases in repose (static rhytides). Increasing severity in the appearance of facial lines has been associated with a patient's perception of reduced attractiveness and a negative effect on self-esteem and sense of well-being (Koblenzer 1996). Furthermore, the appearance of these facial lines can lead to a miscommunication of an emotional state of anger, anxiety, disapproval, or sadness (Khan 2001), causing distress and affecting social interactions (Finn 2003).

Evidence supports that unattractive or aging skin is indeed related to psychological and psychosocial impacts (Farage 2010). Psychological or psychosocial impacts can be characterized as changes in confidence, attractiveness, self-esteem, emotional burdensomeness, self-perceptions of appearance or age, emotional distress, and state of bother. The evaluation of psychological or psychosocial impacts associated with aging facial skin should be assessed from patients' perspectives since these impacts are dependent on their perceptions.

The popularity of BoNT/A cosmetic treatment of GL in adults is related to its proven efficacy for reducing moderate to severe facial lines (Beer 2006); well documented safety profile (Brin 2009); and positive impact on psychological well-being and the resulting psychosocial benefits (Finn 2003).

When injected at therapeutic doses, it is expected that BoNT/E, like BoNT/A, produces partial chemical denervation of the muscle, resulting in localized reduction in muscle activity. Because GL result from muscular activity, the muscle relaxation leads to a temporary relief of facial lines. While it was previously thought that these facial lines were structural and permanent, the effects of these injections demonstrate the lines are part functional and may be associated with persistent increased muscle tone (Garcia 1996; Le Louarn 2007).

Based on published data for BoNT/E, in addition to preclinical and clinical experiences with AGN-151586, it is anticipated that at a clinically efficacious dose, AGN-151586 will exhibit a faster onset of improvement in GL severity compared with BoNT/A, with shorter duration of treatment effect.

AGN-151586

AGN-151586 (previously referred to as EB-001) is a BoNT/E and has been evaluated in clinical studies for various indications up to a total dose of [redacted] U. These studies are briefly summarized below. For additional information and details, please refer to the IB.

The first-in-human study (EB001-GL201) determined that over a limited range of doses up to [redacted] U, AGN-151586 was well tolerated when injected in the glabellar complex (procerus and bilateral corrugator muscles) and exhibited a trend of fast onset (within 24 hours) and a limited duration of clinical effect (approximately 2 weeks) compared with the well characterized clinical profile of BoNT/A for the treatment of GL.

In a Phase 2 exploratory study (EB001-SR201), a single dose of [redacted] U AGN-151586 was administered as 5 injections (divided equally) to the frontalis muscle during Mohs surgery in the forehead. The data suggested favorable safety and tolerability at the tested dose. During the wound healing and acute scar formation phase (up to Day 30), descriptive results of some of the exploratory analyses were consistent with the hypotheses that AGN-151586 may improve overall scar appearance, decrease itch and pain associated with the surgical wound, and improve the scar color and stiffness. However, it should be noted that only a single dose of AGN-151586 was evaluated, which may not have been sufficient to capture the optimal efficacy response for postsurgical scar reduction.

The safety and efficacy of AGN-151586 injections in reducing postsurgical musculoskeletal pain in participants undergoing elective augmentation mammoplasty was evaluated in

Study EB001-MA201. Six doses of AGN-151586 (ranging from [redacted] U) were evaluated. No dose response was observed, and there was no statistically significant difference in pain reduction between any dose group compared with placebo. This study showed favorable safety and tolerability.

The safety and efficacy of AGN-151586 in reducing musculoskeletal pain was also evaluated in Study EB001-ABD201 in participants undergoing elective abdominoplasty. This study evaluated 3 doses of AGN-151586 ranging from [redacted] U. The study was terminated early as a result of a business decision. The available data suggested favorable safety and tolerability, but no efficacy conclusion could be drawn.

AGN-151586 has been evaluated in a series of pharmacology and nonclinical toxicology studies in mice, rats, and monkeys. In addition to faster onset and shorter duration of effect when compared with BoNT/A in these animal models, it is also less potent in terms of extent of muscle paralysis at peak efficacy. The magnitude of lower potency of BoNT/E compared with BoNT/A is varied, depending on the species and on the assays (Donald 2018). Higher doses may be needed to achieve demonstrable therapeutic responses.

For additional information, please refer to the IB.

2.3. Benefit/Risk Assessment

Generally, the popularity of BoNT/A cosmetic treatment of GL in adults is related to its proven efficacy for reducing moderate to severe facial lines (Beer 2006); well documented safety profile (Brin 2009); and positive impact on psychological well-being and the resulting psychosocial benefits (Finn 2003). Compared with the general class of BoNT/A treatments, AGN-151586 may provide additional benefits. For one, it is provided as a ready-to-use liquid product and requires no reconstitution. Secondly, it offers the potential for faster onset of efficacy compared with the BoNT/A products.

Four controlled, Phase 2 clinical studies with AGN-151586 have been completed. In total, 103 participants have received a single study intervention cycle of AGN-151586 (highest exposure was [redacted] U, and 41 participants have received placebo (identical to AGN-151586 but without toxin). Of those who received AGN-151586, headache (n = 2), vital capacity decreased (n = 2), pruritus/pruritus generalized (n = 2), and nausea (n = 1) were the only adverse events considered treatment-related by the investigator. These adverse events were mild to moderate in severity and resolved. The adverse event profile associated with AGN-151586 showed no unusual findings; no safety signal was identified.

The relevant anatomy and any alterations to the anatomy due to prior surgical procedures must be understood prior to administering AGN-151586, and care should be taken when injecting in or near vulnerable anatomic structures. Caution should also be exercised when AGN-151586 is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle. As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoesthesia, tenderness, swelling/edema, erythema, localized infection, bleeding, and/or bruising may be associated with the injection of

AGN-151586 or placebo. Needle-related pain and/or anxiety could result in vasovagal responses, including transient symptomatic hypotension and syncope.

In some cases, botulinum toxin effect may be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary retention, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have an underlying condition that would predispose them to these symptoms.

Reduced blinking has been reported after BoNT/A product injection to the orbicularis muscle, and can lead to corneal exposure, persistent epithelial defect, and corneal ulceration with perforation. For treatment of blepharospasm using a BoNT/A product, corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect. Although these effects mentioned above have not been reported for BoNT/E, these may be anticipated because the mechanism of action of BoNT/E is similar to BoNT/A.

In addition to investigator and the sponsor's MSP oversight, a DMC has been instituted to provide oversight in this study. The dose-escalation design of this study allows for careful review of select safety and efficacy data by the DMC to perform informed risk/benefit assessments prior to escalation to the next higher dose. The DMC may recommend proceeding with the nominal dose for the next cohort, request additional data, request to repeat the current dose or a lower dose, request an intermediate dose be evaluated (between the dose of the current cohort and the nominal dose for the next cohort), or request dose escalation be terminated.

More detailed information about the known and expected benefits and risks, reasonably expected adverse events of AGN-151586, and measures to control these risks can be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Efficacy: To compare the efficacy between placebo and a range of doses of AGN-151586 for the treatment of GL in participants with moderate to severe GL • Safety: To compare the safety between placebo and a range of doses of AGN-151586 for the treatment of GL in participants with moderate to severe GL	• Achievement of a ≥ 2-grade improvement from baseline on the FWS according to investigator assessments of GL severity at maximum frown at any postintervention timepoint through Day 7. • Incidence of adverse events; change from baseline in hematology/chemistry/urinalysis laboratory, vital sign, and ECG parameters; and presence of antidrug antibodies

Nonprimary assessments are specified in the SAP and COA SAP.

