21 May 2026
EMADOC-1829012207-53048
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Boey

International non-proprietary name: trenibotulinumtoxinE

Procedure No. EMEA/H/C/006420/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
PD	Pharmacodynamics
PK	Pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk management plan
SmPC	Summary of product characteristics
AE	Adverse event
BoNT/A	Botulinum toxin type A
BoNT/E	Botulinum toxin type E
CBC	Complete blood count
CBPA	Cell Based Potency Assay
CI	Coordinating Investigator
COVID-19	Coronavirus disease – 2019
CRF	Case report form
ECG	Electrocardiogram
eCOA	Electronic clinical outcomes assessments
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FDA	Food and Drug Administration
FLO-11©	11-item Facial Line Outcomes
FLSQ©	Facial Line Satisfaction Questionnaire
FSFV	First Subject First Visit
FTUQ	Future Treatment Use Questionnaire
FWS	Facial Wrinkle Scale
FWS-A	Facial Wrinkle Scale with Asian Photonumeric Guide
GAC-GL	Global Assessment of Change in Glabellar Lines
GCP	Good clinical practice
GL	Glabellar lines
Hr	Hour

HCP	Healthcare Professional
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IRB	Institutional review board
IM	Intramuscular
ITT	Intent-to-treat
LD	Lethal dose
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-Observed-Adverse-Effect Level
PCI	Potentially clinically important
PCQ	Procedure Comfort Questionnaire
PD	Pharmacodynamics
PDSOT	Possible distant spread of toxin
PK	Pharmacokinetics
PT	Preferred term
QTcF QT	Interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SIMOA	Single Molecule Enzyme-Linked Immunosorbent Assay
SOC	System organ class
SPA	Self-perception of Age
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TK	Toxicokinetics
US	United States

1. regulatory information and recommendations on the procedure

1.1. Scientific advice

Table 1: Scientific advice and protocol assistance

Date	*Topic (quality/ non-clinical/ clinical)*	*Reference number / Coordinator(s)*	*Brief summary of the advice*
27 September 2021	Quality / Non-Clinical / Clinical	EMA/SA/0000063027	The Scientific advice pertained to the following quality, non-clinical, and clinical aspects: -comparability between the Phase 2 and the Phase 3 Drug Substance and Drug Product. - two-tier cell banking system and stability testing schedule Choice of animal species to conduct a pivotal repeat-dose toxicology study, repeat-dose animal toxicity study - Design of two pivotal Phase 3 controlled, safety and efficacy studies including primary and secondary endpoints, dosing, safety and immunogenicity assessments, sample size, missing data handling, hierarchical testing strategy, statistical analysis plan.
4 March 2022	Quality / Clinical	EMA/SA/0000074624	The Scientific advice pertained to the following quality and clinical aspects: - Purity determination in the drug product analytical comparability plan to support the changes being introduced to the Phase 3 clinical trial material; spore enumeration testing during stability for both the Phase 3 drug substance and the proposed two-tier cell banking system - Facial Line Outcomes questionnaire (FLO-11) Psychological Impact cut-off criteria; revised design a Phase 3, multicentre,

			open-label study to evaluate the safety of investigational product AGN-151586 for the treatment of glabellar lines (study M21-509); design of Phase 3 studies (M21-500, M21-508, M21-509) including sample sizes, analysis populations, safety neurological assessments; revised size of the safety database.

1.2. Eligibility to the centralised procedure

The applicant AbbVie Deutschland GmbH & Co. KG submitted on 27 June 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Boey (trenibotulinumtexinE), through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 2023.

The applicant applied for the following indication: *temporary improvement in the appearance of moderate to severe lines between the eyebrows seen at maximum frown (glabellar lines), when the severity has an important psychological impact in adult patients as*

• *an intermittent treatment and/or*

• *a trial option before initiating VISTABEL*

The applicant was updated to AbbVie Limited during the evaluation of the application.

1.3. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies and bibliographic literature substituting/supporting certain test(s) or study(ies).

1.4. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision EMEA-003190-PIP01-22 on the granting of a (product-specific) waiver.

1.5. Information on orphan market exclusivity

1.5.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5.2. New active substance status

The applicant requested the active substance trenibotulinumtoxinE contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5.2.1. CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that trenibotulinumtoxinE is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Steps taken for the assessment of the product

The rapporteur and co-rapporteur appointed by the CHMP were:

rapporteur:	Alexandre Moreau
Co-rapporteur:	Grzegorz Cessak

The application was received by the EMA on	27 June 2025
The procedure started on	17 July 2025
The CHMP rapporteur's first assessment report was received on	06 October 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	08 October 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	20 October 2025
The Biologics working party agreed on the Assessment Overview during their meeting on	05 November 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	13 November 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 January 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	03 March 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	26 March 2026
The applicant submitted the responses to the CHMP list of outstanding issues on	21 April 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	04 May 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Boey on	21 May 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see appendix on NAS)	21 May 2026

1.7. CHMP outcome

1.7.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

1.7.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.7.3. Opinion (positive)

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Boey is favourable in the following indication(s):

Boey is indicated for the temporary improvement in the appearance of moderate to severe lines between the eyebrows seen at maximum frown (glabellar lines), when these have an important psychological impact in adult patients.

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.7.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.7.5. Other conditions and requirements of the marketing authorisation

1.7.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

1.7.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.7.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.7.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. Introduction

2.1. Therapeutic context

Glabellar lines (GL) are furrows in the glabellar area of the face and result from the repetitive functional action of the underlying facial musculature during animation. The development of facial lines (such as GL) is an age-related change of the face that occurs because of the repetitive muscle contractions that are associated with common facial expressions. Thus, these facial lines can be observed with contraction (dynamic rhytides) or in more severe cases in repose (static rhytides). The appearance of these facial lines can lead to a miscommunication of an emotional state of anger, anxiety, disapproval, or sadness causing distress and affecting social interactions. The psychosocial impact of increasing severity in the appearance of facial lines has been associated with a negative effect on self-esteem, a decrease in perceived attractiveness and a diminished sense of well-being.

There are limited published data on the incidence or prevalence of GL. However, the prevalence of GL by age group was reported in a population of French (n = 160) and Chinese (n = 160) women. Prevalence of GL in French women by age group was, 20 to 30 years ~ 10%, 31 to 40 years ~70%; 41 to 50 years ~100%; 51 to 60 years ~100%. Prevalence of GL in Asian women was, 20 to 30 years ~10%, 31 to 40 years ~20%; 41 to 50 years ~ 54%; 51 to 60 years ~100%.

Botulinum neurotoxins are a class of neuromodulator agents that, when injected intramuscularly at therapeutic doses, produce partial chemical denervation of the muscle, thereby resulting in localized reduction in muscle activity.

There are 7 antigenically-distinct botulinum neurotoxin serotypes (A, B, C1, D, E, F, and G) that are similar in structure and action and produced by different strains of the anaerobic bacterium *Clostridium botulinum*. Of all the 7 serotypes, botulinum neurotoxin serotype A (BoNT/A) was the first botulinum neurotoxin isolated and is the most extensively characterized. Several products based on purified pharmaceutical preparations of BoNT/A have been approved by several health authorities for cosmetic/aesthetic and therapeutic indications.

BoNT/A blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals and enters the nerve terminals via endocytosis. Once inside the cell, the enzymatic domain (light chain) of the toxin cleaves SNAP-25 which is part of the SNARE complex involved in mediating neuroexocytosis and vesicular recycling. This cleavage prevents the fusion of synaptic vesicles with the plasma membrane and, thereby, inhibits the release of acetylcholine. This basic mechanism of action is responsible for its activity in focal skeletal and smooth muscle relaxation.

Similar to BoNT/A, trenibotulinumtoxinE (also designated as AGN-151586, or Botulinum neurotoxin type E (BoNT/E)) prevents acetylcholine release from presynaptic nerve terminals and as a result has been shown to inhibit muscle contraction, albeit with a faster onset and shorter duration compared

with BoNT/A. Moreover, BoNT/E inhibits neuromuscular transmission by cleaving SNAP-25, but at a different amino acid position in the protein compared with BoNT/A.

It is hypothesized that the duration of BoNT/E differs from that of BoNT/A due to the shorter persistence of the BoNT/E light chain (LC/E) within the neuron. This is likely due to LC/E being cytoplasmic, whereas the BoNT/A light chain (LC/A) is membrane-anchored and unable to recruit de-ubiquitinating enzymes (DUBs) that could otherwise slow its degradation, unlike LC/A, for which DUBs have been identified.

Additionally, results from epidemiologic studies indicate an earlier onset of the BoNT/E effect compared with BoNT/A. Humans who contracted botulism due to BoNT/E exhibited classic signs of systemic disease characterized by flaccid paralysis, with onset occurring earlier than in cases of classic botulism caused by BoNT/A.

There are currently several treatments currently available to improve the appearance of GL. In addition to botulinum neurotoxin injections such as Vistabel (also known as Botox Cosmetic; and hereafter referred to as BOTOX), options include dermal fillers, resurfacing, chemical peels, and energy-based treatments (e.g., ablative laser).

However, these treatments are associated with risks such as vascular occlusion, infection, inflammation, redness, and extended recovery times, which make botulinum neurotoxin injection a popular treatment option.

Currently, BoNT/A, such as BOTOX, is commonly used to treat GL. BoNT/A typically exhibits a gradual onset of effect, with noticeable improvements within a few days to a week after injection. The peak effect is usually reached around 4 weeks, when the injected muscles are fully relaxed. The duration of effect lasts approximately 3 to 4 months in most patients, after which muscle activity gradually resumes, and the GL reappears.

2.2. Aspects of development

The clinical development program supporting this submission included 6 studies which evaluated the safety and efficacy of trenibotulinumtoxinE (also designated as AGN-151586, or Botulinum neurotoxin type E (BoNT/E)) for improvement in the appearance of moderate to severe GL.

The clinical programme comprises the following studies:

- One dose-escalation, single-treatment placebo-controlled study (2034-201-008) of AGN-151586 in US and one supportive dose-escalation study (M24-040) in Japan;
- Two placebo controlled single-treatment trials of AGN-151586: M21-500 (US and Europe) and M21-508 (US and Canada), which aimed to recruit subjects where GL are associated with significant psychological impact;
- One open label repeat treatment study (M21-509) of AGN-151586 for aesthetic treatment of GL (up to 3 treatment periods) in US and Puerto Rico;
- One study (M23-365) with sequential administration of AGN-151586 700 U and BOTOX 20 U at Day 30 in US.

2.3. Description of the product

Botulinum neurotoxin type E (BoNT/E) is a new product developed for the treatment of GL and is not currently approved in any country.

Botulinum neurotoxin type E (BoNT/E) causes transient muscle paralysis through blockade of neurotransmission at motor nerve terminals. BoNT/E has been demonstrated to temporarily reduce the activity of the motor nerve and thereby reduce muscle contractions.

BoNT/E, like BOTOX (botulinum neurotoxin type A, BoNT/A), exerts its functional effects on motor nerves via a four-step sequential process:

1) receptor-specific binding to the presynaptic nerve terminal,

2) internalization into the terminal via endocytosis,

3) translocation of the light-chain (LC/E) portion into the cytosol,

4) enzymatic cleavage of intracellular synaptosomal-associated protein of 25 kDa (SNAP25206) to form the inactive SNAP25180 BoNT/E-cleaved product.

This protein is part of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex involved in mediating neuroexocytosis and vesicular recycling. Thus, BoNT/E exerts its effects on neuromuscular transmission in a manner comparable to that of BOTOX (both cleave SNAP25, at different amino acid sites). Alteration of SNAP25 disrupts the SNARE complex, and the motor nerve is incapable of releasing its vesicle packaged neurotransmitter, acetylcholine. Over time (days/weeks), BoNT/E-cleaved SNAP25 is replaced with uncleaved SNAP25 and motor nerve neurotransmission is re-established.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection was required.

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection was required.

2.4.3. Good clinical practice (GCP) inspection(s)

No inspection was required.

3. Quality aspects

3.1. Introduction

The finished product (FP) is presented as powder for solution for injection containing 1400 Units of trenibotulinumtoxinE as active substance (AS). After reconstitution with 1 mL of 0.9% sodium chloride solution, the final finished product has a concentration of 1400 U/mL after reconstitution.

Other ingredients are: trehalose dehydrate, poloxamer 188, L-Methionine, L-Histidine, L-Histidine hydrochloride monohydrate and sodium chloride.

The product is available in Type I glass vials fitted with a stopper (chlorobutyl rubber) and a seal (aluminium).

3.2. Active substance

3.2.1. General information

TrenibotulinumtoxinE protein is the 150 kDa subunit of the native 300 kDa complex expressed in Clostridium botulinum type E which is subsequently purified and activated during the purification (or "nicked") to produce the active neurotoxin molecule.

TrenibotulinumtoxinE protein contains 1248 amino acids. A 100 kDa heavy chain (HC) is connected to a 50 kDa light chain (LC) by a single interchain disulfide bond. The domain structure is shown in ***Figure 1***. The precursor of trenibotulinumtoxinE is activated with trypsin via enzymatic cleavage that removes G420, I421, and R422 resulting in a light chain and a heavy chain with a disulfide linkage between C412 of light chain and C426 of heavy chain.

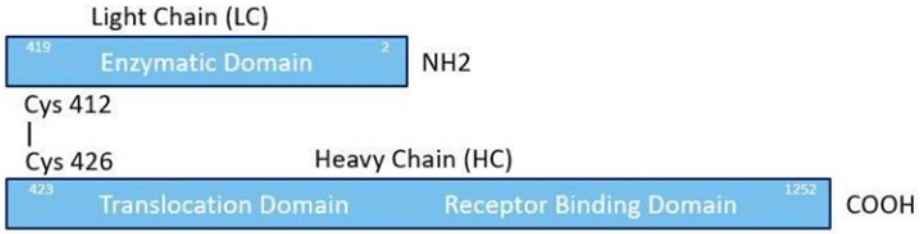


Figure 1. TrenibotulinumtoxinE Domain Structure

The HC contains a receptor-binding domain and a translocation domain, while the LC contains a catalytic domain encoding the zinc-dependent endopeptidase that proteolytically cleaves an endogenous synaptosomal-associated protein 25 (SNAP25) between amino acids 180 (Arg) and 181 (Ile), thereby disrupting the normal function of the SNARE complex, preventing docking of synaptic vesicles, and the release of acetylcholine into the neuromuscular junction, effectively inhibiting muscle contraction.

3.2.2. Manufacture, process controls and process development

The trenibotulinumtoxinE AS is manufactured in accordance with current Good Manufacturing Practices (cGMP) at Allergan Sales, LLC, located in Irvine, California, USA, also responsible for control testing and release.

Valid proof of GMP compliance has been provided for the involved sites.

Description of manufacturing process and process controls

The manufacturing process is divided into two stages:

- Fermentation and harvest
- Purification

A single batch of AS is manufactured from a single Working Cell Bank (WCB) vial. The process is initiated when a WCB vial is thawed and used to propagate the C. botulinum Type E seed culture. The entire seed culture is used to inoculate a single-use production fermentation vessel. At the end of fermentation, following depth filtration, the toxin is purified. Purification consists of multiple chromatography and filtration steps, and an activation step. The formulated trenibotulinumtoxinE AS is filtered and dispensed into vials.

The active substance manufacturing process has been adequately described. For each step, process parameters and in-process controls (IPC) are detailed with either their associated proven acceptable

ranges (PARs) / normal operating ranges (NORs), or their pre-defined action limits / acceptance criteria. The active substance manufacturing process is considered acceptable. Reprocessing will be allowed in the event of an equipment failure or in the event of a filter integrity test failure.

Control of materials

Adequate information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including analytical procedures) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin (yeast extract and recombinant trypsin) used in the establishment of cell substrate.

TrenibotulinumtoxinE active substance is manufactured using Clostridium botulinum Type E. History of the cell line was satisfactorily detailed. A two-tiered cell banking system is used and sufficient information is provided regarding testing of Master Cell Bank (MCB) and WCB and release of future WCBs. Genetic stability has been demonstrated for cells at and beyond the limit of cell age.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process validation

The active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the process consistently produces trenibotulinumtoxinE of reproducible quality that complies with the predetermined specification and in-process acceptance criteria. Additional data was provided to confirm consistent and robust removal of spores during the process and their absence in the clarified harvest.

Impurity clearance was suitability addressed by monitoring during purification. Consistent reduction of these impurities to acceptable levels was demonstrated in the PPQ batches.

Validation of the process is further supported by additional studies including batch uniformity, hold times for process intermediates, and shipping validation. A concurrent validation protocol has also been established for reprocessing of the filtration.

Manufacturing process development

The trenibotulinumtoxinE AS manufacturing process was developed to achieve improvements in product quality, process performance, and to scale-up to anticipated commercial need. The initial process, Process A, was developed and used for the manufacture of AS and FP to supply non-clinical and Phase 2 clinical studies. The intended commercial process, Process B, was further developed by AbbVie for the development scale and scaled up to supply Phase 3 clinical trial material as well as primary stability samples to support product shelf life.

The material used for the phase 3 pivotal clinical study derives from the same manufacturing process (Process B) as the one intended for commercial active substance. Minor modifications were implemented for enhanced process robustness and facility fit in later stages, but these modifications are without potential impact on process performance and product quality. Therefore, the pivotal

clinical material can be considered as representative of the commercial one.

For each process version, a comparability study has been carried out demonstrating that, apart from some expected differences, the change did not have a significant influence on the quality of the product.

The manufacturing process development included an assessment of the critical quality attributes (CQAs) and their relationship to the trenibotulinumtoxinE active substance manufacturing process. Process parameters and CQAs have been considered for each manufacturing step in process characterisation studies (i.e., small-down models and pilot-scale models). The results were then used to establish normal operating ranges (NORs) and proven acceptable ranges (PARs). Process parameters that have been determined to be critical due to their impact on the CQAs are classified as critical process parameters. The available development data, the proposed control strategy and batch analysis data support the proposed PARs and NORs.

3.2.3. Characterisation

The trenibotulinumtoxinE active substance has been sufficiently characterised by orthogonal physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure and biological activity. The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants.

Product-related impurities and process-related impurities have been sufficiently identified and characterised. The amounts of product-related impurities are efficiently and reproducibly controlled by the purification process as demonstrated by the results from historical and validation batches. Similarly, the impurity clearance data for process-related impurities indicate that residual levels are sufficiently low to ensure patient safety. Outcome summary of risk assessment for the clearance of process-related impurities derived from raw materials (i.e, fermentation media components and purification process buffers) has been given. In summary, the amount of each raw material remaining in a dose of FP is well below the threshold of toxicological concern (TTC) of 1.5 mg established in ICH M7 for an individual impurity dosed daily for greater than 10 years.

In summary, the characterisation is considered appropriate.

3.2.4. Control of active substance

The active substance release and shelf life specification was developed in line with ICH Q6B and includes tests for general properties, identity, quantity, biological activity (cell-based assay), charge heterogeneity, purity, and safety (bioburden and bacterial endotoxins).

The proposed analytical procedures and corresponding limits are adequate for routine control of the active substance at release and shelf life. They are generally in line with ICH guidelines, and Ph. Eur. The proposed acceptance criteria for trenibotulinumtoxinE active substance were justified based on preclinical and clinical experience, batch release and stability studies, process understanding gained throughout development, analytical capability, and process capability. For quantitative tests, a statistic based-approach was considered where sufficient data is available. The acceptance criteria are aligned for batch release and shelf-life.

In summary, the proposed tests and associated acceptance criteria are considered adequate to ensure control of the physicochemical and biological attributes of trenibotulinumtoxinE AS. As requested, the commercial acceptance criteria have been revised. The newly proposed acceptance criteria are considered acceptable.

Analytical procedures and reference standards

The analytical procedures used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented. Future Working Reference Standard candidates will be qualified from a representative AS batch that passed all acceptance criteria, and all activities will be performed under relevant protocols.

In the interest of animal welfare, a Cell Based Potency Assay (CBPA) was developed and implemented to replace the mLD50 for release and stability testing. CBPA reflects the in vivo mechanism of action of trenibotulinumtoxinE, including binding to the cell-surface receptors, internalization, translocation of the light chain (LC) into the cytosol, and LC-mediated proteolytic cleavage of synaptosome-associated protein of 25 kilodaltons (SNAP25). Cross-validation of CBPA against mLD50 demonstrated that both methods are equivalent for specific potency testing of trenibotulinumtoxinE AS.

The LAL test method is currently used to monitor bacterial endotoxins. The Applicant indicates that method development and robustness studies are planned in 2026 using a recombinant cascade reagent (rCR) in order to reduce the reliance on horseshoe crabs.

Batch analysis

Analytical data for batches of the active substance manufactured at commercial scale are provided. The results are within the specifications and confirm consistency of the manufacturing process.

3.2.5. Stability

The claimed shelf-life for the active substance is mainly based on data from primary stability batches (PSB).

36-month stability are available for PSB batches. In addition, 36-months stability data generated from supportive batch produced at smaller scale was also provided.

The parameters tested are the same as for release. All tested parameters were within the specifications. The stability indicating nature of the methods have been proven by forced degradation and validation studies.

Overall, the results of stability studies have met the acceptance criteria for all tests performed.

Based on data available, the proposed shelf-life for the active substance is agreed.

Additional stability studies were conducted to assess the effect of freeze/thaw and light on trenibotulinumtoxinE AS. The results demonstrated that the AS is stable when exposed to repeated freeze/thaw cycles (up to 9) with no impact to product quality. In the opposite, trenibotulinumtoxinE was found sensitive to exposure to cool white light and UV light and care should be taken while handling AS to minimize unnecessary exposure to light.

Finally, the proposed post-approval stability protocol is appropriate for annual GMP stability testing.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

Description of the product

TrenibotulinumtoxinE Finished Product is supplied as 1400 Unit (U) of powder for solution for

injection in Type I glass vials fitted with a stopper (chlorobutyl rubber) and a seal (aluminium). It is reconstituted with 1 mL of 0.9% sodium chloride solution. The lyophilized powder may also sometimes appear as a broken cake in the vial. The final FP has a concentration of 1400 U/mL after reconstitution.

Other ingredients are: trehalose dehydrate, poloxamer 188, L-Methionine, L-Histidine, L-Histidine hydrochloride monohydrate and sodium chloride.

One unit corresponds to the calculated intraperitoneal median lethal dose (LD50) in mice. The units by which the potency of the preparation of trenibotulinumtoxinE is being measured are not interchangeable with other commercial preparations of botulinum toxin.

The composition of the finished product per vial (lyophilized powder) and per mL (reconstituted solution) is described.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The FP selected container closure system is a Type I glass fitted with a coated chlorobutyl rubber stopper and aluminum crimp seal. The vials and rubber stoppers are in compliance with the appropriate Ph. Eur. monographs for primary containers (Ph. Eur. 3.2.1) and closures (Ph. Eur. 3.2.9). Specifications, certificates of analysis and representative drawings of the vial, stopper and cap, including the dimensions of each component, are provided.

The choice of materials and physical aspects of the container closure are well justified, addressing the various key attributes such as container closure integrity and functionality, compatibility, robustness during shipment and safety regarding extractables and leachables. The FP is packaged in a carton. The intended secondary packaging material is sufficient for protection from light.

The FP is a sterile, non-pyrogenic, single use lyophilized product without added anti-microbial preservatives. Microbiological quality is ensured by multiple control steps throughout the manufacture including tests for bioburden, sterility, and bacterial endotoxins. In addition, the manufacturing process and the manufacturing facilities are designed to minimize risk of microbiological contamination, and regular environmental monitoring is performed. The FP is sterile filtered followed by aseptic filing into sterile glass containers.

FP reconstituted with preservative-free 0.9% sodium chloride solution for injection is compatible with the primary packaging through 24 hours at 2 – 8°C. Reconstituted FP is compatible with polypropylene (PP) and polycarbonate (PC) syringes and stainless-steel hypodermic needle when stored for up to 1 hour at RT/RL.

Pharmaceutical development

The development of the FP was guided by previous experience with lyophilized formulations of neurotoxin finished products, as well as experience during process development characterisations.

The quality target product profile (QTPP) was suitably defined and the critical quality attributes were identified.

Detailed description of formulation development has been presented. Development covers selection of pH, selection of excipients and their concentrations, selection of protein concentration, selection of container closure system, as well as formulation robustness studies and effect of residual moisture content on the stability of trenibotulinumtoxinE FP. The chosen formulation satisfies the presented QTPP and is also robust at the intended long-term storage temperature of 2-8°C and post-reconstitution for product administration (intramuscular injection).

Pivotal clinical studies were conducted with the proposed commercial formulation.

Sufficiently detailed data in relation to overfill studies have been presented. A 1.0 mL reconstitution was chosen to reduce error risk and deliver the correct 0.5 mL dose.

Manufacturing process development

The manufacturing process development has been evaluated through the use of risk assessments, prior manufacturing knowledge, and extensive process characterisation studies to identify the critical product quality attributes and critical process parameters. Critical quality attributes and critical process parameters have been adequately identified. The control strategy is considered acceptable.

3.3.2. Manufacture of the product and process controls

Abbvie Deutschland GmbH & Co. KG in Germany is responsible for the FP batch release.

For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The FP manufacturing process consists of compounding of the bulk excipient solution (BES), followed by filtration. The AS is then diluted with the BES to produce bulk product at the target concentration. This compounded bulk product solution is then sterile filtered, aseptically filled into vials, partially stoppered, lyophilized, and sealed with flip-off caps. The vials then undergo 100% visual inspection. The process is considered to be a standard manufacturing process.

The manufacturing process and its control, as well as critical equipment have been described in sufficient detail. Acceptance criteria/ranges for the in-process controls and the claimed hold-times are adequately justified.

The process has been validated on consecutive batches.

The PPQ confirmed the process parameters and critical process parameters of the FP batches were all within the proven acceptable range and the results supported the process hold times. Samples were collected at beginning, middle and end of filling of each PPQ batch to confirm the filling process lot uniformity. Homogeneity of results throughout the lyophilizer chamber was also satisfactorily addressed to demonstrate the process is robust and consistent.

Additional validation activities like microbial retention study, media fill runs, and shipping qualification were also conducted to complete the process validation strategy.

The manufacturing process has been adequately validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

3.3.3. Control of Finished Product

Specifications

The finished product release and shelf life specification are developed in line with ICH Guideline Q6B. It includes tests for: appearance, general properties, microbial assurance (bacterial endotoxins and sterility), identity, particulate matter, water content, container closure integrity, concentration and potency. Purity is controlled at the AS level as the low amount of AS in FP vial does not afford direct monitoring of this property.

The acceptance criteria are based on process development, batch data, stability studies for

trenibotulinumtoxinE FP, as well as regulatory requirements.

The proposed analytical procedures and corresponding specification limits are adequate for routine control of the finished product at release and shelf life. They are in line with ICH guidelines and Ph. Eur. and batch data.

The potential presence of elemental impurities in the finished product was adequately assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed according to the applicable guidance, however, the Applicant has presented very short summary information. A Major Objection (MO) was raised and the Applicant was requested to provide a detailed risk evaluation concerning the presence of nitrosamine impurities in the product in question taking into account the findings and principles outlined in the Article 5(3) referral on nitrosamine impurities in human medicinal products CHMP assessment report (EMA/369136/2020) and the current version of "Questions and answers for marketing authorization holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products". In responses to D120, comprehensive risk assessments of the manufacturing processes of the AS and FP, excipients, and primary packaging were provided. In addition, the potential introduction of nitrosamine impurities via cross-contamination from other sources has been considered. No risk of nitrosamine impurity formation or introduction was identified and the MO was considered resolved.

Analytical procedures and reference standards

The analytical procedures used to control the quality of the finished product have been provided. Non-compendial methods are appropriately validated in accordance with the ICH guidelines. Additional validation data were provided for the ELISA method to demonstrate the dilution procedure is accurate and precise. Satisfactory information regarding the reference standards used for assay testing has been presented and is presented in the active substance section.

Batch analysis

Batch analysis data (clinical, stability, and process performance qualification (PPQ)/ pre-PPQ batches) of the finished product are provided. The results are within the specifications and confirm consistency of the manufacturing process.

3.3.4. Stability of the product

A shelf-life of 2 years was initially proposed for the lyophilized finished product when stored at the long-term storage condition of 2°C to 8°C. As updated stability data was provided during assessment phase, a shelf life to 3 years is claimed.

This claim is mainly based on formal stability studies conducted on three primary batches in accordance with ICH guidelines. The primary stability batches were produced using the commercial manufacturing process at the intended commercial manufacturing facility. Samples from these stability studies are stored in the commercial primary packaging. In addition, stability studies are being performed on three process performance qualification (PPQ) batches.

The parameters tested are the same as for release. The analytical procedures used were the same as for release and were stability indicating as demonstrated through studies under forced conditions.

All results from these batches have met the acceptance criteria for all tests performed at the available time points. No significant changes in any assay result, including physical appearance, pH,

osmolality, residual water content, particulate matter, vacuum, ID, potency, sterility, bacteria endotoxin, container closure integrity, and reconstitution time were observed at the long-term storage condition at 2°C to 8°C.

Therefore, the stability results justify the proposed FP shelf life of 3 years at 2-8°C in the proposed container.

Additionally, stability studies conducted at the accelerated condition show that excursions to 25°C up to 45 days do not adversely affect the quality of the FP. Photostability testing following the ICH guideline Q1B was performed and results indicate that the FP needs protection from light.

In-use stability studies were performed to assess compatibility with solvent (i.e. 0.9% sodium chloride solution) and relevant administration devices. Overall, the compatibility data support that finished product, reconstituted with preservative-free 0.9% sodium chloride solution for injection, is stable when stored in its primary container for 24 hours at 2 – 8°, as described in the SmPC.

3.3.5. Post approval change management protocol(s)

Not applicable

3.3.6. Adventitious agents

TSE and viral adventitious agents risks are deemed negligible: TrenibotulinumtoxinE AS is manufactured using Clostridium botulinum; all raw materials used in MCB, WCB and AS manufacturing are declared animal-origin-free; data related to raw materials of biological origin used during precursor cell banks establishment to MCB are acceptable.

3.4. Discussion on chemical, pharmaceutical and biological aspects

TrenibotulinumtoxinE active substance is thoroughly characterised, manufacturing process is well controlled, specifications are set according to ICHQ6B, and stability is demonstrated. Manufacturing process validation data assures that the AS manufacturing process is appropriately validated and can produce batches of consistent quality. The AS process control strategy is properly justified A Major Objection relating to nitrosamines risk assessment has been adequately addressed during the procedure.

A MO on the NAS claim was duly justified and considered resolved. The NAS claim has been further substantiated with results from BLASTP search on NCBI. Based on the review of available data, it is considered that trenibotulinumtoxinE is to be qualified as a new active substance.

Reference standards are sufficiently described and characterised. A comprehensive risk assessment on impurities has been provided and found acceptable.

The finished product is a powder for solution for injection and each FP vial contains 1 400 units of trenibotulinumtoxinE produced in Clostridium botulinum cells. The excipients are of Ph. Eur. quality

Finished product's development data covers formulation development, manufacturing process development and overfill justification. FP manufacturing process is well controlled and validated. The FP specifications are set according to ICHQ6B and Ph.Eur. monograph on Botulinum Toxin A, which is endorsed. Stability of the FP is adequately demonstrated and justifies the proposed shelf-life.

The quality part of the dossier is sufficient and adequate. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality

characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

3.5.1. Recommendation(s) for future quality development

Not applicable

4. Non-clinical aspects

4.1. Analytical methods

Systemic exposure was assessed using a sensitive SIMOA-based ELISA method qualified in mouse, rat, and monkey serum. The method demonstrated adequate selectivity and linearity across most concentration ranges, with an LLOQ considered appropriate for this type of product. However, accuracy and precision were poor at the lowest concentrations in rat serum.

4.2. Pharmacology

4.2.1. Pharmacodynamics

4.2.1.1. Primary pharmacodynamics

The pharmacodynamic data demonstrate in mouse Digit Abduction Score assays that BoNT/E exhibits a characteristic dose-dependent neuromuscular blocking effect with a distinct profile differentiating it from BoNT/A products:

1. Clear dose-response relationship, confirmed across three studies with rather consistent ED50 values (~51 U/kg)
2. Rapid onset of action within 3–4 hours
3. Short duration of effect with complete recovery within 3–4 days in mice
4. 5.3-fold lower potency compared to BOTOX on a unit basis

The pharmacodynamics profile is consistent with the known mechanism of action of BoNT/E.

4.2.1.2. Secondary pharmacodynamics

No data provided.

4.2.1.3. Safety pharmacology

The safety pharmacology package is composed of two studies. A GLP single-dose study in cynomolgus monkeys addressed cardiological and neurological endpoints and a non-GLP single-dose in CD-1 mice for respiratory endpoints. No evidence of BoNT/E-related cardiovascular effects was found, consistent with the known mechanism of action of botulinum neurotoxins. The documented

clinical neurological effects (limb weakness, abnormal gait) at 3 ng/kg are consistent with expected pharmacology. Respiratory safety pharmacology studies in mice demonstrated dose-dependent effects, with sustained reductions in tidal volume observed only at 150 U/kg, a dose associated with mortality. At 125 U/kg, respiratory changes were transient and inconsistent, and at 100 U/kg only isolated, non–test-article–related alterations were detected. Repeat dosing at 100 U/kg was not tolerated, though without direct respiratory correlates.

From a regulatory perspective, the respiratory safety pharmacology study is not considered acceptable as it was not conducted in compliance with GLP. However, this limitation is considered addressed by the assessment of respiratory endpoints included in the repeat dose toxicity studies, in accordance with the guideline ICH S6 (R1).

4.2.1.4. Pharmacodynamic drug interactions

No data provided.

4.2.2. Pharmacokinetics

No classical non-clinical pharmacokinetic studies to characterize absorption, distribution, metabolism, or excretion were conducted, which is acceptable under ICH S6 given the nature of the product.

Toxicokinetic data were generated in CD-1 mice, the most sensitive species in toxicology studies, following intramuscular administration. Systemic concentrations were generally low or below the limit of quantification. A few sporadic values were detected, including a mean concentration of 20.4 pg/mL at 1 h (corresponding to ~1 U/mL based on the reported potency), while concentrations were already below the limit of quantification by 4 h and are not correlated with any clinical sign, thus no clinical significance is expected. Moreover, approximately 18% of serum samples were reported as hemolyzed, and one high value (1362 pg/mL) was excluded as an outlier, both of which reduce confidence in the dataset. Due to sporadic and inconsistent values, AUC and other PK parameters could not be calculated.

Given the intended local mechanism of action and the overall negligible systemic exposure, this limitation is not unexpected but lead to some uncertainty regarding the potential for systemic leakage.

4.3. Toxicology

4.3.1. Single-dose toxicity

The toxicity studies for Botulinum neurotoxin serotype E (also AGN-151586, trenibotulinumtoxinE and EB-001) have been performed in line with ICH S6 (R1) using mice, rats and monkeys via intramuscular (IM, in the left gastrocnemius muscle) injection route, the proposed route of administration in clinics. Single dose toxicity studies were performed on mice, rats and monkeys. Generally, in all animal species, expected effect of weakness in the injected limb was observed leading to abnormal gait. Abdominal swelling was also observed as well as abdominal distension in mice. Body weight gain was decreased along with food consumption at higher doses and in a dose-dependent manner. In non-tolerated doses, further spread or the toxin lead to involvement of ipsilateral limb indicating spread, labored breathing, weakness, decreased activity and lastly, death.

In SD rats, AGN-151586 induced limited usage of injected limb and abnormal gait and all. Coordination deficits, decreased muscular tone, decreased activity, labored breathing, tremor, convulsion, prostration, and/or involvement of contralateral musculature indicating spread of the toxin,

chromodacryorrhea, chromorhinorrhea, piloerection, decreased weight gain and food consumption, and weakness were noted at non-tolerated doses. Other effects are common for IM higher dose groups or for IV and IM; clinical pathology: increase white blood cell and lymphocyte count decrease in reticulocyte count during the study, later increased at the end of studies 2034-T01-065 and 5001680 indicating a possible bone marrow response, increase in glucose and triglycerides, shortening of activated partial thromboplastin time, mild decrease in alkaline phosphatase, increases in red cell parameters, total protein, albumin, globulin, and urea in males given. At NOAEL, there is still an atrophy of left and right gastrocnemius muscle indicating spread with persistence in the left injected muscle, and in the right side for 2 males at D27 however minimal at the end of recovery, but no reported adverse events.

In cynomolgus monkeys, limited usage of the left hindlimb/hindpaw and abnormal gait was observed. Decreased activity, muscle tone, and lack of coordination revealed spread of the toxin. Adverse systemic reactions after IM injections at non tolerated dose : hunched posture, decreased activity, decreased muscle tone, labored breathing, limited usage of the hindlimbs, and abnormal gait. Up to 200 U/kg observed effects were local and consisted in limb disuse, this dose level was considered to be the monkey NOAEL.

4.3.2. Repeat-dose toxicity

Based on tolerated single doses, mice were determined to be the most sensitive species, more sensitive than monkeys which are, also, more sensitive than rats. Therefore, repeated-dose toxicology studies were conducted on mice. Common to toxicological studies, both single and repeated dose, was limited usage of the injected limb (related to pharmacological effect) and swelling (mild to severe at 75 U/kg) of the treated left hindlimb in all treatment groups starting two hours postdose and continuing up to five days following each dose then resolved in tolerated doses, with a dose-dependent increase in number of animals affected, duration of swelling and limited limb usage. This effect is directly linked to PD effect of BoNT/E in inducing muscle paralysis. In 14-day study with 3 IM injections of 100 U/kg, dose was not tolerated. There was no consistent systemic exposure, and most samples were below LOQ.

