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Protocol for Study M21-500

Medical Aesthetics: A Phase 3, Multicenter Study to Evaluate the Safety and Efficacy of AGN-151586 for the Treatment of Glabellar Lines

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1 SYNOPSIS

Title: A Phase 3, Multicenter Study to Evaluate the Safety and Efficacy of AGN-151586 for the Treatment of Glabellar Lines	
Background and Rationale:	AGN-151586 is an investigational product being developed for the treatment of glabellar lines (GL). AGN-151586 offers the potential for faster onset of efficacy compared with the Botulinum Neurotoxin Serotype A (BoNT/A) products. The rationale for the use of AGN-151586 to treat GL is the same as that for BoNT/A in that by inhibiting the release of the neurotransmitter acetylcholine at peripheral cholinergic nerve endings, the overactivity of the muscles responsible for these lines can be reduced, thus eliminating or diminishing the appearance of GL.
Objectives and Endpoints:	The objective of this pivotal study is to evaluate the safety and efficacy of AGN-151586 for the treatment of GL in subjects with moderate to severe GL. **Primary Efficacy Endpoints** For US FDA: Composite: • ≥ 2-grade improvement from baseline on the Facial Wrinkle Scale (FWS) according to both **investigator and subject assessments** of GL severity at maximum frown at Day 7 For EU regulatory agencies: Coprimary: • ≥ 2-grade improvement from baseline on the FWS according to **subject assessment** of GL severity at maximum frown at Day 7 • ≥ 2-grade improvement from baseline on the FWS according to **investigator assessment** of GL severity at maximum frown at Day 7 **Secondary Efficacy Endpoints** For US FDA: a. Key secondary endpoint: ≥ 2-grade improvement from baseline on the FWS according to **investigator assessment** of GL severity at maximum frown over time (double-blind period)* b. Key secondary endpoint: ≥ 2-grade improvement from baseline on the FWS according to **subject assessment** of GL severity at maximum frown over time (double-blind period)* c. *Mostly satisfied* or *Very satisfied* on the Facial Line Satisfaction Questionnaire (FLSQ) follow-up version Item 5 (overall satisfaction) for GL at Day 7 d. *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) for GL at Hour 24 e. *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version

	Item 4 (natural look) for GL at Day 7 For EU Regulatory Agencies: a. Key secondary endpoint: ≥ 20-point improvement from baseline in 11-item Facial Line Outcomes (FLO-11©) total scores for GL at Day 7 b. ≥ 2-grade improvement from baseline on the FWS according to **subject assessment** of GL severity at maximum frown at Hour 24 c. ≥ 2-grade improvement from baseline on the FWS according to **investigator assessment** of GL severity at maximum frown at Hour 24 d. ≥ 1-grade improvement from baseline on the FWS according to **subject assessment** of GL severity at maximum frown at Hour 24 e. ≥ 1-grade improvement from baseline on the FWS according to **investigator assessment** of GL severity at maximum frown at Hour 24 f. *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) for GL at Hour 24 g. *Mostly satisfied or Very satisfied* on the FLSQ follow-up version Item 4 (natural look) for GL at Day 7 h. Time to the first ≥ 1-grade improvement from baseline on the FWS according to **subject assessments** of GL severity at maximum frown (double-blind period)* i. Time to the first ≥ 1-grade improvement from baseline on the FWS according to **investigator assessments** of GL severity at maximum frown (double-blind period)* j. ≥ 2-grade improvement from baseline on the FWS according to **subject assessments** of GL severity at maximum frown over time (double-blind period)* k. ≥ 2-grade improvement from baseline on the FWS according to **investigator assessments** of GL severity at maximum frown over time (double-blind period)* l. Time to return to baseline FWS according to **subject assessments** of FWS at maximum frown (double-blind period)* m. Time to return to baseline FWS according to **investigator assessments** of FWS at maximum frown (double-blind period)* n. *Mostly satisfied or Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) for GL over time* o. ≥ 4-point improvement from baseline in FLO-11 Item 10 (look angry) for GL at Day 7 p. ≥ 4-point improvement from baseline in FLO-11 Item 5 (look less attractive) for GL at Day 7 q. Subject-reported global assessment of change in GL based on

	the Global Assessment of Change in Glabellar Lines (GAC-GL) over time* * Endpoints will be excluded from hierarchical testing **Safety Endpoints:** • Incidence of adverse events (including any abnormality found during neurological assessment and physical examination) • Change from baseline in vital sign parameters • Change from baseline in ECG parameters • Change from baseline in laboratory evaluations (hematology and chemistry) • Presence of binding and neutralizing antidrug antibodies
Investigators:	Multicenter
Study Sites:	Approximately 38 sites
Study Population and Number of Subjects to be Enrolled:	Approximately 600 healthy subjects with moderate to severe GL will be enrolled. Enrollment will be approximately balanced for moderate and severe GL severity at maximum frown. At least 60% of subjects will be enrolled with a baseline FLO-11 questionnaire transformed total score ≤50.
Investigational Plan:	This is a 12-week, multicenter, Phase 3 study designed to evaluate the safety and efficacy of AGN-151586 treatment in adult subjects with moderate to severe GL. Eligible subjects will receive 1 double-blind treatment of either AGN-151586 or placebo on Baseline Day 1 and, if they meet retreatment criteria, 1 open-label treatment with AGN-151586 at Day 43.
Key Eligibility Criteria:	Adult male or female, ≥ 18 years of age, having moderate or severe GL at maximum frown (as assessed by the evaluating investigator and subject using the FWS at Screening and Baseline Day 1). The investigator and subject ratings must match within a visit but do not have to match between Screening and Baseline Day 1.
Study Drug and Duration of Treatment:	Based upon randomization, on Baseline Day 1, subjects will receive either [redacted] AGN-151586 or placebo (3:1 randomization ratio) administered as 5 intramuscular injections in the glabellar complex. Randomization will be stratified by investigator site, toxin use history (for aesthetic purpose), and baseline GL severity at maximum frown (the scores from the investigator and subject must match on Baseline Day 1 per eligibility criteria). Based on meeting the retreatment criteria, subjects may also receive an open-label treatment with [redacted] of AGN-151586 on Day 43.
Date of Protocol Synopsis:	01 August 2022

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

AGN-151586 is an investigational product being developed for the treatment of glabellar lines (GL). Facial lines that develop from repeated facial expression, such as GL, are typically treated by selectively weakening specific muscles with small quantities of botulinum toxin.[1-5] Botulinum toxins reversibly block presynaptic acetylcholine release at the neuromuscular or neuroglandular junction.

There are 8 antigenically-distinct botulinum neurotoxin serotypes (A, B, C1, D, E, F, G, and H) that are similar in structure and action and produced by different strains of the anaerobic bacterium *Clostridium botulinum*. Botulinum Neurotoxin Serotype A (BoNT/A) is popular as a cosmetic treatment of GL in adults due to its proven efficacy for reducing moderate to severe facial lines,[6] well documented safety profile,[7] and positive impact on psychological well-being and the resulting psychosocial benefits.[8]

Botulinum Neurotoxin Serotype E is the active ingredient of AGN-151586. The rationale for the use of AGN-151586 to treat GL is the same as that for BoNT/A in that by inhibiting the release of the neurotransmitter acetylcholine at peripheral cholinergic nerve endings,[9,10] the overactivity of the muscles responsible for these lines can be reduced, thus eliminating or diminishing the appearance of GL. AGN-151586 offers the potential for faster onset of efficacy compared with the BoNT/A products.[9] The purpose of this study is to evaluate the safety and efficacy of AGN-151586 for the treatment of GL in subjects with moderate to severe GL.

2.2 Benefits and Risks to Subjects

Allergan (an AbbVie company) completed 1 dose ranging study (Study 2034-201-008) to explore the safety and efficacy of single cycle treatments at doses ranging from [redacted] AGN-151586-specific units for the treatment of GL in adults. Units of biological activity of AGN-151586 cannot be converted to those of other neurotoxin products.