4. Study Design

4.1. Overall Design

- This is a multicenter, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the safety and efficacy of a single study intervention cycle of AGN-151586 in participants with moderate to severe GL.
- Participants are adults 18 to 65 years old, with moderate to severe GL at maximum frown (as assessed by the investigator using the FWS).
- Up to 5 doses of AGN-151586 will be evaluated and compared with placebo in a sequential cohort design, starting with the lowest dose.
- Each cohort will enroll a balanced distribution of participants with moderate or severe GL severity at maximum frown per investigator assessment (at least 40% and no more than 60% of either).
- The primary efficacy measure is the investigator's assessments of GL at maximum frown using the FWS.
- Participants will undergo a Screening Visit up to 30 days before randomization on Day 1. All screening data must be available to the investigator prior to randomization on Day 1.
- On Day 1, participants will be randomly assigned in a 3:1 ratio to receive AGN-151586 or placebo. Enrollment stratification will be by baseline GL severity at maximum frown, assessed by the clinician (principal investigator or physician subinvestigator) using the FWS.
- Study intervention on Day 1 will be administered as 5 injections in the glabellar complex (1 in the procerus and 2 in each corrugator).
- Participants will attend the following visits:
    - Screening (up to 30 days before randomization)
    - Day 1
        - Hour 0 (randomization and administration of study intervention)
        - Hour 4
        - Hour 8
        - Hour 12
    - Follow-up visits:
        - Day 2, Hour 24
        - Day 2, Hour 36

- Day 3, Hour 48
- Day 3, Hour 60
- Weekly (Days 7, 14, 21, 28, and 35)

- Exit (Day 42)

- Participants will remain in the clinic for the first 12 hours after administration of study intervention for serial assessments at Hours 4, 8 and 12. The total duration of study participation for each participant is up to approximately 72 days.

Data Monitoring Committee

An internal DMC, independent from the study team, has been instituted to provide oversight in this study. Starting with Cohort 1, the DMC will convene to review select safety and efficacy data after the first subset of participants in Cohort 1 have completed the Day 14 visit. Following this review, the DMC will determine whether the study will proceed to Cohort 2 of dose escalation. After Cohort 2 proceeds, a similar review process will occur to determine whether Cohort 3 will proceed. This pattern repeats prior to the start of each new cohort. At each DMC review, data through Day 14 from a subset of participants ($n \geq 16$) for any given cohort will be reviewed. Additionally, cumulative data from participants from the prior cohort(s) will also be included in the DMC review.

At each DMC review, the DMC may recommend proceeding with the nominal dose for the next cohort, request additional data (eg, data from additional participants in the cohort, data from visits after Day 14), request to repeat the current dose or a lower dose, request an intermediate dose be evaluated (between the dose of the current cohort and the nominal dose for the next cohort), or request dose escalation be terminated.

The dose-escalation design of this study allows for careful review of select safety and efficacy data by the DMC to assess risk/benefit prior to escalation to the next higher dose. Details of the activities and composition of the DMC are further described in the DMC charter.

4.1.1. Clinical Hypotheses

Efficacy: A single study intervention cycle of AGN-151586 within the dose range evaluated is more effective than placebo in the treatment of GL, measured by investigators' assessments of GL severity at maximum frown using the FWS.

Safety: A single study intervention cycle of AGN-151586 has an acceptable safety profile at the doses evaluated.

4.2. Scientific Rationale for Study Design

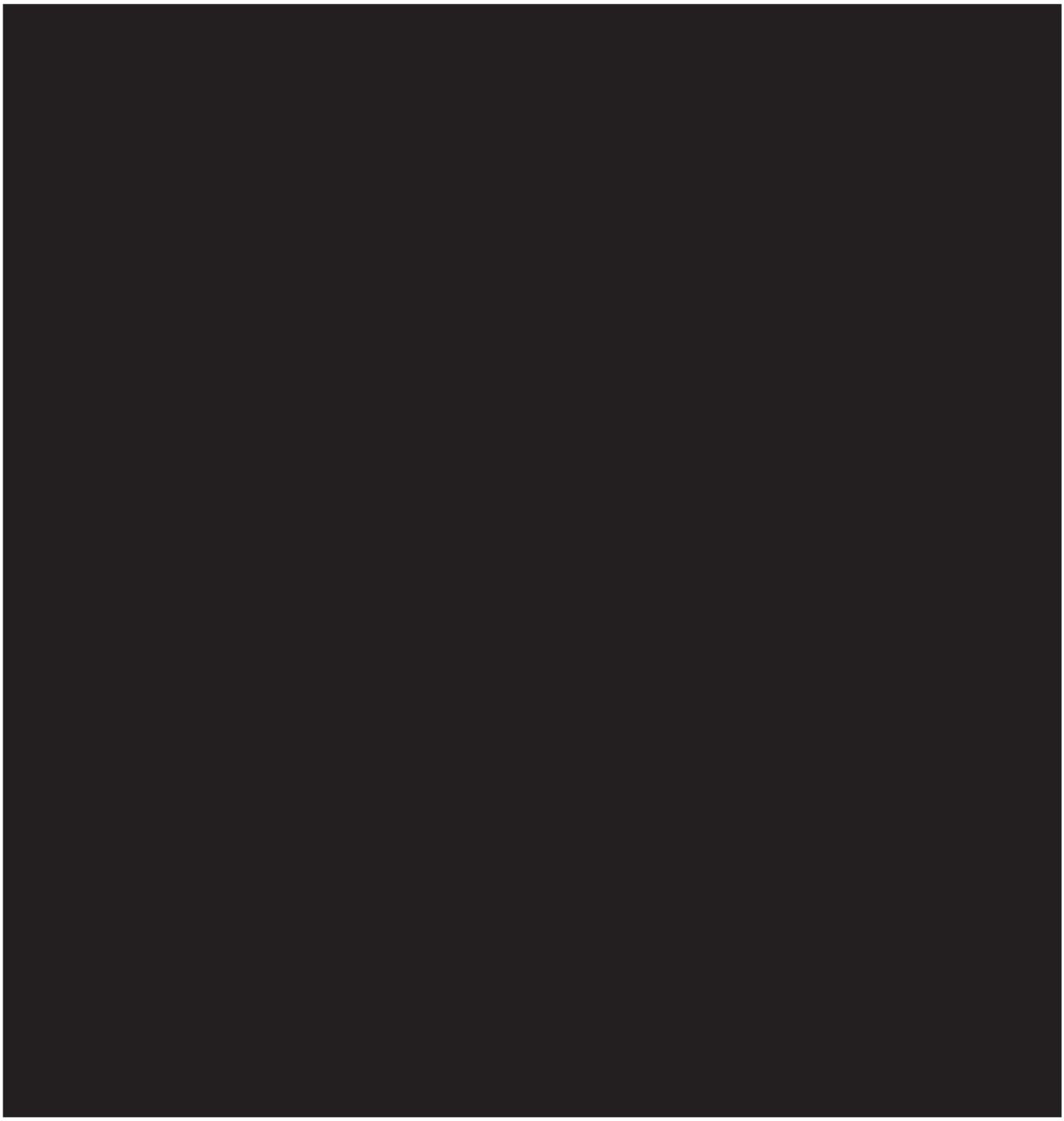
AGN-151586 is a BoNT/E product being developed for IM injections in the treatment of GL. Currently, this indication is commonly treated with BoNT/A products. AGN-151586 may offer a different treatment option to patients with its potential for faster onset of treatment effect. This study is designed to evaluate the tolerability and efficacy profiles of AGN-151586 for the

treatment of GL over a range of doses, and to fully characterize the onset and duration of treatment effect at various doses.