In GLP repeated-dose toxicology, at interim necropsy, scattered myofiber necrosis with focal areas of regeneration were observed, evidenced by increased size and density of myofiber nuclei, with a more open chromatin conformation, and were characterized by increased eosinophilia with cytoplasmic fragmentation and/or mononuclear phagocytic infiltration. At interim necropsy, myofiber regeneration was minimal to mild, accompanied in some cases by minimal myofiber necrosis that was not considered adverse based on the low severity, limited extent, regenerative nature, and the recovery of clinical observations of limited use of left hindlimb. Increased use of the injected limb led to increase muscle weight of left biceps brachii significant for the 25 U/kg/group in males. Following the 7th injection, at terminal necropsy on day 176, there was a non-significant, but likely AGN-151586-related decrease in the weight of the injected left gastrocnemius muscle in males at all doses, but not in females. Minimal to mild myofiber atrophy was noted histologically. Minimal to mild myofiber regeneration was observed in left gastrocnemius and was similar to this observed at interim necropsy in terms of severity. Regeneration was also present in adjacent hindlimb muscles at all doses. Findings were all considered non adverse.

4.3.3. Genotoxicity

Genotoxicity studies with AGN-151586-DP have not been conducted. This approach is consistent with the recommendations of ICH S6 (R1).

4.3.4. Carcinogenicity

Based on the infrequent administration of AGN-151586, its structure, class and biologic origin, and in consideration of ICH S6 Guideline, there is no reasonable cause for carcinogenic concern.

4.3.5. Developmental and reproductive toxicity

In a GLP-compliant dose range-finding embryofetal development study conducted in mice, 2/8 high dams at the top dose level of 75 U/kg were found dead on the day following the second intramuscular injection. In surviving litters, no treatment-related embryofetal lethality or malformations (external, visceral) were noted.

4.3.6. Toxicokinetics and exposure margins

Not applicable.

4.3.7. Local tolerance

Not applicable.

4.3.8. Other toxicity studies

Not applicable

4.3.9. Ecotoxicity/environmental risk assessment

Table 2: Summary of main study results: Phase I

Substance (INN/Invented Name):	AGN-151586 / BOEY
CAS-number (if available):	1350492-91-9
PBT/vPvB screening	
PBT/vPvB statement:	AGN-151586 is considered to be not PBT, nor vPvB

Phase I			
Parameter	***Value***	***Unit***	***Conclusion***
PEC_{sw}	0.000000058 µg/L	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)	N/A	N/A	N/A

$PEC_{surfacewater}$ is below the action limit of 0.01 µg/L. Consequently, a Phase II risk assessment is not required.

4.4. Overall discussion and conclusions on non-clinical aspects

4.4.1. Discussion

The application relies partially on available literature data regarding pharmacology and toxicology of botulinum toxin. The applicant provided data demonstrating reduction of twitch tension and recovery

of rat skeletal muscle following intramuscular (IM) administration of BoNT/A or BoNT/E at paralytic doses.

The applicant conducted Digit Abduction Score (DAS) studies in mice. AGN-151586 demonstrated a dose-dependent response in the mouse DAS assay with an ED50 value of 50.99 U/kg. This potency value was 5.3-fold less potent than that of BOTOX. Furthermore, AGN-151586 exhibited a dose-dependent kinetic profile for the DAS duration of action, showing a relatively fast onset and short duration of response at each dose.

The pharmacodynamics package sufficiently characterised AGN-151586.

The safety pharmacology program shows the expected profile for AGN-151586. No cardiological nor Central Nervous System toxicity was found, respiratory toxicity was found at supraclinical doses.

The applicant did not conduct a separate safety pharmacology study but evaluated respiratory parameters in a single-dose study in mice. Mice received a single IM injection of 0 (vehicle), 100, 125, or 150 U/kg or 3 IM injections (with a 14-day interval) of 100 U/kg AGN 151586-DP to their left gastrocnemius muscle. A single IM injection of 150 U/kg/day AGN-151586-DP resulted in a reduction of tidal volume from 28 through 56-hour postdosing and an increase in minute volume at 10 hours postdosing. A single IM injection of 125 U/kg/day AGN-151586-DP resulted in an increase in minute volume from 8 to 12 hours post-dosing. There was no statistically significant change in minute volume, but minute volume was reduced for all 3 treatment groups at 56 hours postdosing compared to control values. Of note, there were no changes in respiratory function following single IM administration of AGN-151586-DP at 100 U/kg through 56 hours post dose in CD-1 mice.

Assessment of safety neurological and cardiovascular endpoints were performed in the GLP toxicology study in monkeys. The AGN-151586-DP doses of 0.3, 0.9, and 3.0 ng/kg, were given by IM injection into the gastrocnemius muscle. There were no AGN-151586-DP-related neurological changes on Day 2, prior to clinical sign onset. There were several neurological abnormalities observed on later timepoints, but the relation to AGN-151586-DP treatment was not clear. There were no AGN-151586-DP-related electrocardiographic or neurological abnormalities reported in monkeys given the single IM doses of up to 134 U/kg and 55 U/kg for males and females, respectively.

It is agreed that hERG assay can be waived based on the fact that botulinum neurotoxins do not affect the potassium channel. Evaluation of ECG in the definitive GLP toxicity studies in monkeys is considered acceptable. No secondary pharmacology studies have been conducted. This is considered acceptable.

Pharmacokinetics of AGN-151586 was assessed in mice following intramuscular injection in Study 2034-P01-065. 50 female CD-1 mice were dosed with 100 U/kg IM dose of AGN-151586, and blood was collected from 5 animals per timepoint for up to 168 hours post dose. Due to sporadic concentrations measured throughout the time course of this study, PK parameters could not be calculated. The highest mean concentration measured in serum was observed at 1-hour post dose.

No classical ADME study was provided in line with ICH S6, but one absorption assay was included in the non-clinical PK package.

The toxicity studies have been performed in line with ICH S6 (R1) using mice, rats and monkeys via intramuscular. Generally, in all animal species, expected effect of weakness in the injected limb was observed leading to abnormal gait. Abdominal swelling was also observed as well as abdominal distension in mice. Body weight gain was decreased along with food consumption at higher doses and in a dose-dependent manner. In non-tolerated doses, further spread or the toxin led to involvement of ipsilateral limb indicating spread, labored breathing, weakness, decreased activity and lastly, death. No major objection was identified.

In the 3-month repeat dose toxicity study 2034-T08-065, CD-1 mice were exposed to 3 IM injections approximately every 28 days of 0 (vehicle), 25, or 100 U/kg of AGN-151586 to their left gastrocnemius

muscle. No AGN-151586-related effects on serum chemistry, organ weights, or macroscopic evaluations were reported. 2 animals from 100U/kg dose died. Both deaths were considered to be drug related. However, there were no clear differences in clinical observations between 25 or 100 U/kg doses, lameness/weakness in the injected left limb, often leading to an abnormal gait were observed. In histopathological examination there were no changes in muscle weights in AGN-151586-treated animals. However, minimal to mild necrosis of individual myofibers in the left gastrocnemius muscle were reported. Nevertheless, four-weeks after injection there were no AGN-151586-related histologic findings.

In Study 2034-T09-065, potential toxicity of AGN-151586 after administration of up to 7 total doses into the left gastrocnemius muscle once monthly to male and female Crl:CD1® (ICR) mice was assessed. Moreover, the potential reversibility of any findings after 97 days of recovery was assessed. There were no AGN-151586-related unscheduled deaths or early terminations. However, 11 animals were euthanized early or were found dead. Nevertheless, these deaths were considered unlikely to be related to AGN-151586 administration based on the macroscopic and/or microscopic evaluation, the timing of the clinical observations requiring early termination. However, it is noted that there was a minimal, but likely AGN-151586-related decrease in the absolute and relative weight of the injected muscle in males at all doses but not in females at the Terminal necropsy, which was attributed to the differences in in total delivered dose per animal between males and females The No-Observed-Adverse-Effect Level (NOAEL) for AGN-151586 was 75 U/kg which was the highest dose administered.

Possible consequences of several consecutive injections of AGN-151586 on muscle tissue were discussed, and due to short duration of action, generally IM treatment with AGN-151586-DP should be expected to have limited effect on muscle tissue.

Evaluation of anti-drug antibodies was negative. No genotoxicity and carcinogenicity studies with AGN-151586-DP have been conducted. This is considered acceptable.

The applicant provided the results of a GLP-compliant dose range-finding embryofetal development study in mice. No embryofetal lethality or malformations (external, visceral) were reported. There were 2/8 maternal animals found dead at the high dose level reported both with 100% postimplantation loss (all dead fetuses) at necropsy. While it can be difficult to disentangle developmental from maternal toxicity, it is generally considered that fetal deaths observed exclusively in decedent animals are secondary to the cessation of maternal physiological support rather than a direct embryo-fetal effect. In the present case, this is further supported by the absence of any treatment-related increase in postimplantation loss in the 6/8 surviving litters including no fetal death. Consequently, these findings do not indicate a selective developmental hazard. In view of the nonclinical and clinical data available with BOTOX shown to have a mode of action similar to that if AGN-151586-DP, and considering that AGN-151586-DP could not be detected in peripheral blood after intramuscular injection to patients (see SmPC 5.2), it is agreed that additional reproduction toxicity studies are not required with SmPC section 5.3 indicating that conventional developmental and reproduction toxicity studies were not performed and SmPC section 4.6 reporting that animals studies are insufficient with respect to reproductive toxicity. In addition, adverse effects on male fertility and female estrous cycling and fertility reported with BOTOX (see e.g. EPAR for Nuceiva) are taken into consideration in SmPC 4.6. The lack of juvenile animal studies is acceptable as therapeutic indication is restricted to adult patients.

In the ERA section, AGN-151586's PECsw did not trigger a phase II.

4.4.2. Conclusions

The pharmacological profile of trenibotulinumtoxinE is well characterised in *in vivo* study and the provided literature.

The systemic exposure in animals appears negligible, consistent with the intended local pharmacology. The toxicokinetics data are limited in robustness due to methodological issues, sporadic quantifiable concentrations, and the absence of biodistribution studies. Consequently, the non-clinical safety assessment relies primarily on toxicology findings.

In toxicology studies, the incidence of most findings was not significantly higher than in control animals and were therefore not attributed to treatment. Expected toxicological effects such as weakness in the injected limb leading to abnormal gait, abdominal swelling and abdominal distension in mice were observed and related to injection and mechanism of action. In non-tolerated doses, symptoms of toxin spread appeared such as involvement of ipsilateral limb, labored breathing, weakness, decreased activity and lastly, death.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

5.1.2. Tabular overview of clinical trials

Table 3: Tabular overview of main clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
Phase 2b 2034-201-008	26 Sept 2019 to 22 Oct 2020 (US) 198/200 subjects (40x5) (AGN-151586 30 vs pbo 10 100 U: 32 vs pbo 8 250 U: 28 vs pbo 12 400 U: 27 vs pbo 11 600 U: 30 vs pbo 10 **750** U: 31 vs pbo 9	Multicentre, randomised, double-blind, placebo-controlled ascending dose-ranging	AGN-151586 (IM) 100 U, 250 U, 400 U, 600 U, **750** U	- Adults (18-65 years) with moderate to severe GL at maximum frown - Any of the following procedures or treatments occurring in the specified period before randomization (Day 1): • 3 months: any facial non-ablative resurfacing laser, light or ultrasound treatment, microdermabrasion, monopolar radiofrequency, or superficial peels • 6 months: any facial cosmetic procedure with medium depth or deep depth chemical peels; periorbital, mid-facial, or upper-facial skin resurfacing; or permanent make-up in the

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
				mid-facial or upper facial areas • 12 months: any periorbital, mid-facial, or upper-facial treatment with non-permanent soft tissue fillers
Phase 1/2 M24-040	05 January 2024 to 03 April 2024 (Japan) 8 subjects per dose Ratio 3:1	Randomised, Double-Blinded, Placebo-Controlled	3 doses tested 400 U, 600 U and 750 U vs placebo	Japanese Subjects with Moderate to Severe GL at maximum frown as assessed by the investigator using the FWS-A 18-64 years
Phase 3 studies				
M21-500	16 March 2022 to 17 March 2023 (US, Canada, Germany, Hungary and Poland) 790 screened 638 randomised	Double-blind period with placebo-controlled, safety and efficacy and open-label period with AGN-151586 retreatment	Dose of 750 U IM at D0 Retreatment at D43	Adults with moderate to severe GL at maximum frown Subject **must not** have received any of the following procedures or treatments occurring in the specified period before baseline (Day 1) visit: - 3 months: any periorbital, mid-facial, or upper-facial cosmetic procedures with superficial resurfacing /planning, superficial chemical peels, or nonablative energy-based facial treatments. - 6 months: any periorbital, mid-facial or upper-facial cosmetic procedure with medium depth or deep depth resurfacing or deep depth chemical peels, microneedling, ablative energy-based facial treatments, or permanent /semi-permanent make-up. - 12 months: any periorbital, mid-facial, or upper-facial treatment with nonpermanent soft tissue fillers.

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
M21-508	08 March 2022 to 01 February 2023 (US) 372 screened 309 randomised			Same inclusion and exclusion criteria + **Toxin-naïve subjects**
M23-365	30 August 2022 to 30 May 2023 (US) No formal hypothesis testing 112 screened 90 randomised	Double-blind, placebo-controlled, safety and efficacy in Treatment Period 1 with open-label BOTOX in Treatment Period 2	AGN-151586 and Botox 20 U vs placebo 700U of AGN-151586 IM at Day 0 followed at Day 30 by 20 U of Botox	Same inclusion and exclusion criteria + Botulinum neurotoxin naïve subjects
M21-509	25 February 2022 to 26 June 2023 (US and Puerto Rico) 1179 screened 992 randomised	Open-label and safety in up to 3 treatment periods	3 treatment cycles 750 U IM at D0 then retreatment at D43 and/or D85 and/or D126	Adults with moderate to severe GL at maximum frown

5.2. Clinical pharmacology

5.2.1. Methods

Classical non-clinical pharmacokinetic studies to characterize absorption, distribution, biotransformation, and elimination have not been conducted with AGN-151586.
Instead, the applicant developed a sensitive, bead-based enzyme linked immunosorbent assay (ELISA) to quantitate AGN-151586 in mouse and rat serum using a qualified Quanterix single molecule array (SIMOA) platform. This method enabled measurement of AGN-151586 in serum for assessment of systemic exposure following IM dosing (see non-clinical section above).

5.2.2. Pharmacokinetics

No PK studies in human were performed.

5.2.3. Pharmacodynamics

No PD studies *in vitro* or in humans were performed.

5.2.3.1. Immunological events

See Clinical Safety section.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Not applicable.

5.2.5. Dose selection and therapeutic window

Not applicable.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

The chemical complexity of AGN-151586 combined with its extreme potency limits the opportunity to study its pharmacokinetic profile in humans. Systemic bioavailability after administration per os or intravenous injection is without clinical relevance.

No PK and PD studies have been conducted by the applicant. However, this is considered acceptable given the characteristic of the product.

5.2.6.2. Conclusions

The absence of PK and PD studies is acceptable. No systemic passage is expected.

5.3. Clinical efficacy

The clinical programme comprises the following studies:

- One dose-escalation, single-treatment placebo-controlled study (2034-201-008) of AGN-151586 in US and one supportive dose-escalation study (M24-040) in Japan

- Two placebo controlled single-treatment trials of AGN-151586: M21-500 (US and Europe) and M21-508 (US and Canada), which aimed to recruit subjects where GL are associated with significant psychological impact

- One study (M23-365) with sequential administration of AGN-151586 700 U and BOTOX 20 U at Day 30 in US.

- One open label repeat treatment study (M21-509) of AGN-151586 for aesthetic treatment of GL (up to 3 treatment periods) in US and Puerto Rico.

5.3.1. Dose response studies

Study 2034-201-008 and supportive study M24-040 were provided.

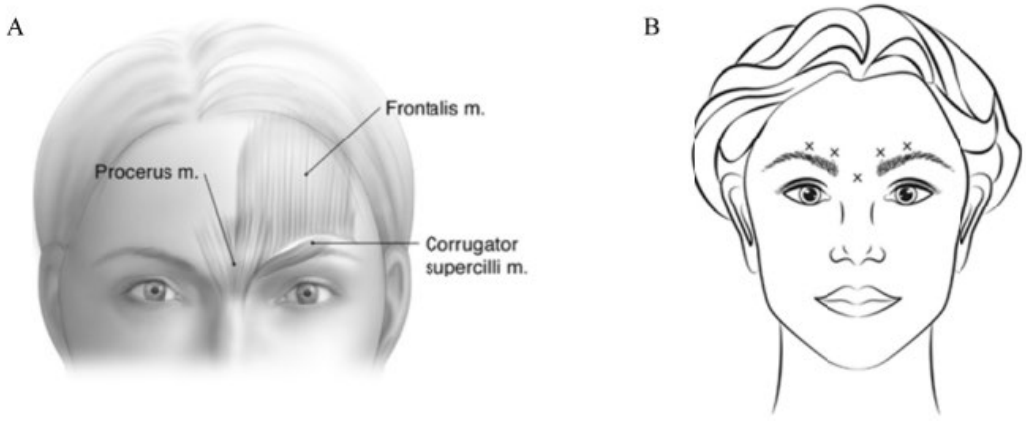
Study 2034-201-008 was a multicentre, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the safety and efficacy of a single study intervention cycle of AGN-151586 in participants with moderate to severe GL. Participants were to be adults 18 to 65 years old, with moderate or severe GL at maximum frown (as assessed by the investigator and participant using the FWS at the Screening Visit).

Five doses of AGN-151586 were evaluated (100, 250, 400, 600 and 750 U) and compared with placebo in a sequential cohort design, starting with the lowest dose (in 5 cohorts).

The primary efficacy measure was the investigator's assessments of GL at maximum frown using the FWS (Facial Wrinkle Scale with photonumeric guide: 4-point scale for grading glabellar lines severity: 0=none, 1=mild, 2=moderate, 3=severe).

Study intervention on Day 1 was administered as 5 injections in the glabellar complex (1 in the procerus muscle and 2 in each corrugator muscle).

Figure 6–1 (A) The Procerus and Corrugator (Glabellar Line Area) on 1 Side of the Face and (B) Locations of the 5 Glabellar Line Injections



In total, 148 subjects in mITT received AGN-151586 and 50 received placebo:

- cohort 1 testing 100 U: 32 vs 8 subjects
- cohort 2 testing 250 U: 28 vs 12 subjects
- cohort 3 testing 400 U: 27 vs 11 subjects
- cohort 4 testing 600 U: 30 vs 10 subjects
- cohort 5 testing 750 U: 31 vs 9 subjects

The efficacy endpoints were analysed based on the mITT population.

mITT population was defined as all randomized participants who received the study intervention and who had at least one post-intervention investigator-rated FWS measurement at maximum frown.

Endpoint	Cohort 1		Cohort 2		Cohort 3		Cohort 4		Cohort 5	
	Placebo (N = 8)	AGN-151586 (100 U) (N = 32)	Placebo (N = 12)	AGN-151586 (250 U) (N = 28)	Placebo (N = 11)	AGN-151586 (400 U) (N = 27)	Placebo (N = 10)	AGN-151586 (600 U) (N = 30)	Placebo (N = 9)	AGN-151586 (750 U) (N = 31)
Primary Endpoint										
Achievement of a ≥ 2-grade improvement from baseline on the FWS according to investigator assessments of GL severity at maximum frown at any postintervention timepoint through Day 7, n (%)	0 (0.0)	13 (40.6)	0 (0.0)	13 (46.4)	2 (18.2)	19 (70.4)	2 (20.0)	25 (83.3)	1 (11.1)	30 (96.8)
Secondary Endpoints										
Achievement of a ≥ 2-grade improvement from baseline on the FWS according to participant assessments of GL severity at maximum frown at any postintervention timepoint through Day 7, n (%)	0 (0.0)	11 (34.4); p = 0.0662	1 (8.3)	15 (53.6)	2 (18.2)	19 (70.4)	3 (30.0)	16 (53.3); p = 0.3406	1 (11.1)	22 (71.0)
Achievement of a composite ≥ 2-grade improvement from baseline on the FWS at maximum frown as rated concurrently by the investigator and participant by timepoint, n (%)[a]	0 (0.0)	4 (12.5); p = 0.3066	0 (0.0)	9 (32.1)	1 (10.0)	12 (50.0)	0 (0.0)	14 (46.7)	0 (0.0)	20 (66.7)

P-values were < 0.05 (unless otherwise specified) for all between-group comparisons of placebo versus AGN-151586 for each cohort.
[a] For comparison purposes, results related to the composite endpoint are provided only for Day 7 in the current table.
Source: Table 14.2-1.1, Table 14.2-2.1, Table 14.2-2.13

Exploratory Endpoints

- Onset of Effect: To examine the onset of improvement of GL severity at maximum frown using the FWS, the proportion of participants at each post-intervention timepoint at which they first achieved an improvement of GL severity at maximum frown per investigator's assessment was evaluated for each cohort. When examining participants with a ≥ 1-grade improvement, results showed that for each dose cohort, at least half of the responders achieved a ≥ 1-grade improvement within the first 24 hours after treatment.

  When examining participants' first achievement of a none or mild rating at maximum frown on the FWS per investigator assessment, the onset of effect relative to achievement of a ≥ 1-grade response was slightly delayed. Most participants (≥ 50%) in the AGN-151586 groups achieved a none or mild rating by Hour 36 for each cohort except for Cohort 1 (100 U), which reached that threshold by Hour 48.

- Duration of Treatment Benefit: In participants who achieved a ≥ 1-grade improvement from baseline in GL severity at maximum frown on the FWS through Day 7 per investigator's assessment, the mean duration of improvement before returning to baseline grade was at least 14 days across all AGN-151586 doses and increased moderately with AGN-151586 dose increase. It reached approximately 25 to 26 days for the 3 cohorts receiving the highest AGN-151586 doses (i.e. Cohorts 3 [400 U], 4 [600 U], and 5 [750 U]).

  The same applied for participants who achieved none or mild rating on the FWS at maximum frown per investigator through Day 7: mean duration of improvement was at least 18 days

across AGN-151586 doses, with the 3 highest AGN-151586 doses reaching durations at approximately 25 to 26 days.

- FWS ≥ 1-grade Responder at Rest: The proportions of responders achieving a ≥ 1-grade improvement on the FWS of GL severity at rest from baseline through Day 7 per investigator's assessment among those participants with at least a moderate rating on the FWS at baseline was **greater** for the AGN-151586 compared with the placebo group only in Cohort 3 (400 U) (placebo: 40.0%; AGN-151586: 91.7%; $p < 0.05$, unadjusted).

  No statistical difference was observed between the AGN-151586 and placebo groups in Cohorts 1 (100 U), 2 (250 U), 4 (600 U), and 5 (750 U) ($p > 0.05$, unadjusted).

  Per participant assessment, AGN-151586 groups did not differ statistically from the placebo groups in any cohort when evaluating ≥ 1-grade improvements on the FWS of GL severity at rest from baseline through Day 7 among those participants with at least a moderate rating on the FWS ($p > 0.05$, unadjusted).

- Participant-reported Outcomes (FLO-11 and FLSQ): Participant-reported emotional and appearance-related impact of GL was assessed using the FLO-11 GL version and participant-reported treatment satisfaction with GL with FLSQ baseline and follow-up GL versions.

M24-040: Supportive dose-escalation study

M24-040 conducted in Japan (n=24) was a 6-week, single-centre, double-blind study designed to evaluate the safety and efficacy of AGN-151586 over a range of doses in treating GL in Japanese adult subjects (18 to 64 years of age, inclusive) with moderate to severe GL at maximum frown as assessed by the investigator using the FWS-A (with Asian photonumeric guide).
Three doses were administered (370, 560 or 700 U) for Cohort 1, Cohort 2, or Cohort 3, respectively in 8 subjects per cohort with 2 receiving placebo and 6 receiving AGN-15186.

The primary efficacy endpoint was % of subjects with ≥ 2-grade improvement from baseline at any timepoint through Day 7 with FWS-A at maximum frown assessed by the investigator.

Table 6. Subjects with ≥ 2 -Grade Improvement from Baseline on the FWS-A – mITT Population

	Cohort 1		Cohort 2		Cohort 3		
Timepoint	Cohort 1 Placebo (N=2)	AGN-151586 370 U (N=6)	Cohort 2 Placebo (N=2)	AGN-151586 560 U (N=6)	Cohort 3 Placebo (N=2)	AGN-151586 700 U (N=6)	Total Placebo (N=6)
Through Day 7							
Responder rate, n/N1[a] (%)	0/2 (0.0)	1/6 (16.7)	0/2 (0.0)	5/6 (83.3)	0/2 (0.0)	4/6 (66.7)	0/6 (0.0)
95% CI (%)	(0.0, 0.0)	(0.0, 46.5)	(0.0, 0.0)	(53.5, 100.0)	(0.0, 0.0)	(28.9, 100.0)	(0.0, 0.0)
vs. Total Placebo							
Difference (%)		16.7		83.3		66.7	
95% CI (%)		(-13.2, 46.5)		(53.5, 100.0)		(28.9, 100.0)	

a. N1 = Number of subjects with data at Baseline and at least 1 post-baseline timepoint through Day 7.

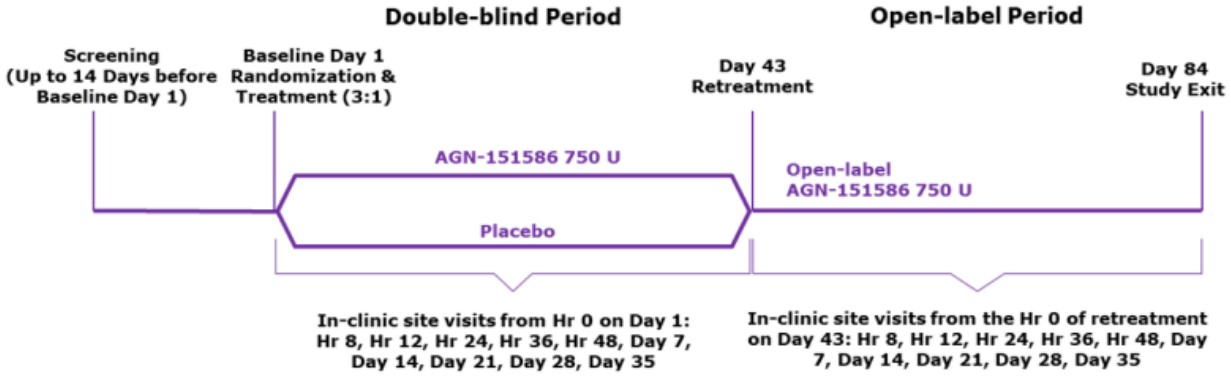
Note: See Section 9.2.1 for Clarification of Doses (approximately 370 U, 560 U, or 700 U for Cohort 1, Cohort 2, or Cohort 3, respectively).
A subject is considered a responder if a ≥ 2-grade improvement from Baseline is achieved at any post-baseline visit through the Day 7 visit according to the investigator assessment of the FWS-A at maximum frown. Analysis is presented as-observed.

Source: Table 14.2-1

5.3.2. Main studies

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

5.3.2.1.1. Study design



Hr = hour

Treatment

All subjects received 700 U of AGN-151586 or matching placebo administered on Baseline Day 1. Based on meeting the retreatment criteria, the subject may be retreated at Day 43.

For each treatment, a total of 5 injections (0.1 mL per injection) was administered, for a total injection volume of 0.5 mL. The first injection was made in the procerus muscle in the midline, and the next 4 injections were made bilaterally (i.e., 2 injections per side) into each corrugator muscle (see the injection pattern below). The corrugators were injected inferomedially near the origin of the supratrochlear nerve and superolaterally/superomedially into the superior middle aspect ≥ 1 cm above the bony orbital rim. The needle was to be oriented away from the eye, and with the bevel tip up, to reduce the occurrence of ptosis.

Randomisation

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

Randomization was stratified by investigator site, toxin use history (for aesthetic purpose), and baseline GL severity at maximum frown. Additionally, enrolment was approximately balanced for moderate and severe GL severity at maximum frown, according to the Baseline Day 1 evaluations by both the investigator and the subject.

In addition, at least 60% of subjects enrolled will demonstrate psychological burden as a result of their GL as measured by a baseline FLO-11 questionnaire total score ≤ 50. To support this, the site manually entered the subject's Baseline Day 1 FWS score (moderate or severe; per eligibility criteria, the investigator and subject FWS assessments must have been 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.

Blinding

All AbbVie personnel with direct oversight of the conduct and management of the trial, the investigator, study site personnel, and the subject remained blinded to each subject's treatment throughout the study.

To maintain the blind, AGN-151586 / matching placebo provided for the study was identical in appearance. The IRT provided access to unblinded subject treatment information in the case of a medical emergency.

Patient population

The study population was adult subjects with moderate or severe GL (FWS=2 or 3) at maximum frown as assessed by both the investigator and subject using the FWS.

Main inclusion criteria

Adult male or female, at least 18 years old

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

Enrolment was to be at least 40% and no more than 60% for each moderate and severe GL severity at maximum frown, according to the Baseline Day 1 evaluations by both the investigator and the subject.

In addition, at least 60% of subjects enrolled should have demonstrated psychological burden as a result of their GL as measured by a baseline FLO-11 questionnaire total score ≤ 50.

Main exclusion criteria

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 prior to Baseline Day 1.

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.

Subjects must not have received any of the any periorbital, mid-facial or upper-facial cosmetic procedures with resurfacing (superficial, with medium depth or deep depth) or non-permanent treatment soft tissue fillers occurring before Baseline Day 1 Visit.

Subjects must not have clinically relevant or significant ECG abnormalities, including ECG with QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec (males) or > 470 msec (females), or personal or family history of prolonged QT interval.

5.3.2.1.2. Objectives and estimands

Primary objective

The objective of both phase 3 studies was to evaluate the safety and efficacy of AGN-151586 for the treatment of GL in subjects with moderate to severe GL for M21-500 and in toxin-naïve subjects with moderate to severe GL for M21-508.

The clinical hypotheses were:

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

Estimand for the primary objective

Table 4: Estimand for primary objective

Population	Adult patients, with moderate or severe Gabellar Lines at maximum frown (as assessed by the evaluating investigator and subject using the FWS at Screening and Baseline Day 1) who would encounter the Intercurrent Event of study discontinuation or no FWS assessment if assigned to AGN-151586 or Placebo.
Treatment condition	Assignment of 750 U of AGN-151586 administered as 5 intramuscular injections in the glabellar complex, in the hypothetical scenario of no study discontinuation and/or absence of FWS assessment compared to assignment to matching placebo in the hypothetical scenario of no study discontinuation and/or absence of FWS assessment.
Co- primary Endpoints (variables)	- 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 rates of patients presenting this achievement in both treatment arms - 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 and rates of patients presenting this achievement in both treatment arms
Population-level summary	- Difference between AGN-151586 and placebo in the rate of patients achieving the primary endpoint **according to subject's assessment** - Difference between AGN-151586 and placebo in the rate of patients achieving the primary endpoint **according to investigator's assessment** CMH test stratified by site, toxin use history for aesthetic purposes and baseline FWS severity will be used for the rates comparison
Intercurrent events and strategy to handle them	
Study discontinuation	Hypothetical strategy using multiple imputations for missing data
No FWS assessment	Hypothetical strategy using multiple imputations for missing data

Statistical methods for estimation and sensitivity analysis on primary estimands

For the EU regulatory agencies: The co-primary responder endpoints for ≥ 2-grade improvement from baseline in the FWS will be analysed separately using the CMH method stratified by investigator site, toxin use history (for aesthetic purpose), and baseline FWS after using multiple imputation for missing data. Both co-primary endpoints must meet $p \leq 0.05$ to be considered successful.

The evaluation of the equality of the proportions of responders for the primary composite or co-primary endpoints at Day 7 will be based on the CMH test stratified by investigator site, toxin use history (for aesthetic purpose), 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. The Breslow-Day homogeneity of the odds-ratio test will be conducted to provide a 2-sided test of treatment-by-baseline severity interaction, in which a p-value ≤ 0.1 will be claimed as statistically significant for homogeneity. The 95% confidence interval for the treatment response rate differences will be constructed using the normal approximation to the binomial distribution.

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 NRI) analysis, stratified by baseline FWS and by investigator site are planned for sensitivity analyses.

In addition, a tipping point analysis will be used to explore different missing data assumptions for the primary endpoint analysis. The tipping point analysis will be performed when the primary endpoint is deemed statistically significant to assess the impact of the missing data assumption used in the primary analysis. Various scenarios of pattern of missing data will be explored to find the scenario that "tips" the conclusion of the primary analysis in terms of the p-value. If the primary endpoint is not statistically significant, no sensitivity analysis for tipping point will be necessary.

For example, when performing multiple imputation to impute missing data for the primary endpoint analysis, a shift parameter value with values between 0 and 3 (for the range of the FWS scale) will be added to the imputed data at Day 7 only for subjects in the AGN-151586 treatment group after any intercurrent event, so that the imputed values in the active treatment group will be worse by an indicated amount. The dataset with imputed values and applied shift parameter will be analysed using the same model as the primary analysis for between-treatment group comparison. The estimated test results and response rate differences from the 30 MI imputed data sets will be combined with SAS PROC MIANALYZE to produce the overall estimate for Day 7, together with the corresponding p-value and two-sided 95% confidence interval.

Secondary objectives

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)

Additional exploratory efficacy endpoints

- ≥ 1-grade improvement from baseline on the FWS according to subject assessment of GL severity at rest at Day 7
- ≥ 1-grade improvement from baseline on the FWS according to investigator assessment of GL severity at rest at Day 7
- ≥ 1-grade improvement from baseline based on subject assessment using FWS at rest at all collected timepoints
- ≥ 1-grade improvement from baseline based on investigator assessment using FWS at rest at all collected timepoints
- *None* or *mild* on the FWS according to subject assessment using FWS at maximum frown at all follow-up visits
- *None* or *mild* on the FWS according to investigator assessment using FWS at maximum frown at all follow-up visits
- Composite ≥ 2-grade improvement from baseline based on investigator and subject assessment using FWS at maximum frown at all follow-up visits
- ≥ 4-point improvement from baseline in FLO-11 Item 3 (feel unattractive) for GL at Day 7
- Improvement from baseline (≥ 20-point improvement for total scores, ≥ 4-point improvement for item scores) for FLO-11 total and item scores at all follow-up visits
- FLO-11 total scores (transformed) and item scores at all follow-up visits
- FLSQ item and domain scores at all follow-up visits
- Self-perception of Age (SPA) based on the SPA at all follow-up visits
- Likelihood to continue neurotoxin treatment at end of study, based on the Future Treatment Use Questionnaire (FTUQ) at study exit
- Procedure comfort reported at 24 hours after each treatment based on the Procedure Comfort Questionnaire (PCQ)

Estimand for the secondary objective

For the European Union 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 (hypothetical strategy). Intercurrent events accounted for are the following:

study discontinuation in the double-blind period, study discontinuation prior to hour 24 assessments, prior to hour 24 or day 7 for FLSQ follow up assessments, absence of FLSQ follow up, absence of FLO-11 day 7 assessments, absence of GAC-GL assessments.

5.3.2.1.3. Results

Participant flow and numbers analysed

A total of 638 subjects were enrolled, randomised, and treated across 36 sites in the United States, Canada, Germany, Hungary, and Poland.

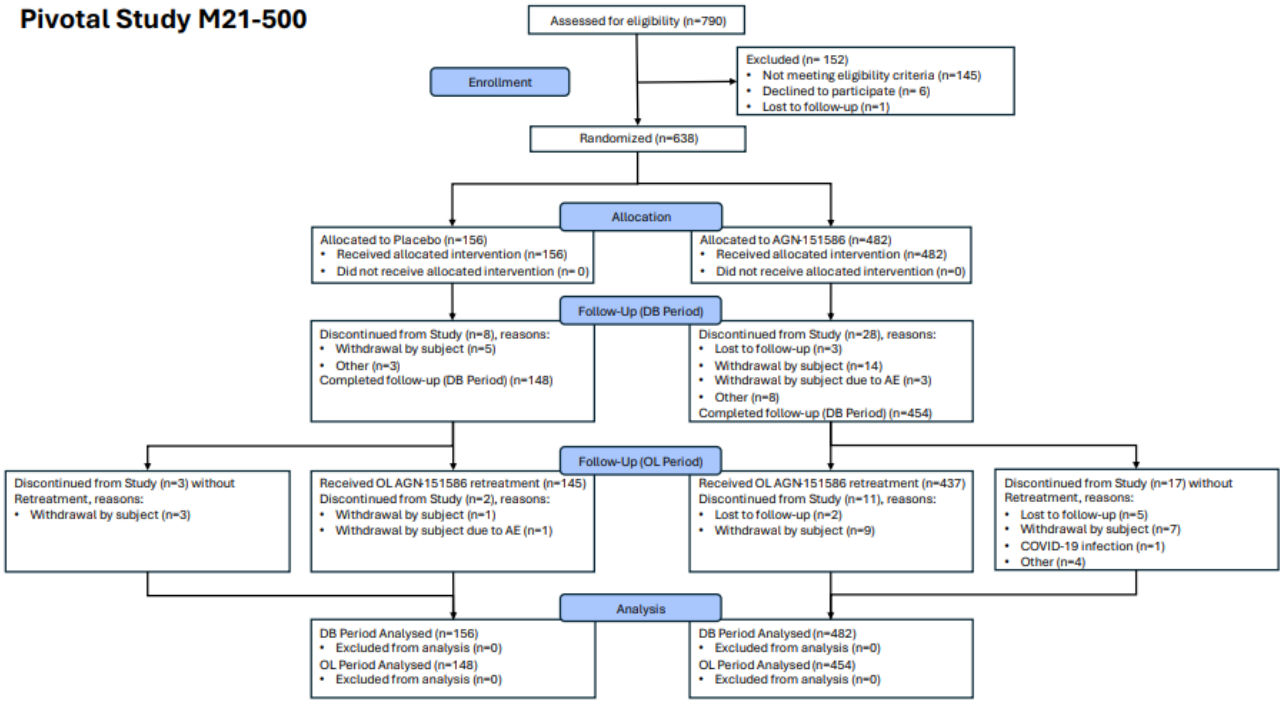


Table 14.1-3
Analysis Populations

	DB Period		OL Period				
	Placebo	AGN-151586	Placebo/ None	Placebo/ AGN-151586	AGN-151586/ None	AGN-151586/ AGN-151586	Total
Intent-to-Treat Population, N	156	482	3	145	17	437	638
Safety Population, N	156	482	3	145	17	437	638

Baseline analyses and efficacy analyses for the US FDA and EU Regulatory agency were performed on the ITT Population, consisting of all randomized subjects.

