



Protocol for Study M21-509

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

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SPONSOR:	AbbVie Inc.*	PLANNED NUMBER OF SITES:	Approximately 45 sites
ABBVIE INVESTIGATIONAL PRODUCT:	AGN-151586	EudraCT:	Not applicable

FULL TITLE: A Phase 3, Multicenter, Open-label Study to Evaluate the Safety of AGN-151586 for the Treatment of Glabellar Lines

Incorporating Versions 1.0, 2.0, 3.0 and 4.0 and Administrative Change 1.

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

SPONSOR/EMERGENCY MEDICAL CONTACT:*

[REDACTED] MD, MPH
Allergan Aesthetics, an AbbVie Company
2525 Dupont Drive
Irvine, CA 92612, USA

Mobile:

Email:

EMERGENCY 24-hour Number: +1 (973) 784-6402

SPONSOR/NON-EMERGENCY CONTACT:

[REDACTED] PhD
Allergan Aesthetics, an AbbVie Company
2525 Dupont Drive
Irvine, CA 92612, USA

Mobile:

Email:

* The specific contact details of the AbbVie legal/regulatory entity (person) within the clinical trial agreement with the Investigator/Institution. Additional study contact information can be found in the Operations Manual ([Appendix F](#)).

TABLE OF CONTENTS

1	SYNOPSIS	5
2	INTRODUCTION	6
2.1	BACKGROUND AND RATIONALE	6
2.2	BENEFITS AND RISKS TO SUBJECTS	6
3	OBJECTIVES AND ENDPOINTS	7
3.1	OBJECTIVES, HYPOTHESES, AND ESTIMANDS	7
3.2	PRIMARY ENDPOINTS	7
3.3	SECONDARY ENDPOINT	8
3.4	ADDITIONAL EFFICACY ENDPOINTS	8
3.5	SAFETY ENDPOINTS	8
3.6	IMMUNOGENICITY ASSESSMENTS	8
4	INVESTIGATIONAL PLAN	8
4.1	OVERALL STUDY DESIGN AND PLAN	8
4.2	DISCUSSION OF STUDY DESIGN	10
5	STUDY ACTIVITIES	10
5.1	ELIGIBILITY CRITERIA	10
5.2	RETREATMENT CRITERIA	13
5.3	CONTRACEPTION RECOMMENDATIONS	14
5.4	PROHIBITED MEDICATIONS AND THERAPY	15
5.5	PRIOR AND CONCOMITANT THERAPY	16
5.6	WITHDRAWAL OF SUBJECTS AND DISCONTINUATION OF STUDY	18
5.7	FOLLOW-UP AFTER SUBJECT DISCONTINUATION OF STUDY DRUG OR FROM STUDY	19
5.8	STUDY DRUG	20
5.9	RANDOMIZATION/DRUG ASSIGNMENT	20
5.10	PROTOCOL DEVIATIONS	20
5.11	DATA MONITORING COMMITTEE	20
6	SAFETY CONSIDERATIONS	21
6.1	COMPLAINTS AND ADVERSE EVENTS	21

6.2	OTHER SAFETY DATA COLLECTION	24
7	STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE	24
7.1	STATISTICAL AND ANALYTICAL PLANS	24
7.2	DEFINITION FOR ANALYSIS POPULATIONS	25
7.3	HANDLING POTENTIAL INTERCURRENT EVENTS FOR THE PRIMARY ENDPOINTS	25
7.4	STATISTICAL ANALYSES FOR EFFICACY	25
7.5	STATISTICAL ANALYSES FOR SAFETY	26
7.6	OVERALL TYPE I ERROR CONTROL	27
7.7	SAMPLE SIZE DETERMINATION	27
8	ETHICS	27
8.1	INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD (IEC/IRB)	27
8.2	ETHICAL CONDUCT OF THE STUDY	27
8.3	SUBJECT CONFIDENTIALITY	28
9	SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION	28
10	DATA QUALITY ASSURANCE	28
11	COMPLETION OF THE STUDY	28
12	REFERENCES	28