In this Phase 2b Study, a clinical dose response was observed, demonstrating that the proportion of responders (i.e., subjects having ≥ 2-grade improvement from baseline as assessed by investigator through Day 7) increased with increasing AGN-151586 dose. The responder rate was approximately 95% for the cohort dosed with [redacted] The overall incidence of study drug-related treatment-emergent adverse event (TEAEs) was similar between the placebo group (18.0%) compared with the AGN-151586 group (20.9%). There were no safety trends or patterns identified with increasing dose of AGN-151586. Overall, AGN-151586 had a favorable safety profile with [redacted] showing the most robust benefit and thus, [redacted] was selected for Phase 3 pivotal studies.

Based on the Phase 2b Study results, there are no known adverse drug reactions (ADRs) for AGN-151586. Since AGN-151586 is given as an intramuscular injection, injection site reactions (e.g., pain, bruising, swelling, etc.) are anticipated. In addition, the mechanism of action of AGN-151586 is similar to BOTOX and thus, adverse reactions associated with BOTOX, when injected into the glabellar

region, may also occur with AGN-151586. These ADRs include facial pain, facial paresis, eyelid ptosis, and muscular weakness.

The overall benefit:risk profile is anticipated to be favorable.

For further details, please see findings from completed studies, including safety data in the current AGN-151586 Investigator's Brochure.

Considering the coronavirus disease – 2019 (COVID-19) pandemic, and based on the information to date, no additional risk to study participants is anticipated with the use of AGN-151586. While AbbVie does not consider COVID-19 to be a safety concern for AGN-151586 or BOTOX due to their mechanism of action and route of administration, the marketing authorization holder is monitoring COVID-19 events during the pandemic closely. A recent review of COVID-19 events for the period of 01 January 2019 through 31 December 2021 did not identify any new or significant safety findings for the patients receiving BOTOX treatment with onabotulinumtoxinA-branded products (BOTOX, BOTOX Cosmetic, VISTABEL®, VISTABEX®, and BOTOX Vista 50®) or botulinum toxin type A products (in which the manufacturer was not identified). Overall, the clinical course and presentation of patients with COVID-19 infection coincident with onabotulinumtoxinA-branded products and botulinum toxin type A products is consistent with what has been described for the general population. The same results are expected with AGN-151586 since onabotulinumtoxinA-branded products, botulinum toxin type A products, and AGN-151586 have a similar mechanism of action.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Overall Objective

The objective of this pivotal study is to evaluate the safety and efficacy of AGN-151586 for the treatment of GL in subjects with moderate to severe GL.

The clinical hypotheses are:

- AGN-151586 is more effective than placebo in treating GL, as measured by both **investigator** and **subject assessments** of GL severity at maximum frown using the Facial Wrinkle Scale (FWS).
- AGN-151586 has an acceptable safety profile after single and repeat treatments.

Estimands: Primary Endpoints

The attributes of the estimands corresponding to the coprimary efficacy endpoints are summarized in Table 1. In addition, the attribute of treatment is a single dose of AGN-151586 or placebo.

Table 1. Summary of the Estimand Attributes of the Primary Efficacy Endpoints

Attributes of the Estimand				
Estimand Label	**Variable (Endpoint)**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Hypothetical estimand for composite primary endpoint (US FDA)	Achievement of at least a 2-grade improvement from baseline on the FWS according to both the investigator and subject assessments (composite) of GL severity at maximum frown on Day 7	Intent-to-treat (ITT) (all randomized)	Subjects who discontinue study prior to Day 7 assessments, or who do not have FWS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between AGN-151586 and placebo treatment groups; Cochran-Mantel-Haenszel (CMH) test [redacted]
Hypothetical estimand for coprimary endpoints (EU)	• Achievement of at least a 2-grade improvement from baseline on the FWS according to subject's assessment of GL severity at maximum frown at Day 7, and • Achievement of at least a 2-grade improvement from baseline on the FWS according to investigator's assessment of GL severity at maximum frown at Day 7	ITT	Subjects who discontinue study prior to Day 7 assessments, or who do not have FWS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between AGN-151586 and placebo treatment groups; CMH test [redacted]

CMH = Cochran-Mantel-Haenszel; Estimands = Secondary Endpoints; EU = European Union; FDA = Food and Drug Administration; FWS = Facial Wrinkle Scale; GL = glabellar lines; ITT = intent-to-treat; US = United States

Estimands: Secondary Endpoints

The attributes of the estimands corresponding to the secondary efficacy endpoints are summarized in Table 2. Treatment is the same as for the primary efficacy endpoints. For the US Food and Drug Administration (FDA) variables/endpoints, the population is the intent-to-treat (ITT) population (all randomized); for the European Union (EU) variables/endpoints, the population is also the ITT population. For the EU, subgroup analyses will be performed for the primary and key secondary endpoints for the ITT population that also has baseline 11 item Facial Line Outcomes (FLO-11) total scores ≤ 50. The variables/endpoints listed have the same handling of intercurrent events and statistical

summary (including population-level summary and analysis methods) within their respective analysis populations for the US FDA and EU, per estimand label.

Table 2. Summary of the Estimand Attributes of the Secondary Efficacy Endpoints

Estimand Label	Attributes of the Estimand		
	Variables (Endpoints)	**Handling of Intercurrent Events**	**Statistical Summary**
Hypothetical estimand for secondary categorical endpoints (US FDA and EU)	Key (US FDA): Achievement of at least a 2-grade improvement from baseline on the FWS according to investigator assessment of GL severity at maximum frown over time (double-blind period)*	Subjects who discontinue study in the double-blind period, or who do not have FWS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between AGN-151586 and placebo treatment groups at each time point; CMH test [redacted] Endpoints will be evaluated outside of the gated hierarchical testing.
Hypothetical estimand for secondary categorical endpoints (US FDA and EU)	Key (US FDA): Achievement of at least a 2-grade improvement from baseline on the FWS according to subject assessment of GL severity at maximum frown over time (double-blind period)*	Subjects who discontinue study in the double-blind period, or who do not have FWS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between AGN-151586 and placebo treatment groups at each time point; CMH test [redacted] Endpoints will be evaluated outside of the gated hierarchical testing.

Estimand Label	Attributes of the Estimand		
	Variables (Endpoints)	**Handling of Intercurrent Events**	**Statistical Summary**
Hypothetical estimand for secondary categorical endpoints (EU only)	• Achievement of at least a 2-grade improvement from baseline in GL severity at maximum frown based on subject assessment using FWS at Hour 24 • Achievement of at least a 2-grade improvement from baseline in GL severity at maximum frown based on investigator assessment using FWS Hour 24	Subjects who discontinue study prior to Hour 24 assessments, or who do not have FWS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between AGN-151586 and placebo treatment groups; CMH test [redacted] Gated hierarchical testing will be conducted.
Hypothetical estimand for secondary categorical endpoints (EU only)	• Achievement of at least a 1-grade improvement from baseline in GL severity at maximum frown based on subject assessment using FWS at Hour 24 Achievement of at least a 1-grade improvement from baseline in GL severity at maximum frown based on investigator assessment using FWS at Hour 24	Subjects who discontinue study prior to Hour 24 assessments, or who do not have FWS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between AGN-151586 and placebo treatment groups; CMH test [redacted] Gated hierarchical testing will be conducted.
Hypothetical estimand for secondary categorical endpoints (US FDA only)	• *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) for GL at Day 7	Subjects who discontinue study prior to Day 7 for the FLSQ follow-up assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between AGN-151586 and placebo treatment groups; CMH test [redacted] Gated hierarchical testing will be conducted.

Estimand Label	Attributes of the Estimand		
	Variables (Endpoints)	**Handling of Intercurrent Events**	**Statistical Summary**
Hypothetical estimand for secondary categorical endpoints (US FDA; EU)	• *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) for GL at Hour 24 • *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 4 (natural look) for GL at Day 7	Subjects who discontinue study prior to Hour 24 or Day 7 respective assessments for the FLSQ follow-up assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between AGN-151586 and placebo treatment groups; CMH test [redacted] Gated hierarchical testing will be conducted.
Hypothetical estimand for secondary categorical endpoints (EU)	*Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) for GL over time*	Subjects who discontinue study or who do not have FLSQ follow-up version Item 5 will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between AGN-151586 and placebo treatment groups at each time point; CMH test [redacted] Endpoints will be evaluated outside of the gated hierarchical testing.
Hypothetical estimand for secondary categorical endpoints (EU only)	• Key: Achievement of at least a 20-point improvement from baseline in FLO-11 total scores for GL at Day 7 • Achievement of at least a 4-point improvement from baseline in FLO-11 Item 10 (look angry) for GL at Day 7 • Achievement of at least a 4-point improvement from baseline in FLO-11 Item 5 (look less attractive) for GL at Day 7	Subjects who discontinue study prior to Day 7 assessments or who do not have FLO-11 Day 7 assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between AGN-151586 and placebo treatment groups; CMH test [redacted]. Gated hierarchical testing will be conducted.