4.3. Justification for Dose

AGN-151586 was evaluated in humans in a Phase 2a GL study (EB001-GL201), which indicated that the dose range studied [redacted]. There were no SAEs, and only one TEAE of headache was considered by the investigator to be related to treatment. By investigator assessments, [redacted]. The responder rate for the primary endpoint of a ≥ 2-grade improvement from baseline at any time point was [redacted]

In addition to the GL study (Study EB001-GL201), 3 other clinical studies have been completed with AGN-151586 (EB001-SR201, EB001-MA201, and EB001-ABD201). In total, AGN-151586 has been evaluated in 103 participants at doses ranging from [redacted] (Table 4-1). Across these indications and dose ranges studied, there have been no reports of treatment-related SAEs, or discontinuations from the study due to treatment-related TEAEs. [redacted]



likely minimal and clinically relevant effective dose for treatment of moderate to severe GL. Data from this study will inform the dose selection for future clinical studies.

Following review of safety and efficacy data at each cohort review, the DMC may recommend proceeding with the nominal dose for the next cohort, request additional data (eg, data from additional participants in the cohort, data from visits after Day 14), request to repeat the current dose or a lower dose, request an intermediate dose be evaluated (between the dose of the current cohort and the nominal dose for the next cohort), or request dose escalation be terminated.

4.4. End of Study Definition

The end of the study is defined as the date of exit for the last participant in the study.

A participant is considered to have completed the study if he/she has completed all phases of the study (screening, randomization, follow-up) including the last visit.

5. Study Population

Adult participants with GL of moderate to severe rating at maximum frown, as assessed using the FWS by the investigator and participant.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age**
1.01	Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.
2.	**Type of Participant and Characteristics**
2.01	Moderate to severe GL at maximum frown (as assessed by the investigator and participant) at Screening and on Day 1 prior to study intervention administration using the FWS
2.02	Participants must have sufficient visual acuity without the use of eyeglasses (contact lens use acceptable) to accurately assess their facial lines, in the opinion of the investigator.
3.	**Sex**
3.01	Male or female
4.	**Contraceptives**
4.01	Female participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up period (at least 10 weeks after study intervention)
4.02	A female participant is eligible to participate if she is 1) not a WOCBP*, or 2) a WOCBP who is not pregnant (ie, has a negative pregnancy test at the Screening Visit and prior to randomization; see Appendix 7), is not breastfeeding, is not planning a pregnancy during the study, and agrees to follow the contraceptive guidance in Appendix 7 during the study and for at least 4 weeks after study completion (at least 10 weeks after administration of study intervention). *A woman is considered NOT to be of childbearing potential if she is premenarchal, postmenopausal (at least 12 consecutive months of amenorrhea), or surgically sterilized (eg, hysterectomy or bilateral oophorectomy).

4.03	Nonvasectomized male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the study and for at least 6 weeks after administration of study intervention: • Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent • Agree to use a male condom with spermicide plus partner use of a contraceptive method with a failure rate of < 1% per year as described in Appendix 7 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant In addition, nonvasectomized male participants must refrain from donating sperm for the duration of the study and for at least 6 weeks after study intervention. Nonvasectomized male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the study and for at least 6 weeks after administration of study intervention.
5.	**Informed Consent**
5.01	Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and this protocol
5.02	Written informed consent from the participant has been obtained prior to any study-related procedures
5.03	Written documentation has been obtained in accordance with the relevant local privacy requirements, where applicable.
6.	**Other**
6.01	Participants in good health as determined by medical history, physical examination, neurological assessment, clinical laboratory evaluations, ECG, vital signs, and investigator's judgment
6.02	Ability to follow study instructions, including completing study assessment tools without any assistance or alteration to the assessment tools and likely to complete all required visits

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	Medical Conditions
1.01	Any condition that precludes a participant's ability to comply with study requirements, including completion of the study visits or inability to read, understand, and/or self-assess GL severity using the FWS
1.02	Known immunization or hypersensitivity to any botulinum neurotoxin serotype
1.03	Known allergy or sensitivity to any of the components of the study interventions or any materials used in the study procedures
1.04	Any medical condition that may put the participant at increased risk with exposure to AGN-151586, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with neuromuscular function
1.05	Any history of significant cardiovascular disease, family history of long QT syndrome, or a clinically significant ECG abnormality at the Screening Visit
1.06	Marked facial asymmetry, dermatochalasis, deep dermal scarring, excessively thick sebaceous skin, or the inability to substantially lessen facial lines even by physically spreading them apart, as determined by the investigator
1.07	Any brow or eyelid ptosis, as determined by the investigator
1.08	Infection or skin disorder at the injection sites
1.09	History of facial nerve palsy
1.10	Any uncontrolled systemic disease
1.11	Any medical condition that, in the opinion of the investigator, puts the participant at undue safety risk
1.12	History of alcohol or drug abuse within 3 months of randomization based on the investigator's judgment
1.13	Anticipated need for treatment with botulinum neurotoxin of any serotype for any reason during the study (other than study intervention)
1.14	Anticipated need for surgery or overnight hospitalization during the study

2.	**Prior/Concomitant Therapy**
2.01	Reported use of any botulinum neurotoxin of any serotype for aesthetic treatment within the last 6 months prior to screening and for therapeutic treatment within the last 12 months prior to screening.
2.02	Any of the following procedures or treatments occurring in the specified period before randomization (Day 1): 3 months: any facial nonablative resurfacing laser, light or ultrasound treatment, microdermabrasion, monopolar radiofrequency, or superficial peels 6 months: any facial cosmetic procedure with medium depth or deep depth chemical peels (eg, TCA and phenol); periorbital, mid-facial, or upper-facial skin resurfacing; or permanent make-up in the mid-facial (extending from inferior orbital margin to level of the nasal base) or upper facial areas 12 months: any periorbital, mid-facial, or upper-facial treatment with nonpermanent soft tissue fillers
2.03	Participants on topical retinoid therapy and/or topical hormone cream applied to the face, who have not been on a consistent dose regimen for at least 6 months before randomization and who are unable to maintain the same regimen for the study
2.04	Participants on oral retinoid therapy within 1 year before study enrollment
2.05	Prior periorbital surgery, facial lift (full face or mid-face), thread lift, brow lift, or related procedures (eg, eyelid [blepharoplasty] and/or eyebrow surgery)
2.06	Prior facial treatment with permanent soft tissue fillers, synthetic implantation (eg, Gore-Tex®), and/or autologous fat transplantation
3.	**Prior/Concurrent Clinical Study Experience**
3.01	Current enrollment in an investigational drug or device study or participation in such a study within 30 days of Screening
4.	**Other**
4.01	Participants who plan for an extended absence away from the immediate area of the study site that would preclude them from returning for all protocol-specified study visits
4.02	Participants who, in the investigator's opinion, are unable or unwilling to maintain their standardized skin care regimen throughout the study period

4.03	Participants who have tattoos, jewelry, or clothing which obscure the target area of interest and cannot be removed
4.04	Participants who are directly or indirectly involved in the conduct and administration of this study as a principal investigator, subinvestigator, study coordinator, or other study staff member; or employee of the sponsor, or a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study
4.05	The participant has a condition or is in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with participation in the study.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes indicating screen failure as reason for ending the study, demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the eligibility criteria for participation in this study (screen failures) may be allowed to be rescreened. Rescreening of participants must only occur after discussion with the sponsor. Rescreened participants must be assigned new participant identification numbers. Rescreening can only occur once for any given potential participant.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

The current study does not allow retreatment of study intervention. In this protocol, the study intervention is AGN-151586 or placebo administered to a study participant.