LIST OF TABLES

TABLE 1.	IDENTITY OF INVESTIGATIONAL MEDICINAL PRODUCT	20
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LIST OF FIGURES

FIGURE 1.	STUDY SCHEMA	9
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LIST OF APPENDICES

APPENDIX A.	STUDY-SPECIFIC ABBREVIATIONS AND TERMS	30
APPENDIX B.	RESPONSIBILITIES OF THE INVESTIGATOR	32

APPENDIX C.	LIST OF PROTOCOL SIGNATORIES	33
APPENDIX D.	ACTIVITY SCHEDULE	34
APPENDIX E.	PROTOCOL SUMMARY OF CHANGES	37
APPENDIX F.	OPERATIONS MANUAL	38

1 SYNOPSIS

Title: A Phase 3, Multicenter, Open-label Study to Evaluate the Safety 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. The purpose of this study is to evaluate the safety of AGN-151586 over multiple repeat treatments of the study drug to improve the appearance of GL.
Objective(s) and Endpoint(s):	The primary objective for this study is to evaluate the safety of AGN-151586 over multiple repeat treatments in subjects with moderate to severe GL. Primary Endpoints: • Incidence of adverse events (AEs) • Change from baseline in vital sign parameters • Change from baseline in 12-lead electrocardiogram (ECG) parameters • Presence of binding and neutralizing antidrug antibodies
Investigator(s):	Multicenter
Study Site(s):	Approximately 45 sites
Study Population and Number of Subjects to be Enrolled:	Approximately 940 to 1100 healthy, adult subjects with moderate to severe GL. In case the dropout rate is higher than estimated, additional subjects may be enrolled until approximately 800 subjects complete the study with 3 study treatments.
Investigational Plan:	This is an 18-week, multicenter, open-label, Phase 3 study designed to evaluate the safety of AGN-151586 over multiple repeat treatments of the study drug in adult subjects with moderate to severe GL. Eligible subjects may receive up to 3 treatments with AGN-151586, based on meeting retreatment criteria.
Key Eligibility Criteria:	Adult male or female, ≥ 18 years of age, having moderate or severe GL at maximum frown (as assessed by both the investigator and subject using the Facial Wrinkle Scale [FWS] at screening and Baseline Day 1 visit).
Study Drug and Duration of Treatment:	All subjects will receive open-label [REDACTED] of AGN-151586 administered as 5 intramuscular injections in the glabellar complex on Baseline Day 1. Based on meeting the retreatment criteria, the subject may receive up to 2 additional cycles of open-label treatments.
Date of Protocol Synopsis:	14 December 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 (BoNT/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 of AGN-151586 over multiple repeat treatments of the study drug to improve the appearance of 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] to [REDACTED] AGN-151586-specific units for the treatment of GL in adults. Units of biological activity of AGN-151586 cannot be compared with 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 events (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 due to its 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 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

Primary

The primary objective for this study is to evaluate the safety of AGN-151586 over multiple repeat treatments of the study drug in subjects with moderate to severe GL.

The clinical hypothesis is that AGN-151586 [REDACTED] has an acceptable safety profile over multiple repeat treatments of the study drug.

Secondary

There are no secondary objectives in the current study.

3.2 Primary Endpoints

The primary endpoints in this study include:

- Incidence of adverse events (AEs)
- Change from baseline in vital sign parameters
- Change from baseline in 12-lead electrocardiogram (ECG) parameters
- Presence of binding and neutralizing antidrug antibodies

No estimands are provided.

3.3 Secondary Endpoint

There are no secondary endpoints in the study.

3.4 Additional Efficacy Endpoints

Glabellar lines severity, along with change from baseline, as assessed by investigators and subjects using the Facial Wrinkle Scale (FWS) will be collected and analyzed as additional efficacy endpoints. No estimands are provided.

3.5 Safety Endpoints

Safety evaluations include AE monitoring, vital sign measurements, 12-lead ECG collection, neurological assessment (examination to consist of assessment of cranial nerves II through VII), and physical examination as measures of safety for the entire study duration.