Table 14.1-1
Disposition of Subjects
Screened Population

Disposition	DB Period		OL Period				Total
	Placebo n (%)	AGN-151586 n (%)	Placebo/ None n (%)	Placebo/ AGN-151586 n (%)	AGN-151586/ None n (%)	AGN-151586/ AGN-151586 n (%)	n (%)
Number of Subjects Screened							790
Number of Subjects Enrolled (Randomized)	156 (100.0)	482 (100.0)					638 (100.0)
Number of Subjects Treated	156 (100.0)	482 (100.0)	0 (0.0)	145 (100.0)	0 (0.0)	437 (100.0)	638 (100.0)
Number of Subjects who Completed Study	148 (94.9)	454 (94.2)	0 (0.0)	143 (98.6)	0 (0.0)	426 (97.5)	569 (89.2)
Number of Subjects who Discontinued from Study	8 (5.1)	28 (5.8)	3 (100.0)	2 (1.4)	17 (100.0)	11 (2.5)	69 (10.8)
Reasons for Discontinuation							
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-Up	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	5 (29.4)	2 (0.5)	10 (1.6)
Withdrawal by Subject	5 (3.2)	14 (2.9)	3 (100.0)	1 (0.7)	7 (41.2)	9 (2.1)	39 (6.1)
Withdrawal by Subject due to Adverse Event	0 (0.0)	3 (0.6)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	4 (0.6)
Study Terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Site Terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	1 (0.2)
COVID-19 Logistical Restrictions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	3 (1.9)	8 (1.7)	0 (0.0)	0 (0.0)	4 (23.5)	0 (0.0)	15 (2.4)

Deviations from study plan

Table 4. Protocol Deviations: Number (%) of Subjects with Protocol Deviations – ITT Population

Protocol Deviation Category	DB Period		OL Period				Total
	Placebo (N=156) n (%)	AGN-151586 (N=482) n (%)	Placebo/ None (N=3) n (%)	Placebo/ AGN-151586 (N=145) n (%)	AGN-151586/ None (N=17) n (%)	AGN-151586/ AGN-151586 (N=437) n (%)	(N=638) n (%)
Subjects With At Least One Protocol Deviation	51 (32.7)	151 (31.3)	1 (33.3)	47 (32.4)	5 (29.4)	135 (30.9)	202 (31.7)
Didn't Satisfy Study Entry Criteria	21 (13.5)	60 (12.4)	1 (33.3)	19 (13.1)	1 (5.9)	54 (12.4)	81 (12.7)
Eligibility Criteria Not Met [1]							
Criterion number 5	8 (5.1)	22 (4.6)	0 (0.0)	7 (4.8)	0 (0.0)	20 (4.6)	30 (4.7)
Criterion number 6	3 (1.9)	16 (3.3)	0 (0.0)	3 (2.1)	1 (5.9)	12 (2.7)	19 (3.0)
Criterion number 9	1 (0.6)	2 (0.4)	0 (0.0)	1 (0.7)	0 (0.0)	2 (0.5)	3 (0.5)
Criterion number 16	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.3)
Criterion number 17	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Criterion number 18	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)
Criterion number 20	6 (3.8)	18 (3.7)	1 (33.3)	5 (3.4)	0 (0.0)	17 (3.9)	24 (3.8)
Criterion number 21	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Criterion number 23	2 (1.3)	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)	2 (0.3)
Criterion number 24	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Criterion number 27	2 (1.3)	3 (0.6)	0 (0.0)	2 (1.4)	0 (0.0)	3 (0.7)	5 (0.8)
Met Withdrawal Criteria But Not Withdrawn	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wrong Treatment Or Incorrect Dose Of Study Treatment	5 (3.2)	17 (3.5)	0 (0.0)	5 (3.4)	0 (0.0)	17 (3.9)	22 (3.4)
Prohibited Concomitant Medication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Percentages based on total number of subjects in each treatment group.
[1] Eligibility criteria: 5 = Healthy, 6 = FWS moderate or severe, 9 = Medical condition, 16 = Surgical or lifting procedure (protocol version 1), 17 = Facial treatment (protocol version 1), 18 = ECG abnormality or not done (protocol version 1), 20 = Pregnancy test (protocol version 1), 21 = Birth control (protocol version 1), 23 = Investigational treatment received (protocol version 1), 24 = Investigational drug received (protocol version 1), 27 = Pregnancy test (protocol version 2)

Baseline data

Table 14.1-4.1
Demographics
Intent-to-Treat Population

Parameter	DB Period		OL Period					
	Placebo (N=156)	AGN-151586 (N=482)	Placebo/ None (N=3)	Placebo/ AGN-151586 (N=145)	AGN-151586/ None (N=17)	AGN-151586/ AGN-151586 (N=437)	Any AGN-151586 (N=627)	Total (N=638)
Age (years)								
Mean (SD)	47.6 (12.48)	47.1 (12.75)	45.0 (6.08)	47.4 (12.59)	46.5 (11.67)	47.3 (12.73)	47.2 (12.70)	47.2 (12.68)
Median	48.0	48.0	42.0	48.0	46.0	48.0	48.0	48.0
Q1, Q3	39.0, 56.5	38.0, 57.0	41.0, 52.0	38.0, 56.0	38.0, 50.0	39.0, 57.0	38.0, 57.0	38.0, 57.0
Min, Max	21, 79	21, 81	41, 52	21, 79	26, 70	21, 81	21, 81	21, 81
n	156	482	3	145	17	437	627	638
Age (years), n(%)								
< 65	142 (91.0)	444 (92.1)	3 (100.0)	133 (91.7)	16 (94.1)	403 (92.2)	577 (92.0)	586 (91.8)
>= 65	14 (9.0)	38 (7.9)	0 (0.0)	12 (8.3)	1 (5.9)	34 (7.8)	50 (8.0)	52 (8.2)
Sex, n (%)								
Male	19 (12.2)	53 (11.0)	0 (0.0)	18 (12.4)	2 (11.8)	46 (10.5)	71 (11.3)	72 (11.3)
Female	137 (87.8)	429 (89.0)	3 (100.0)	127 (87.6)	15 (88.2)	391 (89.5)	556 (88.7)	566 (88.7)
Ethnicity, n (%)								
Hispanic or Latino	14 (9.0)	49 (10.2)	0 (0.0)	12 (8.3)	1 (5.9)	45 (10.3)	61 (9.7)	63 (9.9)
Not Hispanic or Latino	142 (91.0)	433 (89.8)	3 (100.0)	133 (91.7)	16 (94.1)	392 (89.7)	566 (90.3)	575 (90.1)
Race, n (%)								
White	142 (91.0)	432 (89.6)	3 (100.0)	133 (91.7)	17 (100.0)	392 (89.7)	565 (90.1)	574 (90.0)
Black or African American	5 (3.2)	21 (4.4)	0 (0.0)	4 (2.8)	0 (0.0)	20 (4.6)	25 (4.0)	26 (4.1)
Asian	3 (1.9)	16 (3.3)	0 (0.0)	3 (2.1)	0 (0.0)	13 (3.0)	19 (3.0)	19 (3.0)
Japanese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chinese	3 (1.9)	1 (0.2)	0 (0.0)	3 (2.1)	0 (0.0)	1 (0.2)	4 (0.6)	4 (0.6)
Korean	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	3 (0.5)	3 (0.5)
Taiwanese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	13 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	11 (2.5)	13 (2.1)	13 (2.0)
American Indian or Alaska Native	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Native Hawaiian or Other Pacific Islander	2 (1.3)	2 (0.4)	0 (0.0)	2 (1.4)	0 (0.0)	2 (0.5)	4 (0.6)	4 (0.6)

Table 14.1-4.2
Baseline and Disease Characteristics
Intent-to-Treat Population

Parameter	Placebo (N=156)	AGN-151586 (N=482)	Total (N=638)
Weight (kg)			
Mean (SD)	74.98 (15.840)	74.35 (16.555)	74.50 (16.373)
Median	72.29	71.49	72.00
Q1, Q3	63.80, 85.61	62.00, 83.00	62.14, 83.91
Min, Max	44.9, 134.6	43.1, 139.7	43.1, 139.7
n	156	482	638
Height (cm)			
Mean (SD)	166.5 (8.40)	165.8 (8.49)	166.0 (8.46)
Median	165.6	165.1	165.1
Q1, Q3	160.0, 172.4	160.0, 170.2	160.0, 170.2
Min, Max	147, 192	135, 193	135, 193
n	156	482	638
BMI (kg/m**2)			
Mean (SD)	27.02 (5.289)	27.00 (5.528)	27.01 (5.467)
Median	26.52	25.87	26.14
Q1, Q3	23.43, 28.88	23.12, 29.80	23.14, 29.66
Min, Max	16.6, 49.1	17.1, 48.2	16.6, 49.1
n	156	482	638
BMI (kg/m**2), n(%)			
< 25	54 (34.6)	198 (41.1)	252 (39.5)
>= 25	102 (65.4)	284 (58.9)	386 (60.5)

BMI = body mass index, weight in kg divided by height in meters squared.
FWS = Facial Wrinkle Scale, FLSQ = Facial Line Satisfaction Questionnaire, FLO-11 = 11-Item Facial Line Outcomes
For FWS, higher scores (range 0 to 3) indicate worse outcomes; for FLO-11 (transformed score, range 0 to 100), higher scores (range 0 to 100) indicate better outcomes; for FLSQ impact (transformed score, range 0 to 100), higher scores (range 0 to 100) indicate facial lines having higher negative impact; for FLSQ treatment expectations (transformed score, range 0 to 100), higher scores (range 0 to 100) indicate higher treatment expectations.
[1] FWS stratification is the FWS at maximum frown as assessed by the investigator at baseline. Subjects with an investigator assessed FWS at maximum frown at baseline lower than a rating of moderate (i.e., none or mild) will be included in all stratified analyses as part of the 'Moderate' stratum.

Table 14.1-4.2
Baseline and Disease Characteristics
Intent-to-Treat Population

Parameter	Placebo (N=156)	AGN-151586 (N=482)	Total (N=638)
Nicotine Use, n (%)			
Never	101 (64.7)	330 (68.5)	431 (67.6)
Current	26 (16.7)	60 (12.4)	86 (13.5)
Former	29 (18.6)	92 (19.1)	121 (19.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Alcohol Use, n (%)			
Never	36 (23.4)	112 (23.5)	148 (23.5)
Current	107 (69.5)	330 (69.2)	437 (69.3)
Former	11 (7.1)	35 (7.3)	46 (7.3)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Prior Aesthetic Toxin Use, n (%)			
Yes	46 (29.5)	147 (30.5)	193 (30.3)
No	110 (70.5)	335 (69.5)	445 (69.7)
Region, n (%)			
North America	120 (76.9)	378 (78.4)	498 (78.1)
EU	36 (23.1)	104 (21.6)	140 (21.9)
Fitzpatrick Skin Type, n (%)			
I	3 (1.9)	19 (3.9)	22 (3.4)
II	63 (40.4)	175 (36.3)	238 (37.3)
III	59 (37.8)	179 (37.1)	238 (37.3)
IV	21 (13.5)	79 (16.4)	100 (15.7)
V	6 (3.8)	23 (4.8)	29 (4.5)
VI	4 (2.6)	7 (1.5)	11 (1.7)

Table 14.1-4.2
Baseline and Disease Characteristics
Intent-to-Treat Population

Parameter	Placebo (N=156)	AGN-151586 (N=482)	Total (N=638)
FWS Stratification, n [1] (%)			
2 = Moderate	42 (26.9)	151 (31.3)	193 (30.3)
3 = Severe	114 (73.1)	331 (68.7)	445 (69.7)
FWS at Maximum Frown - Subject, n (%)			
0 = None	0 (0.0)	0 (0.0)	0 (0.0)
1 = Mild	1 (0.6)	3 (0.6)	4 (0.6)
2 = Moderate	41 (26.3)	149 (30.9)	190 (29.8)
3 = Severe	114 (73.1)	330 (68.5)	444 (69.6)
FWS at Maximum Frown - Investigator, n (%)			
0 = None	0 (0.0)	0 (0.0)	0 (0.0)
1 = Mild	1 (0.6)	2 (0.4)	3 (0.5)
2 = Moderate	41 (26.3)	149 (30.9)	190 (29.8)
3 = Severe	114 (73.1)	331 (68.7)	445 (69.7)
FWS at Rest - Subject, n (%)			
0 = None	26 (16.7)	85 (17.6)	111 (17.4)
1 = Mild	54 (34.6)	174 (36.1)	228 (35.7)
2 = Moderate	49 (31.4)	156 (32.4)	205 (32.1)
3 = Severe	27 (17.3)	67 (13.9)	94 (14.7)
FWS at Rest - Investigator, n (%)			
0 = None	27 (17.3)	88 (18.3)	115 (18.0)
1 = Mild	60 (38.5)	177 (36.7)	237 (37.1)
2 = Moderate	47 (30.1)	156 (32.4)	203 (31.8)
3 = Severe	22 (14.1)	61 (12.7)	83 (13.0)

Table 14.1-4.2
Baseline and Disease Characteristics
Intent-to-Treat Population

Parameter	Placebo (N=156)	AGN-151586 (N=482)	Total (N=638)
FLSQ Baseline Version - Treatment Expectations Domain Score			
Mean (SD)	60.2 (13.75)	59.1 (14.97)	59.4 (14.68)
Median	60.8	58.3	58.3
Q1, Q3	50.4, 70.0	49.2, 70.0	50.0, 70.0
Min, Max	27, 93	17, 100	17, 100
n	156	480	636
FLSQ Baseline Version - Impact Domain Score			
Mean (SD)	54.4 (23.76)	53.6 (23.37)	53.8 (23.45)
Median	60.0	55.0	55.0
Q1, Q3	37.5, 75.0	35.0, 70.0	35.0, 70.0
Min, Max	0, 100	0, 100	0, 100
n	156	480	636
FLO-11 Total Transformed Score			
Mean (SD)	31.1 (20.91)	34.5 (21.83)	33.6 (21.64)
Median	27.3	32.7	30.9
Q1, Q3	16.4, 40.9	18.2, 50.0	17.3, 48.2
Min, Max	0, 91	0, 95	0, 95
n	156	481	637
FLO-11 Total Transformed Score, n (%)			
<= 50	130 (83.3)	368 (76.3)	498 (78.1)
> 50	26 (16.7)	113 (23.4)	139 (21.8)
Missing	0 (0.0)	1 (0.2)	1 (0.2)

BMI = body mass index, weight in kg divided by height in meters squared.
FWS = Facial Wrinkle Scale, FLSQ = Facial Line Satisfaction Questionnaire, FLO-11 = 11-Item Facial Line Outcomes
For FWS, higher scores (range 0 to 3) indicate worse outcomes; for FLO-11 (transformed score, range 0 to 100), higher scores (range 0 to 100) indicate better outcomes; for FLSQ impact (transformed score, range 0 to 100), higher scores (range 0 to 100) indicate facial lines having higher negative impact; for FLSQ treatment expectations (transformed score, range 0 to 100), higher scores (range 0 to 100) indicate higher treatment expectations.
[1] FWS stratification is the FWS at maximum frown as assessed by the investigator at baseline. Subjects with an investigator assessed FWS at maximum frown at baseline lower than a rating of moderate (i.e., none or mild) will be included in all stratified analyses as part of the 'Moderate' stratum.

Outcomes and estimation

Double-blind period results

Primary endpoints

For the EU regulatory agency, the co-primary efficacy endpoints were the achievement of ≥ 2-grade improvement of GL severity at maximum frown from Baseline at Day 7 according to (1) subject's self-assessment using FWS and (2) investigator's assessment using FWS, among subjects who had a baseline FLO-11 total transformed score ≤ 50.

For the US FDA, the primary composite efficacy endpoint was achievement of Grade 0 or 1 (None or Mild) and ≥ 2-grade improvement on both the investigator and subject FWS assessments of GL severity at maximum frown from Baseline at Day 7.

Table 6. Primary Efficacy Endpoints

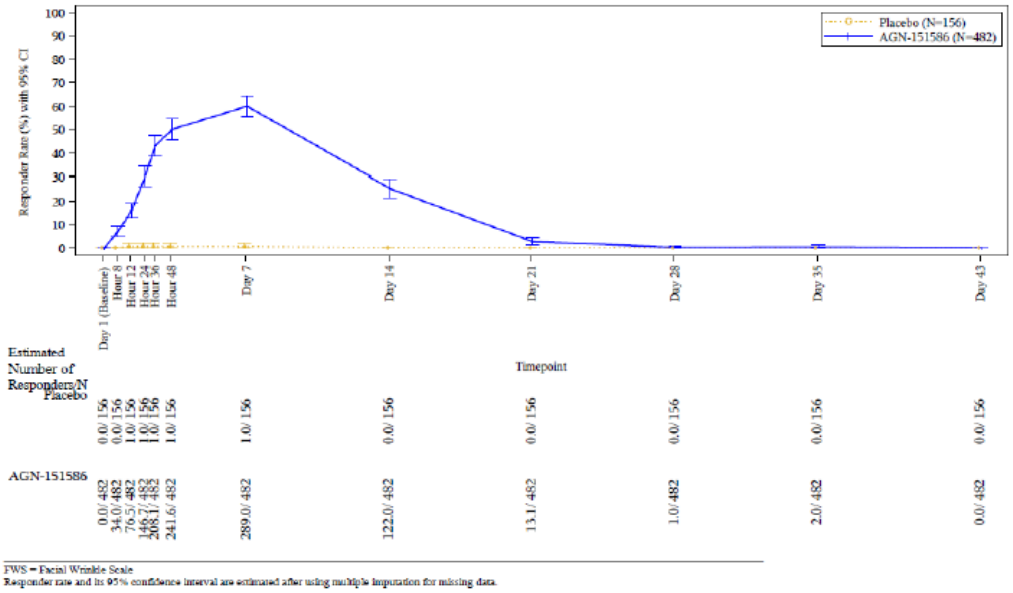
	Placebo	AGN-151586	Difference[a] (95% CI)	p-value
US FDA Primary Composite (ITT)	**N = 156**	**N = 482**		
Grade 0 or 1 (None or Mild) and ≥ 2-grade improvement from Baseline on the FWS at maximum frown by investigator and subject at Day 7, % (95% CI)[b]	0.6% (0.0%, 1.9%)	60.0% (55.5%, 64.4%)	59.3% (54.7%, 63.9%)	*p < 0.0001*
EU Regulatory Agencies Co-primary (ITT[c])	**N = 130**	**N = 368**		
≥ 2-grade improvement from Baseline based on FWS at maximum frown as assessed by subject at Day 7, % (95% CI)[b]	0.8% (0.0%, 2.3%)	61.0% (55.9%, 66.0%)	60.2% (54.9%, 65.4%)	*p < 0.0001*
≥ 2-grade improvement from Baseline based on FWS at maximum frown as assessed by investigator at Day 7, % (95% CI)[b]	0.8% (0.0%, 2.3%)	72.1% (67.5%, 76.7%)	71.4% (66.5%, 76.2%)	*p < 0.0001*

a. Estimated responder rate difference for AGN-151586 vs. placebo group.
b. Estimated responder rate after using multiple imputation for missing data.
c. For EU regulatory agencies, the analysis population is the ITT population with baseline FLO-11 total transformed scores ≤ 50.
Source: Table 14.2-1.1, Table 14.2-3.1

Secondary endpoints

US FDA Key Secondary Endpoint: FWS at Maximum Frown According to Investigator and Subject Assessment over Time (Double-blind Period)

FWS at Maximum Frown – Investigator and Subject: Percentage of Subjects with Composite Achievement of Grade 0 or 1 (None or Mild) and ≥ 2-Grade Improvement from Baseline Over Time – Double-blind Period (ITT Population)



FWS = Facial Wrinkle Scale
Responder rate and its 95% confidence interval are estimated after using multiple imputation for missing data.

in ITT population:

Table 8. EU Regulatory Agencies Secondary Efficacy Endpoints

	Placebo N = 130	AGN-151586 N = 368	Difference[a] (95% CI)	p-value
Key Secondary Efficacy Endpoint[b]				
≥ 20-Point Improvement from Baseline in FLO-11 Total Transformed Scores for GL at Day 7, % (95% CI)[c]	8.5% (3.7%, 13.2%)	66.6% (61.8%, 71.5%)	58.2% (51.3%, 65.0%)	*p < 0.0001*
Secondary Efficacy Endpoints[b]				
≥ 2-Grade Improvement from Baseline in FWS at Maximum Frown as Assessed by Subject at Hour 24, % (95% CI)[c]	0.8% (0.0%, 2.3%)	30.9% (26.2%, 35.7%)	30.1% (25.2%, 35.1%)	*p < 0.0001*
≥ 2-Grade Improvement from Baseline in FWS at Maximum Frown as Assessed by Investigator at Hour 24, % (95% CI)[c]	0.8% (0.0%, 2.3%)	36.5% (31.5%, 41.4%)	35.7% (30.5%, 40.9%)	*p < 0.0001*
≥ 1-Grade Improvement from Baseline in FWS at Maximum Frown as Assessed by Subject at Hour 24, % (95% CI)[c]	11.5% (6.0%, 17.0%)	64.1% (59.2%, 69.1%)	52.6% (45.2%, 60.0%)	*p < 0.0001*
≥ 1-Grade Improvement from Baseline in FWS at Maximum Frown as Assessed by Investigator at Hour 24, % (95% CI)[c]	13.8% (7.9%, 19.8%)	72.5% (67.9%, 77.1%)	58.6% (51.1%, 66.1%)	*p < 0.0001*
Mostly Satisfied or *Very Satisfied* on the FLSQ Follow-up Item 5 (overall satisfaction) at Hour 24, % (95% CI)[c]	16.2% (9.8%, 22.5%)	58.7% (53.6%, 63.7%)	42.5% (34.4%, 50.6%)	*p < 0.0001*
Mostly satisfied or *Very satisfied* on the FLSQ Follow-up Item 4 (natural look) at Day 7, % (95% CI)[c]	7.7% (3.1%, 12.3%)	77.7% (73.3%, 82.0%)	70.0% (63.7%, 76.3%)	*p < 0.0001*

In the population with psychosocial impact (FLO-11 score ≤50):

Table 8. EU Secondary Efficacy Endpoints (ITT Population with Baseline FLO-11 Total Transformed Score ≤ 50)

	Placebo N = 63	AGN-151586 N = 164	Difference (95% CI)	p-value[a]
Key Secondary Efficacy Endpoint[b]				
FLO-11 Total Transformed Scores for GL ≥ 20-Point Improvement from Baseline at Day 7, % (95% CI)[c]	7.9% (1.3% 14.6%)	61.9% (54.4%, 69.3%)	54.0% (43.9%, 64.0%)	*p < 0.0001*
Secondary Efficacy Endpoints[b]				
FWS as assessed by subject: ≥ 2-grade improvement from baseline at Hour 24, % (95% CI)[c]	0.3% (0.0%, 2.0%)	39.8% (32.3%, 47.3%)	39.6% (31.8%, 47.3%)	*p < 0.0001*
FWS as assessed by investigator ≥ 2-grade improvement from baseline at Hour 24, % (95% CI)[c]	0.0% (0.0%, 0.0%)	44.7% (37.1%, 52.4%)	44.7% (37.1%, 52.4%)	*p < 0.0001*
FWS as assessed by subject ≥ 1-grade improvement from baseline at Hour 24, % (95% CI)[c]	14.2% (5.6%, 22.9%)	72.4% (65.5%, 79.3%)	58.2% (47.1%, 69.3%)	*p < 0.0001*
FWS as assessed by investigator ≥ 1-grade improvement from baseline at Hour 24, % (95% CI)[c]	10.2% (2.6%, 17.9%)	78.7% (72.4%, 85.0%)	68.5% (58.6%, 78.4%)	*p < 0.0001*
FLSQ follow-up version Item 5 (overall satisfaction) *Mostly Satisfied* or *Very Satisfied* at Hour 24, % (95% CI)[c]	9.9% (2.4%, 17.5%)	68.5% (61.3%, 75.6%)	58.5% (48.1%, 69.0%)	*p < 0.0001*
FLSQ follow-up version Item 4 (natural look) *Mostly Satisfied* or *Very Satisfied* at Day 7, % (95% CI) [c]	7.9% (1.3%, 14.6%)	86.0% (80.6%, 91.4%)	78.1% (69.5%, 86.7%)	*p < 0.0001*
FLO-11 Item 10 (look angry) ≥4-point improvement from baseline at Day 7[d], % (95% CI)[c]	n= 57 7.0% (0.4%, 13.6%)	n = 159 55.9% (48.2%, 63.6%)	48.9% (38.7%, 59.1%)	*p < 0.0001*
FLO-11 Item 5 (look less attractive) ≥ 4-point improvement from baseline at Day 7[d], % (95% CI)[c]	n = 59 8.5% (1.4%, 15.6%)	n = 160 48.9% (41.1% 56.7%)	40.4% (29.9%, 51.0%)	*p < 0.0001*

a. p-value derived from CMH test stratified by site and baseline FWS at maximum frown.

b. Secondary endpoints that are within gated hierarchical testing.

c. Estimated responder rate after using multiple imputation for missing data.

d. Amongst subjects able to improve at least 4 points from Baseline.

Source: Tables 14.2-4.1 through 14.2-4.7, Table 14.2-4.15, Table 14.2-4.16

Other secondary endpoints

Table 7. US FDA Secondary Efficacy Endpoints

	Placebo N = 156	AGN-151586 N = 482	Difference[a] (95% CI)	p-value
Mostly Satisfied or *Very Satisfied* on the FLSQ follow-up Item 5 (overall satisfaction) at Day 7, % (95% CI)[b]	5.1% (1.7%, 8.6%)	77.6% (73.9%, 81.4%)	72.5% (67.4%, 77.6%)	*p < 0.0001*
Mostly Satisfied or *Very Satisfied* on the FLSQ follow-up Item 5 (overall satisfaction) at Hour 24, % (95% CI)[b]	17.3% (11.4%, 23.2%)	59.2% (54.8%, 63.6%)	41.9% (34.5%, 49.3%)	*p < 0.0001*
Mostly Satisfied or *Very Satisfied* on the FLSQ follow-up Item 4 (natural look) at Day 7, % (95% CI)[b]	9.0% (4.5%, 13.5%)	78.5% (74.8%, 82.2%)	69.5% (63.7%, 75.3%)	*p < 0.0001*

a. Estimated responder rate difference for AGN-151586 vs. placebo group.

b. Estimated responder rate after using multiple imputation for missing data.

Note: Endpoints within the gated hierarchical testing are presented in this table.

Source: Table 14.2-2.3, Table 14.2-2.4, Table 14.2-2.5

Time to loss of primary EU endpoint from investigator and subject assessments

Table 14.2-4.13.1
FWS at Maximum Frown - Investigator: Time to Loss of a 2 Grade Improvement Achieved on Day 7, Double-blind Period
Intent-to-Treat Population
Baseline FLO-11 Total Transformed Score: <= 50

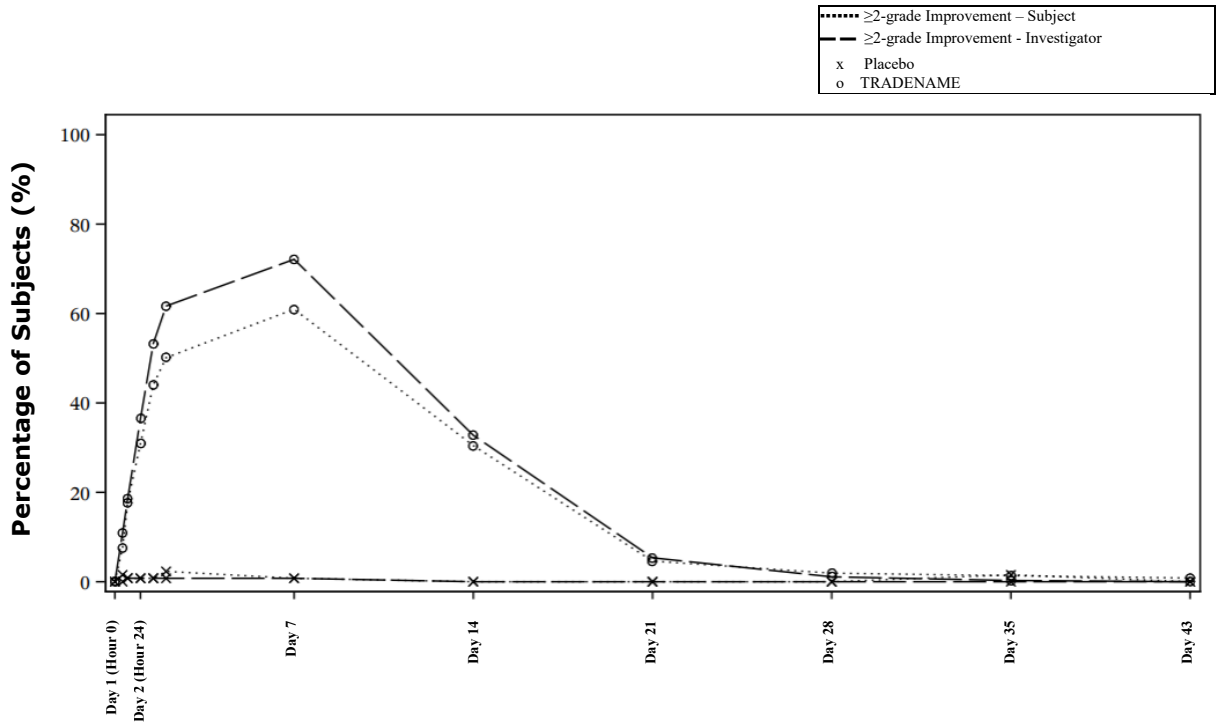
	DB Period	
	Placebo (N=130)	AGN-151586 (N=368)
Time to Event (Days)		
Mean (SD)	15.0 (NA)	19.0 (4.99)
Median	15.0	16.0
Q1, Q3	15.0, 15.0	15.0, 22.0
Min, Max	15, 15	8, 50
n	1	252
vs. Placebo		
Difference (Days)		4.0
95% CI (Days)		(-5.9, 13.8)
P-value [1]		0.0253

Table 14.2-4.12.1
FWS at Maximum Frown - Subject: Time to Loss of a 2 Grade Improvement Achieved on Day 7, Double-blind Period
Intent-to-Treat Population
Baseline FLO-11 Total Transformed Score: <= 50

	DB Period	
	Placebo (N=130)	AGN-151586 (N=368)
Time to Event (Days)		
Mean (SD)	15.0 (NA)	19.1 (4.92)
Median	15.0	17.0
Q1, Q3	15.0, 15.0	15.0, 22.0
Min, Max	15, 15	8, 50
n	1	213
vs. Placebo		
Difference (Days)		4.1
95% CI (Days)		(-5.6, 13.8)
P-value [1]		0.1336

FWS = Facial Wrinkle Scale, FLO-11 = 11-Item Facial Line Outcomes
For subjects who maintained their response, censoring occurred at the latest visit during the treatment period for which FWS was available from the subject. Subjects who did not meet the responder definition on Day 7 were excluded from the analysis; analysis was limited to those that responded.
Time to loss of response is computed as loss of response date - Day 1 date + 1.
[1] P-value derived from log-rank test stratified by site, toxin use history, and baseline FWS at maximum frown, using data as-observed.

≥2-grade improvement from baseline on the FWS according to subject and investigator assessments of glabellar lines severity at maximum frown over time (double-blind period)



Open-label period results

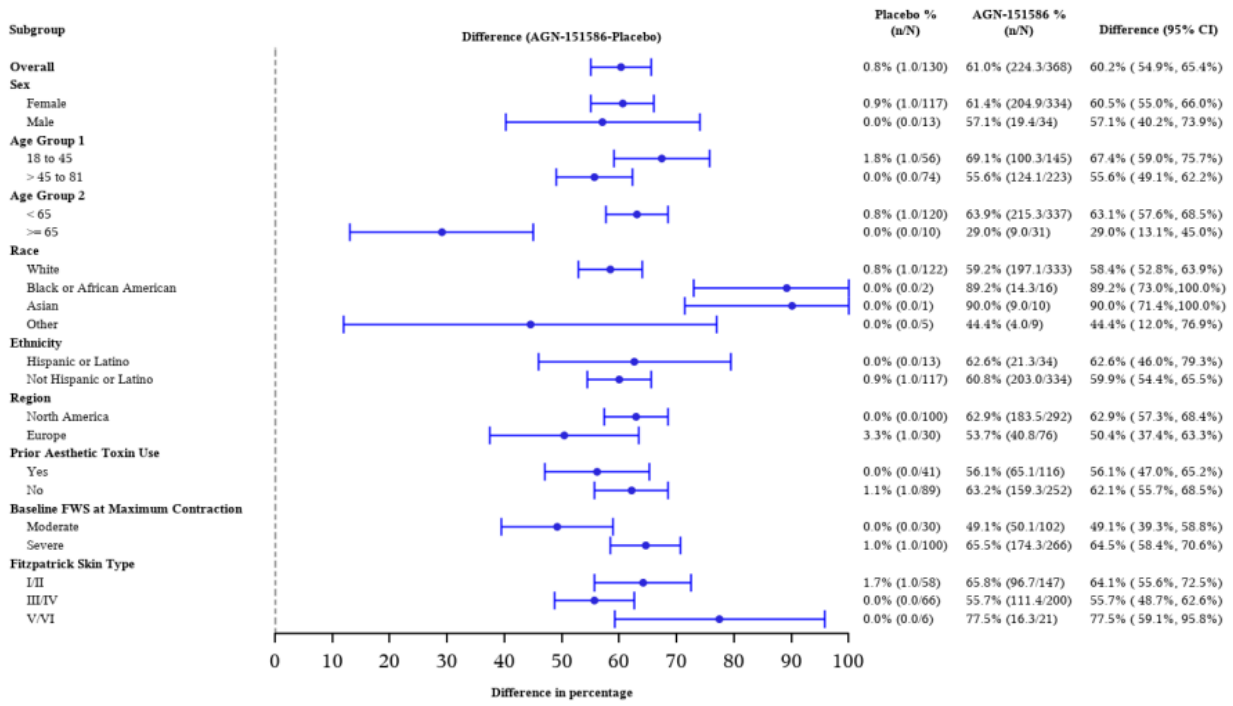
FWS at Maximum Frown: Number (%) of Subjects with Ratings of None or Mild Over Time, Open-label Period Intent-to-Treat Population Baseline FLO-11 Total Score: ≤50

Timepoint **Day 43 / Day 7**	**Placebo/None**	**Placebo/AGN-151586** **1st cycle of injection of AGN-151586**	**AGN-151586/None** **Only 1 cycle of injection of AGN-151586**	**AGN-151586/AGN-151586** **2nd cycle of injection of AGN-151586**
	(N=3)	(N=120)	(N=13)	(N=335)
Subject				
Responder rate, n/N1[1](%) 95% CI (%)	0/1 (0.0) (0.0, 0.0)	84/114 (**73.7**) (65.6, 81.8)	0/7 (0.0) (0.0, 0.0)	235/315 (**74.6**) (69.8, 79.4)
Investigator				
Responder rate, n/N1[1](%) 95% CI (%)	0/1 (0.0) (0.0, 0.0)	93/115 (**80.9**) (73.7, 88.1)	0/7 (0.0) (0.0, 0.0)	258/315 (**81.9**) (77.7, 86.2)

FWS = Facial Wrinkle Scale, FLO-11 = 11-Item Facial Line Outcomes Day 43 (Retreatment) is the baseline visit for FWS for subjects who are retreated on Day 43
[1] N1 = Number of subjects with data at the timepoint. Sources: tables 14.2-2.5.2 and 14.2-2.6.2

Pre-defined and post-hoc subgroup analyses

Figure 1.2-3.2.1f
Forest Plot: Responder Rate Difference of Co-primary Endpoints: FWS at Maximum Frown - Subject: Number (%) of Subjects with >= 2-Grade Improvement from Baseline at Day 7 by Subgroups
Phase 3 Single Treatment Placebo-Controlled Baseline FLO-11 Total Transformed Score <= 50 Dataset (ISE Group 2: M21-500)

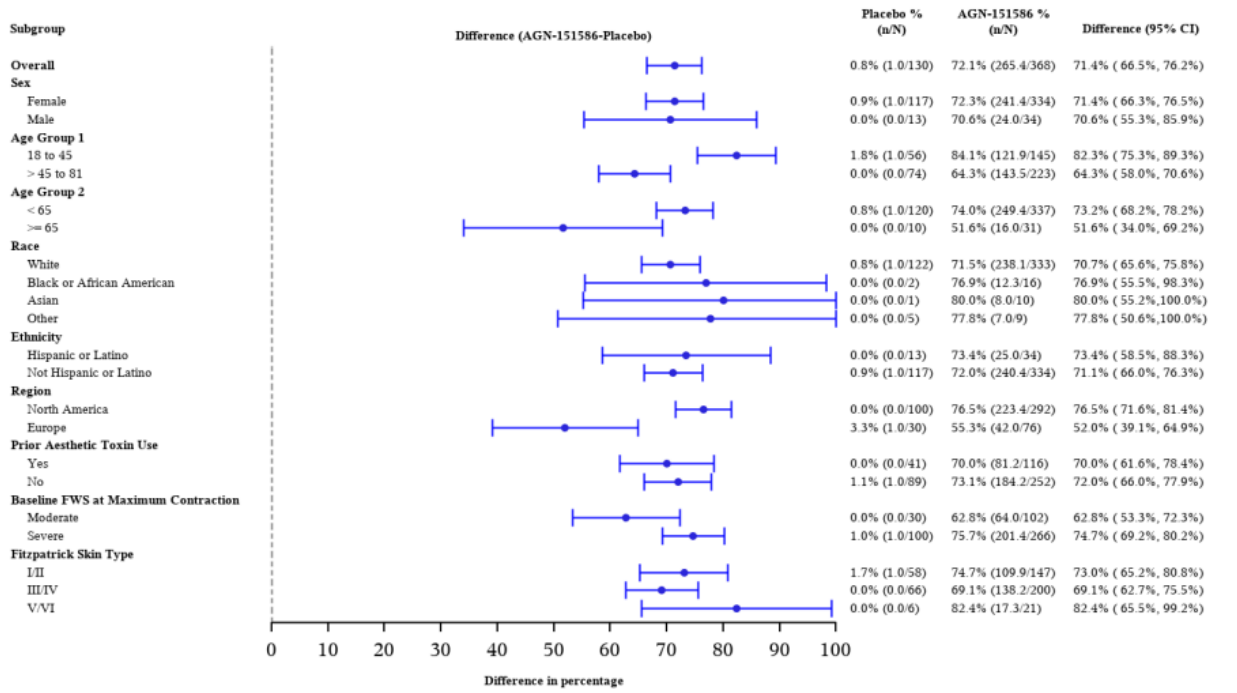


FWS = Facial Wrinkle Scale, FLO-11 = 11-Item Facial Line Outcomes
Responder rate and its 95% confidence interval are estimated after using multiple imputation for missing data.
n/N: n = Number of subjects with achievement within the treatment group after using multiple imputation for missing data, N = Number of subjects within the treatment group.