6.1. Study Interventions Administered

Study Intervention Name	AGN-151586	Placebo
Dosage Formulation	Sterile injectable solution	
Concentration/Injection	Cohort 1 [redacted] per 0.1 mL Cohort 2 [redacted] per 0.1 mL Cohort 3 [redacted] per 0.1 mL Cohort 4 [redacted] per 0.1 mL Cohort 5 [redacted] per 0.1 mL	Cohort 1 (0 U): 0 U per 0.1 mL Cohort 2 (0 U): 0 U per 0.1 mL Cohort 3 (0 U): 0 U per 0.1 mL Cohort 4 (0 U): 0 U per 0.1 mL Cohort 5 (0 U): 0 U per 0.1 mL
Volume per Intervention	[redacted]	
Route of Administration	IM	
Number of Injection Sites	5 (1 in the procerus, 2 in each of the bilateral corrugators)	
Dose	[redacted]	0 U
Packaging and Labeling	Study intervention will be provided in identical appearing vials. Each vial will be labeled as required per US FDA requirement.	
Blinding	Study intervention will be provided in identical appearing vials.	
Number and Timing of Interventions	Single double-blind study intervention on Day 1	

AGN-151586 and placebo are supplied in [redacted] fill volume, and the concentration of AGN-151586 in the supplied vial is [redacted] Step-wise dilution is required to approximate the nominal doses for each cohort. The step-wise dilution may lead to slight variations between the nominal dose and the actual dose in some cohorts. Further information can be found in the study manual.

6.1.1. Study Supplies

The following will be provided by the sponsor:

- Study intervention
- Syringe labels
- Mirror for participant assessment of FWS
- Facial Wrinkle Scale with Photonumeric Guide (investigator and participant versions)

- Photographic equipment (including headbands and drapes) will be provided by a qualified third-party vendor
- Laboratory sample kits (for immunogenicity, hematology/chemistry, and urine sampling) will be provided by a qualified third-party vendor
- Electrocardiogram equipment and supplies will be provided by a qualified third-party vendor
- Tablets for electronic FWS and COA administration will be provided by a qualified third-party vendor

The following will be provided by the investigator:

- Urine pregnancy test kits (sensitivity of 25 mIU/mL)
- Cotton pads and make-up remover
- Appropriately sized (recommended size: 1.5 inch) 21-gauge sterile needles fitted to 1 mL sterile syringes with 0.01 mL demarcations for extraction of study intervention and diluent from vials
- Half-inch 30-gauge sterile needles fitted to 1 mL sterile syringes with 0.01 mL demarcations for study intervention injection
- Alcohol wipes
- Protective gloves
- Paper towel and aluminium foil
- Penlight
- Covered container for medical waste (Sharps box)
- [redacted]
- Freezer that does not automatically defrost to store blood samples at −20°C or colder.
- Centrifuge for separation of serum
- Internet connection (high speed connection for eCRF completion)
- Monitor with video playback from a USB port or with a video player (eg, laptop, USB media player) for viewing participant instructions

6.1.2. Instructions for Use and Administration

Only a qualified physician trained in the study-specific injection technique may administer study intervention.

Study intervention is administered as IM injections at 5 injection sites in the glabellar complex, 1 in the procerus and 2 in each corrugator muscle (Figure 6-1A).

Participants must be observed for adverse events for at least 30 minutes after study intervention injection.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the study manual.

6.4. Study Intervention Compliance

Participants will receive all doses under the direct supervision of study center personnel. Study intervention compliance will not be calculated because participants will receive all doses under the direct supervision of study center personnel.

The study site will keep an accurate drug disposition record that specifies the amount of study intervention administered to each participant and the date of administration.

6.5. Concomitant Therapy

Concomitant therapy and/or medications considered necessary for the study participant's welfare may be given at the discretion of the investigator.

The use of any medication during the study (including prescription or over-the-counter medication, vitamins, and/or herbal supplements) is to be recorded on the participant's eCRF at each visit along with the reason the medication is taken, dates of use, and dosing regimen.

Study site personnel must notify the sponsor immediately if a participant uses any concomitant medications not permitted by the protocol. Participants who admit to using prohibited concomitant medications may be discontinued from the study at the discretion of the investigator or sponsor.

6.5.1. Prohibited Interventions

The decision to administer a prohibited medication/treatment is done with the safety of the participant as the primary consideration. When possible, the sponsor must be notified before the prohibited medication/treatment is administered. Co-administration of aminoglycosides or agents that could interfere with neuromuscular transmission (eg, curare-like agents) or muscle relaxants must be used with caution as the effects of the toxin, theoretically, could be potentiated.

No other facial cosmetic procedures or treatments are to be performed throughout the duration of the study. Prohibited treatments and procedures include, but are not limited to:

- Oral retinoids
- New or changes to regimen of topical hormone cream to the face
- New or changes to regimen of topical retinoids to the face
- Microdermabrasion to the face
- Medium depth to deep facial chemical peels (ie, TCA and phenol)
- Energy-based facial treatments (eg, intense pulsed light, Clear + Brilliant®, monopolar radiofrequency, microfocused ultrasound)
- Facial lift (mid or full face)
- Blepharoplasty
- Synthetic implantation (eg, Gore-Tex) to the upper half of the face

- Autologous fat transplantation to the face
- Soft-tissue fillers to the face
- Permanent make-up to the face
- Concurrent treatment with botulinum neurotoxin of any serotype for any indication (other than the study intervention)

6.5.2. Permitted Interventions

Any medication (including prescription or over-the-counter medication, vaccines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration, including start and end dates
- Dosage information including dose, frequency, and route of administration

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/intervention is in question, please contact the sponsor.

The sponsor must be contacted if there are any questions regarding concomitant or prior therapy.

Any medication taken during the study between the date of the first dose of study intervention and the date of the end of study visit will be recorded in the eCRF as a concomitant medication; any medication started after the End-of-Study Visit will not be considered a concomitant medication and should not be captured in the eCRF.

6.5.3. Rescue Medicine

Not applicable.

6.6. Dose Modification

Any deviation from the planned doses are only at the request of the DMC. After review of safety and efficacy data, the DMC may recommend proceeding with the nominal dose for the next cohort, request additional data (eg, data from additional participants in the cohort, data from visits after Day 14), request to repeat the current dose or a lower dose, request an intermediate dose be evaluated (between the dose of the current cohort and the nominal dose for the next cohort), or request dose escalation be terminated.

6.7. Intervention after the End of the Study

No interventions after the end of study are planned.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and is dosed ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate case report form.