The safety endpoints evaluated in the current study are the primary endpoints discussed in Section [3.2](#).

3.6 Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected from all subjects treated with AGN-151586 at predetermined timepoints 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 an 18-week, multicenter, open-label, Phase 3 study designed to evaluate the safety of AGN-151586 over multiple repeat treatments of the study drug in adult subjects with moderate to severe GL.

To be eligible for this study, subjects must be at least 18 years of age with moderate to severe GL at maximum frown as assessed independently by both the investigator and subject using the FWS at Screening and Baseline Day 1 in-clinic site visit. The investigator and subject GL severity ratings at maximum frown do not need to match for a subject to be enrolled into the study. Screening will occur up to 14 days prior to Baseline Day 1. Treatment will occur on Baseline Day 1. Eligible subjects may receive up to 3 treatments with AGN-151586, based on meeting retreatment criteria.

All eligible subjects will receive the first treatment on Baseline Day 1. Thereafter, subjects will be followed [REDACTED]

The planned retreatment in-clinic site visits are [REDACTED]. The [REDACTED] will occur [REDACTED] and the [REDACTED]

[REDACTED] Subjects who meet the retreatment criteria at each retreatment reassessment (see the Eligibility Criteria Section 5.1) will receive treatment with open-label [REDACTED] AGN-151586. If the subject does not meet the retreatment criteria at the [REDACTED] OR declines retreatment despite meeting the retreatment criteria at [REDACTED], the subject may be discontinued from the study after Early Exit Visit procedures are completed. If the subject becomes pregnant, the 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.

After each retreatment, the same posttreatment visit schedule (i.e., [REDACTED] will be followed for the next reassessment/retreatment site visit ([REDACTED]) and will be followed by the End of Study visit ([REDACTED] or Early Exit Visit).

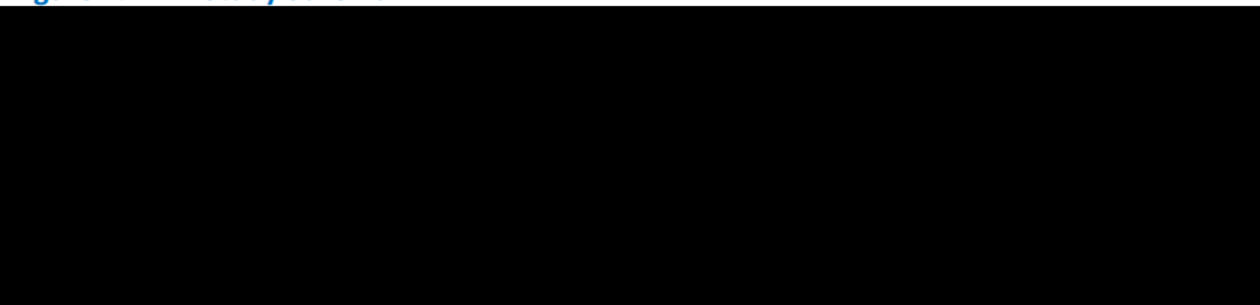
After each study treatment administrations, subjects must remain in the clinic for at least 30 minutes for observation of any AEs.

To assess the safety of AGN-151586 treatment for improving GL severity, the following safety measures are collected in the study: AEs, physical examination, vital sign measurements, 12-lead ECGs, neurological assessment [REDACTED] and anti-drug antibodies to AGN-151586. In addition, efficacy measures including investigator FWS and subject FWS will also be collected and analyzed as additional endpoints.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Study Activities Table (Appendix D) and in the Operations Manual.

See Section 5 for information regarding eligibility criteria.

Figure 1. Study Schema



4.2 Discussion of Study Design

Choice of Control Group

No control group is used for this open-label study.

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 and at Baseline Day 1 of the current study to ensure subject safety.