Figure 1.2-3.2.2f

Forest Plot: Responder Rate Difference of Co-primary Endpoints: FWS at Maximum Frown - Investigator: Number (%) of Subjects with >= 2-Grade Improvement from Baseline at Day 7 by Subgroups

Phase 3 Single Treatment Placebo-Controlled Baseline FLO-11 Total Transformed Score <= 50 Dataset (ISE Group 2: M21-500)



FWS = Facial Wrinkle Scale, FLO-11 = 11-Item Facial Line Outcomes
Responder rate and its 95% confidence interval are estimated after using multiple imputation for missing data.
n/N: n = Number of subjects with achievement within the treatment group after using multiple imputation for missing data, N = Number of subjects within the treatment group.

Ancillary analyses

Not applicable.

5.3.2.2. M21-508: A Phase 3, Multicentre Study to Evaluate the Safety and Efficacy of AGN-151586 for the Treatment of Glabellar Lines in Toxin-Naïve Subjects

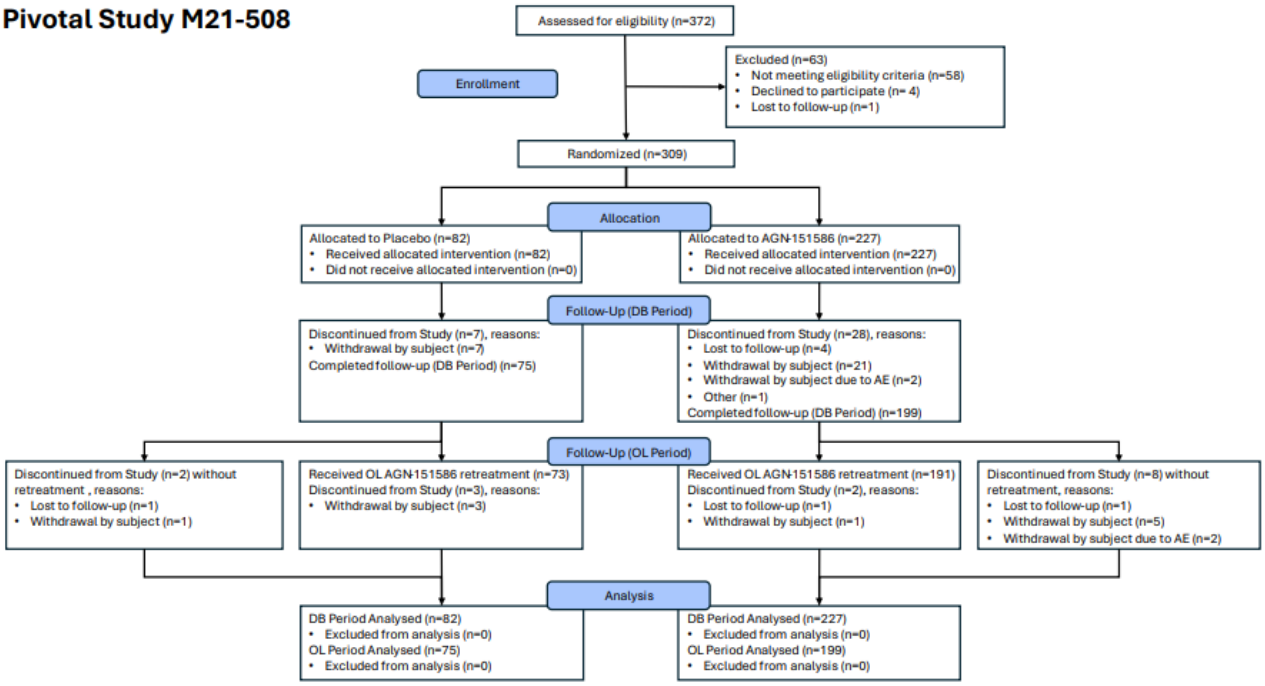
The study design, treatment, randomisation, blinding, objectives and estimands and statistical methods are identical to M21-500.

5.3.2.2.1. Results

Participant flow and numbers analysed

A total of 309 subjects were enrolled, randomized, and treated across 16 sites in 2 countries (US and Canada).

Pivotal Study M21-508



Analysis Populations

	DB Period		OL Period				
	Placebo	AGN-151586	Placebo/ None	Placebo/ AGN-151586	AGN-151586/ None	AGN-151586/ AGN-151586	Total
Intent-to-Treat Population, N	82	227	2	73	8	191	309
Safety Population, N	82	227	2	73	8	191	309

Table 14.1-1
Disposition of Subjects
Screened Population

	DB Period		OL Period				
Disposition	Placebo n (%)	AGN-151586 n (%)	Placebo/ None n (%)	Placebo/ AGN-151586 n (%)	AGN-151586/ None n (%)	AGN-151586/ AGN-151586 n (%)	Total n (%)
Number of Subjects Screened							372
Number of Subjects Enrolled (Randomized)	82 (100.0)	227 (100.0)					309 (100.0)
Number of Subjects Treated	82 (100.0)	227 (100.0)	0 (0.0)	73 (100.0)	0 (0.0)	191 (100.0)	309 (100.0)
Number of Subjects who Completed Study	75 (91.5)	199 (87.7)	0 (0.0)	70 (95.9)	0 (0.0)	189 (99.0)	259 (83.8)
Number of Subjects who Discontinued from Study	7 (8.5)	28 (12.3)	2 (100.0)	3 (4.1)	8 (100.0)	2 (1.0)	50 (16.2)
Reasons for Discontinuation							
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-Up	0 (0.0)	4 (1.8)	1 (50.0)	0 (0.0)	1 (12.5)	1 (0.5)	7 (2.3)
Withdrawal by Subject	7 (8.5)	21 (9.3)	1 (50.0)	3 (4.1)	5 (62.5)	1 (0.5)	38 (12.3)
Withdrawal by Subject due to Adverse Event	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)	4 (1.3)
Study Terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Site Terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 Logistical Restrictions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Deviations from study plan

Table 14.1-2
Protocol Deviations: Number (%) of Subjects with Protocol Deviations
Intent-to-Treat Population

Protocol Deviation Category	DB Period		OL Period				
	Placebo (N=82) n (%)	AGN-151586 (N=227) n (%)	Placebo/ None (N=2) n (%)	Placebo/ AGN-151586 (N=73) n (%)	AGN-151586/ None (N=8) n (%)	AGN-151586/ AGN-151586 (N=191) n (%)	Total (N=309) n (%)
Subjects With At Least One Protocol Deviation	28 (34.1)	75 (33.0)	1 (50.0)	25 (34.2)	2 (25.0)	59 (30.9)	103 (33.3)
Didn't Satisfy Study Entry Criteria	16 (19.5)	33 (14.5)	0 (0.0)	16 (21.9)	1 (12.5)	27 (14.1)	49 (15.9)
Eligibility Criteria Not Met [1]							
Criterion number 1	3 (3.7)	7 (3.1)	0 (0.0)	3 (4.1)	0 (0.0)	4 (2.1)	10 (3.2)
Criterion number 5	5 (6.1)	10 (4.4)	0 (0.0)	5 (6.8)	1 (12.5)	9 (4.7)	15 (4.9)
Criterion number 6	2 (2.4)	9 (4.0)	0 (0.0)	2 (2.7)	0 (0.0)	8 (4.2)	11 (3.6)
Criterion number 16	1 (1.2)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.3)
Criterion number 18	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.6)
Criterion number 20	6 (7.3)	7 (3.1)	0 (0.0)	6 (8.2)	0 (0.0)	6 (3.1)	13 (4.2)
Criterion number 21	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Criterion number 23	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Criterion number 27	1 (1.2)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.3)
Met Withdrawal Criteria But Not Withdrawn	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wrong Treatment Or Incorrect Dose Of Study Treatment	0 (0.0)	8 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	8 (4.2)	8 (2.6)
Prohibited Concomitant Medication	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.6)

Baseline data

Parameter	DB Period		OL Period					
	Placebo (N=82)	AGN-151586 (N=227)	Placebo/ None (N=2)	Placebo/ AGN-151586 (N=73)	AGN-151586/ None (N=8)	AGN-151586/ AGN-151586 (N=191)	Any AGN-151586 (N=300)	Total (N=309)
Age (years)								
Mean (SD)	43.0 (13.08)	43.2 (13.10)	50.0 (9.90)	43.7 (13.20)	45.9 (12.60)	43.7 (13.07)	43.3 (13.11)	43.1 (13.08)
Median	42.5	42.0	50.0	43.0	45.5	43.0	42.5	42.0
Q1, Q3	32.0, 52.0	32.0, 53.0	43.0, 57.0	33.0, 54.0	37.0, 56.5	32.0, 54.0	32.0, 53.5	32.0, 53.0
Min, Max	20, 71	22, 76	43, 57	20, 71	26, 63	22, 76	20, 76	20, 76
n	82	227	2	73	8	191	300	309
Age (years), n(%)								
< 65	74 (90.2)	217 (95.6)	2 (100.0)	65 (89.0)	8 (100.0)	182 (95.3)	282 (94.0)	291 (94.2)
>= 65	8 (9.8)	10 (4.4)	0 (0.0)	8 (11.0)	0 (0.0)	9 (4.7)	18 (6.0)	18 (5.8)
Sex, n (%)								
Male	18 (22.0)	46 (20.3)	1 (50.0)	16 (21.9)	1 (12.5)	37 (19.4)	62 (20.7)	64 (20.7)
Female	64 (78.0)	181 (79.7)	1 (50.0)	57 (78.1)	7 (87.5)	154 (80.6)	238 (79.3)	245 (79.3)
Ethnicity, n (%)								
Hispanic or Latino	8 (9.8)	26 (11.5)	0 (0.0)	7 (9.6)	2 (25.0)	21 (11.0)	33 (11.0)	34 (11.0)
Not Hispanic or Latino	74 (90.2)	201 (88.5)	2 (100.0)	66 (90.4)	6 (75.0)	170 (89.0)	267 (89.0)	275 (89.0)
Race, n (%)								
White	68 (82.9)	189 (83.3)	2 (100.0)	62 (84.9)	8 (100.0)	159 (83.2)	251 (83.7)	257 (83.2)
Black or African American	4 (4.9)	14 (6.2)	0 (0.0)	2 (2.7)	0 (0.0)	13 (6.8)	16 (5.3)	18 (5.8)
Asian	4 (4.9)	16 (7.0)	0 (0.0)	4 (5.5)	0 (0.0)	14 (7.3)	20 (6.7)	20 (6.5)
Japanese	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.7)	2 (0.6)
Chinese	2 (2.4)	4 (1.8)	0 (0.0)	2 (2.7)	0 (0.0)	4 (2.1)	6 (2.0)	6 (1.9)
Korean	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	1 (0.3)
Taiwanese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (2.4)	9 (4.0)	0 (0.0)	2 (2.7)	0 (0.0)	7 (3.7)	11 (3.7)	11 (3.6)
American Indian or Alaska Native	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.7)	2 (0.6)
Native Hawaiian or Other Pacific Islander	2 (2.4)	2 (0.9)	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.5)	3 (1.0)	4 (1.3)
Multiple [1]	4 (4.9)	4 (1.8)	0 (0.0)	4 (5.5)	0 (0.0)	2 (1.0)	8 (2.7)	8 (2.6)

Age relative to informed consent date.
[1] Subjects who reported multiple races are only included in the 'Multiple' category.

Baseline and Disease Characteristics

Parameter	Placebo (N=82)	AGN-151586 (N=227)	Total (N=309)
Weight (kg)			
Mean (SD)	78.43 (18.332)	76.05 (17.368)	76.68 (17.630)
Median	75.52	73.48	73.48
Q1, Q3	64.64, 87.09	63.59, 86.18	64.30, 86.18
Min, Max	46.3, 135.2	45.8, 144.9	45.8, 144.9
n	82	227	309
Height (cm)			
Mean (SD)	168.0 (8.70)	166.7 (9.94)	167.1 (9.63)
Median	167.0	167.0	167.0
Q1, Q3	162.6, 172.7	160.0, 172.7	160.0, 172.7
Min, Max	151, 196	124, 196	124, 196
n	82	227	309
BMI (kg/m**2)			
Mean (SD)	27.68 (5.564)	27.40 (6.183)	27.47 (6.017)
Median	26.47	25.72	25.91
Q1, Q3	23.55, 30.48	23.33, 30.38	23.43, 30.38
Min, Max	17.5, 47.0	17.5, 54.8	17.5, 54.8
n	82	227	309
BMI (kg/m**2), n(%)			
< 25	30 (36.6)	100 (44.1)	130 (42.1)
>= 25	52 (63.4)	127 (55.9)	179 (57.9)
Nicotine Use, n (%)			
Never	55 (67.1)	153 (67.4)	208 (67.3)
Current	8 (9.8)	32 (14.1)	40 (12.9)
Former	19 (23.2)	42 (18.5)	61 (19.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Alcohol Use, n (%)			
Never	15 (18.3)	32 (14.1)	47 (15.2)
Current	58 (70.7)	175 (77.1)	233 (75.4)
Former	9 (11.0)	20 (8.8)	29 (9.4)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Fitzpatrick Skin Type, n (%)			
I	3 (3.7)	16 (7.0)	19 (6.1)
II	34 (41.5)	75 (33.0)	109 (35.3)
III	27 (32.9)	80 (35.2)	107 (34.6)
IV	10 (12.2)	35 (15.4)	45 (14.6)
V	5 (6.1)	15 (6.6)	20 (6.5)
VI	3 (3.7)	6 (2.6)	9 (2.9)
FWS Stratification, n [1] (%)			
2 = Moderate	25 (30.5)	60 (26.4)	85 (27.5)
3 = Severe	57 (69.5)	167 (73.6)	224 (72.5)

Parameter	Placebo (N=82)	AGN-151586 (N=227)	Total (N=309)
FWS at Maximum Frown - Subject, n (%)			
0 = None	0 (0.0)	0 (0.0)	0 (0.0)
1 = Mild	0 (0.0)	0 (0.0)	0 (0.0)
2 = Moderate	25 (30.5)	58 (25.6)	83 (26.9)
3 = Severe	57 (69.5)	169 (74.4)	226 (73.1)
FWS at Maximum Frown - Investigator, n (%)			
0 = None	0 (0.0)	0 (0.0)	0 (0.0)
1 = Mild	0 (0.0)	0 (0.0)	0 (0.0)
2 = Moderate	25 (30.5)	60 (26.4)	85 (27.5)
3 = Severe	57 (69.5)	167 (73.6)	224 (72.5)
FWS at Rest - Subject, n (%)			
0 = None	19 (23.2)	39 (17.2)	58 (18.8)
1 = Mild	27 (32.9)	83 (36.6)	110 (35.6)
2 = Moderate	28 (34.1)	84 (37.0)	112 (36.2)
3 = Severe	8 (9.8)	21 (9.3)	29 (9.4)
FWS at Rest - Investigator, n (%)			
0 = None	17 (20.7)	38 (16.7)	55 (17.8)
1 = Mild	30 (36.6)	93 (41.0)	123 (39.8)
2 = Moderate	26 (31.7)	77 (33.9)	103 (33.3)
3 = Severe	9 (11.0)	19 (8.4)	28 (9.1)

Parameter	Placebo (N=82)	AGN-151586 (N=227)	Total (N=309)
FLSQ Baseline Version - Treatment Expectations Domain Score			
Mean (SD)	53.3 (14.70)	54.6 (15.56)	54.2 (15.32)
Median	52.5	53.3	53.3
Q1, Q3	44.2, 62.5	43.3, 65.0	43.8, 64.6
Min, Max	26, 93	16, 100	16, 100
n	82	226	308
FLSQ Baseline Version - Impact Domain Score			
Mean (SD)	49.9 (23.59)	50.8 (24.37)	50.6 (24.13)
Median	50.0	50.0	50.0
Q1, Q3	35.0, 65.0	30.0, 70.0	30.0, 70.0
Min, Max	0, 95	0, 100	0, 100
n	82	226	308
FLO-11 Total Transformed Score			
Mean (SD)	37.9 (20.23)	36.9 (23.54)	37.1 (22.68)
Median	36.4	33.6	33.6
Q1, Q3	24.5, 50.0	18.2, 51.8	20.0, 51.8
Min, Max	0, 100	0, 93	0, 100
n	82	227	309
FLO-11 Total Transformed Score, n (%)			
<= 50	63 (76.8)	164 (72.2)	227 (73.5)
> 50	19 (23.2)	63 (27.8)	82 (26.5)

Outcomes and estimation

Double-blind period results

Efficacy analyses for the US FDA and EU Regulatory agencies were performed on the ITT Population, consisting of all randomized subjects.

Double-blind period results

Primary endpoints

For the US FDA, the primary composite efficacy endpoint was achievement of Grade 0 or 1 (None or Mild) and ≥ 2-grade improvement on both the investigator and subject FWS assessments of GL severity at maximum frown from Baseline at Day 7.

For the EU regulatory agency, the co-primary efficacy endpoints were the achievement of ≥ 2-grade improvement of GL severity at maximum frown from Baseline at Day 7 according to (1) subject's self-assessment using FWS and (2) investigator's assessment using FWS, among subjects who had a baseline FLO-11 total transformed score ≤ 50.

Table 6. Primary Efficacy Endpoints

	Placebo	AGN-151586	Difference (95% CI)	p-value[a]
US FDA Primary Composite (ITT)	**N=82**	**N=227**		
Grade 0 or 1 (None or Mild) and ≥ 2-grade improvement from baseline on the FWS at maximum frown by investigator and subject at Day 7, % (95% CI)[b]	1.2% (0.0%, 3.6%)	65.7% (59.5%, 71.9%)	64.5% (57.9%, 71.1%)	*< 0.0001*
EU Co-primary (ITT[c])	**N = 63**	**N = 164**		
≥ 2-grade improvement from baseline based on FWS at maximum frown as assessed by subject at Day 7, % (95% CI)[b]	0.0% (0.0%, 0.0%)	67.9% (60.7%, 75.0%)	67.9% (60.7%, 75.0 %)	*< 0.0001*
≥ 2-grade improvement from baseline based on FWS at maximum frown as assessed by investigator at Day 7, % (95% CI)[b]	0.0% (0.0%, 0.0%)	73.6% (66.8%, 80.4%)	73.6% (66.8%, 80.4%)	*< 0.0001*

a. p-value derived from CMH test stratified by site and baseline FWS at maximum frown.

b. Estimated responder rate after using multiple imputation for missing data.

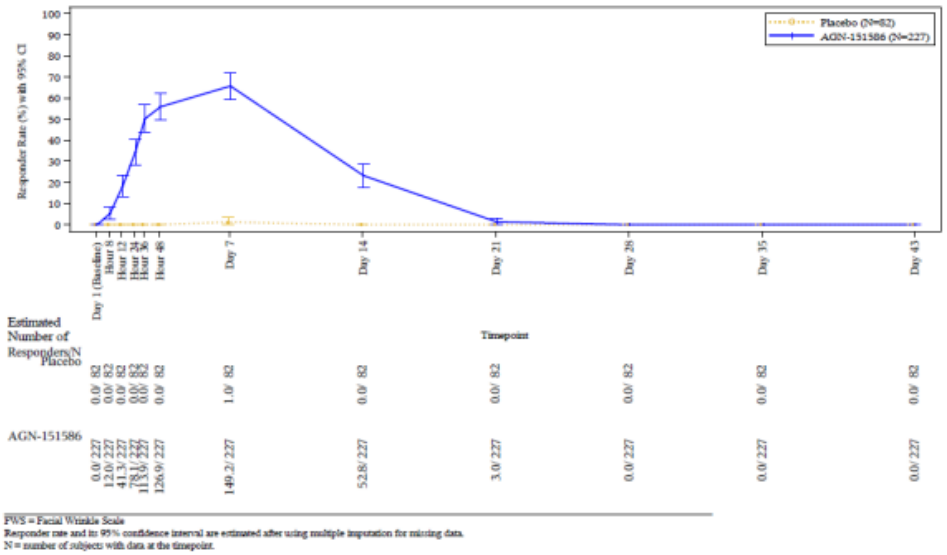
c. For EU regulatory agencies, the analysis population is the ITT population with baseline FLO-11 total transformed scores ≤ 50.

Source: Table 14.2-1.1, Table 14.2-3.1

Secondary endpoints

US FDA Key Secondary Endpoint: FWS at Maximum Frown According to Investigator and Subject Assessment over Time (Double-blind Period)

FWS at Maximum Frown – Investigator and Subject: Percentage of Subjects with Composite Achievement of Grade 0 or 1 (None or Mild) and ≥ 2-Grade Improvement from Baseline Over Time, Double-Blind Period (ITT Population)



EU Key Secondary Endpoint: FLO-11 Total Score ≥ 20-Point Improvement from Baseline at Day 7

Table 8. EU Secondary Efficacy Endpoints (ITT Population with Baseline FLO-11 Total Transformed Score ≤ 50)

	Placebo N = 63	AGN-151586 N = 164	Difference (95% CI)	p-value[a]
Key Secondary Efficacy Endpoint[b]				
FLO-11 Total Transformed Scores for GL ≥ 20-Point Improvement from Baseline at Day 7, % (95% CI)[c]	7.9% (1.3% 14.6%)	61.9% (54.4%, 69.3%)	54.0% (43.9%, 64.0%)	*p < 0.0001*

Secondary Efficacy Endpoints[b]				
FWS as assessed by subject: ≥ 2-grade improvement from baseline at Hour 24, % (95% CI)[c]	0.3% (0.0%, 2.0%)	39.8% (32.3%, 47.3%)	39.6% (31.8%, 47.3%)	*p < 0.0001*
FWS as assessed by investigator ≥ 2-grade improvement from baseline at Hour 24, % (95% CI)[c]	0.0% (0.0%, 0.0%)	44.7% (37.1%, 52.4%)	44.7% (37.1%, 52.4%)	*p < 0.0001*
FWS as assessed by subject ≥ 1-grade improvement from baseline at Hour 24, % (95% CI)[c]	14.2% (5.6%, 22.9%)	72.4% (65.5%, 79.3%)	58.2% (47.1%, 69.3%)	*p < 0.0001*
FWS as assessed by investigator ≥ 1-grade improvement from baseline at Hour 24, % (95% CI)[c]	10.2% (2.6%, 17.9%)	78.7% (72.4%, 85.0%)	68.5% (58.6%, 78.4%)	*p < 0.0001*
FLSQ follow-up version Item 5 (overall satisfaction) *Mostly Satisfied* or *Very Satisfied* at Hour 24, % (95% CI)[c]	9.9% (2.4%, 17.5%)	68.5% (61.3%, 75.6%)	58.5% (48.1%, 69.0%)	*p < 0.0001*
FLSQ follow-up version Item 4 (natural look) *Mostly Satisfied* or *Very Satisfied* at Day 7, % (95% CI) [c]	7.9% (1.3%, 14.6%)	86.0% (80.6%, 91.4%)	78.1% (69.5%, 86.7%)	*p < 0.0001*
FLO-11 Item 10 (look angry) ≥4-point improvement from baseline at Day 7[d], % (95% CI)[c]	n= 57 7.0% (0.4%, 13.6%)	n = 159 55.9% (48.2%, 63.6%)	48.9% (38.7%, 59.1%)	*p < 0.0001*
FLO-11 Item 5 (look less attractive) ≥ 4-point improvement from baseline at Day 7[d], % (95% CI)[c]	n = 59 8.5% (1.4%, 15.6%)	n = 160 48.9% (41.1% 56.7%)	40.4% (29.9%, 51.0%)	*p < 0.0001*

a. p-value derived from CMH test stratified by site and baseline FWS at maximum frown.

b. Secondary endpoints that are within gated hierarchical testing.

c. Estimated responder rate after using multiple imputation for missing data.

d. Amongst subjects able to improve at least 4 points from Baseline.

Source: Tables 14.2-4.1 through 14.2-4.7, Table 14.2-4.15, Table 14.2-4.16

Other secondary endpoints

Table 7. Secondary Efficacy Endpoints for the US FDA (ITT Population)

	Placebo N = 82	AGN-151586 N = 227	Difference (95% CI)	p-value[a]
FLSQ follow-up Version Item 5 (overall satisfaction; *Mostly Satisfied* or *Very Satisfied*) at Day 7, % (95% CI)[b]	9.8% (3.3%, 16.2%)	84.9% (80.1%, 89.6%)	75.1% (67.1%, 83.1%)	*p < 0.0001*
FLSQ follow-up version Item 5 (overall satisfaction; *Mostly Satisfied* or *Very Satisfied*) at Hour 24, % (95% CI)[b]	13.7% (6.2%, 21.3%)	69.3% (63.3%, 75.3%)	55.6% (45.9%, 65.2%)	*p < 0.0001*
FLSQ follow-up version Item 4 (natural look; *Mostly Satisfied* or *Very Satisfied*) at Day 7, % (95% CI)[b]	13.4% (6.0%, 20.8%)	84.7% (79.9%, 89.5%)	71.3% (62.5%, 80.1%)	*p < 0.0001*

Note: Secondary endpoints that are within gated hierarchical testing.

a. p-value derived from CMH test stratified by site and baseline FWS at maximum frown.

b. Estimated responder rate after using multiple imputation for missing data

Source: Table 14.2-2.3, Table 14.2-2.4, Table 14.2-2.5

Time to loss of primary EU endpoint from investigator and subject assessments

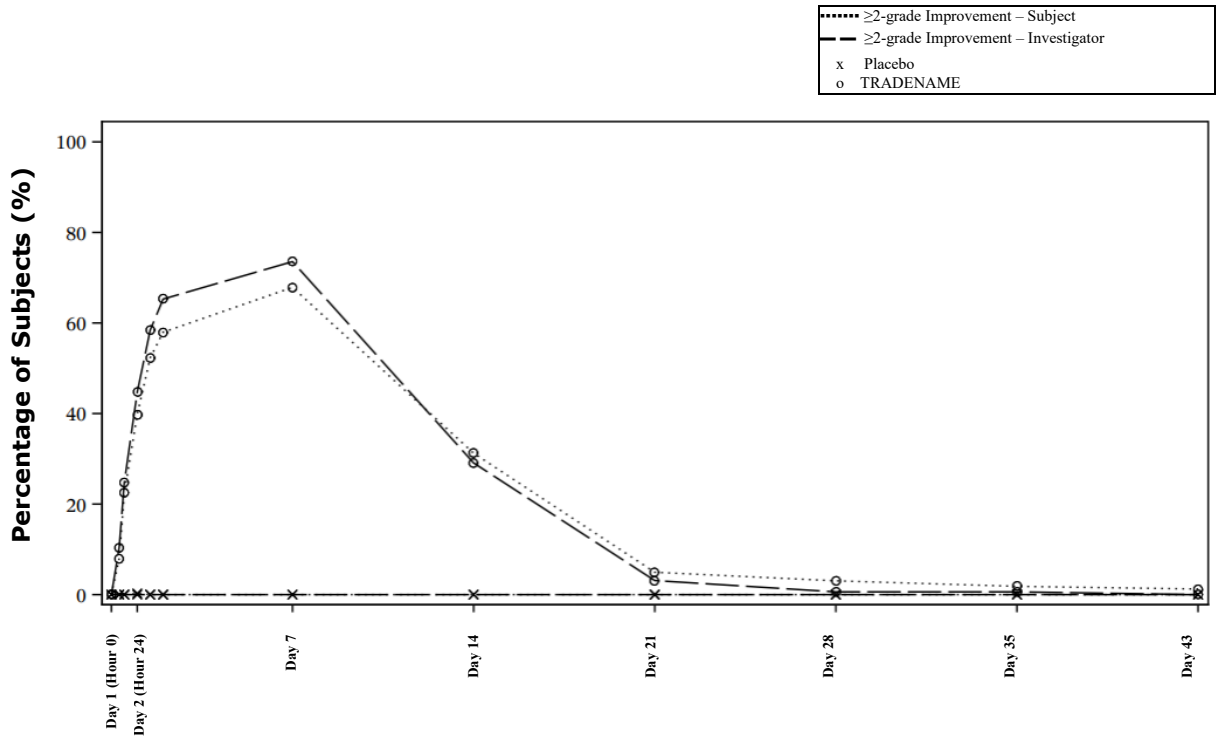
Table 14.2-4.13.1
FWS at Maximum Frown - Investigator: Time to Loss of a 2 Grade Improvement Achieved on Day 7, Double-blind Period
Intent-to-Treat Population
Baseline FLO-11 Total Transformed Score: <= 50

	DB Period	
	Placebo (N=63)	AGN-151586 (N=164)
Time to Event (Days)		
Mean (SD)		18.0 (3.91)
Median		16.0
Q1, Q3		15.0, 22.0
Min, Max		14, 30
n	0	118
vs. Placebo		
Difference (Days)		NE
95% CI (Days)		(NE, NE)
P-value [1]		NE

Table 14.2-4.12.1
FWS at Maximum Frown - Subject: Time to Loss of a 2 Grade Improvement Achieved on Day 7, Double-blind Period
Intent-to-Treat Population
Baseline FLO-11 Total Transformed Score: <= 50

	DB Period	
	Placebo (N=63)	AGN-151586 (N=164)
Time to Event (Days)		
Mean (SD)		18.6 (4.69)
Median		16.0
Q1, Q3		15.0, 22.0
Min, Max		14, 43
n	0	109
vs. Placebo		
Difference (Days)		NE
95% CI (Days)		(NE, NE)
P-value [1]		NE

≥2-grade improvement from baseline on the FWS according to subject and investigator assessments of glabellar lines severity at maximum frown over time (double-blind period)



Open-label period results

Analyses were done also for endpoints during the open-label period: 2 cycles of injections, placebo or AGN-151586 were performed first at Day 7 then at Day 43 if eligibility criteria for repeated administration were met.

FWS at Maximum Frown: Number (%) of Subjects with Ratings of None or Mild Over Time, Open-label Period Intent-to-Treat Population Baseline FLO-11 Total Transformed Score: <= 50

Timepoint **Day 43 / Day 7**	**Placebo/None**	**Placebo/AGN-151586** **1st cycle of** **injection of AGN-151586**	**AGN-151586/None** **Only 1 cycle of injection of AGN-151586**	**AGN-151586/AGN-151586** **2nd cycle of injection of AGN-151586**
	(N=2)	(N=73)	(N=8)	(N=191)
Subject				
Response rate, n/N1[1](%) 95% CI (%)	0/0 (NA) (NA)	50/69 (72.57) (61.9, 83.0)	0/7 (0.0) (0.0, 0.0)	124/183 (67.8) (61.0, 74.5)
Investigator				
Response rate, n/N1[1](%) 95% CI (%)	0/0 (NA) (NA)	57/89 (82.6) (73.7, 88.1)	0/7 (0.0) (0.0, 0.0)	139/182 (76.4 (70.2, 82.5)

FWS = Facial Wrinkle Scale, FLO-11 = 11-Item Facial Line Outcomes Day 43 (Retreatment) is the baseline visit for FWS for subjects who are retreated on Day 43

[1] N1 = Number of subjects with data at the timepoint. Sources: tables 14.2-2.1.2 and 14.2-2.2.2

Pre-defined and post-hoc subgroup analyses

In the Intent-to-Treat Population and in the population with a baseline FLO-11 Total Transformed Score ≤ 50, the response rate was analysed according to the gender, the age, the severity of GL at baseline.

Female

Table 14.2-8.2.1
FLO-11 (Subgroup Analysis): Number (%) of Subjects with >= 20 Point Improvement from Baseline Total Transformed Score at Day 7
Intent-to-Treat Population
Baseline FLO-11 Total Transformed Score: <= 50, Sex: Female

	DB Period	
Timepoint	Placebo (N=52)	AGN-151586 (N=136)
Day 7		
Responder rate, n/N1 [1] (%)	3/52 (5.8)	87/133 (65.4)
95% CI (%)	(0.0, 12.1)	(57.3, 73.5)
Model		
Estimated responder rate, n/N [2] (%)	3.0/52 (5.8)	89.5/136 (65.8)
95% CI (%)	(0.0, 12.1)	(57.8, 73.8)
vs. Placebo		
Difference (%)		60.0
95% CI (%)		(49.8, 70.3)
P-value [3]		<0.0001

Male

	DB Period	
Timepoint	Placebo (N=11)	AGN-151586 (N=28)
Day 7		
Responder rate, n/N1 [1] (%)	2/11 (18.2)	12/26 (46.2)
95% CI (%)	(0.0, 41.0)	(27.0, 65.3)
Model		
Estimated responder rate, n/N [2] (%)	2.0/11 (18.2)	12.0/28 (42.9)
95% CI (%)	(0.0, 41.0)	(24.5, 61.2)
vs. Placebo		
Difference (%)		24.7
95% CI (%)		(-4.6, 53.9)
P-value [3]		0.2189

≥ 65 years:

Table 14.2-8.1.4
Co-primary Endpoints (Subgroup Analysis): FWS at Maximum Frown - Subject, Investigator: Number (%) of Subjects with >= 2 Grade Improvement from Baseline at Day 7
Intent-to-Treat Population
Baseline FLO-11 Total Transformed Score: <= 50, Age: >=65

	DB Period	
Timepoint	Placebo (N=7)	AGN-151586 (N=7)
Subject FWS, Day 7		
Responder rate, n/N1 [1] (%)	0/7 (0.0)	5/7 (71.4)
95% CI (%)	(0.0, 0.0)	(38.0, 100.0)
Model		
Estimated responder rate, n/N [2] (%)	0.0/7 (0.0)	5.0/7 (71.4)
95% CI (%)	(0.0, 0.0)	(38.0, 100.0)
vs. Placebo		
Difference (%)		71.4
95% CI (%)		(38.0, 100.0)
P-value [3]		0.0531
Investigator FWS, Day 7		
Responder rate, n/N1 [1] (%)	0/7 (0.0)	6/7 (85.7)
95% CI (%)	(0.0, 0.0)	(59.8, 100.0)
Model		
Estimated responder rate, n/N [2] (%)	0.0/7 (0.0)	6.0/7 (85.7)
95% CI (%)	(0.0, 0.0)	(59.8, 100.0)
vs. Placebo		
Difference (%)		85.7
95% CI (%)		(59.8, 100.0)
P-value [3]		0.0194

< 65 years

Table 14.2-8.2.3
FLO-11 (Subgroup Analysis): Number (%) of Subjects with >= 20 Point Improvement from Baseline Total Transformed Score at Day 7
Intent-to-Treat Population
Baseline FLO-11 Total Transformed Score: <= 50, Age: < 65

	DB Period	
Timepoint	Placebo (N=56)	AGN-151586 (N=157)
Day 7		
Responder rate, n/N1 [1] (%)	4/56 (7.1)	95/152 (62.5)
95% CI (%)	(0.4, 13.9)	(54.8, 70.2)

Baseline FWS at maximum frown

Moderate

	DB Period	
Timepoint	Placebo (N=16)	AGN-151586 (N=33)
Day 7		
Responder rate, n/N1 [1] (%)	2/16 (12.5)	21/31 (67.7)
95% CI (%)	(0.0, 28.7)	(51.3, 84.2)

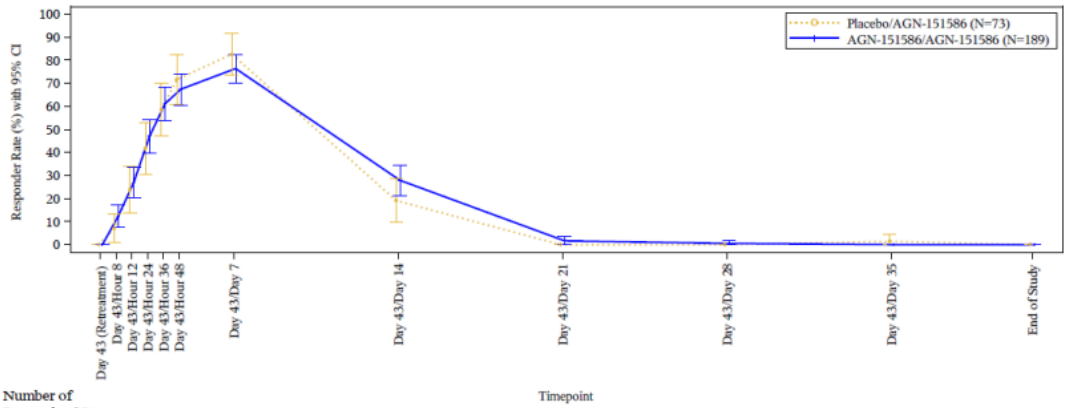
Severe

	DB Period	
Timepoint	Placebo (N=47)	AGN-151586 (N=131)
Day 7		
Responder rate, n/N1 [1] (%)	3/47 (6.4)	78/128 (60.9)
95% CI (%)	(0.0, 13.4)	(52.5, 69.4)

Efficacy of repeated administration: retreatment was possible at Day 43 is eligibility criteria were met

During the open-label period, subjects who were eligible for retreatments in both AGN-151586 and placebo groups received AGN-151586 treatments.