Definitions of the standard terms are provided in Appendix 5.

Reasons for discontinuation of the study intervention and/or from the study may include the following commonly used terms:

Commonly Used Terms
Adverse event
Completed
Lack of efficacy
Lost to follow-up
Other
Physician decision
Pregnancy[a]
Protocol deviation
Site terminated by sponsor
Study terminated by sponsor
Withdrawal by participant

[a] Women who test positive for urine pregnancy test prior to randomization will NOT receive study intervention and will be discontinued from the study.

7.1. Discontinuation of Study Intervention

If a participant does not tolerate study injections, the participant will be observed until the intolerability has either resolved or satisfactorily stabilized in the judgement of the investigator, and the participant may choose to exit the study or to remain in the study for all safety follow-up assessments through the End of Study Visit.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- Women who test positive for urine pregnancy test prior to randomization will NOT receive study intervention and will be discontinued from the study.

7.3. Lost to Follow Up

A participant 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 site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study for clinical laboratory and immunogenicity tests, including any extra assessments that may be required, will not exceed 250 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

[redacted]

[redacted]

[redacted]

8.1.3. Facial Photography

Standardized digital facial photography will be performed prior to injection of study intervention for all participants and at the times shown in the SoA (Section 1.3). Images will be taken of each participant's face from the front at rest and at maximum frown. Each site will receive documented training and instructions on taking photographs.

Conditions of photography will be standardized across all photographs, including camera equipment, exposure, background, lighting, and focal length. Ideally, the same photographer will take all required photographs. A qualified third-party vendor will provide instructions for taking photographs and processing digital photographs. All digital images will be transferred to the sponsor at the end of the study.

Photographs will be taken for research purposes, and may also be used for education, commercial, and/or marketing purposes. To participate in this study, the participant must consent to having photographs taken for research but may still participate if he/she declines use of the photographs for other purposes. The sponsor shall have full ownership rights to any photographs derived from the study.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1. Adverse Events

The investigator will question the participant to ascertain whether any adverse events were experienced since the previous visit. Additionally, the participants will be observed for at least 30 minutes following study intervention. All pertinent information regarding adverse events (ie, date of onset and stop date, duration, outcome, seriousness, severity, relationship to study intervention, treatment required, action taken with study intervention, etc) will be obtained and recorded in the source documents and appropriate eCRF page.

8.2.2. Physical Examinations

A full physical examination will be conducted at the Screening Visit and at the End-of-Study/Early Exit Visit and includes the assessment of general appearance, HEENT, heart/cardiovascular function, lungs, abdomen, extremities, back, musculoskeletal function, lymphatic function, neurologic function, and skin. *Abbreviated physical examinations* will be conducted throughout the study as described in the SoA and limited to an examination of general appearance, heart, lungs, and abdomen.

Before study intervention, if the physical examination finding is clinically significant, the finding must be captured in the medical history eCRF. After study intervention, if the pre-existing finding becomes worse and is clinically significant or the new physical examination finding is clinically significant, it must be captured as an adverse event in the adverse event eCRF.

8.2.3. Neurologic Assessment

The neurologic assessment comprises 2 elements, a Focused Symptoms Questionnaire and Focused Neurologic Examination that will be performed by trained physician investigators as described in the SOA. The neurologic assessment must be performed prior to randomization on Day 1, and is to be performed after adverse event assessment at all subsequent timepoints. See Appendix 8 for instructions for both elements.

Participants with any abnormal findings at Screening or Day 1 (prior to randomization), which meet exclusion criteria or may impact a participant's safety or the interpretation of efficacy, will be excluded from the study. For participants who meet the inclusion/exclusion criteria, images of the face at natural smile and at rest will be captured at Day 1 (prior to randomization) in order to document baseline gross facial symmetry. These images will be referenced for the Focused Neurologic Examination.

8.2.4. Vital Signs

Vital signs will be assessed as follows:

- Pulse rate (beats per minute): Participants are to be seated for at least 2 minutes, and pulse rate will be counted over 60 seconds and recorded in the source document and eCRF as beats per minute.
- Blood pressure (mm Hg): Participants are to be seated for at least 2 minutes, and systolic/diastolic blood pressure will be measured.

- Respiration rate (breaths per minute): Participants are to be seated for at least 2 minutes, and breaths will be counted for 30 seconds and multiplied by 2.
- When applicable, vital sign data will be collected prior to blood draws.
- Body temperature will be taken.

Before study intervention, if the vital sign finding is clinically significant, it must be captured in the medical history eCRF. After study intervention, if the pre-existing finding becomes worse and is clinically significant or the new vital sign finding is clinically significant, it must be captured as an adverse event in the adverse event eCRF.

8.2.5. Electrocardiograms

- All participants will undergo conventional 12-lead ECG using standardized equipment and electrode placement at the visits outlined in the SoA. Participants are to be in a semirecumbent position for at least 10 minutes prior to starting the tracing. During screening, a 12-lead ECG trace will be taken to assess entry eligibility.
- A qualified third-party vendor will read the ECGs and report the findings as normal, abnormal, or unable to evaluate.
- For screening ECGs, prespecified significant abnormal findings will be flagged as exclusion alerts, and a third-party vendor will generate an exclusion alert for the site and the sponsor. Exclusion alerts are considered exclusionary for study eligibility (see Exclusion Criterion 1.05 in Section 5.2 which excludes any participant with a 'clinically significant ECG abnormality at the Screening Visit'). For all subsequent ECGs, a qualified third-party vendor will also report the appearance of any new, prespecified significant abnormal findings and generate a protocol alert for the site and the sponsor.
- The cardiologists will be blinded to participant study intervention assignments. If the ECG finding is abnormal, they will specify the abnormality or give a diagnosis, whenever it is possible. Electrocardiogram reports will be provided to the investigator and the sponsor via a secure portal within 24 hours of screening and within 72 hours for all other visits.
- Before study intervention, if the ECG finding is clinically significant, it must be captured in the medical history eCRF. After study intervention, if the pre-existing finding becomes worse and is clinically significant or the new ECG finding is clinically significant, it must be captured as an adverse event in the adverse event eCRF. Hard copies of the ECG tracings will be kept in the study files at the investigator's site.
- The ECG will be assessed for the following: heart rate, QRS duration, QT interval, QTcB interval, QTcF interval, ST segment, RR interval, PR interval, and qualitative results.

8.2.6. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

- At screening, the investigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significant during participation in the study, including the End-of-Study/Early Exit Visit, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or MSP.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or adverse event or dose modification), then the results must be recorded in the eCRF.

8.2.7. Urine Pregnancy Test

Urine dipstick kits will be used to conduct pregnancy tests at the timepoints specified in the SoA, or more frequently at the investigator's discretion.

8.2.8. Suicidal Risk Monitoring

Suicidal risk monitoring is not applicable for this study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an adverse event or SAE can be found in Appendix 3.