Estimand Label	Attributes of the Estimand		
	Variables (Endpoints)	Handling of Intercurrent Events	Statistical Summary
Hypothetical estimand for secondary categorical endpoints (EU only)	• Subject-reported global assessment of change in GL based on the GAC-GL over time*	Subjects who discontinue study or who do not have the GAC-GL assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Responses and mean and their differences between AGN-151586 and placebo treatment groups at each time point; CMH test and ANOVA models [redacted] Endpoints will be evaluated outside of the gated hierarchical testing.
Hypothetical estimand for secondary continuous endpoints (EU only)	• Time to the first ≥1-grade improvement from baseline on the FWS according to subject assessment* • Time to the first ≥1-grade improvement from baseline on the FWS according to investigator assessment* • Time to return to baseline FWS according to subject assessment of FWS (double-blind period)* • Time to return to baseline FWS according to investigator assessment of FWS (double-blind period)*	Subjects who discontinue study or do not have FWS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	[redacted] Endpoints will be evaluated outside of the gated hierarchical testing.

ANOVA = analysis of variance; CMH = Cochran-Mantel-Haenszel; EU = European Union; FDA = Food and Drug Administration; FLO-11 = 11-item Facial Line Outcomes; FLSQ = Facial Line Satisfaction Questionnaire; FWS = Facial Wrinkle Scale; GAC-GL = Global Assessment of Change in Glabellar Lines; GL = Glabellar lines; US = United States

* Endpoints will be excluded from hierarchical testing.

3.2 Primary Endpoints

For US FDA, the primary composite endpoint is:

- ≥ 2-grade improvement from baseline on the FWS according to both **investigator and subject assessments** of GL severity at maximum frown at Day 7

For EU regulatory agencies, the coprimary endpoints are:

- ≥ 2-grade improvement from baseline on the FWS according to **subject assessment** of GL severity at maximum frown at Day 7
- ≥ 2-grade improvement from baseline on the FWS according to **investigator assessment** of GL severity at maximum frown at Day 7

3.3 Secondary Endpoints

For US FDA, the secondary endpoints are:

a. Key secondary endpoint: ≥ 2-grade improvement from baseline on the FWS according to **investigator assessment** of GL severity at maximum frown over time (double-blind period)*

b. Key secondary endpoint: ≥ 2-grade improvement from baseline on the FWS according to **subject assessment** of GL severity at maximum frown over time (double-blind period)*

c. *Mostly satisfied* or *Very satisfied* on the Facial Lines Satisfaction Questionnaire (FLSQ) follow-up version Item 5 (overall satisfaction) for GL at Day 7

d. *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) for GL at Hour 24

e. *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 4 (natural look) for GL at Day 7

For EU Regulatory Agencies, the secondary endpoints are:

a. Key secondary endpoint: ≥ 20-point improvement from baseline in FLO-11 total scores for GL at Day 7

b. ≥ 2-grade improvement from baseline on the FWS according to **subject assessment** of GL severity at maximum frown at Hour 24

c. ≥ 2-grade improvement from baseline on the FWS according to **investigator assessment** of GL severity at maximum frown at Hour 24

d. ≥ 1-grade improvement from baseline on FWS according to **subject assessment** of GL severity at maximum frown at Hour 24

e. ≥ 1-grade improvement from baseline on FWS according to **investigator assessment** of GL severity at maximum frown at Hour 24

f. *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) for GL at Hour 24

g. *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 4 (natural look) for GL at Day 7

h. Time to the first ≥ 1-grade improvement from baseline on the FWS according to **subject assessment** of GL severity at maximum frown (double-blind period)*

i. Time to the first ≥ 1-grade improvement from baseline on the FWS according to **investigator assessment** of GL severity at maximum frown (double-blind period)*

j. ≥ 2-grade improvement from baseline on the FWS according to **subject assessment** of GL severity at maximum frown over time (double-blind period)*

k. ≥ 2-grade improvement from baseline on the FWS according to **investigator assessment** of GL severity at maximum frown over time (double-blind period)*

l. Time to return to baseline FWS according to **subject assessment** of FWS at maximum frown (double-blind period)*

m. Time to return to baseline FWS according to **investigator assessment** of FWS at maximum frown (double-blind period)*

n. *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) for GL over time*

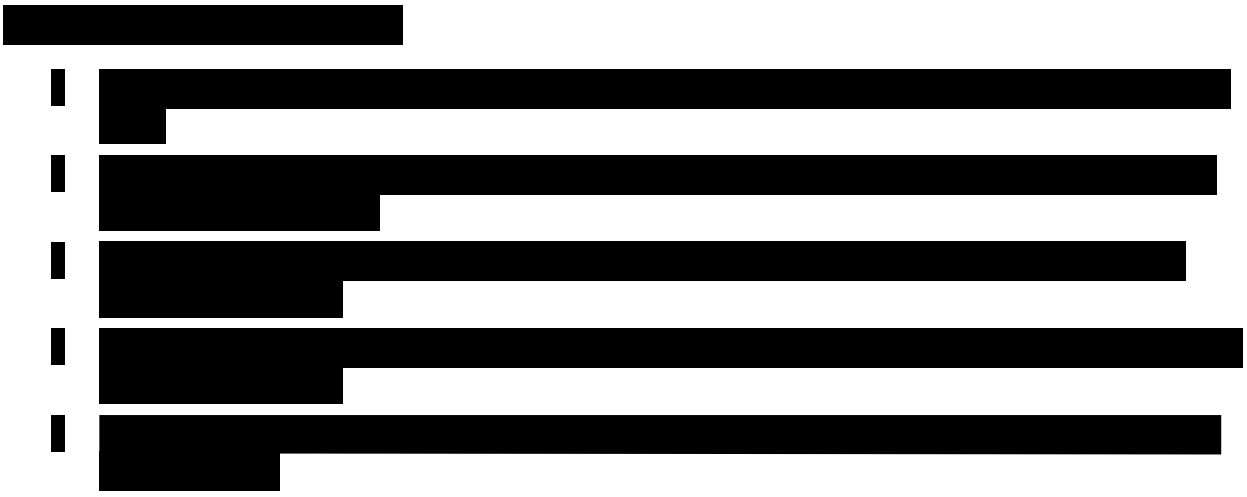
o. ≥ 4-point improvement from baseline in FLO-11 Item 10 (look angry) for GL at Day 7