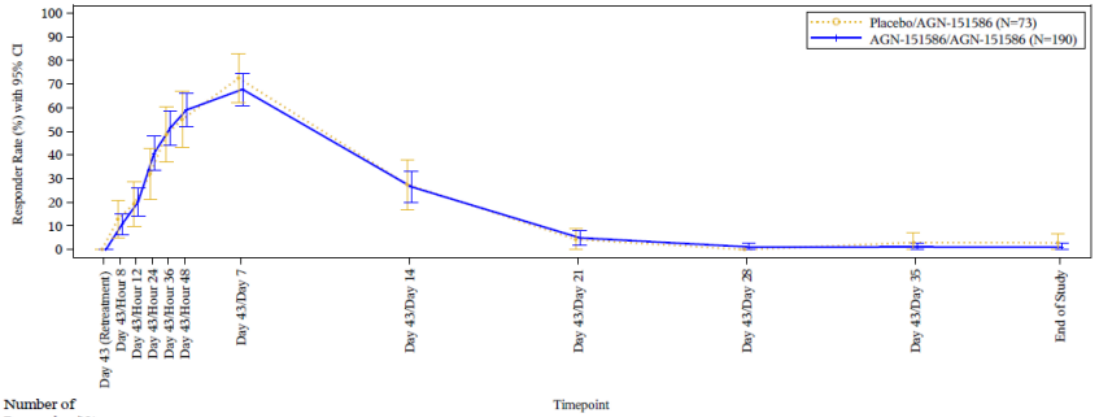
FWS at Maximum Frown – Investigator: Percentage of Subjects with Achievement of Grade 0 or 1 (None or Mild) and ≥ 2-Grade Improvement from Baseline Over Time, Open-Label Period (ITT Population)



Number of Responders/N1	Day 43 (Retreatment)	Day 43/Hour 8	Day 43/Hour 12	Day 43/Hour 24	Day 43/Hour 36	Day 43/Hour 48	Day 43/Day 7	Day 43/Day 14	Day 43/Day 21	Day 43/Day 28	Day 43/Day 35	End of Study
Placebo/AGN-151586	0/73	5/70	16/67	30/72	41/70	48/67	57/69	13/68	0/69	0/69	1/68	0/70
AGN-151586/AGN-151586	0/189	23/186	48/178	86/183	107/175	122/181	139/182	48/172	3/178	1/182	0/175	0/187

FWS = Facial Wrinkle Scale
Day 43 (Retreatment) is the baseline visit for FWS for subjects who are retreated on Day 43.
Responder rate is calculated using data as-observed.
N1= number of subjects with data at the timepoint.

FWS at Maximum Frown – Subject Percentage of Subjects with Achievement of Grade 0 or 1 (None or Mild) and ≥ 2-Grade Improvement from Baseline Over Time, Open-Label Period (ITT Population)



Number of Responders/N1	Day 43 (Retreatment)	Day 43/Hour 8	Day 43/Hour 12	Day 43/Hour 24	Day 43/Hour 36	Day 43/Hour 48	Day 43/Day 7	Day 43/Day 14	Day 43/Day 21	Day 43/Day 28	Day 43/Day 35	End of Study
Placebo/AGN-151586	0/73	9/70	13/67	23/72	34/70	38/69	50/69	19/69	3/70	0/69	2/68	2/70
AGN-151586/AGN-151586	0/190	20/187	36/179	75/184	91/177	108/183	124/183	47/177	9/182	2/183	2/178	2/189

FWS = Facial Wrinkle Scale
Day 43 (Retreatment) is the baseline visit for FWS for subjects who are retreated on Day 43.
Responder rate is calculated using data as-observed.
N1 = number of subjects with data at the timepoint.

Ancillary analyses

Not applicable.

5.3.2.3. M23-365: Sequential administration of AGN-151586

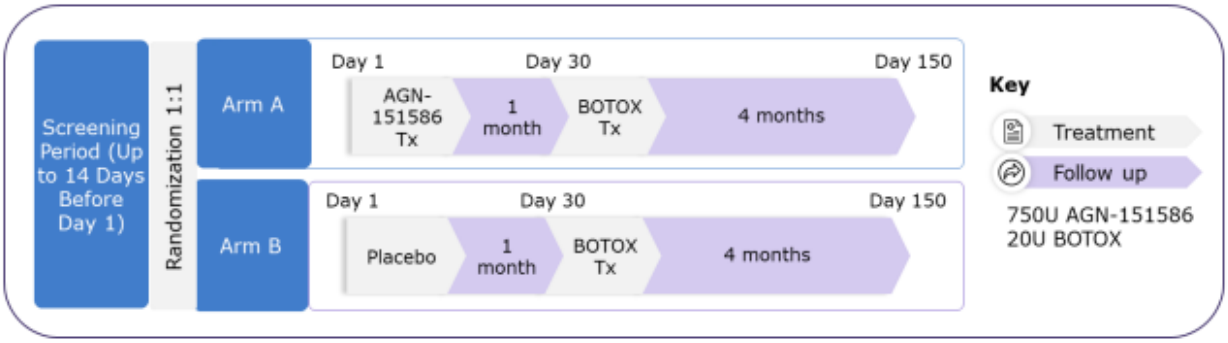
Study M23-365 was a 150-day, multicentre, double-blind, placebo-controlled study to assess the safety and efficacy of sequential administration of AGN-151586 700 U and BOTOX 20 U (units were toxin-specific), in which BOTOX was administered at the Day 30 study visit after AGN-151586 (or placebo) administration on Baseline Day 1, in subjects with moderate to severe GL. Subjects were adults (≥ 18 years of age) with moderate to severe GL at maximum frown as assessed independently by the investigator and the subject using the FWS at the Screening and Baseline Day 1 visits (matching not required).

The objective of this Phase 1 study was to assess the safety and efficacy of sequential administration of AGN-151586 700 U and BOTOX 20 U, in which BOTOX was administered 30 days after AGN-151586 administration for the treatment of GL in subjects with moderate to severe GL.

The first treatment period (Day 1 to Day 30) was a randomized, placebo-controlled, single-treatment design and the second treatment period (Day 30 to Study exit) consisted of treatment with one dose of BOTOX 20 U for subjects who met eligibility criteria. Over the duration of the study, a maximum of 2 study treatments could be administered to subjects.

Subjects were 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 at the Screening and Baseline Day 1 visits, with no reported use of any botulinum neurotoxin of any serotype (including any investigational botulinum neurotoxin product) within the last 12 months prior to screening.

Figure 1. Study Design Schematic



The primary efficacy endpoint for this study was the achievement of None or Mild according to investigator FWS assessment of GL severity at maximum frown at Day 60 (30 days after BOTOX administration).

A total of 90 subjects were enrolled, randomized, and treated across 10 sites in the US. Overall, most subjects completed the study. The most common reason for study discontinuation was lost to follow-up and withdrawal by subject in Treatment Period 1 and Treatment Period 2, respectively.

No formal hypothesis testing was performed. The results after AGN-151586 injections observed at Day 7 (period 1) and the results of Botox injections observed at Day 60 (period 2) are presented as observed.

Primary endpoint

Period 2: response rate assessed by investigator at Day 60 (Botox efficacy)

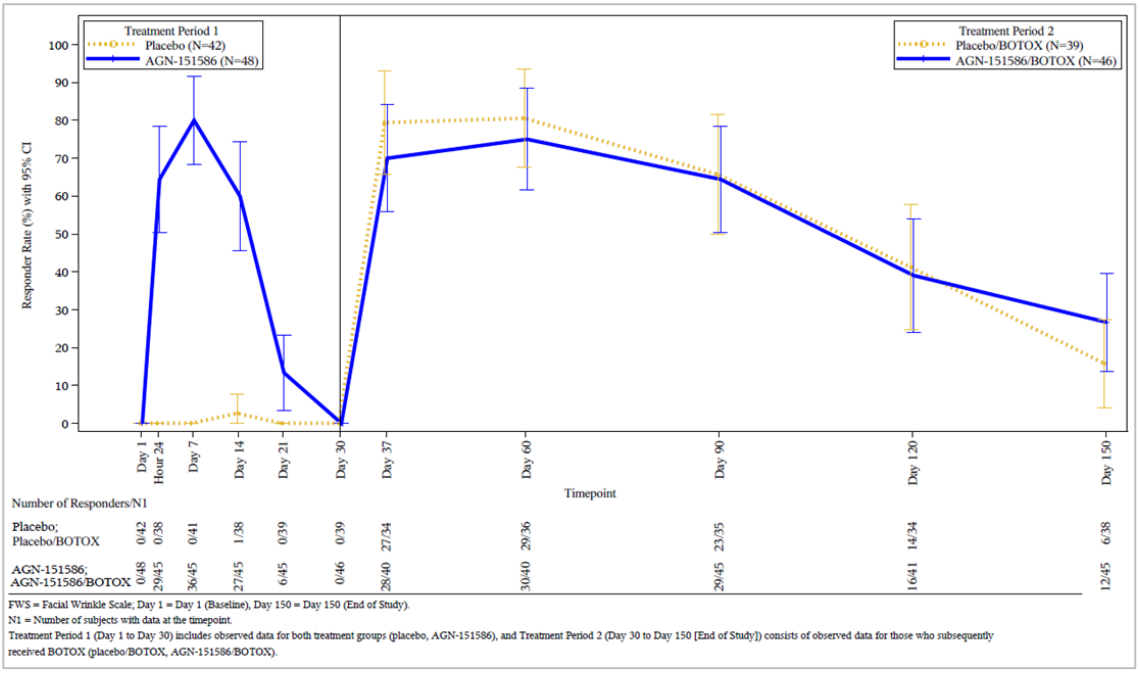
Table 14.2-1
Primary Endpoint: FWS at Maximum Frown – Investigator: Number (%) of Subjects with Ratings of None or Mild at Day 60
Intent-to-Treat Population

Timepoint	Placebo/BOTOX (N=39)	AGN-151586/BOTOX (N=46)
Day 60		
Responder rate, n/N1 [1] (%)	29/ 36 (80.6)	30/ 40 (75.0)
95% CI (%)	(67.6, 93.5)	(61.6, 88.4)
vs. Placebo/BOTOX		
Difference (%)		-5.6
95% CI (%)		(-24.2, 13.1)

Period 2: response rate assessed by subject at Day 60 (Botox efficacy)

	Treatment Period 2	
Timepoint	Placebo/BOTOX (N=39)	AGN-151586/BOTOX (N=46)
Day 37		
Responder rate, n/N1 [1] (%)	25/ 34 (73.5)	27/ 41 (65.9)
95% CI (%)	(58.7, 88.4)	(51.3, 80.4)
Day 60		
Responder rate, n/N1 [1] (%)	22/ 36 (61.1)	29/ 40 (72.5)
95% CI (%)	(45.2, 77.0)	(58.7, 86.3)

Secondary endpoint



FWS at Maximum Frown – Investigator: Percentage of Subjects with Ratings of None or Mild Over Time, Treatment Periods 1 & 2

Other efficacy endpoint

Period 1: response rate assessed by investigator at Day 7 (**AGN-151586 efficacy**)

Table 14.2-2.1
FWS at Maximum Frown – Investigator: Number (%) of Subjects with Ratings of None or Mild Over Time, Treatment Period 1
Intent-to-Treat Population

	Treatment Period 1	
Timepoint	Placebo (N=42)	AGN-151586 (N=48)
Hour 24		
Responder rate, n/N1 [1] (%)	0/ 38 (0.0)	29/ 45 (64.4)
95% CI (%)	(0.0, 0.0)	(50.5, 78.4)
Day 7		
Responder rate, n/N1 [1] (%)	0/ 41 (0.0)	36/ 45 (80.0)
95% CI (%)	(0.0, 0.0)	(68.3, 91.7)

Period 1: response rate assessed by subject at Day 7 (**AGN-151586 efficacy**)

Table 14.2-3.1
FWS at Maximum Frown - Subject: Number (%) of Subjects with Ratings of None or Mild Over Time, Treatment Period 1
Intent-to-Treat Population

Timepoint	Treatment Period 1	
	Placebo (N=42)	AGN-151586 (N=48)
Hour 24		
Responder rate, n/N1 [1] (%)	0/39 (0.0)	18/45 (40.0)
95% CI (%)	(0.0, 0.0)	(25.7, 54.3)
Day 7		
Responder rate, n/N1 [1] (%)	0/41 (0.0)	31/45 (68.9)
95% CI (%)	(0.0, 0.0)	(55.4, 82.4)

5.3.3. Clinical studies in special populations

Not applicable.

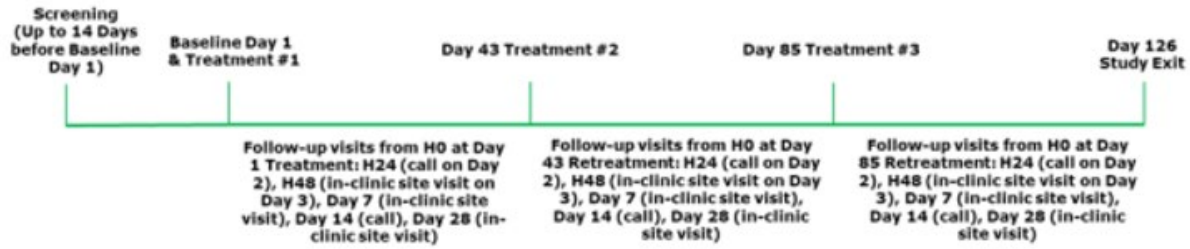
5.3.4. Supportive study: M21-509, sequential administration study

Study M21-509 tested repeated administration of AGN-151586 (up to 3 treatment periods).

It was an 18-week, multicentre, open-label study to evaluate the safety of AGN-151586 over multiple treatments of the study drug in subjects with moderate to severe GL. Subjects were adults (≥ 18 years of age) with moderate to severe GL at maximum frown as assessed independently by the investigator and the subject using the FWS at the Screening and Baseline Day 1 visits (matching not required). A maximum of 3 study treatments could be administered to subjects.

This study included naïve and non-toxin-naïve subjects, in the US with moderate to severe GL.

Study Design Schematic



A total of 992 subjects were enrolled at 41 sites in the USA and Puerto Rico. Overall, most subjects completed the study and the most common reason for study discontinuation was withdrawal by subjects. A total of 985 subjects received at least 1 dose of AGN-151586 (Cycle 1); 916 subjects received at least 2 doses (Cycle 2), and 846 subjects received 3 doses (Cycle 3).

No primary efficacy endpoints were tested. However, the rate of responses after repeated administrations with ≥2 grade improvement from baseline were collected Day 7 as assessed by the investigator and the subject:

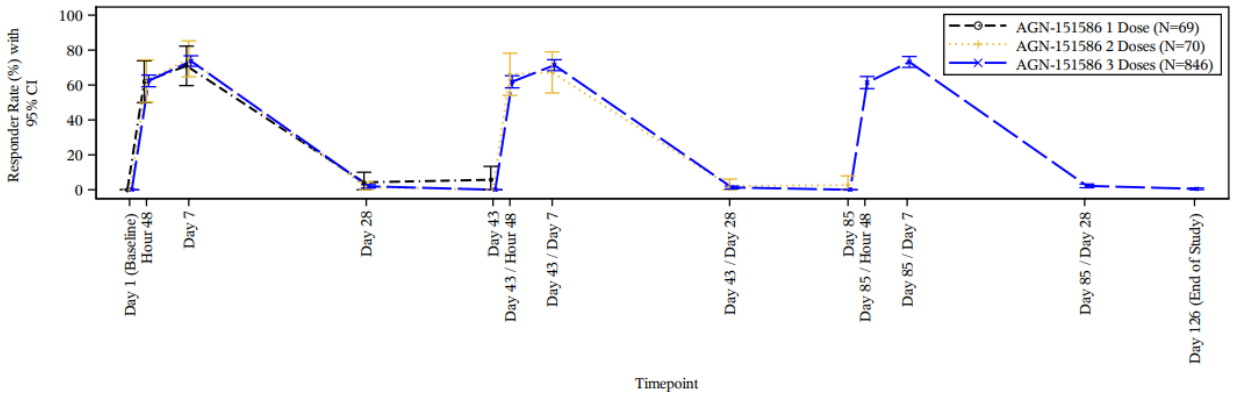
Table 14.2-1
FWS at Maximum Frown - Investigator: Number (%) of Subjects with >= 2 Grade Improvement from Baseline Over Time
Intent-to-Treat Population

Timepoint	AGN-151586 1 Dose (N=69)	AGN-151586 2 Doses (N=70)	AGN-151586 3 Doses (N=846)	Any AGN-151586 (N=985)
Hour 48				
Responder rate, n/N1 [1] (%)	39/63 (61.9)	38/61 (62.3)	500/802 (62.3)	577/926 (62.3)
95% CI (%)	(49.9, 73.9)	(50.1, 74.5)	(59.0, 65.7)	(59.2, 65.4)
Day 7				
Responder rate, n/N1 [1] (%)	44/62 (71.0)	51/68 (75.0)	609/826 (73.7)	704/956 (73.6)
95% CI (%)	(59.7, 82.3)	(64.7, 85.3)	(70.7, 76.7)	(70.8, 76.4)
Day 28				
Responder rate, n/N1 [1] (%)	2/47 (4.3)	1/65 (1.5)	16/813 (2.0)	19/925 (2.1)
95% CI (%)	(0.0, 10.0)	(0.0, 4.5)	(1.0, 2.9)	(1.1, 3.0)
Day 43				
Responder rate, n/N1 [1] (%)	2/35 (5.7)	0/69 (0.0)	0/821 (0.0)	2/925 (0.2)
95% CI (%)	(0.0, 13.4)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.5)
Day 43 / Hour 48				
Responder rate, n/N1 [1] (%)		39/59 (66.1)	465/752 (61.8)	504/811 (62.1)
95% CI (%)		(54.0, 78.2)	(58.4, 65.3)	(58.8, 65.5)
Day 43 / Day 7				
Responder rate, n/N1 [1] (%)		41/61 (67.2)	568/796 (71.4)	609/857 (71.1)
95% CI (%)		(55.4, 79.0)	(68.2, 74.5)	(68.0, 74.1)

Table 14.2-2
FWS at Maximum Frown - Subject: Number (%) of Subjects with >= 2 Grade Improvement from Baseline Over Time
Intent-to-Treat Population

Timepoint	AGN-151586 1 Dose (N=69)	AGN-151586 2 Doses (N=70)	AGN-151586 3 Doses (N=846)	Any AGN-151586 (N=985)
Hour 48				
Responder rate, n/N1 [1] (%)	29/62 (46.8)	39/61 (63.9)	404/806 (50.1)	472/929 (50.8)
95% CI (%)	(34.4, 59.2)	(51.9, 76.0)	(46.7, 53.6)	(47.6, 54.0)
Day 7				
Responder rate, n/N1 [1] (%)	35/62 (56.5)	48/68 (70.6)	521/828 (62.9)	604/958 (63.0)
95% CI (%)	(44.1, 68.8)	(59.8, 81.4)	(59.6, 66.2)	(60.0, 66.1)
Day 28				
Responder rate, n/N1 [1] (%)	0/47 (0.0)	1/65 (1.5)	17/816 (2.1)	18/928 (1.9)
95% CI (%)	(0.0, 0.0)	(0.0, 4.5)	(1.1, 3.1)	(1.1, 2.8)
Day 43				
Responder rate, n/N1 [1] (%)	1/35 (2.9)	0/69 (0.0)	5/821 (0.6)	6/925 (0.6)
95% CI (%)	(0.0, 8.4)	(0.0, 0.0)	(0.1, 1.1)	(0.1, 1.2)
Day 43 / Hour 48				
Responder rate, n/N1 [1] (%)		36/59 (61.0)	407/761 (53.5)	443/820 (54.0)
95% CI (%)		(48.6, 73.5)	(49.9, 57.0)	(50.6, 57.4)
Day 43 / Day 7				
Responder rate, n/N1 [1] (%)		42/61 (68.9)	517/797 (64.9)	559/858 (65.2)
95% CI (%)		(57.2, 80.5)	(61.6, 68.2)	(62.0, 68.3)

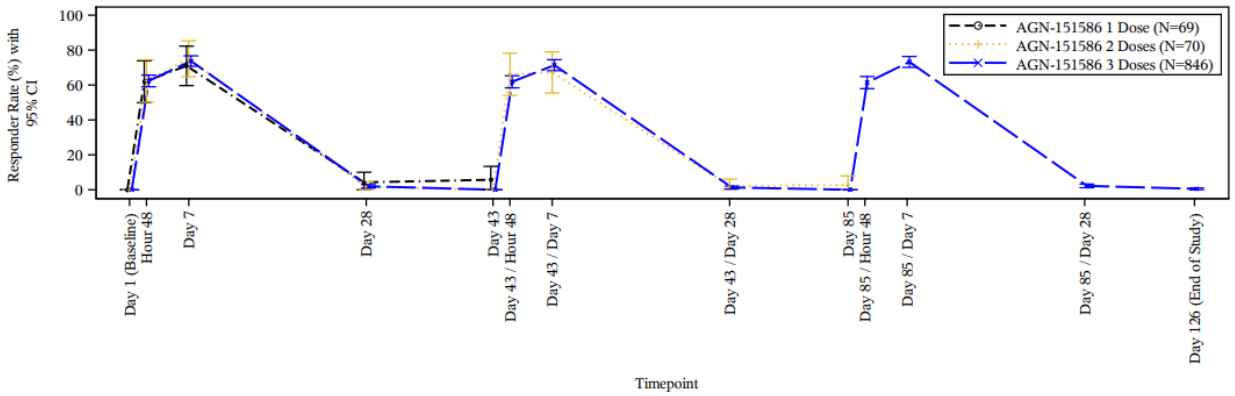
Figure 14.2-1.1f
FWS at Maximum Frown - Investigator: Number (%) of Subjects with >= 2 Grade Improvement from Baseline Over Time
Intent-to-Treat Population



	Number of Responders/N1 [1]													
AGN-151586 1 Dose	0/68	39/63	44/62		2/47		2/35	0/0	0/0		0/0		0/0	0/0	0/0	0/0
AGN-151586 2 Doses	0/70	38/61	51/68		1/65		0/69	39/59	41/61		1/48		1/37	0/0	0/0	0/0	0/0	0/0
AGN-151586 3 Doses	0/843	500/802	609/826		16/813		0/821	465/752	568/796		10/769		0/808	458/746	566/773		17/766	4/785

FWS = Facial Wrinkle Scale
Day 43 and Day 85 are the treatment cycle baselines for subjects who are retreated on Day 43 and Day 85, respectively. Responder rate and its 95% confidence interval are estimated using observed data.
[1] N1 = Number of subjects with data at the treatment cycle baseline and the timepoint.

Figure 14.2-1.1f
FWS at Maximum Frown - Investigator: Number (%) of Subjects with >= 2 Grade Improvement from Baseline Over Time
Intent-to-Treat Population



	Number of Responders/N1 [1]													
AGN-151586 1 Dose	0/68	39/63	44/62		2/47		2/35	0/0	0/0		0/0		0/0	0/0	0/0	0/0
AGN-151586 2 Doses	0/70	38/61	51/68		1/65		0/69	39/59	41/61		1/48		1/37	0/0	0/0	0/0	0/0	0/0
AGN-151586 3 Doses	0/843	500/802	609/826		16/813		0/821	465/752	568/796		10/769		0/808	458/746	566/773		17/766	4/785

FWS = Facial Wrinkle Scale
Day 43 and Day 85 are the treatment cycle baselines for subjects who are retreated on Day 43 and Day 85, respectively. Responder rate and its 95% confidence interval are estimated using observed data.
[1] N1 = Number of subjects with data at the treatment cycle baseline and the timepoint.

5.3.5. Analysis performed across trials (pooled analyses and meta-analysis)

Comparison of EU Co-primary Efficacy Endpoint results: Pivotal Studies M21-500 and M21-508 vs. Integrated Results from Phase 3 Single-Treatment, Placebo-Controlled Baseline FLO-11 Total Transformed Score ≤ 50 Analysis Set

Hierarchical Testing Sequence	M21-500		M21-508		Pooled data	
	Placebo (N = 130)	AGN-151586 (N = 368)	Placebo (N = 63)	AGN-151586 (N = 164)	Placebo (N = 193)	AGN-151586 (N = 532)
EU co-primary endpoint P1: FWS at Maximum Frown – Subject: Number (%) of Subjects with ≥ 2-Grade Improvement from Baseline at Day 7						
Estimated response rate, n/N[a] (%)	1.0/130 (0.8)	224.3/368 (61.0)	0.0/63 (0.0)	111.3/164 (67.9)	1.0/193 (0.5)	335.6/532 (63.1)
Difference (%) vs placebo 95% CI (%)	60.2 (54.9, 65.4)		67.9 (60.7, 75.0)		62.6 (58.3, 66.8)	
P-value[b]	< 0.0001		< 0.0001		< 0.0001	
EU co-primary endpoint P2: FWS at Maximum Frown – Investigator: Number (%) of Subjects with ≥ 2-Grade Improvement from Baseline at Day 7						
Estimated response rate, n/N[a] (%)	1.0/130 (0.8)	265.4/368 (72.1)	0.0/63 (0.0)	120.6/164 (73.6)	1.0/193 (0.5)	386.0/532 (72.6)
Difference (%) vs placebo 95% CI (%)	71.4 (66.5, 76.2)		73.6 (66.8, 80.4)		72.0 (68.1, 76.0)	
P-value[b]	< 0.0001		< 0.0001		< 0.0001	

Comparison of US composite endpoint results (Pivotal Studies M21-500 and M21-508 vs. Integrated Results from Phase 3 Single-Treatment, Placebo-Controlled Analysis Set /ITT

Hierarchical Testing Sequence	M21-500		M21-508		Pooled data	
	Placebo (N = 156)	AGN-151586 (N = 482)	Placebo (N = 82)	AGN-151586 (N = 227)	Placebo (N = 238)	AGN-151586 (N = 709)
US composite endpoint P1: FWS at Maximum Frown – Investigator and Subject: Number (%) of Subjects with Achievement of Grade 0 or 1 (None or Mild) and ≥ 2-Grade Improvement from Baseline at Day 7						
Estimated response rate, n/N[a] (%)	1.0/156 (0.6)	289.0/482 (60.0)	1.0/82 (1.2)	149.2/227 (65.7)	2.0/238 (0.8)	438.2/709 (61.8)
Difference (%) vs placebo		59.3		64.5		61.0
95% CI (%)		(54.7, 63.9)		(57.9, 71.1)		(57.2, 64.7)
P-value[b]		< 0.0001		< 0.0001		< 0.0001

a. Response rate and its 95% confidence interval (CI) are estimated after using multiple imputation for missing data.
b. P-value derived from CMH model stratified by study, investigator site, prior aesthetic toxin use, and baseline FWS at maximum frown for ITT.
FLSQ Item 4: How satisfied are you that your treatment gave you a natural look? FLSQ Item 5: How satisfied are you with the effect your treatment had on your facial lines?
Primary (P1) and Secondary (S1 to S3) endpoints tested in order according to the prespecified gated hierarchical testing sequence.
Pooled data ITT consists of the Phase 3 Studies M21-500 and M21-508 (all randomized subjects).
Source: ISE (R&D/23/2227) Table 1.2-1.1

Key secondary EU endpoint

Table 1.2-2.4

FLO-11: Number (%) of Subjects with >= 20 Point Improvement from Baseline Total Transformed Score at Day 7
Phase 3 Single Treatment Placebo-Controlled Baseline FLO-11 Total Transformed Score <= 50 Analysis Set (ISE Group 2)

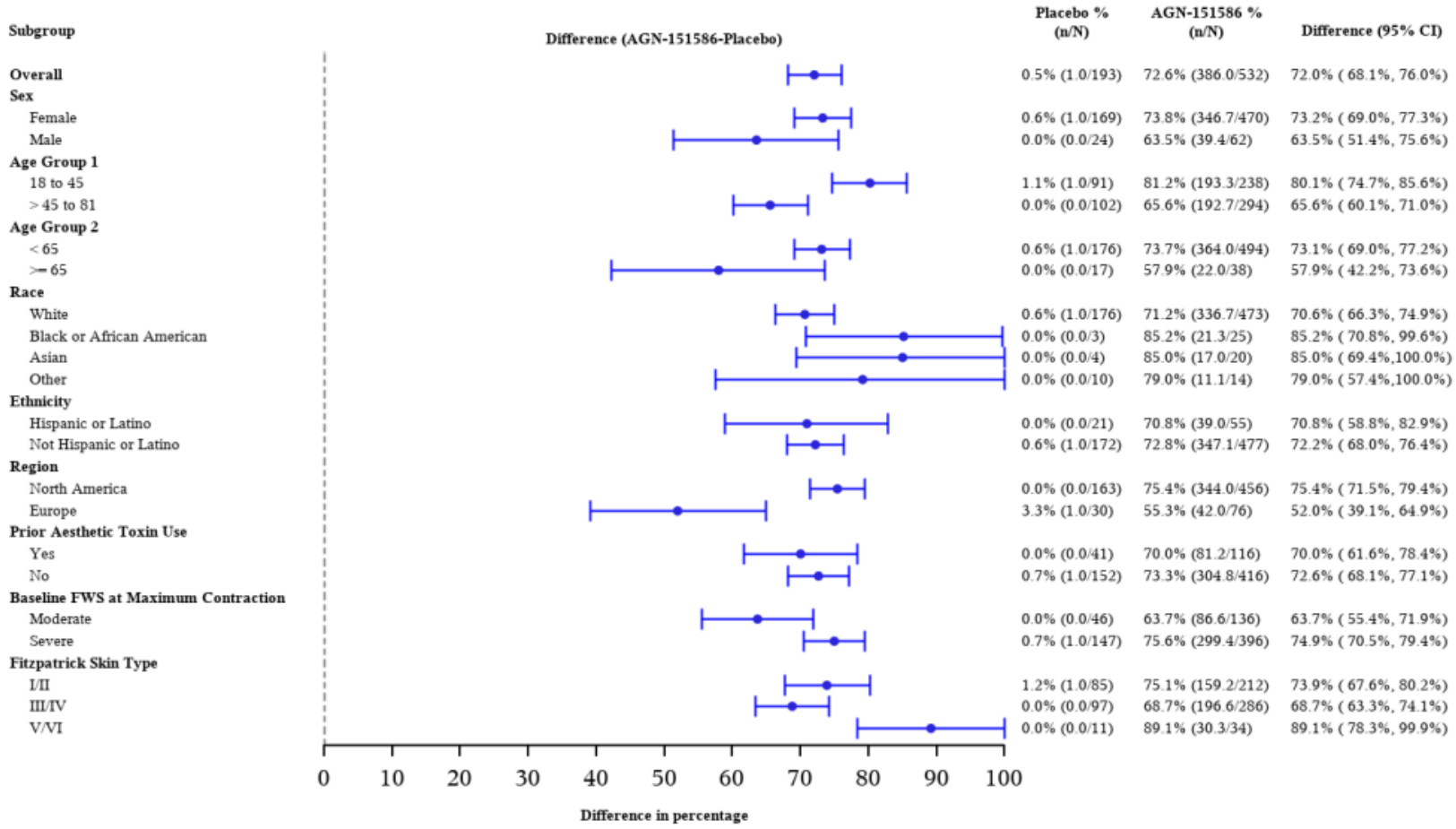
Analysis Visit Statistics	Placebo (N=193)	AGN-151586 (N=532)
Day 7		
Responder rate, n/N1 [1] (%)	16/188 (8.5)	333/512 (65.0)
95% CI (%)	(4.5, 12.5)	(60.9, 69.2)
Model		
Estimated responder rate, n/N [2] (%)	16.0/193 (8.3)	346.6/532 (65.2)
95% CI (%)	(4.4, 12.2)	(61.1, 69.2)
vs. Placebo		
Difference (%)		56.9
95% CI (%)		(51.2, 62.5)
P-value [3]		<0.0001

FLO-11 = 11-Item Facial Line Outcomes
[1] N1 = Number of subjects with data at baseline and the timepoint.
[2] Responder rate and its 95% confidence interval are estimated after using multiple imputation for missing data.
[3] P-value derived from CMH model stratified by study, investigator site, prior aesthetic toxin use, and baseline FWS at maximum frown.
ISE Group 2 consists of the Phase 3 Studies M21-500 and M21-508 (subjects with baseline FLO-11 total transformed score <= 50).

Figure 1.2-3.6.2f

Forest Plot: Responder Rate Difference of Co-primary Endpoints: FWS at Maximum Frown - Investigator: Number (%) of Subjects with >= 2-Grade Improvement from Baseline at Day 7 by Subgroups

Phase 3 Single Treatment Placebo-Controlled Baseline FLO-11 Total Transformed Score <= 50 Analysis Set (ISE Group 2)



FWS = Facial Wrinkle Scale, FLO-11 = 11-Item Facial Line Outcomes

Responder rate and its 95% confidence interval are estimated after using multiple imputation for missing data.

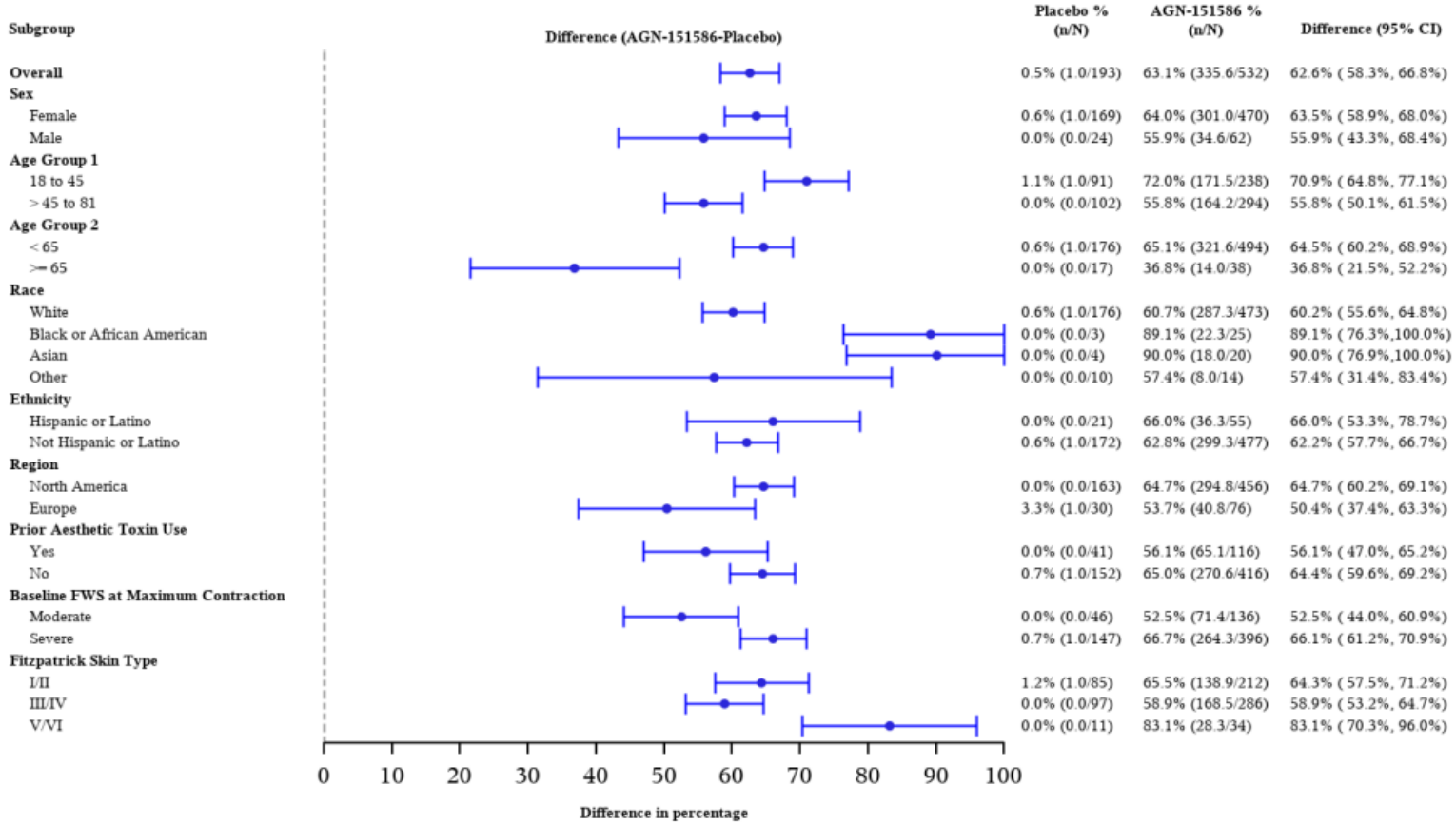
n/N: n = Number of subjects with achievement within the treatment group after using multiple imputation for missing data, N = Number of subjects within the treatment group.

ISE Group 2 consists of the Phase 3 Studies M21-500 and M21-508 (subjects with baseline FLO-11 total transformed score <= 50).

Figure 1.2-3.6.1f

Forest Plot: Responder Rate Difference of Co-primary Endpoints: FWS at Maximum Frown - Subject: Number (%) of Subjects with >= 2-Grade Improvement from Baseline at Day 7 by Subgroups

Phase 3 Single Treatment Placebo-Controlled Baseline FLO-11 Total Transformed Score <= 50 Analysis Set (ISE Group 2)



FWS = Facial Wrinkle Scale, FLO-11 = 11-Item Facial Line Outcomes

Responder rate and its 95% confidence interval are estimated after using multiple imputation for missing data.

n/N: n = Number of subjects with achievement within the treatment group after using multiple imputation for missing data, N = Number of subjects within the treatment group.

ISE Group 2 consists of the Phase 3 Studies M21-500 and M21-508 (subjects with baseline FLO-11 total transformed score <= 50).

5.4. Overall discussion and conclusions on clinical efficacy

5.4.1.1. Discussion

This Marketing Authorisation application is for a new active substance trenibotulinumtoxinE, also referred as AGN-151586.

AGN-151586 is a native, non-recombinant botulinum toxin serotype E (BoNT/E). AGN-151586 is an injectable treatment that has been evaluated as a locally acting therapy to reduce the vertical rhytide of the forehead [glabellar lines (GL)]. The rationale for using AGN-151586 is similar to BoNT/A: it reduces muscle overactivity by inhibiting acetylcholine release, thereby diminishing or eliminating the appearance of GL.

However, AGN-151586 differs from other botulinum toxin products available on the market by a faster onset and shorted duration of action. The onset of effect was already visible at 8 hours, peak effect was described by Day 7, the effect lasted 2-3 weeks.