Selection of Doses in the Study

The dose selection [REDACTED] in this study is based on safety and efficacy data from the Phase 2b study (Study 2034-201-008) in subjects with moderate to severe GL. In addition, the prior clinical experience included 39 subjects who received doses higher than [REDACTED], with no notable safety concerns (Studies EB001-MA201 and EB001-ABD201). 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]



[REDACTED]



[REDACTED]

- ✓ 4. Subjects must be able to accurately assess their facial lines without the use of eyeglasses (contact lens use is acceptable).



[REDACTED]

Disease Activity /Condition

- ✓ 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]

[REDACTED]

Subject History

- ✓ 7. Subjects must not have uncontrolled systemic disease.
- ✓ 8. 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.
- ✓ 9. 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.
- ✓ 10. Subjects must not have a history of facial nerve palsy.
- ✓ 11. Subjects must not have infection or dermatological condition at the treatment injection sites.
- ✓ 12. 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.
- ✓ 13. Subjects must not have any eyebrow or eyelid ptosis at screening or Baseline Day 1 visit.
- ✓ [REDACTED]
- ✓ [REDACTED]
- ✓ [REDACTED]
- ✓ 17. Subjects must not have tattoos, jewelry, or clothing which obscure the glabellar area and cannot be removed.
- ✓ 18. Subjects do not have a known immunization to any botulinum neurotoxin serotype.

- ✓ 19. Subjects do not have reported use of any botulinum neurotoxin of any serotype (including any investigational botulinum neurotoxin product) for aesthetic treatment within the last 6 months prior to screening and for therapeutic treatment within the last 12 months prior to study drug administration.
- ✓ 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]
- [REDACTED]

Contraception Requirements for Females

- ✓ [REDACTED]
- ✓ [REDACTED]
- ✓ 29. Female subject who is not pregnant or breastfeeding, and is 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/Therapy



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



31. Subjects must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) 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).

5.2 Retreatment Criteria

Prior to each retreatment, subjects must be evaluated during the scheduled in-clinic site visit and meet all the retreatment criteria in order to be retreated. Retreatment is not permitted after the scheduled retreatment visit.

Based on meeting all of the following criteria for retreatment on the study specified days, subjects may receive up to 2 additional cycles of treatment:

- Female subjects of childbearing potential must have a negative urine pregnancy test.
- [REDACTED]
- The subject must not have any ongoing eyelid ptosis, eyebrow ptosis, facial paresis, or facial paralysis.
- The subject must not have any ongoing AEs that may place the subject at increased risk following exposure to AGN-151586, as per investigator determination.
- The subject must not have clinically relevant or significant ECG abnormalities as per investigator determination, including ECG with QTcF > 450 msec (males) or > 470 msec (females) or prolonged QT on retreatment day or on any prior ECGs.

- The subject must not have any clinically significant abnormal vital sign value on retreatment day, as per investigator determination.
- The subject must not have any clinically significant abnormality on neurological or physical examination on retreatment day, as per investigator determination.
- The subject must not present with any medical condition that may place the subject at increased risk following exposure to retreatment or interfere with the study evaluation.
- A subject with confirmed (viral test positive) or suspected COVID-19 infection can only be retreated if the following COVID-19 viral clearance criteria are met:
 - At least 10 days since the first PCR test result have passed in asymptomatic patients or 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

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 30 days after the last dose or until the end of study, whichever is longer.
- Among the birth control methods given below, females enrolled in sites located in the European Union (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 (IUS).
 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

In addition to the medications listed in the eligibility criteria, no other facial cosmetic procedures or treatments are to be performed throughout the duration of the study. Some procedures listed below that are prohibited for the mid and upper face may be permitted if they are limited to the lower face (e.g., lips). Prohibited treatments and procedures include, but are not limited to:

- Concurrent treatment with botulinum neurotoxin of any serotype for any indication (other than the study treatment)
- Medium depth to deep facial chemical peels (i.e., trichloroacetic acid and phenol) to the mid or upper face

- Energy-based treatments (e.g., intense pulsed light, Clear + Brilliant®, monopolar radiofrequency, microfocused ultrasound) to the mid or upper face
- Microneedling to the mid or upper face
- Facial lift (partial or full face) or suspension threads
- Rhinoplasty
- Blepharoplasty
- Synthetic implantation (e.g., Gore-Tex) to the mid or upper face
- Autologous fat transplantation to the mid or upper face
- Soft tissue fillers to the mid or upper face
- Permanent make-up to the mid or upper face

During the study, all other investigational drugs are prohibited.