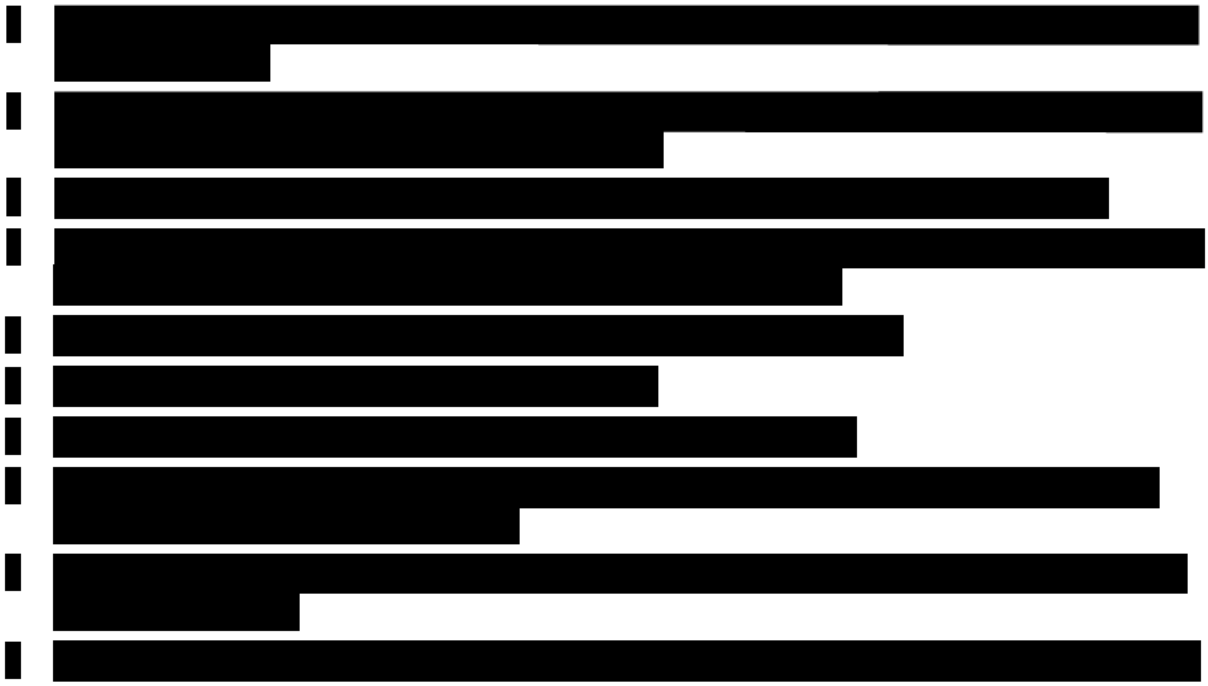
p. ≥ 4-point improvement from baseline in FLO-11 Item 5 (look less attractive) for GL at Day 7

q. Subject-reported global assessment of change in GL based on the Global Assessment of Change in Glabellar Lines (GAC-GL) over time*

* Endpoints will be evaluated outside of the gated hierarchical testing.

3.4 Additional Efficacy Endpoints





3.5 Safety Endpoints

Safety evaluations include adverse event (AE) monitoring, vital sign measurements, 12-lead electrocardiogram (ECG) collection, laboratory evaluations (hematology and chemistry), neurological assessment (examination to consist of assessment of cranial nerves II through VII), and physical examinations as measures of safety. The safety endpoints are:

- Incidence of AEs (including any abnormality found during neurological assessment and physical examination)
- Change from baseline in vital sign parameters
- Change from baseline in ECG parameters
- Change from baseline in laboratory evaluations (hematology and chemistry)
- Presence of binding and neutralizing antidrug antibodies (see Section 3.6 for more details)

3.6 Immunogenicity Assessment

Blood samples for immunogenicity testing will be collected from all subjects according to the Study Activities Table (Appendix D). Collected samples will be processed to yield serum for detection of binding and neutralizing antibodies to AGN-151586 and may also be used for additional characterization of antibody response to other neurotoxin subtypes.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a 12-week, multicenter, Phase 3 study designed to evaluate the safety and efficacy of AGN-151586 in treating GL. Subjects are adults (≥ 18 years of age) with moderate to severe GL at maximum frown as assessed independently by both the investigator and subject using the FWS. The investigator and subject ratings for GL will be done at the Screening Visit and at the Baseline Day 1 Visit. The investigator and subject ratings must match within a visit but do not have to match between Screening and Baseline Day 1. Each eligible subject may receive up to 2 study treatments with AGN-151586. The time of study treatment administration defines Hour 0 for the treatment period (on Day 1 for double-blind period and on Day 43 for open-label period).

Eligible subjects will be enrolled into the study containing 2 treatment periods:

Double-blind Period:
Screening will occur up to 14 days prior to Baseline Day 1. Randomization and treatment will occur on Baseline Day 1 after all other study procedures have been completed. A single treatment of AGN-151586 [redacted] or placebo will be administered on Baseline Day 1, based on randomization (3:1 ratio of AGN-151586:placebo). Randomization will be stratified by investigator site, toxin use history (for aesthetic purpose), and baseline GL severity at maximum frown. All enrolled subjects will receive treatment on Baseline Day 1 and attend in-clinic site visits [redacted] to fully characterize the onset of treatment effect. Thereafter, [redacted] in-clinic site visits [redacted] will be completed to characterize the peak and duration of effect.

The double-blind period will end on Day 43. The Day 43 visit will occur 42 ± 2 days following the Day 1 visit. The study assessments conducted during the Day 43 visit serve as the final assessment for the double-blind period and as the baseline assessment for the open-label period.

Open-label Period:
For subjects meeting all the retreatment criteria on Day 43, a single open-label treatment with AGN-151586 [redacted] will be administered on the same day. The subject will then be followed for approximately 6 weeks (through Day 84). The schedule of the follow-up visits in the open-label period is the same as that in the double-blind period. After each study treatment administration, subjects must remain in the clinic for at least 30 minutes for observation of any AEs.

Retreatment is only permitted on the Day 43 visit.

If the subject does not meet the GL severity criterion at Day 43 visit for retreatment, the subject will be followed weekly as per the Activity Schedule (Appendix D) until the FWS grades assessed by both investigator and subject have returned to moderate or severe (investigator and subject grades do not need to match) before being discontinued from the study after completing either the Early Exit or Study Exit Visit. If the subject becomes pregnant, then study drug may not be administered, and the subject can either be discontinued from the study after Early Exit Visit procedures are completed or remain in the study for all safety follow-up assessments. If the subject declines retreatment despite meeting the retreatment criteria at Day 43 visit, the subject may be discontinued from the study after Early Exit Visit procedures are completed.

The efficacy measures include investigator FWS, subject FWS, FLO-11, FLSQ, GAC-GL, [redacted].

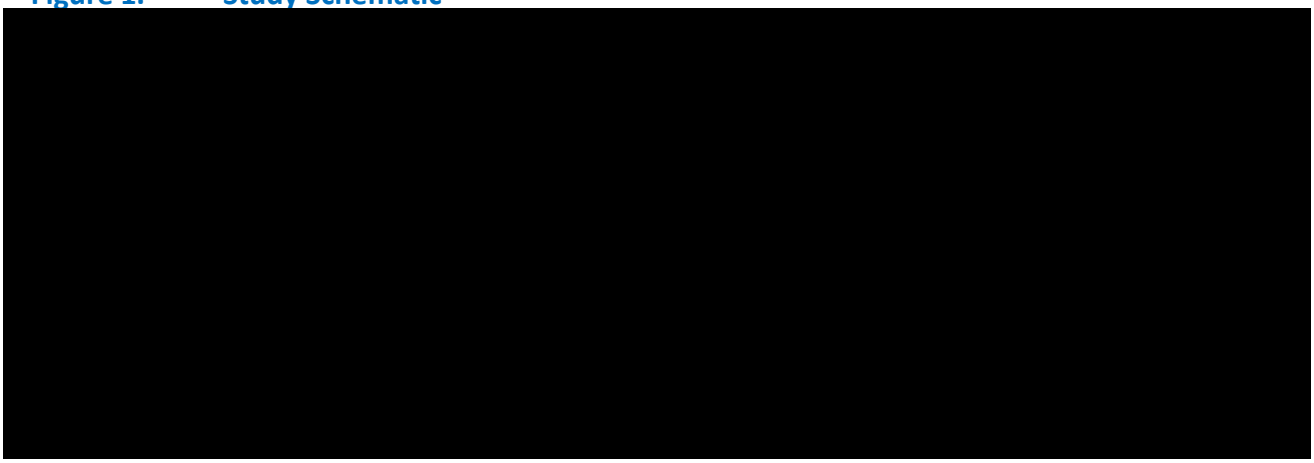
To assess the safety of AGN-151586 for the treatment of GL, the safety measures are collected in the study are AEs, vital sign measurements, ECG, laboratory evaluations (hematology and chemistry), neurological assessment [redacted] physical examinations, and immunogenicity.

Prior to commencing any assessment, all makeup must be removed and care must be taken so that hair does not obscure the upper face. All assessments must be completed before administration of study treatment.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual (Appendix F).

See Section 5 for information regarding eligibility criteria.