The initial claimed indication is "*the temporary improvement in the appearance of moderate to severe lines between the eyebrows seen at maximum frown (glabellar lines) when the severity has an important psychological impact in adult patients as*

- *an intermittent treatment and/or*
- *a trial option before initiating BOTOX."*

The clinical programme to evaluate the efficacy and safety of AGN-151586 comprised data from:

- dose selection phase 2 studies:
  - main study 2034-201-008, a US dose-escalation, single-treatment placebo-controlled study of AGN-151586 testing doses of AGN-151586: 100 U, 250 U, 400 U, 600 U and 750 U in 5 cohorts with 40 subjects each;
  - and supportive data from study M24-440 which performed with Japanese subjects in a small size sample testing 400 U, 600 U and 750 U in cohorts of 8 subjects each with 6 receiving AGN-151586 and 2 in placebo group;
- phase 3 studies consisting of:
  - 2 pivotal studies M21-500 (US and Europe) and M21-508 (US and Canada), to demonstrate the superiority of AGN-151586 vs placebo when injected as a single administration, which corresponds to the 1st part of the indication: AGN-151586 used alone once;
  - 1 study M21-509 (US and Puerto Rico), to demonstrate the reproducibility of the effect with repeated administration (up to 3 treatment periods);
  - 1 study M23-365 (US) testing the sequential administration of AGN-151586 followed by the administration of Botox at Day 30, which corresponds to the 2nd part of the indication: AGN-151586 used before Botox.

Dose-escalation study 2034-201-008

The supportive Phase 2b Study 2034-201-008 was a multicentre, double-blind, randomized, dose-escalation study to evaluate the safety and efficacy of AGN 151586 in the treatment of moderate to severe GL. 198 subjects were adults (18 to 65 years of age) with moderate to severe GL at maximum frown as assessed by both the investigator and subject independently.

AGN-151586 was evaluated at 5 doses (100, 250, 400, 600, and 750 U) and compared with placebo (3:1 randomisation) in a sequential cohort design.

FWS (Facial Wrinkle Scale) is a validated 4-point scale for grading GL severity: 0=none, 1=mild, 2=moderate, 3=severe. This scale has already been used in other Abbvie toxin-A clinical studies provided for marketing authorisation as the primary efficacy measure with the investigator's assessments of GL at maximum frown

which is acceptable.

The primary efficacy endpoint was the improvement of FWS score of ≥ 2-grade from baseline according to investigator assessments of GL severity at maximum frown at any post-intervention timepoint through Day 7.

Doses from 100 U to 750 U showed an increasing effect of AGN-151586 at Day 7 with response's rates from 40.6% to 96.8% as assessed by investigator with statistically significant differences versus placebo.

Subjects in the AGN-151586 groups assessed the improvement in the severity of their GL at maximum frown generally lower compared with investigators, the overall trend was greater proportions of participants in the AGN-151586 compared with placebo groups reported ≥ 2-grade improvements on the FWS. From 100 U to 750 U, subject response rate was 34.4% to 71.0% respectively. It is to note that according to subject assessment, the difference of response rate compared to % in placebo groups was not statistically significant for 100 U and 600 U. This could be explained by the relatively small number of participants in each placebo group (8 to 12 subjects).

Placebo and AGN-151586 treatment groups were compared for each cohort across several secondary and exploratory endpoints with among them:

- Time to ≥ 2-grade responses on the FWS at maximum frown per investigator's assessment: at least half of the responses achieved a ≥ 2-grade improvement within the first 48-60 hours (2-2.5 days) after treatment and within 36 hours for the 750 U cohort, defining the time to the onset of AGN-151586 effect.
- Improvement of FWS ⩾ 1-grade at rest: no statistical difference was observed between the AGN-151586 and placebo groups in Cohorts 1 (100 U), 2 (250 U), 4 (600 U), and 5 (750 U) ($p > 0.05$, unadjusted). Per participant assessment, AGN-151586 groups did not differ statistically from the placebo groups in any cohort when evaluating ⩾ 1-grade improvements on the FWS of GL severity at rest from baseline through Day 7 among those participants with at least a moderate rating on the FWS ($p > 0.05$, unadjusted).
- Patient-reported Outcomes: 2 scores were used, FLO-11 (11-Item Facial Line Outcomes) and FLSQ (Facial Line Satisfaction Questionnaire)
- Participant-reported emotional and appearance-related impact of GL was assessed using the FLO-11 GL version. Descriptive results indicate that participants in the AGN-151586 groups compared with the placebo groups in each cohort reported a greater proportion of participants with positive change from baseline in FLO-11 scores that exceeded the minimally important difference threshold (i.e., ≥ 20-point change from baseline) at Hour 24 and Day 7.
- Participant-reported treatment satisfaction with GL was evaluated with FLSQ: a higher proportion of participants treated with AGN-151586 reported being mostly or very satisfied compared with placebo across all cohorts.

The dose selected was 750 U given the higher response rate obtained compared to the other lower doses.

Placebo-controlled studies: M21-500 (US and Europe) and M21-508 (US and Canada) studies

Both phase 3 studies were 12-week, multicentre, double-blind, placebo-controlled, studies with similar design, participants, inclusion and exclusion criteria.

Subjects were 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 at the Screening and Baseline Day 1 visits. The double-blind Period (Day 1 to Day 43) was a randomized, placebo-controlled, single-treatment design and the open-label Period (Day 43 to Study exit) consisted of retreatment with one dose of AGN-151586 700 U for subjects who met retreatment criteria.

Psychological impact as claimed in the indication labelling, was assessed in main studies based on the results of

FLO-11 questionnaire which score should have to be score ⩽ 50. This is acceptable.

Treatment administration in GL used a standard method with injections of 140 U in 5 sites of the forehead i.e. a total dose of 700 U. Over the duration of the study, a maximum of 2 study treatments could be administered to subjects.

Results

In pivotal Phase 3 Study M21-500, a total of 638 subjects (156 in placebo group and 482 in AGN-151586) were enrolled, randomised, and treated. In total 148 subjects from placebo group and 454 subjects from AGN-151586 group completed the study.

The second pivotal Phase 3 Study M21-508 had an identical design compared to Study M21-500, except that Study M21-508 was conducted only in the US and Canada and subjects had no prior botulinum toxin treatment of any serotype for any indication. 309 subjects were enrolled and randomised with 82 subjects into placebo group and 227 into AGN-151586 group.

The demographics were generally balanced across treatment groups. In the ITT Population, most subjects were female, and the population was primarily White.

For the EU regulatory agency, the co-primary efficacy endpoints were the achievement of ⩾ 2-grade improvement of GL severity at maximum frown from Baseline at Day 7 according to (1) subject's self-assessment using FWS and (2) investigator's assessment using FWS, among subjects who had a baseline FLO-11 total transformed score ⩽ 50. This is in line with the label of the claimed indication to ensure that treated subjects have a psychosocial impact.
This was measured by the FLO-11 which is an 11-item validated PRO measure that assesses appearance-related psychological impacts of GL from the subject perspective: "*bothered, looking older, feeling unattractive, looking less attractive, skin not looking smooth, looking tired, looking stressed, looking angry, and feeling good about facial appearance*".

	M21-500 DB period In subgroup of FLO ≤ 50	**M21-508** DB period In subgroup of FLO ≤ 50	**Pooled data** **(=ITT)**	**Pooled data** In subgroup of FLO ≤ 50
AGN-151586 vs Placebo	N=368 vs N=130	N=164 vs N=63	N=709 vs N=238	N=532 vs N=193
EU co-primary endpoints: Achievement ≥ 2-Grade improvement on investigator and subject FWS assessments of GL severity at maximum frown from Baseline at Day 7 assessed by investigator assessed by subject	 72.1% vs 0.8% 60.2% vs 0.8%	 73.6% vs 0.0% 67.9% vs 0.0%	 -	 72.6% vs 0.5% 63.1% vs 0.5%
EU key secondary endpoint: FLO-11 Total Transformed Score ≥ 20-Point Improvement from Baseline at Day 7	66.3% vs 8.8%	62.3% vs 7.9%	-	65.2% vs 8.3%
EU secondary endpoint: Time to first ≥ 1-grade improvement from Baseline on FWS at maximum frown (mean) assessed by investigator assessed by subject (in days)	 4.2 vs 29.7 5.2 vs 33.5	 3.1 vs 31.1 3.3 vs 31.9	 3.7 vs 30.2 4.4 vs 33.3	 3.8 vs 30.1 4.6 vs 33.0

Statistically significantly higher responder rates were observed in subjects treated with AGN-151586 compared to subjects in the placebo group (each $p < 0.0001$). Sensitivity analyses, including the tipping point analysis, of the co-primary endpoints showed comparable results.

However, it is noted that proportion of subjects maintaining response drops from 14 days after administration. The risk associated with more frequent administration due to multiple injection procedures is therefore reflected in section 4.4 of the SmPC:*"Repeated administrations: Repeated injections of trenibotulinumtoxinE may increase the risk of adverse reactions associated to the injection procedures."*

At all timepoints, the proportion of subjects who were *Mostly satisfied* or *Very satisfied* with the appearance of their GL based on the FLSQ follow-up version Item 5 (overall satisfaction) was greater for the AGN-151586 group compared to the placebo group during the double-blind period.

Descriptive results showed compared to < 65 years, a lower response in ≥ 65 years: response's rate assessed by subject: 36.8% vs 65.1% and assessed by investigator 57.9% vs 73.7%. It is to note that in pooled data group with psychological impact (FLO-11 ≤ 50 at baseline), only 55 subjects were ≥ 65 years with 38 in AGN-151586 group while 670 were < 65 years with 494 in AGN-151586 group. The lower responder rates in ≥ 65 years is reflected in section 5.1 of the SmPC.

During the double-blind period, the US key secondary endpoint: FWS at Maximum Frown According to Investigator and Subject Assessment Over Time confirmed the kinetics of the effect with an early onset from 8 hours after injections, a peak effect at Day 7 and immediate decrease of effect observed at Day 14 and return to baseline at Day 21.

For other US FDA key secondary endpoints of a Grade 0 or 1 (none or mild) and ⩾ 2-grade improvement from Baseline on FWS at maximum frown, the AGN-151586 group showed higher improvements versus placebo over time as early as Hour 8 through Day 21.

In the open-label period, the results showed that the effect of AGN-151586 was similar at the 1st or the 2nd cycle of injections in GL at Day 7 and Day 43. The response rate of placebo group after being injected was null indicating the absence of residual effect of 1st AGN-151586 injections.

Overall, the effect of AGN-151586 starts 8h after injections in GL with a peak at Day 7 and lasts not more than 21 days. It is to note that from Day 2 to Day 7, the response rate is around 60 to 70% and after Day 7, an immediate decrease of the effect without any plateau is observed with a return to baseline state. This effect is reproducible with further injections in GL when repeated at Day 43.

No rationale for a 6-week-interval between two injections of AGN-151586 was not provided and it is for the physician to assess the severity of GL moderate to severe to repeat toxin E administration. In order to give a clear picture of assessed data, the following statement has been added in the SmPC section 4.2: '*Retreatment with Boey at intervals more frequent than every 6 weeks has not been evaluated and should be determined by physician.'*

The response rate **at rest** in the group of subjects corresponding to the EU co-primary endpoints with psychosocial impact is also of interest as moderate to severe GL at rest are more severe than at maximum frown. This is interesting especially as a lack of benefit of AGN-1515986 on GL at rest was observed in the dose-escalation study even at the highest dose. The applicant has provided the number (%) of subjects with achievement of Grade 0 or 1 (None or Mild) when FWS at rest. The treatment difference of responder rates was around 20% for subject and investigator.

Overall, the response rate at Day 7 was lower compared to the investigator's assessment and for every subgroup and also in ≥ 65 years group of subjects.

The efficacy of repeated administration of AGN-151586 was collected during open period: the response rates were similar to those after 1 cycle of injections with almost no difference from AGN-151586 previously treated arm or from previously placebo-treated arm, whether assessed by subject or investigator. The proportion of responders was comparable during the double-blind and open-label periods among subjects who received AGN-151586.

Analysis from pooled data

For the EU, analyses were performed for the primary and secondary endpoints for the ITT Populations that also had baseline FLO-11 Total Transformed Score ≤ 50 in Studies M21-500 and M21-508.

Subgroup analyses were performed for primary and tested key secondary efficacy endpoints in ITT (M21-500 and M21-508) and pooled data (M21-500 and M21-508 with baseline FLO-11 total transformed score $\leq$ 50). The subgroup analyses of primary efficacy endpoints were compared with that of the individual Phase 3 studies.

The demographic characteristics were generally comparable across all integrated analysis sets and generally comparable to the individual study demographics.

In the pooled data group with psychological impact (Baseline FLO-11 Score ≤ 50), the response rate was greater in the AGN-151586 group than the placebo group at Day 7.

A higher percentage of subjects in the AGN-151586 group showed ≥ 20-point improvement from Baseline in FLO-11 total transformed score at Day 7 (P value < 0.0001, unadjusted)

Similar to the individual phase 3 studies, for the integrated analysis (ITT) the AGN-151586 group demonstrated higher response rates in all hierarchical tested EU secondary endpoints compared to the placebo group (P value < 0.0001 for each endpoint, unadjusted).

These results were comparable to the individual study results for the co-primary endpoints. Similar trends were observed in the group of pooled data in subjects with 2 treatments and in the subgroup with psychological impact with 2 treatments.

Repeated administration study: M21-509

This was an 18-week, multicentre, open-label, Phase 3 study designed to evaluate the safety of AGN-151586 over multiple repeat treatments of the study drug in subjects with moderate to severe GL in adults. Each enrolled subject could receive up to 3 treatments with AGN-151586, including the first treatment on Baseline Day 1, and planned retreatment during clinic site visits on Day 43 and Day 85 if the subject met retreatment criteria.

A total of 992 subjects were enrolled. Overall, most subjects completed the study and the most common reason for study discontinuation was withdrawal by subjects. A total of 985 subjects received at least 1 dose of AGN-151586 (Cycle 1); 916 subjects received at least 2 doses (Cycle 2), and 846 subjects received 3 doses (Cycle 3). In total 916 (92.3%) 848 (85.5%) 836 (84.3%) completed Cycle 1, 2 and 3 of the study.

After 1 dose of AGN-151586, most subjects experienced a $\geqslant$ 2-grade improvement from baseline in the FWS at maximum frown as assessed by the investigator (71.0%) and by the subject (56.5%) with peak effect at Day 7 followed by a decrease through Day 43.

There were similar trends of efficacy response during each treatment cycle between subjects who received 1 cycle, 2 cycles, or 3 cycles of AGN-151586 based on investigator (71.0 to 75.0%) as well as subject (56.5 to 70.6%) FWS assessments at maximum frown.

Similar response rates were observed with the US composite efficacy endpoint also.

The overall efficacy profiles were similar across all 3 treatment cycles. However, the repeated administration with an interval of 6-week between injections in GL is not part of the indication since an intermittent treatment is claimed.

5.4.1.2. Conclusions on the clinical efficacy

The efficacy of trenibotulinumtoxinE, compared to placebo, has been demonstrated in the 2 pivotal studies.

However, the data do not support the initially claimed indication as an intermittent treatment of Glabellar Lines and/or as a trial option before initiating Botox: the sequential administration of this trenibotulinumtoxinE as a trial option before Vistabel/Botox does not constitute an indication *per se* and the claimed use of trenibotulinumtoxinE as a trial option before Vistabel/Botox does not meet a medical need.
In addition, the sequential administration of toxin E followed by Vistabel/Botox is based on study M23-365 which had no formal hypothesis testing.

In view of the assessment of data, the indication was updated as foloows: "*Boey is indicated for the temporary improvement in the appearance of moderate to severe lines between the eyebrows seen at maximum frown (glabellar lines), when these have an important psychological impact in adult patients (see section 5.1)".*

TrenibotulinumtoxinE has a different pharmacological profile compared to other botulinum toxins A and the Product Information reflects the data as relevant to enable a well-informed use of Health Care Professionals and patients.

Since trenibotulinumtoxinE is indicated only for administration between the eyebrows, there is a possible risk of administration of a remaining amount of 700U in the vial to other parts of the face**.** It is agreed that clear product labelling, HCP education and training and postmarketing pharmacovigilance are acceptable to mitigate the risk.

5.5. Clinical safety

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.5.1. Safety data collection

The applicant completed two Phase 3 pivotal double-blind, placebo-controlled studies to evaluate the safety and efficacy of AGN-151586 in adult subjects with moderate to severe GL. In addition, an open-label Phase 3 study evaluating safety of repeat treatments, a Phase 1 sequential treatment study, and

two Phase 2 dose escalation studies are included in the submission (Study 2034-201-008 and Study EB001-GL201).

The main analyses were performed using integrated data from pivotal Phase 3 Studies M21-500 and M21-508, and integrated data from 6 studies were used to evaluate safety results (i.e., Studies M21-500, M21-508, M21-509, M23-365, 2034-201-008, and EB001-GL201).

In both pivotal studies, the first treatment period included all visits up to Day 43. The first treatment cycle, which was placebo-controlled, was integrated for these 2 studies for ISS Group 1 and with other placebo-controlled studies for ISS Groups 2 to form placebo controlled analysis sets. During the second treatment period, subjects received open-label AGN 151586 700 U upon meeting retreatment criteria. If a subject did not meet the retreatment criteria at the Day 43 visit, they were not considered for retreatment. In subjects who received AGN-151586 700 U during the first treatment period, the second treatment period was analyzed for safety of repeat treatment in ISS Group 3 (AGN-151586 Treatment Analysis Set).

Across all studies, safety assessments included AEs, ECGs, vital sign measurements, and neurological assessments. In addition, laboratory assessments were conducted in all studies except Study M21-509.

Table 5: Analysis Sets (ISS Groups)

Analysis Set	Description	Studies Included	Subjects Included	Summarized Treatment Groups	Rationale
ISS Group 1	Pivotal Studies Analysis Set	M21-500 M21-508	All subjects who received at least 1 study drug administration	Placebo AGN-151586 700 U	To provide a randomized, controlled assessment of safety of AGN-151586 compared with placebo in placebo-controlled Phase 3 studies in treatment of GL in Treatment Cycle 1 DB Period as well as assessment of laboratory values, vital sign parameters, and ECG parameters in Treatment Cycle 2 OL Period.

ISS Group 2	DB Placebo-Controlled Analysis Set, All DB Studies	M21-500 M21-508 M23-365 2034-201-008 EB001-GL201	All subjects who received at least 1 study drug administration	Placebo AGN-151586 < 700 U AGN-151586 ≥ 700 U	To provide a randomized, controlled assessment of safety of AGN-151586 (< 700 U and ≥ 700 U) compared with placebo in all double blinded studies in treatment of GL. As 700 U is the proposed dose for the GL indication and the sample sizes for the non-700 U groups were small relative to the 700 U group, subjects receiving AGN-151586 were grouped into these 2 categories.
ISS Group 3	AGN-151586 Treatment Analysis Set	M21-500 M21-508 M21-509 M23-365	All subjects who received at least 1 AGN-151586 700 U study drug administration	AGN-151586 700 U	To provide safety assessment of first-time treatment and retreatment of AGN-151586 700 U in treatment of GL

5.5.2. Patient exposure

Table 6: Patient exposure (cut off)

	Patients enrolled (randomized)	**Patients exposed***	**Patients exposed to 700 U**	**Patients with long term** safety data**
Blinded studies (placebo-controlled) *M21-500* *M21-508* *M23-365* *2034-201-008* *EB001-GL201* *M24-008* *M24-040*	1463	1335	1140	2 treatments = 727
Open study *M21-509*	992	985	985	At least 2 treatments = 916 3 treatments = 846

* Received at least 1 dose of AGN-151586 treatment
** Patients with multiple 700 U treatment exposures

A total of 947 subjects were included in ISS Group 1. In the pivotal studies, 709 subjects received AGN-151586 700 U and 238 subjects received placebo in Treatment Cycle 1. A total of 12.6% of

subjects discontinued from the studies, and the most common reasons (≥ 1% total subjects) were withdrawal by subject (8.1%), lost to follow-up (1.8%), and other (1.7%). Eight subjects in the AGN-151586 700 U group discontinued study treatment due to an AE in Treatment Cycle 1. Subjects in both treatment groups were followed for a median of 42.0 days in Treatment Cycle 1.

Most subjects were female (85.6%) and primarily White (87.8%). Age ranged from 20 to 81 years (median 46 years) and 7.4% of subjects were ≥ 65 years. Prior toxin use was similar between placebo group and AGN-151586 700 U group (respectively 18.9% and 19.5%).

Most subjects reported at least 1 medical history term. Overall, the medical history was generally balanced between the AGN-151586 700 U and placebo groups. Some imbalances (> 5% difference) were seen in the SOCs of psychiatric disorders (26.5% in placebo groups vs. 32.2% in AGN-151586 700 U group) in particular history of anxiety (11.8% in placebo group vs. 14.7% in AGN-151586 700 U group) and depression (13.0% in placebo group vs. 15.1% in AGN-151586 700 U group), and vascular disorders (21.0% in placebo group vs. 13.5% in AGN-151586 700 U group) in particular history of hypertension (18.9% in placebo group vs. 12.0% in AGN-151586 700 U group).

In ISS Group 2, 152 subjects received at least 1 dose of AGN-151586 < 700 U, 788 subjects received at least 1 dose of AGN-151586 ≥ 700 U, and 337 subjects received placebo. They were followed for a median of 42.0 days in Treatment Cycle 1 for the placebo and AGN-151586 ≥ 700 U groups and a median of 43.0 days in Treatment Cycle 1 for the AGN-151586 < 700 U group. A total of 10.6% of subjects discontinued from the studies, and the most common reasons (≥ 1% total subjects) were withdrawal by subject (6.4%), other (1.8%), and lost to follow-up (1.6%). Nine subjects discontinued study treatment due to an AE (including 8 subjects in the AGN-151586 ≥ 700 U group and 1 subject in the placebo group).

In ISS Group 3, 1960 subjects received at least 1 treatment with AGN-151586 700 U and were followed for a median of 42.0 days for Treatment Cycle 1; 1544 subjects were followed for a median of 42.0 days for Treatment Cycle 2, and 846 subjects were followed for a median of 43.0 days for Treatment Cycle 3. A total of 12.7% of subjects discontinued from the studies, and the most common reasons (≥ 1% total subjects) were withdrawal by subject (6.6%), other (2.6%), and lost to follow-up (2.5%). Overall, 19 subjects discontinued study treatment due to an AE.

The demographic characteristics of ISS Group 2 and ISS Group 3 were similar to those of ISS Group 1.

In all the studies, subjects ≥ 18 years of age, with moderate (Grade 3) to severe (Grade 4) GL at maximum frown as assessed by both the investigator and subject using Facial Wrinkle Scale were to be enrolled in each placebo controlled study.

In addition, study M24-040 (which was not included in the ISS Groups) included in total 18 subjects in the AGN-151586 groups and 6 subjects in the placebo groups.

5.5.3. Adverse events

Pivotal Studies Analysis Set (ISS Group 1)

This analysis set provides a comprehensive safety analysis of Treatment Cycle 1 DB Period for all subjects who received a single treatment of AGN-151586 700 U or placebo (Treatment Cycle 1) in the pivotal Phase 3 studies (Studies M21-500 and M21 508) with a follow-up period of 6 weeks. Analysis of repeat treatment of AGN 151586 700 U in the pivotal studies (Treatment Cycle 2 OL Period) is included in ISS Group 3 under AGN 151586 Treatment Cycle 2.

The percentage of subjects experiencing at least 1 TEAE was similar between treatment groups with a greater percentage being reported among subjects who received placebo (26.5% in Placebo Group vs.

23.4% in AGN-151586 700 U Group). Most subjects reported TEAEs that were mild in severity (20.6% in Placebo Group vs. 19.7% in AGN-151586 700 U Group) and not related to study treatment (90.8% in Placebo Group vs. 92.4% in AGN-151586 700 U Group).

TEAEs leading to study drug discontinuation were higher in the AGN-151586 700 U group (1.1%) than the placebo group (0.0%).

Table 7: Overview of Subjects with TEAEs in Treatment Cycle 1 in Pivotal Studies Analysis Set (ISS Group 1)

TEAE Category	Placebo (N=238) n (%)	AGN-151586 700U (N=709) n (%)
Treatment-Emergent Adverse Event (TEAE)	63 (26.5)	166 (23.4)
TEAE Related to Study Treatment [1]	22 (9.2)	54 (7.6)
TEAE Related to Study Procedure [1]	22 (9.2)	48 (6.8)
TEAE Related to Study Drug [1]	19 (8.0)	40 (5.6)
Mild TEAE	49 (20.6)	140 (19.7)
Related to Study Treatment [1]	22 (9.2)	52 (7.3)
Moderate TEAE	14 (5.9)	40 (5.6)
Related to Study Treatment [1]	0 (0.0)	2 (0.3)
Severe TEAE	2 (0.8)	4 (0.6)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)
Serious TEAE	1 (0.4)	4 (0.6)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)
TEAE Leading to Study Drug Discontinuation	0 (0.0)	8 (1.1)
Neurological Assessment Associated TEAE	0 (0.0)	1 (0.1)
Possible Distant Spread of Toxin (PDSOT) TEAE	0 (0.0)	1 (0.1)
All Deaths	0 (0.0)	0 (0.0)

Note: ISS Group 1 includes studies M21-500 and M21-508.
Subjects are counted once in each row within a column, regardless of the number of events they may have had.
[1] As assessed by investigator.

The most frequently reported events by SOC level belonged to the SOCs Infections and infestations (9.7% in placebo groups vs. 8.3% in AGN-151586 700 U group), Nervous system disorders (6.3% in placebo groups vs. 6.3% in AGN-151586 700 U group) and General disorders and administration site conditions (5.9% in placebo groups vs. 4.5% in AGN-151586 700 U group).

The most frequently reported TEAEs (≥ 2% of subjects) were headache (5.4%) and COVID-19 (2.4%) among subjects who received AGN-151586 700 U; and headache (5.9%), COVID-19 (2.9%), nasopharyngitis (3.4%), and injection site pain (2.9%) among subjects who received placebo.

The percentage of subjects experiencing at least 1 severe TEAE was similar across treatment groups with a greater percentage being reported among subjects who received placebo (0.8% in placebo groups vs. 0.6% in AGN-151586 700 U group).

Severe TEAEs reported in subjects who received AGN-151586 700 U were cholecystitis, appendicitis, pneumonia, hypocalcaemia (one TEAE each). All these TEAEs were serious and no other serious TEAEs were reported.

The time to onset of treatment-related TEAEs experienced by subjects who received AGN-151586 during Treatment Cycle 1 (Double-blind Period) ranged from 1 to 42 days with a median onset of 1.0 day. The duration of treatment-related TEAEs ranged from 1 to 16 days with a median duration of 2.0 days.

No subjects reported serious or severe TEAEs that were assessed as treatment-related by the investigator.

Double-Blind Placebo-Controlled Analysis Set (ISS Group 2)

This analysis set integrated all subjects who received at least 1 treatment of study drug (AGN 151586 or placebo) in a double-blind, placebo-controlled study to provide a comprehensive safety analysis of all subjects who received 1 treatment of AGN-151586 or placebo over a period of 6 weeks. This analysis set examines the TEAEs of all subjects (AGN-151586 ≥ 700 U, < 700 U, and placebo) for Treatment Cycle 1.

During Treatment Cycle 1, 31.6% of subjects experienced at least 1 TEAE in the AGN-151586 < 700 U group, 23.6% of subjects in the AGN-151586 ≥ 700 U group, and 26.1% of subjects in the placebo group.

Most TEAEs reported were mild in severity. A higher proportion of severe TEAEs was observed in the AGN-151586 < 700 U (3.3%, all related to study treatment) compared to the AGN-151586 ≥ 700 U group (0.8%) and the placebo group (1.5%).

TEAEs leading to study drug discontinuation were higher in the AGN-151586 ≥ 700 U group (1.1%) compared to other groups (0.0%).

Table 8: Overview of Subjects with TEAEs Treatment Cycle 1 - DB Placebo-Controlled Analysis Set (ISS Group 2)

TEAE Category	Placebo (N=337) n (%)	AGN-151586 <700U (N=152) n (%)	AGN-151586 >=700U (N=788) n (%)
Treatment-Emergent Adverse Event (TEAE)	88 (26.1)	48 (31.6)	186 (23.6)
TEAE Related to Study Treatment [1]	32 (9.5)	26 (17.1)	63 (8.0)
TEAE Related to Study Procedure [1]	26 (7.7)	7 (4.6)	51 (6.5)
TEAE Related to Study Drug [1]	28 (8.3)	24 (15.8)	48 (6.1)
Mild TEAE	68 (20.2)	29 (19.1)	154 (19.5)
Related to Study Treatment [1]	27 (8.0)	10 (6.6)	55 (7.0)
Moderate TEAE	25 (7.4)	18 (11.8)	46 (5.8)
Related to Study Treatment [1]	4 (1.2)	12 (7.9)	6 (0.8)
Severe TEAE	5 (1.5)	5 (3.3)	6 (0.8)
Related to Study Treatment [1]	2 (0.6)	5 (3.3)	2 (0.3)
Serious TEAE	1 (0.3)	0 (0.0)	4 (0.5)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)	0 (0.0)
TEAE Leading to Study Drug Discontinuation	0 (0.0)	0 (0.0)	9 (1.1)
Neurological Assessment Associated TEAE	1 (0.3)	2 (1.3)	1 (0.1)
Possible Distant Spread of Toxin (PDSOT) TEAE	1 (0.3)	1 (0.7)	1 (0.1)
All Deaths	0 (0.0)	0 (0.0)	0 (0.0)

Note: ISS Group 2 includes studies 2034-201-008, EB001-GL201, M21-500, M21-508, and M23-365.
Subjects are counted once in each row within a column, regardless of the number of events they may have had. CTCAE severity scale from EB001-GL201 are mapped into AE severity in other studies; Mild (grade 1) = Mild, Moderate (grade 2) = Moderate, and Severe (grade 3) = Severe. There are no Grades 4 and 5 AEs reported in Study EB001-GL201.
[1] As assessed by investigator.

The most frequently reported TEAEs (> 2% of subjects) were headache (5.3%), injection site pain (2.3%), and COVID-19 (2.2%) among subjects who received AGN-151586 ≥ 700 U; injection site pain (11.8%) and headache (7.9%) among subjects who received AGN-151586 < 700 U; and headache (6.2), injection site pain (3.9%), COVID-19 (2.1%), and nasopharyngitis (2.7%) among subjects who received placebo.

Severe (non-serious) TEAEs reported in subjects who received AGN-151586 ≥ 700 U were Injection site pain (n=2, 0.3%) which were related to treatment. Severe and serious TEAEs reported in subjects

who received AGN-151586 ≥ 700 U were cholecystitis (n=1, 0.1%), appendicitis (n=1, 0.1%), pneumonia (n=1, 0.1%), hypocalcaemia (n=1, 0.1%).

The time to onset of treatment-related TEAEs experienced by subjects who received AGN-151586 ≥ 700 U ranged from 1 to 42 days with a median onset of 1.0 day; and 1 to 2 days with a median onset of 1.0 day for the AGN 151586 < 700 U group. The duration of treatment-related TEAEs ranged from 1 to 16 days with a median duration of 1.0 day for the AGN 151586 ≥ 700 U group; and 1 to 17 days with a median duration of 1.0 day for the AGN-151586 < 700 U group.

No subjects reported serious TEAEs that were related to treatment.

AGN-151586 Treatment Analysis Set (ISS Group 3)

This analysis set integrated all subjects who received at least 1 treatment of AGN-151586 700 U in Studies M21-500, M21-508, M21-509, and M23-365 to provide a comprehensive safety analysis of first-time treatment and retreatment of AGN-151586 for treatment of GL. This analysis set examines the TEAEs of all subjects for each AGN-151586 Treatment Cycle.

Across all AGN-151586 treatment cycles, 34.8% of subjects experienced at least 1 TEAE. The incidence of TEAEs trended downward with each subsequent AGN-151586 Treatment Cycle (22.6% during Cycle 1, 19.9% during Cycle 2, 14.7% during Cycle 3).

Across all AGN-151586 treatment cycles, 0.7% of subjects experienced severe TEAEs and 0.6% serious TEAEs.

Table 9: Overview of Subjects with TEAEs by AGN-151586 Treatment Cycles and All AGN-151586 Treatment Cycles – AGN-151586 Treatment Analysis Set (ISS Group 3)

TEAE Category	AGN-151586 Treatment Cycle 1 AGN-151586 700U (N=1960)	AGN-151586 Treatment Cycle 2 AGN-151586 700U (N=1544)	AGN-151586 Treatment Cycle 3 AGN-151586 700U (N=846)	All AGN-151586 Treatment Cycles AGN-151586 700U (N=1960)
Treatment-Emergent Adverse Event (TEAE)	443 (22.6)	307 (19.9)	124 (14.7)	683 (34.8)
TEAE Related to Study Treatment [1]	163 (8.3)	88 (5.7)	42 (5.0)	229 (11.7)
TEAE Related to Study Procedure [1]	145 (7.4)	75 (4.9)	37 (4.4)	200 (10.2)
TEAE Related to Study Drug [1]	128 (6.5)	71 (4.6)	32 (3.8)	178 (9.1)
Mild TEAE	378 (19.3)	242 (15.7)	102 (12.1)	572 (29.2)
Related to Study Treatment [1]	159 (8.1)	81 (5.2)	40 (4.7)	219 (11.2)
Moderate TEAE	98 (5.0)	79 (5.1)	30 (3.5)	196 (10.0)
Related to Study Treatment [1]	5 (0.3)	7 (0.5)	2 (0.2)	13 (0.7)
Severe TEAE	8 (0.4)	3 (0.2)	3 (0.4)	14 (0.7)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE	7 (0.4)	1 (0.1)	4 (0.5)	12 (0.6)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE Leading to Study Drug Discontinuation	15 (0.8)	4 (0.3)	0 (0.0)	19 (1.0)
Neurological Assessment Associated TEAE	8 (0.4)	7 (0.5)	1 (0.1)	16 (0.8)
Possible Distant Spread of Toxin (PDSOT) TEAE	5 (0.3)	7 (0.5)	1 (0.1)	13 (0.7)
All Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: ISS Group 3 includes studies M21-500, M21-508, M21-509, and M23-365.
Subjects are counted once in each row within a column, regardless of the number of events they may have had.
[1] As assessed by investigator.

The most frequently reported TEAEs (≥ 2% of subjects overall) were headache (7.6%), COVID 19 (4.5%), injection site pain (3.7%), and nasopharyngitis (2.9%) for subjects who received AGN 151586 during any AGN-151586 treatment cycle. The sameTEAEs were the highest in AGN-151586 700 U Treatment Cycles 1, 2 and 3.

A similar incidence of severe TEAEs was reported in all 3 AGN 151586 treatment cycles (0.4% during Cycle 1, 0.2% during Cycle 2, 0.4% during Cycle 3). Overall, < 1% of subjects reported severe TEAEs with AGN-151586 700 U. No serious TEAEs were reported.

Overall, the time to onset of treatment-related TEAEs among all subjects ranged from 1 to 43 days with a median onset of 1.0 day. The duration of treatment-related TEAEs ranged from 1 to 125 days with a median duration of 2.0 days. The median time to onset and the median duration of treatment related TEAEs was the same for all 3 AGN-151586 Treatment Cycles.

No severe or serious TEAEs were assessed by the investigator as treatment-related across all treatment cycles.

5.5.4. Adverse events of special interest, serious adverse events and deaths, other significant events

5.5.4.1. Serious adverse events

In ISS Group 1, a similar incidence (<1%) of subjects reported at least 1 serious TEAE (TESAE) in both treatment groups. There were no TESAEs reported by more than 1 subject in either group. Cholecystitis, appendicitis, pneumonia, and hypocalcaemia were each reported once in the AGN-151586 700 U group and invasive ductal breast carcinoma was reported once in the placebo group. There was no treatment related TESAE reported. Overall, most TESAEs were mild to moderate in severity and 3 subjects reported a TESAE that led to study drug discontinuation.

Table 10: Serious TEAEs (ISS group 1)

MedDRA 25.1 System Organ Class Preferred Term	Placebo (N=238) n (%)	AGN-151586 700U (N=709) n (%)
Subjects with at least one Serious TEAE	1 (0.4)	4 (0.6)
Hepatobiliary disorders	0 (0.0)	1 (0.1)
Cholecystitis	0 (0.0)	1 (0.1)
Infections and infestations	0 (0.0)	2 (0.3)
Appendicitis	0 (0.0)	1 (0.1)
Pneumonia	0 (0.0)	1 (0.1)
Metabolism and nutrition disorders	0 (0.0)	1 (0.1)
Hypocalcaemia	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	0 (0.0)
Invasive ductal breast carcinoma	1 (0.4)	0 (0.0)

In ISS Group 2, < 1% of subjects reported at least 1 TESAE in the AGN-151586 ≥ 700 U group, with no TESAEs being reported in the AGN-151586 < 700 U group. There were no TESAEs reported by more than 1 subject in the placebo or AGN-151586 ≥ 700 U group. Cholecystitis, appendicitis, pneumonia, and hypocalcaemia were each reported once in the AGN-151586 ≥ 700 U group and invasive ductal breast carcinoma was reported once in the placebo group. There was no treatment related TESAE reported in ISS Group 2.

Table 11: Serious TEAEs (ISS group 2)

MedDRA 25.1 System Organ Class Preferred Term	Placebo (N=337) n (%)	AGN-151586 <700U (N=152) n (%)	AGN-151586 >=700U (N=788) n (%)
Subjects with at least one Serious TEAE	1 (0.3)	0 (0.0)	4 (0.5)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.1)
Cholecystitis	0 (0.0)	0 (0.0)	1 (0.1)
Infections and infestations	0 (0.0)	0 (0.0)	2 (0.3)
Appendicitis	0 (0.0)	0 (0.0)	1 (0.1)
Pneumonia	0 (0.0)	0 (0.0)	1 (0.1)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (0.1)
Hypocalcaemia	0 (0.0)	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	0 (0.0)	0 (0.0)
Invasive ductal breast carcinoma	1 (0.3)	0 (0.0)	0 (0.0)

In ISS Group 3, a similar incidence (all < 1%) of subjects reported at least 1 TESAEs during AGN-151586 Treatment Cycle 1, Cycle 2, and Cycle 3, with the lowest incidence occurring in AGN-151586 Treatment Cycle 2. There were no TESAEs reported by more than 1 subject overall and in any of the individual AGN-151586 treatment cycles. There was no treatment related TESAE reported in ISS Group 3.