5.5 Prior and Concomitant Therapy

Any medication or non-COVID-19 vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded from 30 days prior to the first dose of study drug through the study exit. However, any prior toxin therapy for aesthetics or therapeutic treatment at any time and COVID-19 vaccination history must be recorded. See below for details on special handling for the COVID-19 vaccine.

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 subject's electronic case report form (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 subject uses a concomitant medication not permitted by the protocol (see Section 5.4). Subjects who use prohibited concomitant medications may be discontinued at the discretion of the investigator or sponsor.

Non-live vaccines may be used during the study, if not contraindicated or medically inappropriate. When possible, study drug should be given at least ± 14 days from vaccine administration.

Co-administration of aminoglycosides or agents that could interfere with neuromuscular transmission (e.g., curare-like agents) or muscle relaxants are to be used with caution as the effects of the toxin, theoretically, could be potentiated.

Systemic and topical hormones and their derivatives (i.e., sex steroids - androgens, estrogens, progesterone) should be maintained throughout study period to avoid changes in skin, including but not limited to:

- Oral birth control
- IUDs/implants/injections

- Oral supplements including testosterone and estrogens and their derivatives, DHEA, etc.
- Topicals (anywhere on the body) including testosterone and estrogens and their derivatives, DHEA, etc.
- Androgel, Axiron, Testim, Fortesta, Vogelxo
- Emepelle (methyl estradiolpropanoate), Rejuvenate, All Natural Bioidentical Estradiol, Emerita Phytoestrogen

Subjects must maintain their skin care regimen throughout the study period.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie non-emergency contact. Information regarding potential drug interactions with AGN-151586 can be located in the AGN-151586 Investigator's Brochure.

Subjects must be able to safely discontinue any prohibited medications as described in the eligibility criteria. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., messenger ribonucleic acid, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening, the treatment period, or follow-up as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of AGN-151586 on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- All doses of study drug AGN-151586, when possible, are preferred to be given at least ± 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

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.
- Subject doesn't meet the GL severity criterion at Day 43 or Day 85 retreatment criteria.
- If the subject becomes pregnant, the 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 the subject declines retreatment despite meeting the retreatment criteria at Day 43 or Day 85 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 in [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 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.
- [REDACTED] 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 prepared at the investigator site as an injectable solution and administered on Baseline Day 1. Based on meeting the retreatment criteria, the subject may receive up to 2 additional cycles of treatments. See Operations Manual (Section 3.10) for information about study drug administration.

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

Table 1. Identity of Investigational Medicinal Product

Investigational Medicinal Product	AGN-151586
Dosage Form	Powder for solution for injection
Strength	██████████
Mode/Route of Administration	Intramuscular injection
Manufacturer	Allergan (an AbbVie company)

AbbVie will provide study drug for AGN-151586. AbbVie-provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

5.9 Randomization/Drug Assignment

Randomization is not applicable since this is an open-label study.

All subjects will be assigned a unique identification number by the interactive response technology (IRT) system at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used.

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 independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

5.11 Data Monitoring Committee

This is an open-label study with safety monitoring throughout the course of the study duration. Hence 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 electronic data capture (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 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. 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 evidence of AEs on a routine basis throughout the study; laboratory testing will be done when indicated, on an as needed basis. 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 an SAE within 24 hours of the site being 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 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 during the study will be encouraged to 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 within 24 hours after the site becomes aware of the event (refer to Section 4.2 of the Operations Manual for reporting details and contact information).

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 (PT) 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 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 the study and the database has been locked.