Figure 1. Study Schematic



4.2 Discussion of Study Design

Choice of Control Group

A placebo-control group is the gold standard for comparative evaluations of safety and efficacy in clinical trials and will be used for the double-blind period of the study. No control group will be used for the open-label period.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are standard for assessing subjects with GL. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

The study population will be adult subjects with moderate or severe GL at maximum frown as assessed by both the investigator and subject using the FWS. Eligibility criteria will be assessed at Screening Visit and Baseline Day 1 Visit to ensure subject safety.

Selection of Doses in the Study

In the previous Phase 2b Study 2034-201-008, a clinical dose response was observed, demonstrating that the proportion of responders (i.e., subjects having ≥ 2-grade improvement from baseline as assessed by investigator through Day 7) increased with increasing AGN-151586 dose. The responder rate was approximately 95% for the cohort dosed with [redacted]. The overall incidence of study drug-related TEAEs was similar between the placebo group (18.0%) compared with the AGN-151586 group (20.9%). There were no safety trends or patterns identified with increasing the dose of AGN-151586. Overall, AGN-151586 had a favorable safety profile and [redacted] AGN-151586 showed the most robust benefit and thus, [redacted] AGN-151586 was selected for the Phase 3 pivotal studies.

The dose selected is expected to be efficacious with an acceptable safety profile.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation. Subjects who do not meet the eligibility criteria for participation in this study (screen failures) may be allowed to be rescreened. Rescreening of subjects must only occur after discussion with the sponsor. Rescreening can only occur once for any given potential subject; however, if the original screen failure was due to ineligible FWS grade(s), the subject will not be permitted to rescreen.

[redacted]

- [redacted]

[redacted]

- 2. Subjects must be adult male or female, at least 18 years old.
- [redacted]
- 4. Subjects must be able to accurately assess their facial lines without the use of eyeglasses (contact lens use is acceptable).
- [redacted]

Disease/Condition Activity

- 6. Subjects must have moderate or severe GL at maximum frown as assessed by both the investigator and subject using the FWS at Screening and Baseline Day 1 Visit. [redacted]

Subject History

- 7. Subjects must not have uncontrolled systemic disease.
- 8. Subjects must not have received treatment with any botulinum neurotoxin of any serotype for aesthetic treatment within the last 6 months prior to Baseline Day 1 and for therapeutic treatment within the last 12 months [redacted]
- 9. Subjects do not present with or have a history of any medical condition that may place the subject at increased risk following exposure to AGN-151586 or interfere with the study evaluation.
- 10. Subjects must not have a diagnosis of myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, or any other significant disease that might interfere with neuromuscular function.
- 11. Subjects must not have a history of facial nerve palsy.
- 12. Subjects must not have infection or dermatological condition at the treatment injection sites.
- 13. Subjects must not have marked facial asymmetry, dermatochalasis, deep dermal scarring, excessively thick sebaceous skin, excessively photodamaged skin, or the inability to substantially lessen facial lines even by physically spreading them apart.
- 14. Subjects must not have any eyebrow or eyelid ptosis at screening or Baseline Day 1 visit as determined by the investigator.
- [redacted]
- [redacted]
- [redacted]
- 18. Subjects must not have tattoos, jewelry, or clothing which obscure the glabellar area and cannot be removed.
- 19. Subjects do not have known immunization to any botulinum neurotoxin serotype.
- 20. Subjects do not have anticipated need for surgery or overnight hospitalization during the study.
- 21. Subjects do not have history of surgical procedures on forehead and/or periorbital areas or affecting these areas including any lifting procedure (e.g., rhinoplasty, facial lift, suture lift, thread lift, brow lift, eyelid and/or eyebrow surgery).

- 22. Subjects do not have history of periorbital, mid-facial, or upper-facial treatment with semi-permanent or permanent soft tissue fillers (e.g., poly-L-lactic acid, polyalkylimide, polymethylmethacrylate, polytetrafluoroethylene, and silicone), synthetic implantation and/or autologous fat transplantation.
- [redacted]
- [redacted]
- 25. No known active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. [redacted]
- [redacted]

Contraception

- [redacted]
- [redacted]
- 29. Female subjects that are not pregnant or breastfeeding, and are not considering becoming pregnant or donating eggs during the study or for approximately 30 days after the last dose of study drug or until the end of study, whichever is longer.

Concomitant Medications

- [redacted]

[redacted]

- 31. Subjects must not have been treated with any investigational drug within 30 days prior to the first dose of study drug or is currently enrolled in another clinical study or was previously enrolled in this study.
- 32. Subjects do not have an anticipated need for treatment with botulinum neurotoxin of any serotype for any reason during the study (other than study drug).

[redacted]

5.3 Contraception Recommendations

Contraception Requirements for Females

Female subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

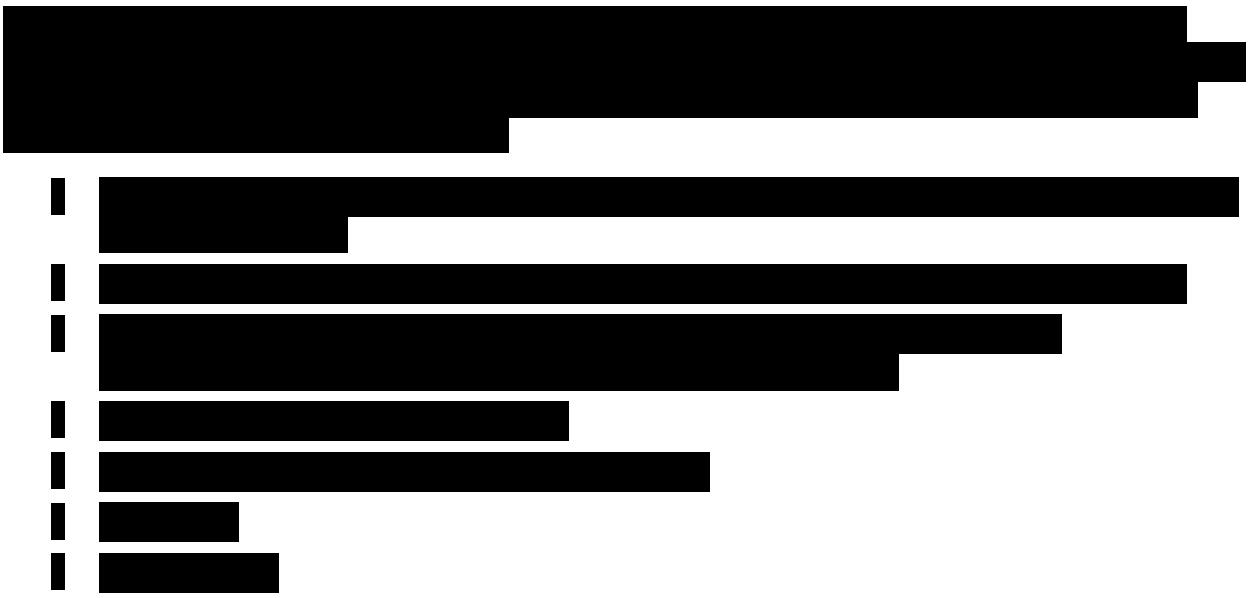
  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
     - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
  2. Postmenopausal female
     - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
       - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt, as determined by the investigator, will be required to use one of the non-hormonal 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.

- Females, of Childbearing Potential
  - Review and document pregnancy avoidance recommendations with females of childbearing potential.
  - Females of childbearing potential must avoid pregnancy during the study and for at least 30 days after the last dose of study drug or until the end of study, whichever is longer.
  - Among the birth control methods given below, females enrolled in sites located in the EU must choose from one of the methods 1 through 7 and subjects enrolled in sites located outside of EU must choose from one of the methods 1 through 10.

1. Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
2. Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
3. Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
4. Intrauterine device (IUD).
5. Intrauterine hormone-releasing system.
6. Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
7. Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).
8. Male or female condom with or without spermicide.
9. Cap, diaphragm, or sponge with spermicide.
10. A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

5.4 Prohibited Medications and Therapy



[redacted]

During the study, all other investigational drugs are prohibited.