Adverse events will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or SAE and remain responsible for following up adverse events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs and adverse events from the signing of the ICF will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention, but after obtaining informed consent will be recorded in the adverse event section of the eCRF and will be considered pretreatment adverse events.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of adverse events and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All adverse events/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the adverse event or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

- Details of all pregnancies, including pregnancy outcome, in female participants and consented female partners of male participants will be collected; pregnancies include those with onset after study intervention, and until 10 weeks after study intervention for female participants and until 6 weeks after study intervention for female partners of male participants.
- At each visit, site personnel must discuss with WOCBP and males with partners who are WOCBP compliance with contraceptive use.
- Urine pregnancy testing will be conducted for WOCBP at the Screening Visit, prior to randomization at Day 1, at the study exit visit, and at the discretion of the investigator. See Appendix 7 for detailed information on definition of WOCBP, use of contraceptives, and pregnancy.
- Women who test positive for urine pregnancy test prior to randomization will NOT receive treatment and will be discontinued from the study.
- If a pregnancy is confirmed after the participant has received study intervention, the participant may choose to exit the study after appropriate safety follow-up or remain in the study for all safety and efficacy follow-up assessments.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Abnormal pregnancy outcomes (eg, spontaneous or elective abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

8.3.6. Adverse Events of Special Interest

There are no AESIs for this study because they are not clinically indicated.

8.3.7. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study intervention
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant)

Medication errors include occurrences of overdose and underdose of the study intervention.

Overdose: Unintentional administration of a quantity of the study intervention given per administration that is above the maximum recommended dose according to the protocol for the study intervention. See Section 8.4 for information of treatment of overdose.

Underdose: Unintentional administration of a quantity of the study intervention given per administration that is under the minimum recommended dose according to the protocol.

8.4. Treatment of Overdose

Overdose of AGN-151586 is a relative term and depends upon dose, site of injection, and underlying tissue properties. Signs and symptoms of overdose are likely not to be apparent immediately postinjection. Excessive doses may produce local, or distant, generalized and profound neuromuscular paralysis.

Because AGN-151586 is administered as injections by physicians, for this study, the chance of overdose is extremely low. Should accidental injection occur or overdose be suspected, the participant should be medically monitored for up to several weeks for progressive signs or symptoms of systemic muscular weakness that could be local or distant from the site of injection, which may include ptosis, diplopia, dysphagia, dysarthria, generalized weakness, or respiratory failure. Eyelid ptosis, diplopia, or vision blurred are known local effects of BoNT/A during treatment of glabellar lines, which may also occur with BoNT/E. These participants should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

If the musculature of the oropharynx and esophagus is affected, aspiration may occur, which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of an overdose, the investigator should:

1. Contact the MSP immediately.
2. Closely monitor the participant for any AE/SAE.
3. Document the quantity of the excess dose in the eCRF.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

Immunogenicity Assessments

Validated assays will be used to assess the presence of antidrug antibodies to AGN-151586, using blood samples collected during the course of the study.

Blood samples for immunogenicity testing will be collected from each participant at Screening, and at the Day 7, Day 28, and End-of-Study visits. Collected samples (approximately 20 mL per sample) will be processed to yield serum for analysis.

Detection of binding antibodies against AGN-151586 in participants' serum will be carried out using the validated ELISA in a 3-tier format (screening, confirmation, and titering). Only samples that are confirmed positive in the confirmatory assay will be stored and analyzed for presence of neutralizing antibodies to AGN-151586 when a validated assay becomes available.

These samples may also be used for additional characterization of antibody response to other neurotoxin subtype(s). The findings from this exploratory analysis will be documented in the clinical study report or in a separate report. The ICF will contain a separate appendix that addresses the use of immunogenicity samples for this optional exploratory research. The investigator or his/her representative will explain to each participant that their participation is voluntary. With regards to using their blood samples for this exploratory characterization of antibody response to other neurotoxin subtype(s), participants may give consent, refuse to give consent, or may give consent and later withdraw their consent at any time and for any reason

during the storage period. A separate signature will be required to document a participant's agreement or refusal to allow specimens to be used for this exploratory research.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The following hypotheses will be used to compare each dose group of AGN-151586 with placebo:

- Null hypothesis: AGN-151586 and placebo are equally effective in the probability of reducing GL severity at maximum frown as measured by a ≥ 2-grade improvement from baseline based on the investigator-rated FWS at any posttreatment timepoint through Day 7.
- Alternative hypothesis: AGN-151586 and placebo are not equally effective in the probability of reducing GL severity at maximum frown as measured by a ≥ 2-grade improvement from baseline based on the investigator-rated FWS at any posttreatment timepoint through Day 7.

9.2. Sample Size Determination

For each cohort, there will be approximately 40 participants (AGN-151586: n = 30; placebo: n = 10) with a 3:1 randomization allocation; up to 5 dose cohorts are planned. For a cohort of 30 participants treated with AGN-151586, there is an approximately 60% chance of detecting an adverse event which occurs at a 3% incidence (eg, eyelid ptosis).

Approximately 200 participants will be randomized to have approximately 180 participants complete the study based on an anticipated dropout rate of 10%. Approximately 150 participants are expected to have a single dose exposure to AGN-151586 with an approximately 78% chance to detect any adverse event at a 1% incidence, and a 95% chance to detect any adverse event at a 2% incidence.

The primary efficacy analysis will be conducted on the mITT population, which consists of randomized participants who have been dosed and have a posttreatment measurement of investigator-rated FWS at maximum frown. A sample size of 40 participants per cohort will have approximately 87% power to detect a difference between an AGN-151586 dose group and the placebo group, assuming a 10% dropout rate and responder rates of 70% for the AGN-151586 study intervention group and 10% for the placebo group.

The calculation is based on a 2-sided Chi-squared test (Fisher's exact test) with a 0.05 significance level using nQuery Advisor version 7.0.

9.3. Populations for Analyses

For the efficacy analyses, the mITT population will be used and include all randomized participants who received study intervention and who had a posttreatment investigator-rated FWS measurement at maximum frown. The safety analysis will be performed using the safety population that includes all participants who received study intervention. All analyses will be performed on an as-treated basis.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and unblinding, and will describe the participant populations to be included in the analyses, along with procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and exploratory endpoints.

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Endpoints

The efficacy endpoint is the achievement of a ≥ 2-grade improvement from baseline on the FWS according to investigator assessments of GL severity at maximum frown at any postintervention timepoint through Day 7.

9.4.1.2. Primary Efficacy Analyses

The purpose of the primary analyses is to test for the primary endpoint, that is, the achievement of a ≥ 2-grade improvement in FWS according to investigator assessments of GL severity at maximum frown from Day 1 through Day 7 for each cohort. Safety will be assessed by the DMC.

- The purpose of the primary analyses will be to test for the primary endpoint (ie, at least a 2-grade improvement response from investigator) during any timepoint after study intervention administration through Day 7 for each AGN-151586 intervention dose group versus placebo group for each cohort. For example, if it is determined by the investigator-rated FWS that participants have at least a 2-grade improvement at any postintervention assessment through Day 7, they will meet the responder definition for each assessment timepoint this applies.
- The proportion of responders for the primary endpoint for each AGN-151586 study intervention group versus placebo will be analyzed using CMH tests stratified by baseline GL severity at maximum frown, using observed data without imputation or adjustment for multiplicity. In addition, 2-sided 95% CIs for the treatment differences in response rates will be provided. Between group comparisons will only be performed for each AGN-151586 group against the placebo group. Nominal p-values will be presented for each statistical test.
- Observed data without imputation will be used with stratification based on baseline GL severity for the primary analysis described above. In addition, sensitivity analyses of the primary efficacy variable will be performed to establish consistency and robustness and further characterize the extent of participants' responses (eg, missing as nonresponder). In addition, placebo groups across cohorts can be pooled to compare with each AGN-151586 group as a supportive analysis. Details will be provided in the SAP.