7.2 Definition for Analysis Populations

The following population sets will be used for the analyses:

- The Intent-to-Treat (ITT) Population includes all enrolled subjects and will be used for all baseline and efficacy analyses.
- The Safety Analysis Set consists of all subjects who were treated with at least 1 dose of study drug (i.e., AGN-151586). The Safety Analysis Set will be used for all safety analyses.

7.3 Handling Potential Intercurrent Events for the Primary Endpoints

The primary endpoints are safety endpoints and will be based on the Safety Analysis Set. No additional methods will be used to address potential intercurrent events, as all subjects who were treated will be included in the Safety Analysis Set with events reported as observed.

Any missing assessments or data due to the COVID-19 pandemic will be considered as missing data in the analyses. Any AEs resultant from COVID-19 will be reported.

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 MedDRA. Prior and concurrent procedures will be summarized by MedDRA high level term and PT.

Summary and Analysis of the Primary Endpoints

The primary endpoints are incidence of AEs, change from baseline in vital signs parameters, and presence of binding and neutralizing antidrug antibodies. The Safety Analysis Set will be used for all of these analyses (see Section 7.5).

Summary and Analysis of Secondary Endpoint

Summary and Analysis of Key Secondary Endpoint

Not applicable.

Summary and Analysis of Additional Efficacy Endpoints

The efficacy endpoints that will be collected and analyzed are the FWS for GL severity at maximum frown and at rest as assessed by the investigator and the subject independently at each assessment timepoint. The ITT population will be used for all analyses of the FWS in each period.

Facial Wrinkle Scale endpoints for GL severity at rest include values at each timepoint.

Facial Wrinkle Scale endpoints for GL severity at maximum frown include values at each timepoint, change from baseline, None or Mild at each timepoint, and responder definitions (e.g., at least 1-grade improvement, at least 2-grades improvement). Details will be provided in the SAP.

7.5 Statistical Analyses for Safety

The safety analyses will be performed using the safety population (i.e., Safety Analysis Set). Safety assessments will include collection of AEs, vital sign measurement, physical examination, 12-lead ECGs, neurological examination (consists of assessment of cranial nerves II through VII), and immunogenicity. For each safety endpoint evaluating change from baseline, 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
4. Any serious TEAE
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 TEAEs 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. Details will be provided in the SAP. 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

There is no formal hypothesis testing to be performed for this study. Data will be presented as observed.

7.7 Sample Size Determination

No formal statistical hypothesis will be tested. The main study objective is to characterize the safety of multiple repeat treatments of AGN-151586. [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 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 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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10. Adler M, Keller JE, Sheridan RE, et al. Persistence of botulinum neurotoxin A demonstrated by sequential administration of serotypes A and E in rat EDL muscle. *Toxicon.* 2001;39(2-3):233-43.

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
BoNT/A	Botulinum Neurotoxin Serotype A
BoNT/E	Botulinum Neurotoxin Serotype E
COVID-19	Coronavirus Disease – 2019
CRF	case report form
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FWS	Facial Wrinkle Scale
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
IUS	Intrauterine hormone-releasing system
MedDRA	Medical Dictionary for Regulatory Activities
PCR	polymerase chain reaction
PDSOT	Possible distant spread of toxin
PRO	Patient-reported outcomes
PTs	preferred terms
QTcF	QT interval corrected for heart rate using Fridericia's formula
RSI	reference safety information

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
SUSAR	Suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
WOCBP	women of childbearing potential

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M21-509: A Phase 3, Multicenter, Open-label Study to Evaluate the Safety of AGN-151586 for the Treatment of Glabellar Lines

Protocol Date: 14 December 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 laws and 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