5.5 Prior and Concomitant Therapy

[redacted]

[redacted]

5.6 Withdrawal of Subjects and Discontinuation of Study

A subject can voluntarily withdraw at any time or will be withdrawn from the study for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the Sponsor. However, when possible, the subject is encouraged to remain in the study for all safety follow-up assessments, even if the subject does not meet retreatment criteria.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.

- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- Subject is significantly noncompliant with study procedures.
- If the subject does not meet the GL severity criterion at Day 43 visit for retreatment, the subject will be followed weekly per the visit schedule (Appendix D) until the FWS grades assessed by both investigator and subject have returned to moderate or severe (investigator and subject grades do not need to match) before being discontinued from the study by completing either the Early Exit or Study Exit Visit.
- If the subject becomes pregnant, then study drug will not be administered, and the subject can either be discontinued from the study after Early Exit Visit procedures are completed or remain in the study for all safety follow-up assessments. If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.
- If the subject declines retreatment despite meeting the retreatment criteria at Day 43 visit, the subject will be discontinued from the study after Early Exit Visit procedures are completed unless the investigator determines the subject should remain in the study for safety follow-up.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

The following events, if applicable, will also cause premature termination of the clinical study:

- Unjustifiable risk and/or toxicity in risk-benefit analysis (decision taken by sponsor representative), e.g., when AEs occur, unknown to date in respect of their nature, severity, duration or frequency in relation to the current established safety profile (substantial changes in risk-benefit considerations), and therefore medical and/or ethical reasons affect the continued performance of the study.
- New scientific evidence becomes available during the study that could affect the patient's safety (benefit-risk analysis no longer positive), e.g., new insights from other clinical trials.
- Request of the sponsor or regulatory agency, e.g., as a consequence of inspection; favorable opinion withdrawn by ethics commission.
- In case of difficulties in the recruitment of the planned number of subjects in the indicated time (insufficient recruitment rate).
- Withdrawal of the license to manufacture or of the permission to import.

AbbVie can terminate this study prematurely, either in its entirety or at any site. The investigator can also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator and appropriate Health Authority.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual (Appendix F), Section 2 and Section 3.

The investigator should contact the sponsor before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

During the study drug dosing period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- At least 10 days since first positive test result have passed in asymptomatic patients or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of early exit from the study drug dosing period. Follow subsequent protocol Section 5.7 for subjects who discontinued study drug.

5.7 Follow-Up After Subject Discontinuation of Study Drug or from Study

For subjects who

- are ineligible for retreatment because of not meeting GL severity criterion on Day 43, the subjects will be followed weekly per the visit schedule (Appendix D) until the FWS grades assessed by both investigator and subject have returned to moderate or severe (investigator and subject grades do not need to match) before being discontinued by completing either the Early Exit or Study Exit Visit.
- are ineligible for retreatment because of pregnancy, the subjects will not receive study drug. They can either be discontinued from the study after Early Exit Visit procedures are completed or remain in the study for all safety follow-up assessments.
- prematurely discontinue study treatment, or who prematurely discontinue study participation (due to withdrawal of informed consent or if the protocol-specified discontinuation criteria are met), the procedures outlined for the Early Exit visit (in Appendix D) should be completed as soon as possible, preferably within 2 weeks, but no sooner than 30 days since last treatment.

5.8 Study Drug

All subjects will receive AGN-151586 or matching placebo, which will be prepared at the investigator site as an injectable solution and administered on Baseline Day 1. Based on meeting the retreatment

criteria, the subject may be retreated at Day 43. See Operations Manual (Section 3.15) for information about study drug administration.

AGN-151586 / matching placebo will be supplied in vials in quantities sufficient to accommodate study design. [redacted] Study drug will only be used for the conduct of this study.

Detailed study drug preparation instructions will be provided to sites in the Pharmacy Manual.

Table 3. Identity of Investigational Medicinal Product

Investigational Medicinal Product	AGN-151586	Placebo for AGN-151586
[redacted]		

5.9 Randomization/Drug Assignment

At the Screening Visit, all subjects will be assigned a unique identification number using the IRT. For subjects who rescreen, the screening number assigned by the IRT at the initial Screening Visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule (3:1 ratio AGN-151586:placebo).

Randomization will be stratified by investigator site, toxin use history (for aesthetic purpose), and baseline GL severity at maximum frown. [redacted] To support this, the site will manually enter the subject's Baseline Day 1 FWS score (moderate or severe; per eligibility criteria, the investigator and subject FWS assessments must be identical), toxin use history (for aesthetic purpose), and the Baseline Day 1 FLO-11 total score (as calculated by the electronic data capture [EDC] after the subject completes the questionnaire) in to the IRT.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the

AGN-151586 / matching placebo provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

5.10 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

5.11 Data Monitoring Committee

A data monitoring committee is not planned for this study.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via EDC. The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or vital sign measurement), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a serious adverse event (SAE) immediately without undue delay, but no later than 24 hours, from when the site is made aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.

Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event.

All AEs reported from the time of study drug administration will be collected for at least 30 days after last dose or until the last follow-up visit, whichever is longer, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an Investigational Medicinal Product (IMP) related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information), and meets one of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the investigational medicinal product (IMP) in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

There are no AEs of special interest in this study.

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE as mild, moderate, or severe.

The investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug and to the injection procedure:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant can either be discontinued from the study after Early Exit Visit procedures or remain in the study for follow-up through study exit but will receive no further treatment with the study drug. If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected. Partner pregnancy information will not be collected.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered an SAE and must be reported to AbbVie immediately without undue delay, but no later than 24 hours, from when the site is made aware of the event.

6.2 Other Safety Data Collection

Possible Distant Spread of Toxin

Possible distant spread of toxin (PDSOT) is defined as a possible pharmacologic effect of botulinum toxin at sites noncontiguous and distant from the site of injection. Utilizing a standardized methodology to assess for PDSOT, Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) that may be associated with botulinum toxin effects have been prospectively identified (the statistical analysis plan [SAP] will include a complete list of these PTs). Adverse events reporting any of these terms will be

medically reviewed on a regular basis throughout the duration of the study and will be summarized in the study clinical study report (CSR).

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and secondary analyses. Complete and specific details of the statistical analysis will be described in the SAP.

The primary analysis will be conducted after all subjects have completed their end of study visit for the purpose of submission.

7.2 Definition for Analysis Populations

The following population sets will be used for the analyses.

The ITT Population includes all randomized subjects. For double-blind period analyses, subjects will be included in the analysis according to the treatment groups to which they were randomized. For open-label period analyses, data will be analyzed according to the treatments randomized in the double-blind period and received in the open-label period (i.e., AGN-151586/AGN-151586, AGN-151586/None, Placebo/AGN-151586, Placebo/None).

Baseline analyses and efficacy analyses for US FDA and EU Regulatory agencies will be performed on the ITT population, consisting of all randomized subjects. Subjects will be included in the double-blind period analysis according to the treatment groups to which they were randomized. For open-label period analyses, data will be analyzed according to the treatments randomized in the double-blind period and received in the open-label period (i.e., AGN-151586/AGN-151586, AGN-151586/None, Placebo/AGN-151586, Placebo/None).

Additionally, for EU regulatory agencies only, subgroup analyses will be performed on the ITT population, that also has a baseline FLO-11 total score ≤ 50. Analyses will consist of the EU primary and key secondary endpoints.

The Safety Analysis Set consists of all subjects who were treated with at least 1 dose of study drug (i.e., AGN-151586 or placebo). All safety analyses will be performed with subjects analyzed by their actual treatment received in double-blind period/open-label period (i.e., AGN-151586/AGN-151586, AGN-151586/None, Placebo/AGN-151586, Placebo/None), and will be presented with overall safety data for the study (i.e., either period), for double-blind period, and for open-label period. The Safety Analysis Set will be used for all safety analyses.