Baseline and posttreatment values will be summarized using descriptive statistics for the AGN-151586 dose groups and placebo group for each cohort at each assessment timepoint. Details will be provided in the SAP.

[redacted]

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population and will be defined in the SAP. The safety parameters will include:

- Incidence of adverse events, including adverse event severity and causality as assessed by the investigator
- Change from baseline and values over time in clinical laboratory tests, physical examinations, vital signs, and ECGs

9.4.2.1. Adverse Events

An adverse event will be considered a TEAE if:

- The adverse event began on or after the date and time of the study intervention; or
- The adverse event was present before the date and time of the study intervention, but increased in severity or became serious on or after the date and time of the study intervention.

An adverse event that occurs after the End-of-Study Visit (Day 42) will not be counted as a TEAE.

An adverse event will be considered a TESAE if it is a TEAE that additionally meets any SAE criteria.

The number and percentage of participants reporting TEAEs in each study intervention group will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity.

The number and percentage of participants reporting treatment-related TEAEs in each study intervention group will be tabulated by system organ class and preferred term.

If more than 1 adverse event is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summaries by severity and causality.

The causality and severity of all adverse events will be assessed by the investigator.

The number and percentage of participants reporting TEAEs that are included in the PDSOT term list will be tabulated by study intervention group. The PDSOT term list will be included in the SAP.

Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to discontinuation if 5 or more participants reported such events. Listings of all adverse events, SAEs, and adverse events leading to discontinuation by participant will be presented.

The definitions of an adverse event and SAE can be found in Appendix 3.

9.4.2.2. Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline (screening) and changes from baseline at each assessment will be presented by study intervention for each clinical laboratory assessment.

The criteria for PCS laboratory values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by study intervention at each assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.4.2.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressure, pulse rate, respiration rate, body temperature) at baseline prior to receiving study intervention (or screening value just prior to baseline if baseline values are not available) and changes from baseline at each assessment will be presented by study intervention.

The criteria for PCS vital signs will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline vital signs will be tabulated by study intervention at each assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.4.2.4. Electrocardiograms

Electrocardiogram evaluations by investigators are captured in the eCRF and are classified into 3 categories: normal, abnormal, or not evaluable. These data will be summarized by study intervention group as the number and percent of participants in each category at each visit. Data listings which include ECG basic parameters and any ECG abnormalities will be produced.

9.4.3. Other Analyses

9.4.3.1. Immunogenicity Analyses

Immunogenicity results, manifested as the presence of binding antibodies, and neutralizing antibodies if a validated assay becomes available, to AGN-151586, will be summarized in a table

and reported for each sampling timepoint. Additional immunogenicity exploratory analyses may be performed; results will be summarized in the clinical study report or in a separate report.

9.5. Interim Analyses

No interim analysis is planned.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH/ISO Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are not required to sign a new ICF if rescreening occurs within 30 days of first signing the ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Posting Clinical Study Data

- Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of the sponsor.
- Clinical study reports, safety updates, and annual reports will be provided to regulatory authorities as required.
- Company-sponsored study information and tabular study results will be posted on the US National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is

responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.
- Definition of what constitutes source data can be found in Section 4.0 of ICH E6, Good Clinical Practice: Consolidated Guidance and must follow ALCOA, ie, records must be attributable, legible, contemporaneous, original, and accurate.
- All study photographs will be uploaded to a secure server via the internet. Secure digital cards will remain at the site and serve as the source documentation for subject photographs.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.9. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. The use of the data collected for the participant will be discussed to determine if the data are to be included in the analysis. The investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1 Protocol-Required Safety Laboratory Assessments[a]

Serum Chemistry	**Hematology**
Total bilirubin	Hemoglobin
AST (SGOT)	Hematocrit (PCV)
ALT (SGPT)	RBC count
GGT	MCV
LDH	RDW
Alkaline phosphatase	MCH
Total protein	MCHC
Albumin	WBC count and differential[c]
Calcium	- Neutrophil count
Creatinine	- Lymphocyte count
BUN	- Monocyte count
Sodium	- Basophil count
Potassium	- Eosinophil count
Bicarbonate	Platelet count
Chloride	
Inorganic phosphate	**Urinalysis**
Uric acid	Color
Glucose	Appearance
Magnesium	pH
	Specific gravity
Other	Glucose
Urine pregnancy[b]	Protein
	Ketone
	Blood
	Urine microscopy[d]

ALT = alanine aminotransferase (= serum glutamic pyruvic transaminase [SGPT]); AST = aspartate aminotransferase (= serum glutamic oxaloacetic transaminase [SGOT]); BUN = blood urea nitrogen; GGT = γglutamyl- transferase; LDH = lactate dehydrogenase; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration; MCV = mean (red) cell volume; PCV = packed cell volume; RBC = red blood cell; RDW = red (cell) distribution width; WBC = white blood cell (leukocyte)

[a] Laboratory samples for hematology, chemistry, and urinalysis testing will be collected under random conditions; participants do not need to be fasting.

[b] Urine pregnancy tests are performed only in females of childbearing potential and must be conducted at the investigational site.

[c] Differential count to be provided as absolute counts for neutrophils, lymphocytes, monocytes, basophils, and eosinophils (rather than as percentages of WBC)

[d] Crystals, casts, RBC, WBC, bacteria

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. **AE of Special Interest (AESI)** There are no AESIs in this study.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease); for example: o The test result is associated with accompanying symptoms, and/or o The test result requires additional diagnostic testing or medical/surgical intervention, and/or o The test result leads to a discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or o The test result is considered to be an AE by the investigator or sponsor. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.
- The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE or SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity/Severity

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment. • For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting of SAEs

SAE Reporting
• Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@allergan.com. • Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295). • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE form, sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the protocol title page.

10.4. Appendix 4: Abbreviations

AESI	adverse event of special interest
AUC	area under the curve
AUC_{12-96}	area under the curve over the period of 12 to 96 hours post-surgery
AUC_{16-96}	area under the curve over the period of 16 to 96 hours post-surgery
BoNT/A	Botulinum Neurotoxin Serotype A
BoNT/E	Botulinum Neurotoxin Serotype E
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
COA	clinical outcome assessment
CONSORT	Consolidated Standards of Reporting Trials
DAS	digital abduction score
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
[redacted]	[redacted]
[redacted]	[redacted]ire
FWS	Facial Wrinkle Scale With Photonumeric Guide
FWS-IA	Facial Wrinkle Scale – Investigator Assessment
GCP	Good Clinical Practice
GL	glabellar lines
HEENT	head, eyes, ear, nose, and throat
IB	investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF	informed consent form
IEC	independent ethics committee
IM	intramuscular

IR-2	Investigator assessment of a 2-grade improvement (reduction) from baseline in GL severity
IRB	institutional review board
ISO	International Organization for Standardization
IWRS	interactive web response system
LCL	lateral canthal lines
mITT	modified intent-to-treat
MSP	medical safety physician
NOAEL	no-observed-adverse-effect level
[redacted]	[redacted]
PCS	potentially clinically significant
PDSOT	possible distant spread of toxin
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
SI	Le Système International d'Unités (International System of Units)
SoA	schedule of assessments
SUSAR	serious adverse reactions
TCA	trichloroacetic acid
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
USB	universal serial bus
VAS	Visual Analog Scale
WOCBP	woman of childbearing potential