Table 12: Serious TEAEs (ISS group 3)

MedDRA 25.1 System Organ Class Preferred Term	AGN-151586 Treatment Cycle 1 AGN-151586 700U (N=1960)	AGN-151586 Treatment Cycle 2 AGN-151586 700U (N=1544)	AGN-151586 Treatment Cycle 3 AGN-151586 700U (N=846)	All AGN-151586 Treatment Cycles AGN-151586 700U (N=1960)
Subjects with at least one Serious TEAE	7 (0.4)	1 (0.1)	4 (0.5)	12 (0.6)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Obstructive pancreatitis	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Hepatobiliary disorders	2 (0.1)	0 (0.0)	1 (0.1)	3 (0.2)
Biliary dilatation	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Cholecystitis	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Cholecystitis acute	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Cholelithiasis	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Hypertransaminasaemia	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Infections and infestations	3 (0.2)	1 (0.1)	0 (0.0)	4 (0.2)
Appendicitis	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Device related infection	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Pneumonia	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Pyelonephritis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Injury, poisoning and procedural complications	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Jaw fracture	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Rib fracture	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Road traffic accident	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Skin laceration	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Spinal column injury	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Metabolism and nutrition disorders	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Hypocalcaemia	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Plasma cell myeloma	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Nervous system disorders	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Transient ischaemic attack	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Bipolar I disorder	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Acute kidney injury	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)

No deaths were reported in the AGN-151586 GL clinical development program.

5.5.4.2. Injection site reactions

In ISS Group 1, a similar percentage of subjects who received AGN-151586 (3.5%) and subjects who received placebo (5.0%) reported injection site reactions. The most common injection site reactions (> 1% of subjects in either group) were injection site pain and injection site erythema; both events were reported with a higher incidence in the placebo group (resp. 2.9% and 1.3%) than in the AGN-151586 group (resp. 1.7% and 0.6%).

In ISS Group 2, the incidence of injection site reactions was highest in the AGN-151586 < 700 U group (11.8%). This difference may be attributed to the high incidence of injection site pain events reported by 1 site (study 2034-201-008); no dose response was seen. All other injection site reaction events occurred with similar incidence (< 1%) across the 3 treatment groups.

In ISS Group 3, the frequency of injection site reactions was comparable across treatment cycles with the most common (> 1.0% of subjects) injection site reactions being injection site pain and injection site bruising. Across all AGN-151586 Treatment Cycles, the time to onset for these injection site reaction events since most recent AGN-151586 treatment ranged from 1 to 9 days with a median onset of 1.0 day. The duration of these events ranged from 1 to 40 days with a median duration of 2.0 days.

All injection site reaction TEAEs were non-serious; the majority of injection site reaction TEAEs resolved by the end of the study, and none led to study drug discontinuation.

5.5.4.3. Possible Distant Spread of Toxin (PDSOT)

PDSOT is defined as a possible pharmacologic effect of botulinum toxin at sites non-contiguous and distant from the site of injection. To identify TEAEs potentially meeting this definition, a standardized methodology was utilized, and MedDRA PTs were identified. These terms were purposely chosen to be broad, knowing that cases would subsequently be further characterized.

According to the applicant, none of the PDSOT TEAEs represented cases of distant spread of toxin but rather were assessed as local diffusion events, inconsistent with pharmacologic effect, and/or confounded by medical history, alcohol use, or concomitant medication. All PDSOT TEAEs were mild in severity.

Table 13: Possible distant spread of toxin TEAEs (ISS Group 3)

MedDRA 25.1 Preferred Term	AGN-151586 Treatment Cycle 1 AGN-151586 700U (N=1960)	AGN-151586 Treatment Cycle 2 AGN-151586 700U (N=1544)	AGN-151586 Treatment Cycle 3 AGN-151586 700U (N=846)	All AGN-151586 Treatment Cycles AGN-151586 700U (N=1960)
Subjects with at least one PDSOT TEAE	5 (0.3)	7 (0.5)	1 (0.1)	13 (0.7)
Eyelid ptosis	2 (0.1)	1 (0.1)	0 (0.0)	3 (0.2)
Vision blurred	2 (0.1)	1 (0.1)	0 (0.0)	3 (0.2)
Dyspnoea	1 (0.1)	2 (0.1)	0 (0.0)	3 (0.2)
Dry mouth	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Dysphagia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Constipation	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)

5.5.4.4. Neurological assessment TEAEs

Neurological assessment comprised of a Focused Symptom Questionnaire and a Focused Neurological Examination was collected in Studies M21-500, M21-508, M21 509, M23 365, and 2034-201-008. In EB001-GL201, a focused neurological examination was performed to evaluate spread of toxin. Neurological assessment-associated TEAEs were summarized by PT, treatment group and treatment cycle for ISS Groups 1, 2 and 3.

Overall, the neurological assessment-associated TEAEs were non-serious and mild to moderate in severity. Most were not related to study treatment and one TEAE led to study drug discontinuation.

Table 14: Neurological assessment TEAEs (ISS Group 3)

MedDRA 25.1 Preferred Term	AGN-151586 Treatment Cycle 1 AGN-151586 700U (N=1960)	AGN-151586 Treatment Cycle 2 AGN-151586 700U (N=1544)	AGN-151586 Treatment Cycle 3 AGN-151586 700U (N=846)	All AGN-151586 Treatment Cycles AGN-151586 700U (N=1960)
Subjects with at least one Neurological Assessment Associated TEAE	8 (0.4)	7 (0.5)	1 (0.1)	16 (0.8)
Visual acuity reduced	3 (0.2)	2 (0.1)	1 (0.1)	6 (0.3)
Vision blurred	2 (0.1)	1 (0.1)	0 (0.0)	3 (0.2)
Eyelid ptosis	1 (0.1)	1 (0.1)	0 (0.0)	2 (0.1)
Brow ptosis	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Halo vision	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Myopia	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Joint range of motion decreased	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)

5.5.4.5. ADRs of special interest, serious ADRs and deaths causally related to the medicinal product.

Serious treatment related TEAE

There was no serious treatment related TEAE reported in the three ISS Groups.

Injection site reactions

The majority of injection site reaction TEAEs were considered to be related to study treatment (study drug and/or study drug administration procedure) by the investigator.

Possible distant spread of toxin

The following PDSOT TEAEs were considered as treatment-related by the investigator: eyelid ptosis, dry mouth, and vision blurred. Onset day of these treatment-related PDSOT events since most recent AGN-151586 treatment ranged from Day 2 to Day 7, with duration ranging from 2 to 15 days.

In addition, 3 subjects who received AGN-151586 700 U reported an event of brow ptosis. In this indication, the event of brow ptosis is considered to be consistent with local diffusion. All events were assessed as treatment related by the investigator. Day of onset since the most recent AGN-151586 treatment ranged from Day 3 to Day 4, with duration ranging from 2 days to ongoing at time of study end.

Neurological Assessment Adverse Events

The following neurological assessment-associated TEAEs were considered as treatment-related by the investigator: brow ptosis (2 events) and 1 event each of eyelid ptosis, vision blurred, and visual acuity reduced. The onset day of these treatment-related events since the most recent AGN-151586 treatment ranged from Day 3 to Day 8, with duration ranging from 6 days to ongoing at time of study end.

5.5.5. Discontinuation due to adverse events

In total, across the 6 studies, 19 subjects treated with AGN-151586 had a TEAE that led to study drug discontinuation; 8 subjects from the Phase 3 pivotal studies, 10 subjects from the open-label safety study (6 subjects from AGN-151586 Treatment Cycle 1 and 4 subjects from Cycle 2), and 1 subject from Study M23-365. No subjects discontinued from Studies 2034-201-008 and EB001-GL201 due to a TEAE.

Overall, the majority of TEAEs leading to study drug discontinuation were electrocardiogram QT prolonged (6 subjects: 2 from Study M21-500, 1 from Study M21-508, 3 from Study M21 509; all asymptomatic) followed by COVID 19/ asymptomatic COVID-19 (3 subjects: 1 from Study M21-500, 2 from Study M21-509). Other TEAEs leading to study drug discontinuation were: Hypocalcaemia, Pneumonia, Anemia, Electrocardiogram T wave amplitude decreased (asymptomatic), Supraventricular tachycardia (asymptomatic), Bundle branch block (asymptomatic), Eyelid ptosis (worsening, mild), Device related infection, Cholecystitis acute, Hemianaesthesia (from arm to feet).

None of the TEAEs leading to study treatment discontinuation was assessed by the investigator as treatment-related.

5.5.6. Safety in special populations

There were no clinically meaningful differences in the TEAE profile amongst the subgroups of sex, race, ethnicity, and age group.

Sex

In ISS Group 1, the percentage of subjects experiencing at least 1 TEAE was similar between sexes for subjects who received AGN-151586 and subjects who received placebo. The most frequently reported treatment-related TEAEs (> 1% of subjects in either subgroup) for female subjects who received AGN 151586 were headache and injection site pain; and injection site pain for male subjects who received AGN-151586.

Table 15: Overview number of subjects with TEAEs by sex (ISS Group 1)

Sex: Female

TEAE Category	Placebo (N=201) n (%)	AGN-151586 700U (N=610) n (%)
Treatment-Emergent Adverse Event (TEAE)	55 (27.4)	147 (24.1)
TEAE Related to Study Treatment [1]	21 (10.4)	49 (8.0)
TEAE Related to Study Procedure [1]	21 (10.4)	44 (7.2)
TEAE Related to Study Drug [1]	18 (9.0)	36 (5.9)
Mild TEAE	45 (22.4)	123 (20.2)
Related to Study Treatment [1]	21 (10.4)	47 (7.7)
Moderate TEAE	10 (5.0)	38 (6.2)
Related to Study Treatment [1]	0 (0.0)	2 (0.3)
Severe TEAE	2 (1.0)	4 (0.7)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)
Serious TEAE	1 (0.5)	4 (0.7)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)
TEAE Leading to Study Drug Discontinuation	0 (0.0)	7 (1.1)
Neurological Assessment Associated TEAE	0 (0.0)	1 (0.2)
Possible Distant Spread of Toxin (PDSOT) TEAE	0 (0.0)	1 (0.2)
All Deaths	0 (0.0)	0 (0.0)

Sex: Male

TEAE Category	Placebo (N=37) n (%)	AGN-151586 700U (N=99) n (%)
Treatment-Emergent Adverse Event (TEAE)	8 (21.6)	19 (19.2)
TEAE Related to Study Treatment [1]	1 (2.7)	5 (5.1)
TEAE Related to Study Procedure [1]	1 (2.7)	4 (4.0)
TEAE Related to Study Drug [1]	1 (2.7)	4 (4.0)
Mild TEAE	4 (10.8)	17 (17.2)
Related to Study Treatment [1]	1 (2.7)	5 (5.1)
Moderate TEAE	4 (10.8)	2 (2.0)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)
Severe TEAE	0 (0.0)	0 (0.0)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)
Serious TEAE	0 (0.0)	0 (0.0)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)
TEAE Leading to Study Drug Discontinuation	0 (0.0)	1 (1.0)
Neurological Assessment Associated TEAE	0 (0.0)	0 (0.0)
Possible Distant Spread of Toxin (PDSOT) TEAE	0 (0.0)	0 (0.0)
All Deaths	0 (0.0)	0 (0.0)

In ISS Group 3, there was a downward trend in TEAE frequency with subsequent AGN-151586 treatment cycles in female subjects, whereas there was no meaningful trend in the frequency of TEAEs with subsequent AGN-151586 treatment cycles in male subjects. This same finding was seen for treatment-related TEAEs; decreasing trend in frequency in females and no meaningful trend in males with subsequent AGN-151586 treatment cycles.

Race group

In ISS Group 1, the percentage of subjects experiencing at least 1 TEAE were similar in subjects who received AGN-151586 and subjects who received placebo in the White race group. In the Black or African American, Asian, and "Other" (including American Indian or Alaska Native, Native Hawaiian, Other Pacific Islander or multiple) groups, the percentage of subjects experiencing at least 1 TEAE was lower in subjects who received AGN-151586 than subjects who received placebo. The most frequently reported treatment-related TEAEs (> 1% in any subgroup and occurring in > 1 subject) in subjects who received AGN-151586 were headache and injection site pain in the White race group, and injection site pain and injection site erythema in the Black or African American race group; no treatment-related TEAEs occurred in more than 1 subject in the Asian and "Other" race groups.

In ISS Group 3, there was a downward trend in overall percentage of TEAEs with subsequent treatment cycles for White, Black or African American, and Asian race groups that was not observed in the "Other" race group, in which no trend was seen with subsequent treatment cycles. The same downward trend in overall percentage of treatment-related TEAEs with subsequent treatment cycles was observed for White and Black or African American groups that was not observed in Asian and "Other" race groups.

Age group

Safety of AGN-151586 for GL has not been established for patients who are under the age of 18; therefore, AGN-151586 for GL is not recommended in this age group.

In ISS Group 1, the percentage of subjects experiencing at least 1 TEAE was lower for subjects ≥ 65 years old who received AGN-151586 than for subjects who received placebo. For subjects < 65 years old, the percentage of subjects experiencing at least 1 TEAE was similar for both treatment groups. Among AGN-151586 treated subjects, a lower percentage of subjects ≥ 65 years old reported at least 1 TEAE compared with subjects < 65 years old.

In ISS Group 1, the percentage of subjects experiencing at least 1 treatment-related TEAE was similar for both treatment groups for subjects < 65 years old; no subject ≥ 65 years old experienced a treatment-related TEAEs in the double-blind period. In subjects < 65 years old, the most frequently reported treatment-related TEAEs (> 1% of subjects) among subjects who received AGN-151586 were headache and injection site pain.

Table 16: Overview number of subjects with TEAEs by age group (ISS Group 1)

Age Group 2: < 65

TEAE Category	Placebo (N=216) n (%)	AGN-151586 700U (N=661) n (%)
Treatment-Emergent Adverse Event (TEAE)	54 (25.0)	160 (24.2)
TEAE Related to Study Treatment [1]	18 (8.3)	54 (8.2)
TEAE Related to Study Procedure [1]	18 (8.3)	48 (7.3)
TEAE Related to Study Drug [1]	15 (6.9)	40 (6.1)
Mild TEAE	41 (19.0)	135 (20.4)
Related to Study Treatment [1]	18 (8.3)	52 (7.9)
Moderate TEAE	13 (6.0)	39 (5.9)
Related to Study Treatment [1]	0 (0.0)	2 (0.3)
Severe TEAE	2 (0.9)	3 (0.5)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)
Serious TEAE	1 (0.5)	3 (0.5)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)
TEAE Leading to Study Drug Discontinuation	0 (0.0)	8 (1.2)
Neurological Assessment Associated TEAE	0 (0.0)	1 (0.2)
Possible Distant Spread of Toxin (PDSOT) TEAE	0 (0.0)	0 (0.0)
All Deaths	0 (0.0)	0 (0.0)

Table 17: Overview number of subjects with TEAEs by age group (ISS Group 1)*

Age Group 2: >= 65

TEAE Category	Placebo (N=216) n (%)	AGN-151586 700U (N=661) n (%)
Treatment-Emergent Adverse Event (TEAE)	9 (40.9)	6 (12.5)
TEAE Related to Study Treatment [1]	4 (18.2)	0 (0.0)
TEAE Related to Study Procedure [1]	4 (18.2)	0 (0.0)
TEAE Related to Study Drug [1]	4 (18.2)	0 (0.0)
Mild TEAE	8 (36.4)	5 (10.4)
Related to Study Treatment [1]	4 (18.2)	0 (0.0)
Moderate TEAE	1 (4.5)	1 (2.1)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)
Severe TEAE	0 (0.0)	1 (2.1)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)
Serious TEAE	0 (0.0)	1 (2.1)
Related to Study Treatment [1]	0 (0.0)	0 (0.0)
TEAE Leading to Study Drug Discontinuation	0 (0.0)	0 (0.0)
Neurological Assessment Associated TEAE	0 (0.0)	0 (0.0)
Possible Distant Spread of Toxin (PDSOT) TEAE	0 (0.0)	1 (2.1)
All Deaths	0 (0.0)	0 (0.0)

**There is an error with number of subjects in this table. It should be: Placebo (N=22), AGN-151586 700 U (N=48)*

In ISS Group 3, 162 subjects treated with AGN-151586 700 U were ≥ 65 years of age. No clinically meaningful differences in TEAE profiles were observed between subjects < 65 years of age and subjects ≥ 65 years of age.

In ISS Group 3, a decreasing trend in the percentage of TEAEs was observed in both age groups (< 65 and ≥ 65) with subsequent AGN-151586 treatment cycles. The same trend was seen with the percentage of treatment-related TEAEs in these 2 age groups.

In ISS Group 1, the percentage of subjects experiencing at least 1 TEAE was similar between subjects 18 to 45 years old and subjects > 45 years old for subjects who received AGN-151586 and for subjects who received placebo. Similar findings were seen with regards to the percentage of subjects experiencing at least 1 treatment-related TEAE. For both age groups, the most frequently reported treatment-related TEAEs (> 1% in either subgroup) in subjects who received AGN-151586 were headache and injection site pain. In ISS Group 3, a decreasing trend in the percentage of TEAEs and the percentage of treatment-related TEAEs was observed in both age groups (18 to 45 years old and > 45 years old) with subsequent AGN-151586 treatment cycles.

Ethnicity

In ISS Group 1, the percentage of subjects experiencing at least 1 TEAE was lower in subjects who received AGN-151586 than subjects who received placebo among those of Hispanic or Latino ethnicity. For subjects in the Not Hispanic or Latino group, the percentage of subjects experiencing at least 1 TEAE was similar in both treatment groups. Similar findings were seen for the percentage of subjects experiencing at least 1 treatment-related TEAE. The most frequently reported treatment-related TEAEs (> 1% in any subgroup and occurring in > 1 subject) in subjects who received AGN-151586 were headache and injection site pain in the Not Hispanic or Latino subgroup; no treatment-related TEAEs occurred in more than 1 subject in the Hispanic or Latino subgroup.

In ISS Group 3, there was a downward trend in TEAE percentage with subsequent AGN-151586 treatment cycles in the Not Hispanic or Latino group, whereas there was no such trend in the percentage of TEAEs with subsequent AGN-151586 treatment cycles in the Hispanic or Latino group. There was also a downward trend in treatment-related TEAE percentage with subsequent AGN- treatment cycles in the Not Hispanic or Latino group, whereas there was an increasing trend in the percentage of treatment-related TEAEs with subsequent AGN-151586 treatment cycles in the Hispanic or Latino group. These differences were not clinically meaningful.

Prior toxin use

In ISS Group 1, the percentage of subjects experiencing at least 1 TEAE were similar between subjects with and without a history of prior toxin use for subjects who received AGN-151586 and subjects who received placebo. The most frequently reported treatment-related TEAEs (> 1% in either subgroup) in subjects who received AGN-151586 were headache, injection site pain, and injection site hemorrhage for subjects with a history of prior toxin use, and headache and injection site pain for subjects with no prior toxin use history.

In ISS Group 3, the incidence in TEAEs and treatment-related TEAEs did not increase in subjects regardless of prior toxin use history with subsequent AGN-151586 treatment cycles; the incidence trended downward with repeat treatment cycles.

There were no clinically meaningful differences in the TEAE profile amongst those with prior toxin use and those without.

Region

In ISS Group 1, the percentage of subjects experiencing at least 1 TEAE were similar between subjects in North America and Europe for subjects who received AGN-151586 and subjects who received placebo. The most frequently reported treatment-related TEAEs (> 1% in either subgroup) in subjects who received AGN-151586 were headache and injection site pain for subjects in North America, and headache and injection site hematoma for subjects in Europe.

In ISS Group 3, the incidence in TEAEs and treatment-related TEAEs did not increase in subjects in both North America and Europe with subsequent AGN-151586 treatment cycles; the incidence trended downward with repeat treatment cycles.

There were no clinically meaningful differences in the TEAE profile based on region

Use in pregnancy and lactation

Safety of AGN-151586 for GL has not been established for patients who are pregnant or lactating, therefore AGN-151586 for GL is not recommended in these groups.

There are no studies or adequate data on the developmental risk associated with use of AGN-151586 in pregnant women. Fertility and early embryonic development studies in animals have not been conducted. AGN-151586 is not recommended during pregnancy.

There is no information on whether AGN-151586 is excreted in human milk.

No subjects in Studies M21-508, M23-365, 2034-201-008, and EB001-GL201 reported a pregnancy. One subject each in Studies M21-500 and M21-509 reported a pregnancy that resulted in live birth with no congenital anomalies or birth defects reported. An additional subject in Study M21-509 reported a pregnancy for which the outcome was unknown despite repeated attempts to contact the subject.

Overdose

According to the applicant, the risk of overdose for AGN-151586 is low due to the fact that it is intended to be administered by a health care provider at the health care provider's facilities.

Drug abuse

AGN-151586 blocks neuromuscular transmission by inhibiting the release of acetylcholine and is not physically addictive.

Withdrawal and rebound

Withdrawal and rebound effects are not applicable.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

According to the applicant, AGN-151586 has negligible influence on the ability to drive and use machines. It may cause eyelid ptosis and visual disturbance. Patients should exercise caution before driving or using machinery until they are reasonably certain that AGN 151586 does not adversely affect performance.

5.5.7. Immunological events

Immunogenicity was evaluated after single (Studies M23-365 and 2034-201-008) and repeat (Studies M21-500, M21-508, M21-509) administration of AGN-151586. For Studies M23-365, M21-500, M21-508, and M21-509, samples confirmed positive for BAbs to AGN-151586 were evaluated for NAbs and cross reactivity to BoNT/A. In addition, subjects with samples confirmed positive at study exit were requested to return to the site for additional blood samples to monitor for persistence of antibody response. For Study 2034-201-008, only antibody response to AGN-151586 was evaluated. No cross reactivity to BoNT/A evaluation was planned as sample volume collected from subjects was sufficient only to analyse for antibody response to AGN-151586. Study Y24-1002 (ABD201, GL201, MA201, and SR201) were conducted by Bonti, Inc. Due to unavailability of validated immunogenicity assays at that time, serum samples were stored per agreement with the FDA and analysed once the assay was developed and validated. Bioanalytical report Y24-1002 includes sample analysis from studies ABD201,

GL201, MA201, and SR201. Due to the differences in drug product and the doses in Units (defined by different assays) used in these studies, data from the Bonti, Inc. studies was not included in the pooled immunogenicity analysis.

5.5.7.1. Clinical Immunogenicity Results by Study

Phase 1 Study M23 365

Blood samples were collected from all subjects at screening, Day 30 (prior to BOTOX administration), Day 60 (30 days after BOTOX administration), and Day 150 (Study Exit/Early Discontinuation) for immunogenicity assessment. All collected samples were analysed for BAb to AGN 151586 and to BOTOX (botulinum toxin type A or BoNT/A). All analysed samples tested negative for BAb to AGN 151586 at all timepoints. Therefore, no samples were tested for NAb. One subject tested positive for BAb to BoNT/A at Screening, Day 60, and Day 150 (Study Exit); this subject tested negative for BAb to BoNT/A at Day 30. This subject was reportedly toxin naïve when enrolled in the study and received AGN 151586 700 units (U) in Treatment Period 1 followed by BOTOX 20 U in Treatment Period 2. Because this subject had pre-existing toxin BAbs (positive BAb to BoNT/A at Screening), the antibody response post treatment (positive BAb to BoNT/A at Day 60 and Day 150) was not considered to be treatment emergent. In addition, the subject's titer value at Screening was high (10935) and continuously decreased at Day 60 (3645) and Day 150 (135) visits, supporting that the Day 60 and Day 150 positive BAb results were not treatment emergent. The positive BAb samples at Screening, Day 60, and Day 150 also tested positive for NAb to BOTOX. The TEAEs experienced by this subject were related to elevated liver function tests (alanine aminotransferase increased, aspartate aminotransferase increased, and gamma glutamyltransferase increased) at the Day 60 visit; the subject was asymptomatic.

Liver function tests were within normal limits at Screening and Day 150 visit; thus, the abnormal liver function tests did not appear related to antibody formation. A review of efficacy data for this subject indicated no relationship between efficacy and presence of Nab.

Phase 2b Study 2034 201 008

Blood samples were collected from all subjects across all cohorts at Screening (Day 1), and post dose at Days 7, 28, and the end of the study. The number of subjects in each cohort ranged from 27 to 32 from whom samples were collected for immunogenicity assessment.

The results indicated that 4 analysed samples were found to have BAbs against AGN 151586. These four samples were collected from the same subject (toxin naïve when enrolled in the study) dosed with 750 U of AGN 151586 (Cohort 5) and had a low titer value of five across all timepoints, including the Screening Visit prior to AGN 151586 administration through the exit visit at Day 43 post AGN 151586 administration. Serum NAbs against AGN 151586 were not detected in samples that were positive to BAbs. Cross reactivity to BoNT/A was not evaluated in this study.

Phase 3 Study M21 500

Blood samples were collected from all subjects at screening, prior to each retreatment at Day 43 and study exit at Day 84. All analysed samples were negative for BAbs to AGN 151586. Therefore, no further testing for NAbs or cross reactivity to BoNT/A was performed.

Phase 3 Study M21-508

Blood samples were collected from all subjects at Screening, prior to each retreatment on Day 43, and study exit at Day 84. All analysed samples were negative for BAbs to AGN 151586. Therefore, no further testing for NAbs or cross reactivity to BoNT/A was performed.

Phase 3 Study M21 509

Blood samples were collected from all subjects at Screening, prior to each retreatment at Day 43 and Day 85, and study exit at Day 126. Two of 985 AGN 151586 treated subjects tested positive for BAbs to AGN 151586. Both subjects were reportedly toxin naïve when enrolled in the study and received all 3 treatment cycles of AGN 151586 700 U.

- One subject tested positive for BAbs to AGN 151586 only at the study exit with a titer value of 180. This subject tested negative for NAbs to AGN 151586 and for BAbs to BoNT/A. This subject reported 1 TEAE of COVID 19 that occurred between first and second treatment.
- One subject (ID 124012) tested positive for BAbs to AGN 151586 at all timepoints including Screening; titer values increased after the second treatment of AGN 151586. This subject tested positive for NAbs to AGN 151586 and for BAbs to BoNT/A (low titer value of 15 at all timepoints), but negative for NAbs to BoNT/A. This subject reported no TEAEs.

Upon review of subject level data, no correlation was observed between antibody formation and safety or efficacy.

Post End of Study Sample Immunogenicity (PEOSI)

Per protocol, additional blood collections post study exit were requested from both subjects due to positive BAb results at study exit. One Subject declined additional blood collections and therefore no PEOSI samples were collected from this subject. The other subject was evaluated with an additional sample taken at post end of study exit at Day 541 to monitor immunogenicity response. The subject tested positive for BAbs to AGN 151586 with a decreased titer value of 1620 compared to the previous titer value of 4860 at study exit Day 126. This sample tested positive for NAbs to AGN 151586 and positive for BAbs to BoNT/A with a low titer value of 15 (unchanged from study exit Day 126). The subject tested negative for NAbs to BoNT/A. Given the samples were collected after study exit, these additional data were not included in the pooled analysis.

Study Y24 1002 (ABD201)

Blood samples were collected at screening, post dose Day 8, and at study exit on Day 29 (Study ABD201). Overall, 1 subject (1/11) had positive BAbs to AGN 151586 at all timepoints (screening, Day 8, and Day 29 including at screening with decreased titer value post treatment (Y24 1002). No NAb to AGN 151586 or cross reactivity to BoNT/A was performed.

Study Y24 1002 (GL201)

Blood samples were collected at screening, post dose Day 7, and at study exit on Day 30 (Study GL201). Based on the results, 2 subjects tested positive for BAbs to AGN 151586. Of these 2 subjects, 1 subject (1/34) had pre-existing antibodies with low titer value of 5 at screening and Day 30. Another subject (1/34) only tested positive at Day 30 with low titer value of 15 (Y24 1002). No NAb to AGN 151586 or cross reactivity to BoNT/A was performed.

Study Y24 1002 (MA201)

Blood samples were collected at screening, post dose Day 8, and at study exit on Day 29 (Study MA201). The results indicated one subject (1/47) had pre-existing BAbs to AGN 151586 with positive BAbs at all timepoints (Y24 1002). The titer value of 15 was reported in all positive samples. No NAb to AGN 151586 or cross reactivity to BoNT/A was performed.

Study Y24 1002 (SR201)

Blood samples were collected at Day 1 (pre surgery), post dose Day 8, and at study exit on Day 30 (Study SR201). All analysed samples were negative for BAbs to AGN 151586 (Y24 1002). No NAb to AGN 151586 or cross reactivity to BoNT/A testing was performed.

5.5.7.2. Pooled Immunogenicity Data across Clinical Studies

Three analysis sets were created for pooled immunogenicity data analysis. Pivotal studies analysis set includes data from Phase 3 Studies M21-500 and M21-508 (ISS Group 1). AGN-151586 700 U treatment analysis set was integrated from studies M21-500, M21-508, M21-509, and M23-365 for pooled analysis (ISS Group 3). The third analysis set included all immunogenicity data from studies included in ISS Group 3 and Phase 2b Study 2034-201-008. A positive subject was determined based on the post baseline formation of BAb among subjects who are negative for BAb at baseline (screening visit) and with non-missing BAb post baseline results. Among the 2104 subjects treated with AGN-151586 across 5 GL studies, analysed in the immunogenicity analysis set ISS Group 3 and Study 2034-201-008, 1 subject (<0.1%) developed BAbs to AGN-151586 post-treatment. This subject received 3 treatments of 700 U AGN-151586 at 6-week interval and was negative for NAbs. Therefore, no subjects developed NAbs post AGN-151586 treatment.

Table 18: Summary of Immunogenicity Assessment Across 3 Analysis Sets

Parameters	ISS Group 1	ISS Group 3	ISS Group 3 + Study 2034-201-008
Studies	M21-500, M21-508 (Pivotal studies; Subjects received AGN-151586 700 U)	M21-500, M21-508, M21-509, and M23-365 (Subjects received AGN-151586 700 U)	2034-201-008, M21-500, M21-508, M21-509, and M23-365 (subjects received AGN-151586 at doses 100 - 750 U)
N1	708	1957	2104
BAb Incidence (treatment emergent) n/N (%)	0/649 (0.0)	1/1884 (<0.1)[a]	1/2028 (<0.1)[b]
NAb Incidence (treatment emergent) n/N (%)	0/649 (0.0)	0/1884 (0.0)	0/2029 (0.0)

N1 = number of subjects that provided samples during the study; n = number of positive incidences; N = number of subjects included in the immunogenicity assessment based on negative and missing samples at Baseline and non-missing samples from post baseline.
a. One subject (M21 509) had pre-existing antibody response and was positive for BAb at baseline and was therefore not included for determining treatment emergent incidence.
b. Two subjects (one subject from each study 2034 201 008 and M21 509) had pre-existing antibody response and were positive for BAb at baseline and were therefore not included for determining treatment emergent incidence.

5.5.7.3. Impact of Immunogenicity on Efficacy and Safety

Immunogenicity impact on efficacy and safety was evaluated by reviewing efficacy data, such as investigator and subject assessed FWS at max frown and at rest over time, as well as safety data such as TEAEs.

The impact on efficacy and safety for the subject with treatment emergent response is as follows: the subject developed treatment emergent BAbs with titer value of 180 at Day 126 (study exit visit) and tested negative for NAbs. The subject achieved peak effect with at least 2 grade improvement from

baseline in the FWS at maximum frown by either the investigator or subject at Day 7 after the first treatment. This subject reported one TEAE of COVID 19 that occurred between the first and second treatment

For the two subjects with pre-existing BAbs, there was no impact of antibody formation on safety and efficacy.

5.5.8. Safety related to drug-drug interactions and other interactions

No studies have been carried out to establish the possibility of clinical interaction with other medicinal products. No drug interactions of clinical significance have been reported.

The effect of administering different botulinum neurotoxin serotypes at the same time is unknown.

Neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

The sequential administration of AGN-151586 and BOTOX were studied in Phase 1 Study M23-365, where AGN-151586 700 U or placebo was administered on Day 1 followed by BOTOX 20 U on Day 30. In this study, treatment with AGN-151586 and BOTOX was well-tolerated. No safety concerns were identified.

5.5.9. Vital signs and laboratory findings

5.5.9.1. Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital signs included systolic and diastolic blood pressure, heart rate, and temperature. In ISS Group 1, there were no clinically meaningful changes in vital signs from Baseline over time during Treatment Cycles 1 and 2.

In ISS Group 1, during Treatment Cycle 1, shifts from Baseline to minimum post-baseline value, shift from Baseline to maximum post-baseline value, and shifts from Baseline to last post-baseline value showed no clinically meaningful differences between the subjects in the AGN-151586 group and those in the placebo group.

In ISS Group 1, during Treatment Cycle 1, no potentially clinically important (PCI) criteria were met for systolic blood pressure, diastolic blood pressure, or increase in heart rate in subjects who received AGN-151586 or placebo. For the rest of the vital sign measurements (decrease in heart rate and increase in temperature), similar incidences of PCI values were observed in subjects who received AGN-151586 compared with subjects who received placebo with all occurring in < 1% of subjects in both treatment groups. During treatment Cycle 2, the number and percentage of subjects with PCI post-baseline vital sign values were low and comparable for subjects who received AGN-151586 regardless of whether they received AGN-151586 or placebo during Treatment Cycle 1.

In ISS Group 3, vital signs included systolic and diastolic blood pressure, heart rate, and temperature. Overall, PCI vital signs values were uncommon with results similar to ISS Group 1; there were no PCI values for systolic blood pressure, diastolic blood pressure, and increase in heart rate. Decrease in heart rate and increase in temperature occurred in 1.0% and 0.2% of subjects, respectively; similar to ISS Group 1 results.

5.5.9.2. Clinical Laboratory Evaluations

In ISS Group 1 (double-blind period), no PCI values were observed for decrease in platelets in subjects who received AGN-151586. For the rest of the complete blood count (CBC) analytes, similar incidence

of PCI values was observed in subjects who received AGN-151586 compared with subjects who received placebo. During Treatment Cycle 1, no PCI criteria were met for decrease in albumin, calcium, glucose or sodium and for increase in alanine aminotransferase, alkaline phosphatase, calcium, cholesterol, creatinine, or sodium. For the rest of the chemistry analytes, similar incidences of PCI values were observed in subjects who received AGN 151586 compared with subjects who received placebo. In addition, all chemistry PCI values occurred with an incidence of ≤ 1% in subjects who received AGN-151586. During Treatment Cycle 2, the incidence of subjects with PCI post-baseline laboratory values were low and comparable for subjects who received AGN-151586 regardless of whether they received AGN-151586 or placebo during Treatment Cycle 1.

In ISS Group 3, similar results were seen for PCI CBC analyte values compared with ISS Group 1, with no PCI values observed for decrease in platelets and a similar incidence of PCI values observed for the rest of the CBC analytes. Similar to ISS Group 1, no PCI criteria were met in ISS Group 3 for decrease in albumin, calcium, glucose, or sodium and for increase in alkaline phosphatase or creatinine. For the rest of the chemistry analytes, similar incidences of PCI values were observed in ISS Group 3 compared with ISS Group 1.

In ISS Group 1, during Treatment Cycle 1, shifts from Baseline to minimum post-baseline value, shifts from Baseline to maximum post-baseline value, and shifts from Baseline to final post-baseline value showed no clinically meaningful differences between the subjects in the AGN-151586 group and those in the placebo group.

In ISS Group 1, the change from Baseline over time of the laboratory analytes revealed no clinically meaningful changes during both Treatment Cycle 1 and Treatment Cycle 2.

5.5.9.3. Electrocardiogram (ECG) Parameters

Electrocardiogram-Associated TEAEs

In ISS Group 1, a similar percentage of subjects who received AGN-151586 700 U had ECG-associated TEAEs (1.1%) compared with subjects who received placebo (0.8%). In ISS Group 3, the frequency of ECG associated TEAEs did not increase with subsequent treatment cycles.

Electrocardiogram QT prolonged

Electrocardiograms were conducted for all subjects enrolled in all 6 studies. In total, across the 6 studies, 8 subjects treated with AGN-151586 had a TEAE of electrocardiogram QT prolonged: 3 subjects from the Phase 3 pivotal studies (Study M21-500: 2 subjects and Study M21-508: 1 subject) and 5 subjects from the open-label safety study (Study M21-509; 3 subjects from AGN-151586 Treatment Cycle 1, 1 from Cycle 2, and 1 from Cycle 3). All subjects were asymptomatic. All AEs were non-serious and considered by the investigator to be mild in severity and not related to study treatment.

In total, 7 asymptomatic subjects discontinued study drug due to the AE of ECG QT prolonged per protocol. Protocol-defined ECG criteria stipulated that if QTcF > 450 msec (males) or > 470 msec (females), the subject was not eligible to receive treatment with study drug.

Incidence

In ISS Group 1 Treatment Cycle 1, the incidence of ECG QT prolonged TEAE was the same for the AGN 151586 and placebo-treated subjects (0.4% of subjects in each group). The same incidence was found in ISS Group 3 in which 0.4% of subjects treated with AGN-151586 (all treatment cycles) had an AE of ECG QT prolonged; 6 subjects in Treatment Cycle 1, 1 subject in Treatment Cycle 2, and 1 subject in Treatment Cycle 3.

Values for Subjects with ECG QT prolonged AE

In ISS Group 1, the absolute change from Baseline in subjects with an AE of ECG QT prolonged was low in AGN-151586 treated subjects: 1 msec, 8 msec, and 21 msec, respectively; the absolute change from Baseline in QTcF was 58 msec in the placebo-treated subject. In all 4 subjects, the QTcF at the time of the AE was < 500 msec.

PCI QTc interval

The PCI QTc interval was defined as:

1. QTcF > 500 msec or increase from Baseline of ≥ 60 msec or
2. QTcB > 500 msec or increase from Baseline of ≥ 60 msec.

In ISS Group 1, during Treatment Cycle 1 (DB Period), no subjects met the PCI QTcF criteria. In Treatment Cycle 2, 1 subject treated with AGN-151586 had a QTcF increase from Baseline of ≥ 60 msec. In ISS Group 3, no subject had QTcF > 500 msec. One subject had a QTcF increase from Baseline of ≥ 60 msec, which is the same subject as in ISS Group 1 noted above.