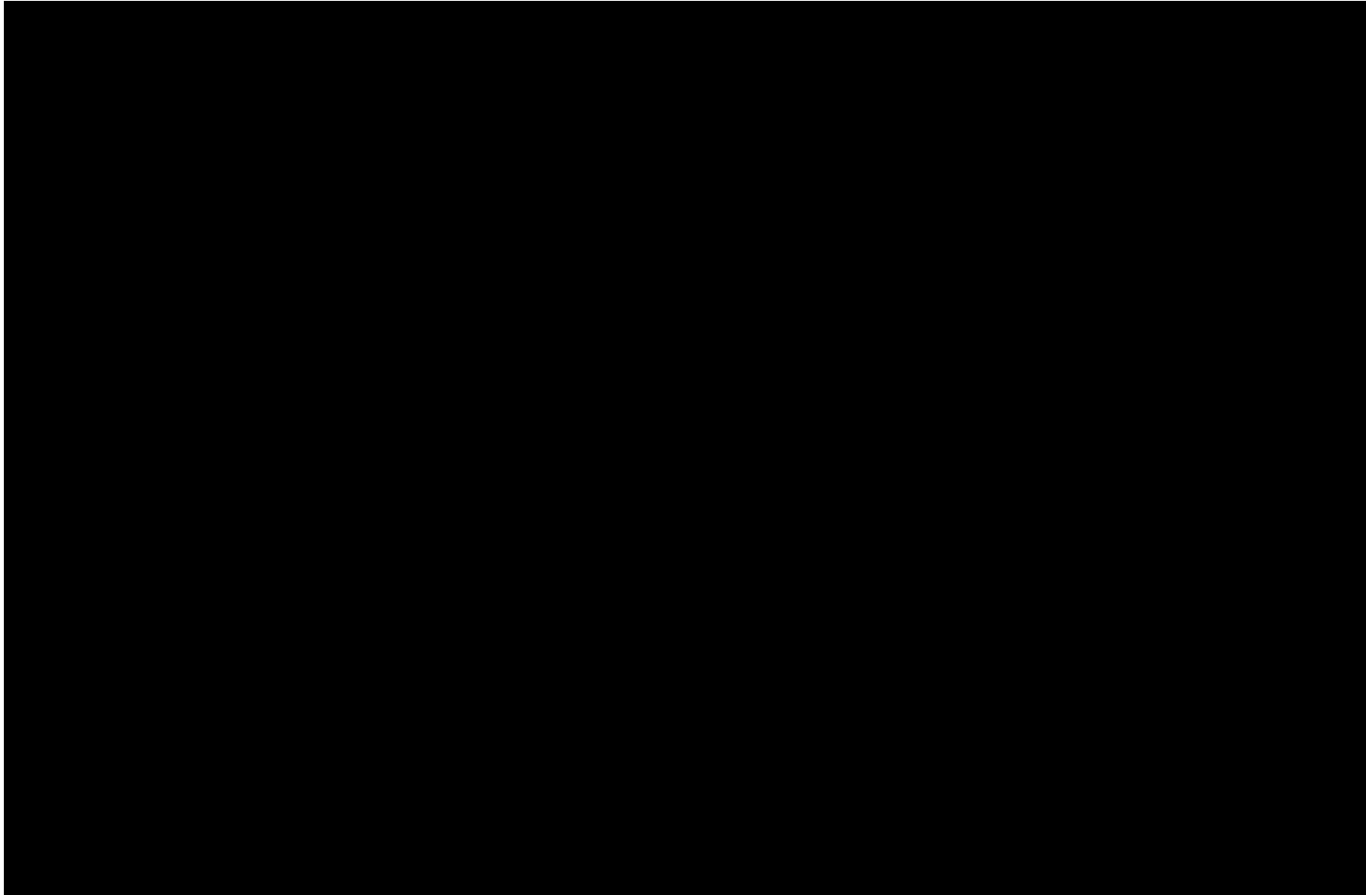
Name of Principal Investigator (printed or typed)