10.5. Appendix 5: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Disease relapse	The return of a disease after a period of remission
Failure to meet randomization criteria	An indication that the participant has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a participant to follow-up
Non-compliance with study drug	An indication that a participant has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion or judgment reached after consideration by a physician with reference to participant (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Progressive disease	A disease process that is increasing in extent or severity (NCI)

CDISC Submission Value	CDISC Definition
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Recovery	A healing process and/or an outcome implying relative health. The term is typically used in the context of direct and indirect effects of sickness or injury. (NCI)
Screen failure	The potential participant who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by parent/guardian	An indication that a study participant has been removed from the study by the parent or legal guardian
Withdrawal by participant	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	A Phase 2b Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of AGN-151586 in Participants With Moderate to Severe Glabellar Lines
	Clinical Study Sponsor	Allergan Sales LLC
	Trial Phase Classification	Phase 2b
	Trial Indication	Glabellar lines
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	72 days (from the Screening to Day 42 visits)
	Planned Country of Investigational Sites	United States
	Planned Number of Participants	200
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	No
Participant information	Diagnosis Group	Presence of GL of moderate to severe rating at maximum frown
	Healthy Participant Indicator	No
	Planned Minimum Age of Participants	18
	Planned Maximum Age of Participants	65
	Sex of Participants	Male or Female
	Stable Disease Minimum Duration	Not applicable

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	AGN-151586 (Botulinum Neurotoxin Serotype E)
	Intervention Type	Drug
	Pharmacological Class of Invest. Therapy	Botulinum Neurotoxin Serotype E
	Dose per Administration	Cohort 1: [redacted] Cohort 2: Cohort 3: Cohort 4: Cohort 5:
	Dose Units	U
	Dosing Frequency	Single treatment
	Route of Administration	Intramuscular
	Current Therapy or Treatment	Not applicable
	Added on to Existing Treatments	No
	Control Type	Placebo
	Comparative Treatment Name	Not applicable
Trial design	Study Type	Interventional
	Intervention Model	Dose-ranging
	Planned Number of Arms	2 per Cohort
	Trial is Randomized	Yes, [redacted]
	Randomization Quotient	3:1
	Trial Blinding Schema	Double blind
	Stratification Factor	Glabellar lines severity, investigator-assessed at baseline
	Adaptive Design	No
	Study Stop Rules	Data monitoring committee

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Male Participants

Nonvasectomized male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the study and for at least 6 weeks after administration of study intervention:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

- Agree to use a male condom with spermicide plus partner use of a contraceptive method with a failure rate of < 1% per year as described in Table 10-2 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

In addition, nonvasectomized male participants must refrain from donating sperm for the duration of the study and for at least 6 weeks after study intervention.

Nonvasectomized male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the study and for at least 6 weeks after administration of study intervention.

[redacted]

Pregnancy Testing:

- Pregnancy testing will be performed according to instructions provided in the pregnancy test kit.
- WOCBP should only be included after a confirmed menstrual period and a negative urine pregnancy test at Day 1.
- Additional pregnancy testing is not required during the study other than at the End-of-Study/Early Exit Visit.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected at the discretion of the investigator.

Collection of Pregnancy Information:

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an adverse event or SAE, any pregnancy complication will be reported as an adverse event or SAE. A spontaneous or elective abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participants who becomes pregnant while participating in the study after receiving study intervention may choose to exit the study after appropriate safety follow-up or remain in the study for all safety and efficacy follow-up assessments.

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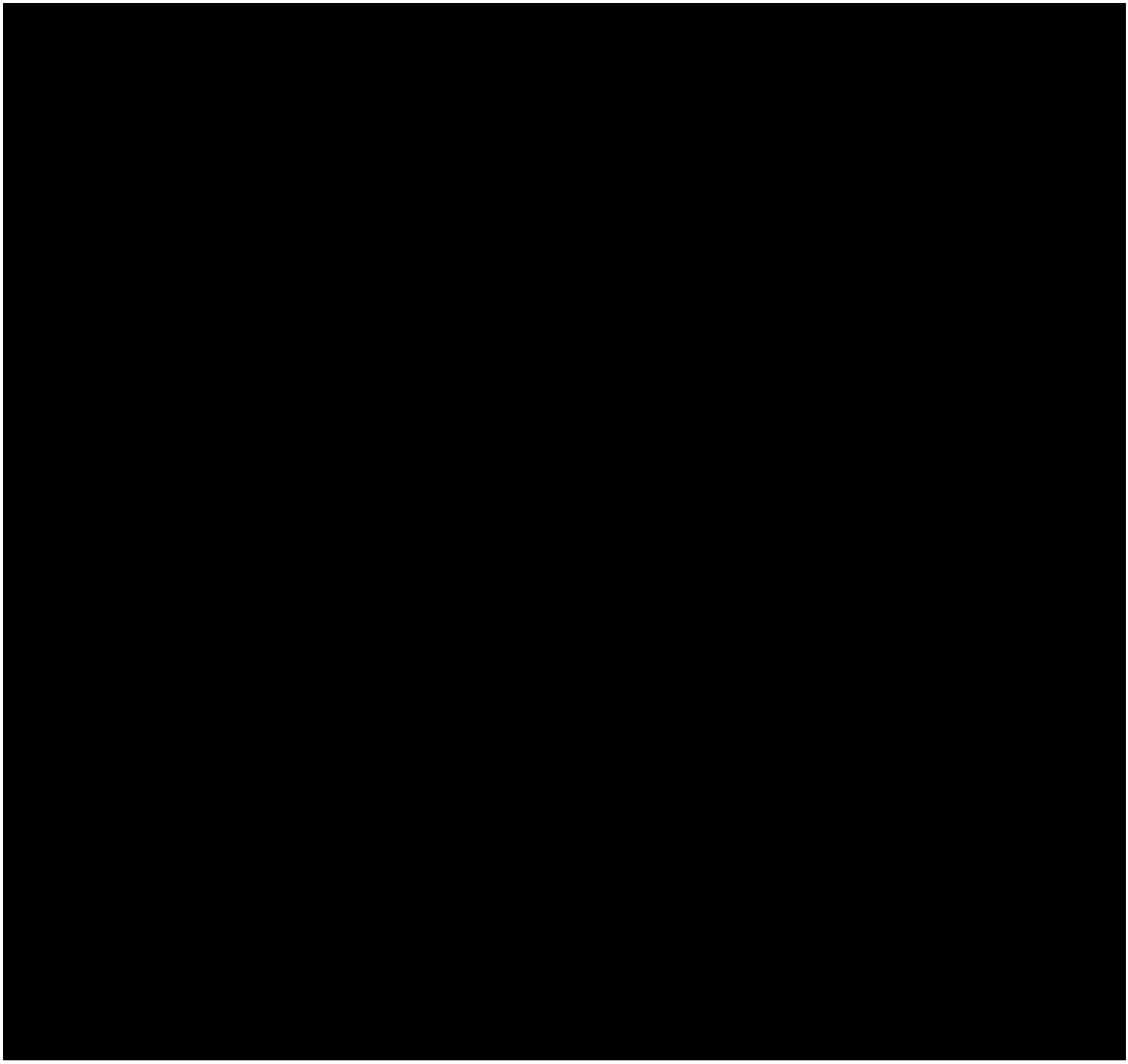

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