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The primary efficacy endpoint of the composite endpoints for the US FDA and the coprimary endpoints for the EU regulatory agencies (defined in Section 3.2), respectively, will be analyzed based on the ITT population and the following methods will be used to address potential intercurrent events:

- Subjects who did not receive any dose of study drug but are randomized will still be included in the ITT population. For the EU, those who also had baseline FLO-11 total score of ≤ 50 will be included in subgroup analyses of the coprimary and key secondary endpoints.
- Subjects who are randomized but prematurely discontinued the study before assessment of the primary endpoints will be considered as part of the ITT population.
- Subjects who die before assessment of the primary endpoints will count as though they hypothetically continued in the study.
- Subjects who are lost to follow-up and are missing data for the primary endpoints will count as though they hypothetically continued in the study.
- Subjects who are missing assessments or data due to the COVID-19 pandemic and are missing data for the primary endpoints will count as though they hypothetically continued in the study.
- Subjects who are missing data for any other reason for the primary endpoints will count as though they hypothetically continued in the study.

The efficacy analysis of secondary endpoints (defined in Section 3.3) will be analyzed based on the same populations as above with similar methods for addressing potential intercurrent events.

7.4 Statistical Analyses for Efficacy

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the ITT population. Medical history data will be reported and summarized separately from prior procedures data for the ITT population. Medical history data and prior procedure data will be coded using the MedDRA. Prior and concurrent procedures will be summarized by MedDRA high level term and PT.

Summary and Analysis of the Primary Endpoints

Analysis of the respective primary endpoints will be conducted on the ITT Population for the US and for the EU regulatory agencies based on treatment as randomized.

The assessments of the severity of GL at maximum frown using the validated FWS is based on the following scale:

- 0 = None
- 1 = Mild
- 2 = Moderate

- 3 = Severe

The composite primary endpoint for FDA is the following:

- ≥ 2-grade improvement from baseline on the FWS according to both **investigator and subject assessments** of GL severity at maximum frown at Day 7

The coprimary endpoints for EU regulatory agencies consist of the following:

- ≥ 2-grade improvement from baseline on the FWS according to **subject assessment** of GL severity at maximum frown at Day 7, and
- ≥ 2-grade improvement from baseline on the FWS according to **investigator assessment** of GL severity at maximum frown at Day 7.

The attributes of the estimands corresponding to the primary efficacy endpoints for the US FDA and EU regulatory agencies are summarized in Section 3.1.

US FDA: The composite primary responder endpoint for at least a 2-grade improvement will be analyzed using the Cochran-Mantel-Haenszel (CMH) method [redacted] The primary endpoint must meet $p \leq 0.05$ to be considered successful.

European Union regulatory agencies: The coprimary responder endpoints for ≥ 2-grade improvement from baseline in the FWS will be analyzed separately using the CMH method [redacted]. Both coprimary endpoints must meet $p \leq 0.05$ to be considered successful.

The evaluation of the equality of the proportions of responders for the primary endpoints at Day 7 will be based on the CMH test stratified by investigator site, toxin use history, and baseline FWS. (Sites may be pooled for stratification purposes if there are too few subjects in a site.) A p-value ≤ 0.05 (2-sided testing) will be claimed as statistically significant. [redacted]

For primary and secondary endpoints, missing data will first be imputed at the visit level using multiple imputation, and then the responder definitions will be applied. Details are provided in the SAP for missing data handling.

Sensitivity analyses of the primary efficacy variables will be performed to establish their consistency and robustness as well as to further characterize the extent of subjects' responses. As-observed data analysis, as well as missing as non-responder (using non-responder imputation [NRI]) analysis, stratified by baseline FWS and by investigator site are planned for sensitivity analyses.

[redacted]

[redacted]

Summary and Analysis of Secondary Endpoints

Secondary efficacy endpoints for the US FDA and EU regulatory agencies are listed in Section 3.3, and include other response definitions for the FWS by investigator and subject, as well as for the FLO-11, FLSQ, and GAC-GL.

The attributes of the estimands corresponding to the secondary efficacy endpoints are summarized in Section 3.1. Analysis of the secondary endpoints will be conducted on the ITT population based on treatment as randomized for the US FDA and the EU regulatory agencies.

For the secondary endpoints, the proportion of responders will be analyzed using the CMH test [redacted]. The continuous variables will be analyzed using analysis of covariance with treatment as the main effect, [redacted].

[redacted]

7.5 Statistical Analyses for Safety

The safety analyses will be performed using the safety population (i.e., Safety Analysis Set). The safety parameters will include AEs, vital sign measurements, 12-lead ECG, laboratory evaluations (hematology and chemistry), neurological assessment (examination to consist of assessment of cranial nerves II through VII), physical examination, and immunogenicity. The last nonmissing safety assessment before study drug administration will be used as the baseline for all analyses of that endpoint.

Treatment-emergent AEs are defined as any AE with the onset that is after the first dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless known to have started prior to study treatment administration.

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

1. Any TEAE
2. Any TEAE related to study treatment according to the investigator (i.e., study drug-related, study injection procedure-related)
3. Any severe TEAE
    a. Any severe TEAE related to study treatment according to the investigator
4. Any serious TEAE
    a. Any serious TEAE related to study treatment according to the investigator
5. Any TEAE leading to discontinuation of study drug
6. Any TEAE leading to death
7. PDSOT TEAEs
8. Neurological assessment TEAEs
9. All deaths

Treatment-emergent AEs will be summarized by system organ class (SOC) and PT; by maximum relationship to study treatment (i.e., study drug related, study injection procedure related) as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific treatment-emergent AEs will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same AE occurs multiple times within a subject, the AE will be counted only once, and the highest severity and level of relationship to investigational product will be reported.

Serious AEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and in listing format.

Possible distant spread of toxin PTs will be identified in the SAP and PDSOT TEAEs will be summarized by PT.

Neurological assessment TEAEs will be summarized by PT.

Vital sign measurements and 12-lead ECG parameters will be summarized for each assessment timepoint, as well as for changes from baseline at each assessment timepoint. In addition, potentially clinically significant vital signs values will be summarized. Details will be provided in the SAP.

Immunogenicity results, manifested as the presence of binding antibodies (positive) and neutralizing antibodies (positive) to AGN-151586, will be summarized in a table for baseline and postbaseline data. Immunogenicity findings (positive) will be tabulated with the number and percentage of subjects at each visit. Percentages will be based on the number of treated subjects with interpretable antibody assays at the specified visit. Immunogenicity results including additional analysis of antibody response to other neurotoxin serotypes will be documented in the CSR or in a separate report.

7.6 Overall Type I Error Control

For the double-blind period, to control the family-wise Type I error rate at 0.05 for multiplicity across the primary and secondary analyses, a hierarchical testing strategy[11] will be used. The hierarchical testing strategy starts with the coprimary endpoint followed by sequential testing of the secondary endpoints. The statistical significance will be evaluated in the following order: if a statistical significance at the 0.05 level (2-sided) is shown for the first endpoint in the ranking order, then the next endpoint in the immediate subsequent order will be evaluated; evaluation of subsequent endpoint will continue in the same manner. If no statistical significance is shown at $\alpha = 0.05$ at any endpoint, then the endpoint and all subsequent endpoints will not be considered statistically significant, regardless of their nominal p-values.

The hierarchical testing order follows for US FDA:

1. Primary: At least a 2-grade improvement from baseline based on the following:
    - **Investigator and subject assessments** (composite) of GL severity at maximum frown at Day 7.
2. Secondary: *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) for GL at Day 7

3. Secondary: *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) for GL at Hour 24
4. Secondary: *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 4 (natural look) for GL at Day 7

For the US FDA, the following secondary endpoints will be evaluated outside of the gated hierarchical testing sequence at each time point:

1. Key Secondary: At least 2-grade improvement from baseline in GL severity at maximum frown according to the **investigator assessment** using the FWS over time (double-blind period)
2. Key Secondary: At least 2-grade improvement from baseline in GL severity at maximum frown according to the **subject assessment** using the FWS over time (double-blind period).