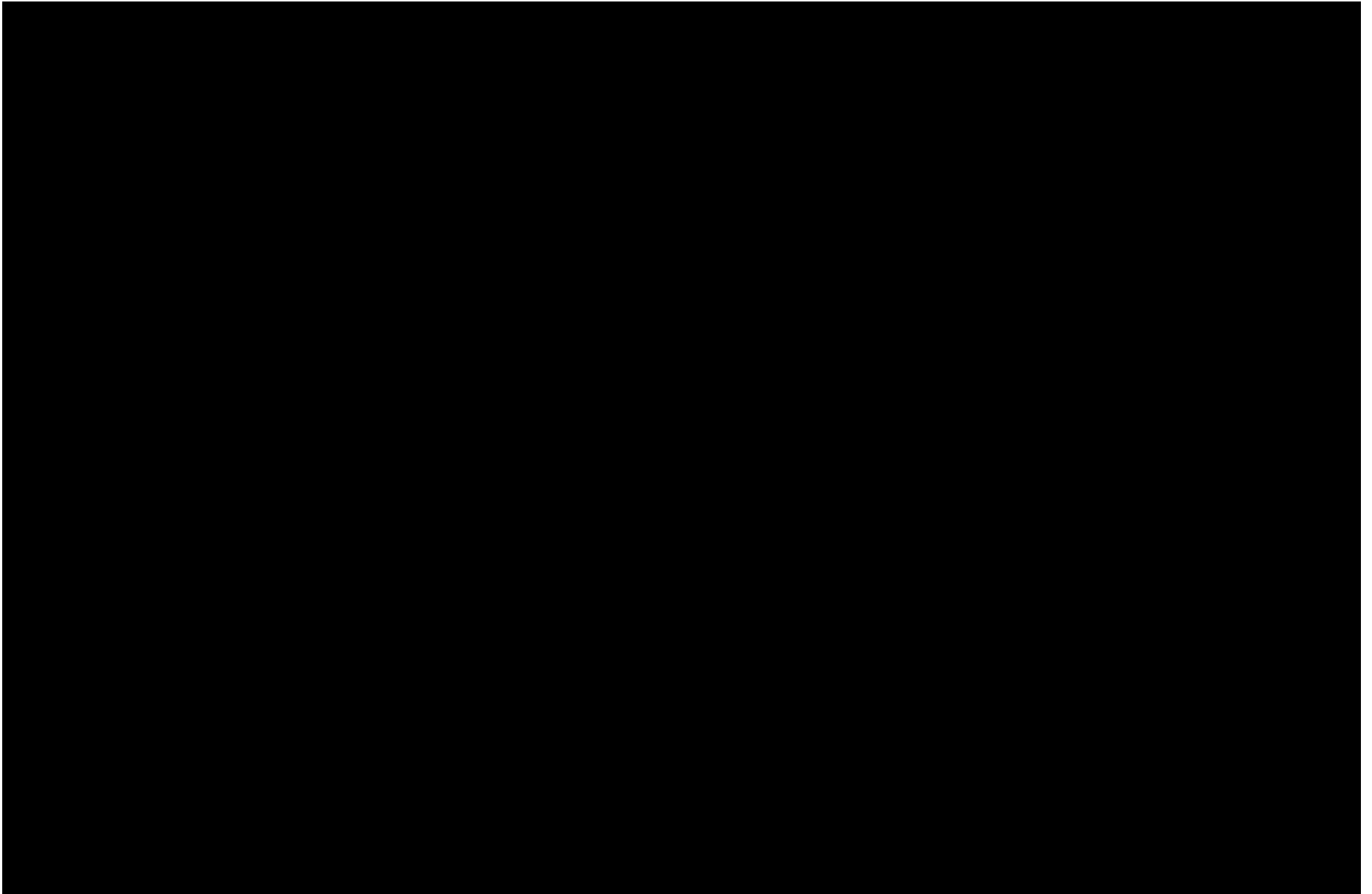
APPENDIX C. LIST OF PROTOCOL SIGNATORIES

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

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the study. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed in the Operations Manual.





APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	03 August 2021
Version 2.0	12 November 2021
Version 3.0	01 August 2022
Administrative Change 1	15 November 2022

The purpose of this version is to correct the following:

- Section 1 and Section 7.7 – Changed the number of subjects to be enrolled from approximately 880 to approximately 940 to 1100 and indicated that additional subjects may be enrolled until approximately 800 subjects complete the study.
- Section 7.7 - Dropout rate adjusted from approximately 10% to about 15% to 27%.