The hierarchical testing order follows for EU regulatory agencies:

1. Coprimary: At least a 2-grade improvement based on the following:
   - **Subject assessment** using FWS at maximum frown at Day 7, and
   - **Investigator assessment** using FWS at maximum frown at Day 7.
2. Key Secondary: At least 20-point improvement from baseline in FLO-11 total scores for GL at Day 7
3. Secondary: At least 2-grade improvement from baseline in GL severity at maximum frown according to the **subject assessment** using the FWS at Hour 24
4. Secondary: At least 2-grade improvement from baseline in GL severity at maximum frown according to the **investigator assessment** using the FWS at Hour 24
5. Secondary: At least 1-grade improvement from baseline in GL severity at maximum frown according to the **subject assessment** using the FWS at Hour 24
6. Secondary: At least 1-grade improvement from baseline in GL severity at maximum frown according to the **investigator assessment** using the FWS at Hour 24
7. Secondary: *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) for GL at Hour 24
8. Secondary: *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 4 (natural look) for GL at Day 7
9. Secondary: *Mostly satisfied* or *Very satisfied* on the FLSQ follow-up version Item 5 (overall satisfaction) over time
10. Secondary: At least 4-point improvement from baseline in FLO-11 Item 10 (look angry) for GL at Day 7
11. Secondary: At least 4-point improvement from baseline in FLO-11 Item 5 (look less attractive) for GL at Day 7

For the EU, the following secondary endpoints will be evaluated outside of the gated hierarchical testing sequence:

1. Secondary: Time to the first ≥ 1-grade improvement from baseline on the FWS according to subject assessments of GL severity at maximum frown (double-blind period)
2. Secondary: Time to the first ≥ 1-grade improvement from baseline on the FWS according to investigator assessments of GL severity at maximum frown (double-blind period).
3. Secondary: At least 2-grade improvement from baseline on the FWS according to subject assessments of GL severity at maximum frown over time (double-blind period)
4. Secondary: At least 2-grade improvement from baseline on the FWS according to investigator assessments of GL severity at maximum frown over time (double-blind period)
5. Secondary: Time to return to baseline FWS according to subject assessments of FWS at maximum frown (double-blind period)
6. Secondary: Time to return to baseline FWS according to investigator assessments of FWS at maximum frown (double-blind period)
7. Secondary: Subject-reported global assessment of change in GL based on the GAC-GL over time

7.7 Sample Size Determination

Approximately 600 subjects will be enrolled at approximately 38 study sites. [redacted] For the US FDA and EU regulatory agencies, the ITT population will consist of all randomized subjects. Additionally, for the EU regulatory agencies, subgroup analyses will be performed for the coprimary and key secondary endpoint with the ITT population that also has a baseline FLO-11 total score ≤50.

For the US FDA, a sample size of 600 subjects with a 3:1 randomization ratio (AGN-151586:Placebo) will have > 99% power to detect a difference on Day 7 between the AGN-151586 group and the placebo group using the composite endpoint of ≥ 2-grade improvement, [redacted]

For the EU regulatory agencies, a sample size of 600 subjects for the ITT population will have >99% power (and the subgroup population of an estimated 360 subjects will provide > 99% power) to detect a difference between the AGN-151586 group and the placebo group at Day 7 for the coprimary endpoints, [redacted]

For the FDA and EU regulatory agencies, a gate-keeping testing strategy will be used to compare the AGN-151586 group versus the placebo group, starting with the primary endpoint(s) and sequentially testing in the endpoint hierarchy at the 0.05 significance level. [redacted]

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end of study is defined as the date of end of study participation by the last subject in the last country where the study was conducted.

12 REFERENCES

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
BoNT/A	Botulinum Neurotoxin Serotype A
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease – 2019
CSR	clinical study report
DHEA	Dehydroepiandrosterone
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FDA	Food and Drug Administration
FLO-11	11-item Facial Line Outcomes
FLSQ	Facial Line Satisfaction Questionnaire
[redacted]	[redacted]
FWS	Facial Wrinkle Scale
GAC-GL	Global Assessment of Change in Glabellar Lines
GCP	good clinical practice
GL	Glabellar lines
HRT	hormone replacement therapy
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
NRI	non-responder imputation
[redacted]	[redacted]

Abbreviation	Definition
PDSOT	possible distant spread of toxin
PRO	patient reported outcome
PTs	preferred terms
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
[redacted]	[redacted]
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
WOCBP	Women of childbearing potential

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M21-500: A Phase 3, Multicenter Study to Evaluate the Safety and Efficacy of AGN-151586 for the Treatment of Glabellar Lines

Protocol Date: 01 August 2022

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly to AbbVie, the ethics committee/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

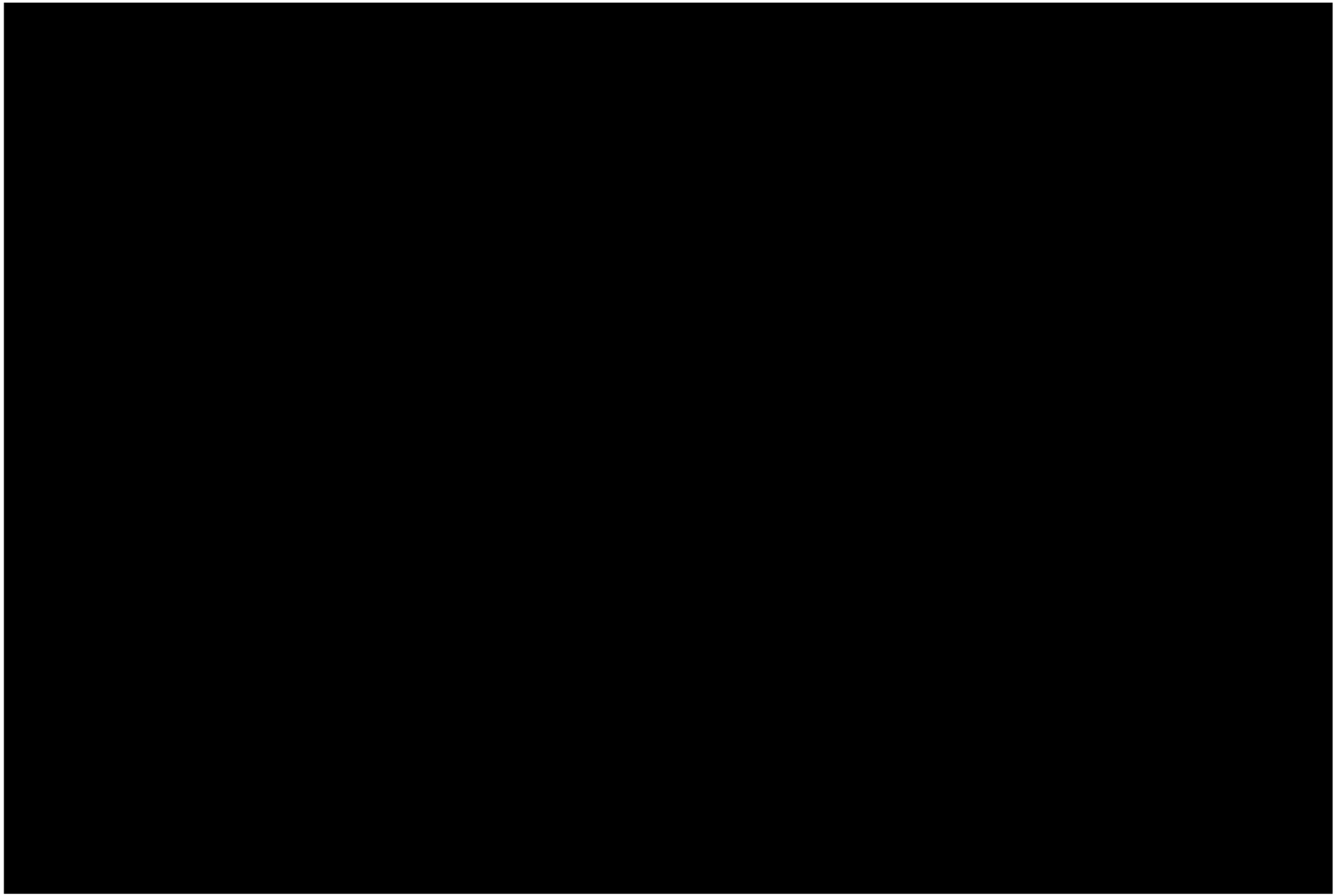
Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Vice President, Head of Clinical Development, Aesthetics Medicine	Therapeutic Area
[redacted]	Executive Director	Statistics

APPENDIX D. ACTIVITY SCHEDULE



APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	10 November 2021
Version 1.1 (Germany Only)	19 July 2022

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following:

[redacted]