In ISS Group 1, the same incidence of QTcB PCI was observed in the AGN-151586 group and in the placebo group during Treatment Cycle 1. A similar incidence of QTcB PCI was observed for AGN-151586 treated subjects in Treatment Cycle 2, regardless of whether they received AGN-151586 or placebo during Cycle 1. In ISS Group 3, similar incidences of QTcB PCI were observed as compared with ISS Group 1.

Change from Baseline

On review of the change from Baseline in QTcF and QTcB, there were no clinically meaningful changes over time for ISS Group 1.

Mean Change from Baseline in ECG Parameters

ECG parameters assessed for mean change from Baseline included heart rate, PR interval, QRS duration, QT interval, QTcB interval, QTcF interval, and RR interval. In ISS Group 1, there were no clinically meaningful changes in ECG parameters from Baseline over time during Treatment Cycles 1 and 2.

Assessment of PCI ECG Values

In ISS Group 1, no PCI values were obtained for QRS interval or QTcF in subjects who received AGN-151586 during Treatment Cycle 1. For the rest of the ECG parameters, the number and percentage of subjects with PCI post-baseline ECG values were low and comparable for subjects who received AGN-151586 and for subjects who received placebo. No PCI criteria were met for QRS interval during Treatment Cycle 2. For the rest of the ECG parameters, the number and percentage of subjects with PCI post-baseline ECG values were low and comparable for subjects who received AGN-151586 regardless of whether they received AGN-151586 or placebo during Treatment Cycle 1.

In ISS Group 3, all PCI ECG values occurred with low incidence (< 1% of subjects) in subjects who received AGN 151586 700 U. No subjects who received AGN-151586 700 U experienced a QTcF value > 500 msec and 1 subject experienced an increase in QTcF ≥ 60 msec.

Categorical Assessment of QTcF and QTcB

In ISS Group 1, Treatment Cycle 1, the percentage of subjects with specified QTcF and QTcB post-baseline values (≤ 450 msec, > 450 to ≤ 480 msec, > 480 to ≤ 500 msec, or > 500 msec) were similar for subjects who received AGN-151586 700 U and subjects who received placebo, with the majority of subjects having QTc values ≤ 450 msec.

In ISS Group 1 Treatment Cycle 1, the percentage of subjects with a specified change from Baseline in QTc interval (≤ 30 msec, > 30 to ≤ 60 msec, or > 60 msec) for subjects who received AGN 151586 700 U were similar to those of subjects who received placebo, with the majority of subjects having values ≤ 30 msec.

In ISS Group 1 during Treatment Cycle 2, the percentage of subjects with specified QTc post-baseline values and the percentage of subjects with a specified change from Baseline in QTc interval were similar in AGN-151586 treated subjects, regardless of whether they received AGN-151586 or placebo during Treatment Cycle 1.

Compared to ISS Group 1 results, differences were observed in ISS Group 3 for both absolute QTc and change from baseline values.

5.5.10. Post-marketing experience

Not applicable.

5.5.11. Overall discussion and conclusions on clinical safety

5.5.11.1. Discussion

5.5.11.1.1. Overall assessment of available safety data

Safety data collection and patient exposure

The main analyses of the safety of AGN-151586 in patients with GL were performed using integrated data from 2 completed pivotal phase 3 double-blind, placebo-controlled studies in adult male or female, at least 18 years old (studies M21-500 and M21-508) (ISS Group 1). This pool was used to provide a randomized, controlled assessment of safety of AGN-151586 700 U (i.e. proposed dosage for this marketing application) compared with placebo in placebo-controlled Phase 3 studies in treatment of GL in Treatment Cycle 1 DB Period with a follow-up period of 6 weeks.

The main difference between pivotal studies is the history of treatment with botulinum neurotoxin. In Study M21-508 subjects were totally naïve of any use of botulinum neurotoxin of any serotype for any indication, whereas in Study M21-500 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 prior to Baseline Day 1. Of note, in studies M21-508 and M21-509, no EU subjects were included. However, it is not expected that this difference in terms of prior use of botulinum toxin will increase the risk of adverse reactions.

In addition, all the data from double-blind, placebo-controlled studies were integrated to form ISS Group 2 (studies M21-500, M21-508, M23-365, 2034-201-008, EB001 GL201) to provide a randomized, controlled assessment of safety of AGN-151586 Cycle 1 (< 700 U and ≥ 700 U) compared with placebo in all double-blind studies in treatment of GL with a follow-up of 6 weeks.

In subjects who received at least 1 dose of AGN-151586 700 U during the first treatment period, the retreatment period (i.e. Cycle 2 at D43 and Cycle 3 at D85) were analysed for safety of repeat treatment in ISS Group 3 (studies M21-500 [open-label period], M21-508 [open-label period], M21-509, M23-365).

Overall, the database is adequate for a safety assessment. Pooling strategies and collection of safety data are acceptable.

It should be noted that a Phase 3 study M24-008 and a Phase 1/2 study M24-040 were recently completed (LSLV on 26 Feb 2025 and 03 Apr 2025, resp.). No safety concerns were identified by the applicant.

In ISS Group 1, 709 subjects were treated with at least one dose of AGN-151586 700 U and 628 received two doses of AGN-151586 700 U. Subjects were followed for a median of 42.0 days in Treatment Cycle 1. In ISS Group 2, same median was found in AGN-151586 ≥ 700 U group.

In ISS Group 3, 1960 subjects received at least one dose of AGN-151586 700 U and were followed for a median of 91.0 days (2 to 267 days). 1544 subjects (78.8%) received at least 2 doses of AGN-151586 700 U (at Day 1 and Day 43) and 846 subjects (43.2%) received 3 doses of AGN-151586 700 U (at Day 1, Day 43 and Day 85).

The exposed patient population of over 2000 patients is consistent with the recommendations in ICH E1 (The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-life-threatening conditions).

The duration of exposure falls somewhat short of the ICH E1 requirement. However, taking into account that other botulinum toxin serotype (i.e. type A) has been marketed for over decades, that AGN-151586 has short duration of effect and is intended for occasional use in patients with GL, the duration of exposure and number of cycles is considered sufficient.

Of note, AGN-151586 was also studied in musculoskeletal pain and in facial scar reduction in the US at different dose units used in the AGN-151586 clinical program for GL. No safety concerns were identified by the MAH.

Adverse events

Based on ISS group 1 and ISS group 2 (placebo-controlled studies), overall TEAEs seems similar between the placebo groups and the AGN-151586 700 U group (26% vs. 23%, resp.). However, in ISS Group 2, TEAEs were higher in the AGN-151586 < 700 U group, which could be explained by the lower number of patients in this group compared to the placebo group and the AGN-151586 ≥ 700 U group. The overall TEAE profile of AGN-151586 700 U in Treatment Cycles 2 and 3 (ISS Group 3) was consistent with the overall TEAE profile in AGN-151586 700 U Treatment Cycle 1. Compared to placebo group, TEAEs leading to study drug discontinuation were higher in patients who received AGN-151586 700 U (n=8).

The most frequently reported TEAEs (≥ 1%) in all the ISS groups among subjects who received AGN-151586 ≥ 700 U were Headache, COVID-19, Nasopharyngitis and Injection site pain. In ISS group 2, the incidence of TEAE Injection site pain was higher in the AGN-151586 < 700 U group (n=18, 11.8% in AGN-151586 < 700 U group vs. 3.9% in placebo group and 2.3% in AGN-151586 ≥ 700 U group). This imbalance could come from one of the sites in study 2034-201-008. As reported in the CSR of this study, of the 30 injection site pain events reported (n=18 with AGN-151586 < 700 U), 27 (90%) were reported by one investigational site (n=15 with AGN-151586 < 700 U). No dose response was observed with the incidence of injection site pain in the AGN-151586 groups across cohorts (100 U, 250 U, 400 U, 600 U and 750 U). The incidence of injection site pain TEAEs reported by this site was similar for placebo and AGN-151586 treated subjects.

In ISS group 1, the percentage of subjects experiencing at least one severe TEAE was similar across treatment groups (0.8% in placebo groups vs. 0.6% in AGN-151586 700 U group). There were 4 subjects who received AGN-151586 700 U that experienced severe TEAEs (Cholecystitis, Appendicitis, Pneumonia, Hypocalcaemia). All severe TEAEs were serious and none were treatment-related. Three subjects had severe (and serious) TEAEs that led to study drug discontinuation (see Section 4.5). In ISS group 2, 2 severe (non-serious) TEAEs (Injection site pain) that were

considered related to study treatment were reported in 2 subjects who received AGN-151586 ≥ 700 U. Other severe TEAEs (all serious, not related to study treatment) that were reported in subjects who received AGN-151586 ≥ 700 U were the same as described in ISS group 1 above. In ISS group 3, a similar incidence of severe TEAEs was reported in the AGN 151586 treatment cycles and < 1% of subjects reported severe TEAEs with AGN-151586 700 U (0.4% during Cycle 1, 0.2% during Cycle 2, 0.4% during Cycle 3). No severe TEAEs were assessed by the investigator as treatment-related across all treatment cycles.

Overall, treatment-related TEAEs were mainly localised and were similarly related to study drug and study procedure. Headache and Injection site pain were the most common treatment-related TEAEs (3.4% and 1.7% in ISS group 1, resp.). The incidence of Headache trends to decrease with repeated injections whereas Injection site pain remains stable. These TEAEs seems to be more related to the injection procedure rather than the study drug and the incidence was higher in the placebo group for both TEAEs. Treatment-related TEAE Brow ptosis was observed in 3 subjects (4 TEAEs). One subject had Brow ptosis during Cycle 1 (study-drug related) and Cycle 2 (study-drug and study-procedure related) of AGN-151586 and 2 subjects had Brow ptosis during Cycle 2 only (study-drug and study-procedure related). The time to onset were between 2 and 3 days for these TEAEs (4) and lasted up to 7 days for 3 TEAEs. One subject has ongoing Brow ptosis at the end of study date which suggest that the TEAE lasted > 40 days. However, this event was noted to have resolved with a duration of no more than 13 days. All the treatment-related TEAEs were mild in severity. In study M24-040, 2 treatment-related TEAEs were reported in the same subject who received AGN-151586 (Eyelid ptosis, Mephisto sign).

In ISS group 1 and ISS group 2, the incidence of serious TEAEs was similar between AGN-151586 groups and placebo groups (0.6% in the ISS group 1 AGN-151586 700 U group). Across all studies (n=6), 21 serious TEAEs were reported in 15 subjects. Among them, 3 subjects reported a serious TEAEs that led to study drug discontinuation ("worsening of hypocalcaemia", "left hip prosthetic joint infection", "acute cholecystitis"), including 1 patient that had life-threatening TEAEs ("acute cholecystitis", "distended bile duct"). The subjects recovered from these TEAEs. There were no signs of hypocalcaemia or worsening of hypocalcaemia in the safety data and for the TEAE related to hip prosthetic infection, the most likely cause seems to be a medical history for Klippel-Trenaunay syndrome and a prior left hip surgery. One additional patient had a serious TEAE Cholecystitis and another patient had serious TEAEs Cholelithiasis ("biliary sludge"), Obstructive pancreatitis ("acute gallstone pancreatitis") and Hypertransaminasaemia ("transaminitis"). The subjects with serious hepatobiliary disorder events possessed risk factors for such an event. Two of the subjects had a contributing medical history and/or family history, the remaining subject had the risk factor of obesity. All of the hepatobiliary serious AEs were assessed as unrelated to study treatment.

There was no treatment-related serious TEAE and no deaths were reported in the AGN-151586 GL clinical development program.

TEAEs of special interest

Except for the high incidence of the TEAE Injection site pain reported in the AGN-151586 < 700 U (ISS group 2) which could be explained by an imbalance in one site (see above), other injection site reactions TEAEs were similar between groups. Although low, incidence of TEAEs Injection site bruising, Injection site haematoma and Injection site haemorrhage were slightly higher in AGN-151586 groups compared to placebo groups in ISS group 1 (resp. 0.7%, 0.3% and 0.6% vs. 0.4%, 0.0% and 0.4%) and ISS group 2 (resp. 0.6%, 0.3% and 0.5% vs. 0.3%, 0.0% and 0.3%). Although treatment-related TEAEs Injection site bruising, Injection site haematoma and Injection site haemorrhage are higher in AGN-151586 groups than placebo groups in ISS group 1 (resp. 0.7%, 0.3% and 0.6% vs. 0.4%, 0.0% and 0.4%) and ISS group 2 (resp. 0.6%, 0.3% and 0.5% vs.

0.3%, 0.0% and 0.3%), the absolute risk differences of these TEAEs is low. These events were infrequent and non-serious, they were generally mild in severity and persisted for a few days. Therefore, they are unlikely to affect the benefits of the product for most patients. A warning in Section 4.4 of the SmPC is included.

Across all studies, there were 14 PDSOT TEAE in the AGN-151586 700 U groups (13 subjects). Reported PDSOT TEAEs consisted of vision blurred (4 events), eyelid ptosis (3), dyspnoea (3), dry mouth (2), dysphagia (1), and constipation (1). There was no serious PDSOT TEAE (all mild severity). One PDSOT TEAE Eyelid ptosis led to study drug discontinuation (see below). PDSOT TEAEs related to study treatment are discussed below. One PDSOT TEAE Vision blurred was reported as treatment-related in a subject in placebo group. Two PDSOT TEAEs Dry mouth (mild severity) were related to AGN-151586 and occurred in 2 patients. According to the narratives, the events occurred 1 day and 4 days after the second study drug treatment cycle and lasted 15 days and 3 days. In both cases, only TEAEs of dry mouth were reported and it was not likely to be distant spread of toxin symptoms (intermittent nature was reported in one case and COVID-19 infection was reported later in the other case). Another PDSOT TEAE related to AGN-151586 Eyelid ptosis occurred in 2 patients. Eyelid ptosis is added to the list of adverse reactions in section 4.8 of the SmPC. The risks of spread of toxin is mentioned in sections 4.4 and 4.9 of the SmPC.

Across all studies, 19 neurological assessment-associated TEAEs were reported in 19 patients. There was no serious neurological assessment-associated TEAEs. Among the 19 neurological assessment-associated TEAEs, 4 were related to AGN-151586 700 U: Eyelid ptosis (1), Brow ptosis (2), Visual acuity reduced (1). The patient who developed visual acuity TEAE reduced had a headache ongoing or recently resolved at the time of the eye examination and the change in visual acuity was probably minimal. Brow ptosis is added to the list of adverse reactions in section 4.8 of the SmPC which is acceptable.

It is known that patients with neuromuscular junction disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise with the use of botulinum toxins. Subjects with history of Myasthenia gravis, Lambert-Eaton syndrome, or amyotrophic lateral sclerosis (ALS) were not included in the pivotal studies and Myasthenia gravis and Lambert-Eaton syndrome are contraindicated with botulinum toxin type A. Myasthenia gravis and Lambert-Eaton syndrome are mentioned as contraindication in section 4.3 of the SmPC. Botulinum toxin has been used to treat various disorders of ALS including sialorrhea, spasticity, and dysphagia. Therefore, a warning regarding increased risk of clinically significant systemic effects in patients with ALS is mentioned in the SmPC.

Across all studies, 19 subjects had a TEAE (n=19) that led to study drug discontinuation. All the subjects were treated with AGN-151586 700 U (no discontinuation in placebo groups or other AGN-151586 doses). None of the TEAEs that led to study treatment discontinuation was assessed by the investigator as treatment-related. One TEAE Eyelid ptosis (worsening) that led to study treatment discontinuation was coded as a Possible Distant Spread of Toxin (PDSOT) event. It is agreed that this case is confounded by the subject's underlying eyelid ptosis and conjunctival cyst recurrence. However, given the time to onset (7 days after the injection) and location of injections into the GL, local spread of toxin cannot be ruled out. Another TEAE Hemianesthesia ("Hemianesthesia of left side of body from arm to feet") that led to study treatment discontinuation was reported under the SOC Nervous system disorders. This TEAE was non-serious and the patient had a medical history of multiple sclerosis (the subject reported that his multiple sclerosis flare would manifest with motor symptoms in the right lower extremity/problems with gait and a tremor). According to the investigator, the event could be a coincidental multiple sclerosis flare (unrelated to the injections) or a result of a poor historian with possible cognitive impairment. Other TEAEs leading to study drug discontinuation were: Hypocalcaemia, Pneumonia, Anaemia, Electrocardiogram T wave amplitude

decreased (asymptomatic), Supraventricular tachycardia (asymptomatic), Bundle branch block (asymptomatic), Device related infection, Cholecystitis acute.

Safety in special populations

In ISS group 1, gender (610 females vs. 99 males), race (621 white vs. 88 non-white) and age (661 < 65 years old vs. 48 ⩾ 65 years old) subgroups were not equally distributed in the AGN-151586 groups. Although, the safety profile is not expected to differ among gender and race subgroups, patients ⩾ 65 years old could have more or serious adverse effects due to their skin and/or concomitant medications (e.g. anti-coagulants). However, among AGN-151586 treated subjects, a lower percentage of subjects ⩾ 65 years old reported at least 1 TEAE compared with subjects < 65 years old (12.5% vs. 24.2%, resp.) and no treatment-related TEAE was reported in subjects ⩾ 65 years old treated with AGN-151586 700 U in the pivotal studies.

In ISS group 1, in subjects with a history of prior toxin use, TEAEs were slightly higher in the placebo group compared to the AGN-151586 700 U group. In subjects without a history of prior toxin use the distribution was similar between the groups except for TEAEs leading to study drug discontinuation which was higher in the AGN-151586 700 U group (n=7) (see above). In general, in both groups, there was more TEAEs in subjects with a history of prior toxin use (27.5% in AGN-151586 700 U group) compared to subjects without a history of prior toxin use (22.4% in AGN-151586 700 U group).

Overall, headache and injection site pain were the most frequently reported treatment-related TEAEs in the different groups of populations.

Use in pregnancy and lactation

AGN-151586 for GL is not recommended in pregnancy and lactation as data on the developmental risk associated with use of AGN-151586 in these groups are limited at this stage of development. A total of three pregnancies were reported during development. Two of these pregnancies resulted in live births with no congenital anomalies or reported birth defects. For the third pregnancy, no outcome information was available.

Drug-drug interactions and other interactions

Administration of AGN-151586 700 U followed by a 30-days post-injection BOTOX 20 U (botulinum toxin type A) was studied in Phase 1 Study M23-365. In this study, during the second treatment period which consisted of an injection of BOTOX 20 U after the first injection of placebo (placebo/BOTOX group) or AGN-151586 700 U (AGN-151586/BOTOX group), the incidence of TEAEs were similar between the placebo/BOTOX group (n=13/39, 33.3%) and the AGN-151586/BOTOX group (n=15/46, 32.6%). There were no cases of serious or severe or treatment-related TEAEs in the AGN-151586/BOTOX group. However, these data are based on a low number of subjects in each group (85 subjects at second treatment period in any BOTOX groups). Taking into account the mechanism of action of botulinum toxin type E, it is not expected that the safety profile will differ from the botulinum toxin type A. The safety related to drug interactions can be further characterise in the future PSURs via routine pharmacovigilance.

Other expected drug-drug interactions are mentioned in the proposed SmPC (muscle relaxants, aminoglycosides and other agents interfering with neuromuscular transmission, and anticholinergic drugs).

Laboratory and other findings

In ISS group 1, during treatment cycle 1 and treatment cycle 2, similar incidences of potentially clinically important (PCI) laboratory values were observed in subjects who received AGN-151586 compared to subjects who received placebo, except for neutrophils count decreased which showed higher incidence of PCI laboratory values in the AGN-151586 group (4.1% during cycle 1, 3.0% during cycle 2) compared to placebo group (2.1% during cycle 1, 1.8% during cycle 2). In ISS group 3, the incidence of neutrophils count decreased were also high (4.7%). However, no increase in incidence was observed following the switch from placebo to AGN-151586 in the ISS Group 1 cycle 2 (2.1% in the ISS Group 1 cycle 1 vs 1.8% in the cycle 2). The slight imbalance between groups persisted across cycles irrespective of treatment exposure. In addition, a similar incidence in the groups (<1.0% difference) was observed at all timepoints tested regarding the percentage of subjects who went from normal baseline to low post-baseline, and the incidence of subjects who went from high baseline to low minimum post-baseline value was essentially the same for the placebo and AGN-151586 treatment groups.

In ISS group 1, proportion of subjects with potentially clinically important vital sign and physical findings were similar between placebo group and AGN-151586 group and consistent with ISS group 3. In ISS Group 1, a similar percentage of subjects who received AGN-151586 700 U had ECG-associated TEAEs (1.1%) compared with subjects who received placebo (0.8%). In ISS Group 3, the frequency of ECG associated TEAEs were consistent with ISS group 1 and decreased with subsequent treatment cycles. Across all studies, 8 subjects had a (asymptomatic) TEAE of Electrocardiogram QT prolonged and 7 discontinued study drug as per protocol. All AEs were non-serious, and considered by the investigator to be mild in severity and not related to study treatment. Differences in ISS Group 3 compared to ISS Group 1 had been observed for both absolute QTc and change from baseline values. However, it is agreed that it could be attributed to differential follow-up and assessments for subjects in ISS Group 3.

Immunogenicity was evaluated in two pivotal Phase 3 studies M21-500 and M21 508, in Phase 2b Study 2034-201-008, in Phase 1 Study M23-365, and in the open-label safety Study M21-509. In total, it has been evaluated in approximately 2000 subjects and a low incidence (1 patient, < 0.1%) of treatment-emergent binding antibody formation was observed. No safety impact was observed related to antibody formation. No hypersensitivity reactions or immune-related events were observed in the one subject who developed antibodies post AGN-151586 treatment. No subjects developed treatment emergent neutralizing antibodies post AGN-151586 treatment. In study M23-365 in which AGN-151586 or placebo was administered at Day 1 followed by botulinum toxin type A (BOTOX/VISTABEL) at Day 30, no subject developed binding or neutralising antibodies to AGN-151586 or botulinum toxin type A. Due to low incidence of antibody formation, no clear relationship was observed between dose, repeat treatment, or prior toxin use and antibody formation. Cross reactivity between botulinum toxin type E and type A (subtype A1) was studied in *in silico* analysis. Overall, botulinum toxin type E and botulinum toxin type A have low similitude in terms of sequence homology, and only two contiguous stretches of ≥ 9 amino acids were found in the botulinum toxin type E heavy chain. Thus, risks of cross reactions between the two toxins seems low. Immunogenicity data are correctly reflected in Section 5.1 of the SmPC.

5.5.11.1.2. Adverse drug reactions (ADRs) in the SmPC

The adverse drug reactions reflected in the SmPC section 4.8 are as follows:

Table 19: ADRs proposed for inclusion in the SmPC by the rapporteur

System Organ Class	Adverse Drug Reaction	Frequency
Eye disorders	Eyelid ptosis	Uncommon
Skin and subcutaneous tissue disorders	Brow ptosis	Uncommon
Musculoskeletal and connective tissue disorders	Mephisto sign	Rare

These effects are widely acknowledged as ADRs based on the mechanism of action of botulinum toxins and are listed in the SmPCs of some botulinum toxins as ADRs.

This is acceptable.

5.5.11.2. Conclusions on clinical safety

The overall size of the safety database is considered adequate and in line with the ICH E1 recommendations.

In the two pivotal Phase 3 studies, the incidence of TEAE was lower in the AGN-151586 700 U group (23.4%) compared to the placebo group (26.5%). Among the subjects who received AGN-151586 700 U, 7.6% had at least one TEAE related to AGN-151586 700 U (similarly related to study procedure and study drug). The most frequently reported treatment-related TEAEs were Headache and Injection site pain. In total (all studies with AGN-151586 700 U), 19 subjects (1.0%) discontinued treatment with AGN-151586 700 U due to TEAEs (0 subject in the placebo group). None of the TEAEs leading to study treatment discontinuation was treatment-related. No serious TEAE were related to AGN-151586.

Among subjects treated with AGN-151589 700 U, a total of 14 PDSOT TEAEs were reported (all mild in severity): vision blurred (4), eyelid ptosis (3), dyspnoea (3), dry mouth (2), dysphagia (1), and constipation (1). None of them was considered distant spread of toxin. The following PDSOT TEAEs were considered as treatment-related: eyelid ptosis and dry mouth. According to the narratives of dry mouth's cases, the events occurred 1 day and 4 days after the second study drug treatment cycle and lasted 15 days and 3 days. In both cases, only TEAEs of dry mouth were reported and it was not likely to be distant spread of toxin symptoms (intermittent nature was reported in one case and COVID-19 infection was reported later in the other case).

It is agreed to list Eyelid ptosis, Brow ptosis and Mephisto sign as adverse reactions in the SmPC section 4.8.

There was no change observed in the overall safety profile with repeat treatments (up to 3) when compared with a single treatment. Immunogenicity of AGN-151586 is expected to be low but could theoretically occur with repeated treatment (see Section 5.1 of the SmPC).

6. Risk management plan

6.1. Safety specification

6.1.1. Safety concerns

The summary of safety concerns in the RMP is as follows:

Table 20. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

6.2. Pharmacovigilance plan

6.2.1.1. Routine pharmacovigilance activities

There are no routine pharmacovigilance activities beyond adverse event reporting and signal detection.

6.2.1.2. Additional pharmacovigilance activities

There are no additional pharmacovigilance activities.

6.3. Plans for post-authorisation efficacy studies

There are no post-authorisation efficacy studies.

6.4. Risk minimisation measures

6.4.1.1. Routine risk minimisation measures

Not applicable.

6.4.1.2. Additional risk minimisation measures

Not applicable.

6.5. RMP summary and RMP annexes overall conclusion

The RMP Part VI and the RMP Annexes are considered acceptable.

6.6. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 1.0 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points.

8. Product information

8.1.1. User consultation

8.1.1.1. Conclusion from the checklist for the review of user consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Boey (trenibotulinumtoxinE) is included in the additional monitoring list since it is a new biological active substance.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

Glabellar Lines (GL) are furrows in the glabellar area of the face and result from the repetitive functional action of the underlying facial musculature during animation. The development of facial lines (such as GL) is an age-related change of the face that occurs because of the repetitive muscle contractions that are associated with common facial expressions. Thus, these facial lines can be observed with contraction (dynamic rhytides) or in more severe cases in repose (static rhytides). The appearance of these facial lines can lead to a miscommunication of an emotional state of anger, anxiety, disapproval, or sadness causing distress and affecting social interactions. The psychosocial impact of increasing severity in the appearance of facial lines has been associated with a negative effect on self-esteem, a decrease in perceived attractiveness and a diminished sense of well-being.

Initially, the claimed indication was "*the temporary improvement in the appearance of moderate to severe lines between the eyebrows seen at maximum frown (glabellar lines) when the severity has an important psychological impact in adult patients as*

- *an intermittent treatment and/or*
- *a trial option before initiating BOTOX."*

The proposed indication was further updated in the view of the available data (see below)

9.1.2. Available therapies and unmet medical need

There are several treatments currently available to improve the appearance of GL. In addition to botulinum neurotoxin type A injections (eg Vistabel, Botox, Nuceiva...), options include dermal fillers, resurfacing, chemical peels, and energy-based treatments (e.g., ablative laser).

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to the respective sections of this document.

Placebo-controlled pivotal studies: M21-500 (US and Europe) and M21-508 (US and Canada) studies

Both phase 3 studies were 12-week, multicentre, double-blind, placebo-controlled, studies with similar design, participants, inclusion and exclusion criteria.

Subjects were 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 at the Screening and Baseline Day 1 visits. The double-blind Period (Day 1 to Day 43) was a randomized, placebo-controlled, single-treatment design and the open-label Period (Day 43 to Study exit) consisted of retreatment with one dose of AGN-151586 700 U for subjects who met retreatment criteria.

Psychological impact as claimed in the indication labelling, was assessed in main studies based on the results of FLO-11 questionnaire which score should have to be score ≤ 50. This is acceptable.

Treatment administration in GL used a standard method with injections of 140 U in 5 sites of the forehead i.e. a total dose of 700 U. Over the duration of the study, a maximum of 2 study treatments could be administered to subjects.

A dose clarification was provided as the higher dose tested was 750 U in the phase 2b study 2034-201-008 while the dose used in both phase 3 studies was 700 U. The equivalence of 750 U used in phase 2 study with 700 U was provided in Quality part and is acceptable.

Results

Most subjects completed the study and the most common reason for discontinuation was withdrawal by subject.

The demographics were generally balanced across treatment groups. In the ITT Population, most subjects were female, and the population was primarily White.

For the EU regulatory agency, the co-primary efficacy endpoints were the achievement of ≥ 2-grade improvement of GL severity at maximum frown from Baseline at Day 7 according to (1) subject's self-assessment using FWS and (2) investigator's assessment using FWS, among subjects who had a baseline FLO-11 total transformed score ≤ 50. This is in line with the label of the claimed indication to ensure that treated subjects have a psychosocial impact. This was measured by the FLO-11 which is an 11-item validated PRO measure that assesses appearance-related psychological impacts of GL from the subject perspective: "*bothered, looking older, feeling unattractive, looking less attractive, skin not looking smooth, looking tired, looking stressed, looking angry, and feeling good about facial appearance*".

Co-primary endpoints results are presented in a subgroup of ITT with FLO-11 total transformed score ≤ 50 at baseline to reflect the claimed indication which mentions this subpopulation. US endpoints are presented in ITT population only.

The pooled ITT results of EU co-primary endpoints were provided.

	M21-500 DB period In subgroup of FLO ≤ 50	**M21-508** DB period In subgroup of FLO ≤ 50	**Pooled data (=ITT)**	**Pooled data** In subgroup of FLO ≤ 50
AGN-151586 vs Placebo	N=368 vs N=130	N=164 vs N=63	N=709 vs N=238	N=532 vs N=193
EU co-primary endpoints: Achievement ≥ 2-Grade improvement on investigator and subject FWS assessments of GL severity at maximum frown from Baseline at Day 7 assessed by investigator assessed by subject	 72.1% vs 0.8% 60.2% vs 0.8%	 73.6% vs 0.0% 67.9% vs 0.0%	 -	 72.6% vs 0.5% 63.1% vs 0.5%
EU key secondary endpoint: FLO-11 Total Transformed Score ≥ 20-Point Improvement from Baseline at Day 7	66.3% vs 8.8%	62.3% vs 7.9%	-	65.2% vs 8.3%
EU secondary endpoint: Time to first ≥ 1-grade improvement from Baseline on FWS at maximum frown (mean days) assessed by investigator assessed by subject	 4.2 vs 29.7 5.2 vs 33.5	 3.1 vs 31.1 3.3 vs 31.9	 3.7 vs 30.2 4.4 vs 33.3	 3.8 vs 30.1 4.6 vs 33.0

Descriptive results showed compared to < 65 years, a lower response in ≥ 65 years: response's rate assessed by subject: 36.8% vs 65.1% and assessed by investigator 57.9% vs 743.7%.

The results for the co-primary endpoints in ITT population for ≥ 65 years and < 65 years subgroups were provided.

During the double-blind period, the US key secondary endpoint: FWS at Maximum Frown According to Investigator and Subject Assessment Over Time confirmed the kinetics of the effect with an early onset from 8 hours after injections, a peak effect at Day 7 and immediate decrease of effect observed at Day 14 and return to baseline at Day 21.

For other US FDA key secondary endpoints of a Grade 0 or 1 (none or mild) and ≥ 2-grade improvement from Baseline on FWS at maximum frown, the AGN-151586 group showed higher improvements versus placebo over time as early as Hour 8 through Day 21.

In the open-label period, the results showed that the effect of AGN-151586 was similar at the 1st or the 2nd cycle of injections in GL at Day 7 and Day 43. The response rate of placebo group after being injected was null indicating the absence of residual effect of 1st AGN-151586 injections.

Overall, the effect of AGN-151586 starts 8h after injections in GL with a peak at Day 7 and lasts not more than 21 days. It is to note that from Day 2 to Day 7, the response rate is around 60 to 70% and after Day 7, an immediate decrease of the effect without any plateau is observed with a return to baseline state. This effect is reproducible with further injections in GL when repeated at Day 43.

Therefore, the rationale of a 42 day-interval between two injections of AGN-151586 was not provided.

It is understood that the applicant prefers not to mention the 6-week interval as a minimal time between 2 injections of toxin E but letting the physician assess the severity of GL moderate to severe to repeat toxin E administration. However, to give a clear picture of data assessed for this Marketing Authorisation, section 4.2 of the SmPC specifies that '*Retreatment with Boey at intervals more frequent than every 6 weeks has not been evaluated and should be determined by physician.'*

The response rate **at rest** in the group of subjects corresponding to the EU co-primary endpoints with psychosocial impact is also of interest as moderate to severe GL at rest are more severe than at maximum frown. The applicant provided the number (%) of subjects with achievement of Grade 0 or 1 (None or Mild) when FWS at rest. It is accepted to mention them in section 5.1 of the SmPC.

The efficacy of a 2nd administration of AGN-151586 was collected during open period: the response rates were similar to those after 1 cycle of injections with almost no difference from AGN-151586 previously treated arm or from previously placebo-treated arm, whether assessed by subject or investigator.

Study 509

This open-label study is considered supportive for efficacy assessment as the objective of this study was to evaluate the safety of repeated sequential administrations at Day 43 and Day 85. The rationale of repeating AGN-151586 every 6 weeks should be provided.

There were no primary or efficacy endpoints analysed in the study. Nevertheless, the rate of responses after repeated administrations with ≥2 grade improvement from baseline were collected Day 7 as assessed by the investigator and the subject showing a response rate from 1st cycle of injections to 3rd cycle, assessed by investigator (71.0%, 75.0%, 73.7%), by subject (56.5%, 70.6%, 62.9%) respectively.

The overall efficacy profiles were similar across all 3 treatment cycles. However, the repeated administration with an interval of 6-week between injections in GL is not considered being part of the indication since an intermittent treatment is claimed which supposes an occasional use of AGN-151586.

9.3. Favourable effects

Both pivotal phase 3 studies showed that AGN-151586 was superior to placebo in terms of improvement of appearance of Glabellar Lines (GL) using FWS score at Day 7. This was expected due the mechanism of action of this new active trenibotulinumtoxinE.

The results are presented in the subgroup of subjects with a psychological impact (with FLO ≤ 50 at baseline) which is in line with the claimed indication. The co-primary endpoints results from pooled data showed a response rate as assessed by investigator of 72.1% vs 0.8% [difference 71.4%, (95%CI 66.5,76.2)] and by subject [61.0% vs 0.8% [difference 60.2% (95%CI 54.9, 65.4)].

In subgroups, descriptive results were consistent with global results.

A 2nd cycle of injections was possible in these studies at Day 43 and the response rates were similar.

Through secondary endpoints, the patient-reported outcomes showed an emotional and appearance-related impact with more than 20-point change from baseline (FLO-11 questionnaire) and a satisfaction of the subject (FLSQ questionnaire).

At all timepoints, the proportion of subjects who were *Mostly satisfied* or *Very satisfied* with the appearance of their GL based on the FLSQ follow-up version Item 5 (overall satisfaction) was greater for the trenibotulinumtoxinE group compared to the placebo group during the double-blind period.

Another phase 3 open-label study evaluated repeated administration every 6 weeks with up to 3 cycles of injections in GL. Similar response rates between cycles were observed without impact of previous administration in terms of efficacy but the rationale of repeating the injections of AGN-151586 every 6 weeks was not provided.

TrenibotulinumtoxinE showed an early onset of effect compared to botulinum toxin A. An effect was observed 8 hours after the injections in GL, the peak effect was attained rapidly at Day 7 then decreased to return to baseline state at Day 21. The duration of the effect of the toxin E is short compared to toxin A, 3 weeks vs 3-4 months. This quick elimination could be a positive in case of undesirable effect.

9.3.1. Uncertainties and limitations about favourable effects

As the effect of trenibotulinumtoxinE is short with the higher improvement of GL between Day 2 to Day 7, the clinical relevance of the treatment effect remains uncertain in terms of target population, psychological state of treated subjects, frequency of administration.

The value of obtaining an effect that disappears after a week is not clearly understood. The applicant has identified two situations, as initially proposed in the claimed indication: *intermittent treatment* and/or as a *trial option before initiating Botox*. However these situations are not supported by clinical studies and with the level of evidence required for a marketing authorisation.

It is noted that the botulinum toxin A indications are harmonised (+/- restriction of indication in ≥ 65 years) in Europe through centralised or MRP procedures with the following wording for Glabellar Lines: "*temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows seen at maximum frown (glabellar lines) when the severity of the facial lines has an important psychological impact."*

It is therefore agreed for the Boey indication to be as follows: *"Boey is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines (vertical lines between the eyebrows) seen at maximum frown,* when *these have an important psychological impact in adult patients. (see section 5.1)."*

In addition, the statement *"Due to its early onset of effect and short duration, Boey should be used occasionally ."* is added in section 4.2 of the SmPC.

In order to clearly reflect the available assessed clinical data, the following statements are also added in section 4.2 of the SmPC:

"*Retreatment of Boey at intervals more frequent than every 6 weeks has not been evaluated and should be determined by physician.*
The efficacy and safety of more than 3 consecutive injections of Boey beyond 18 weeks have not been evaluated.
Administration of another botulinum toxin A less than 30 days after Boey has not been evaluated."

9.4. Unfavourable effects

The safety assessment is based on 947 subjects in the pivotal studies (709 subjects received AGN-151586 700 U and 238 subjects received placebo in Treatment Cycle 1). Subjects were followed for a median of 42.0 days in Treatment Cycle 1. When pooling studies evaluating retreatment, 1960 subjects received at least one dose of AGN-151586 700 U and were followed for a median of 91.0 days (2 to 267 days), 1544 subjects (78.8%) received at least 2 doses of AGN-151586 700 U (at Day 1 and

Day 43) and 846 subjects (43.2%) received 3 doses of AGN-151586 700 U (at Day 1, Day 43 and Day 85).

In the pivotal studies, 26% of subjects reported at least one TEAE in the placebo groups and 23% in the AGN-151586 700 U group. Treatment-related TEAEs were mainly localised and were similarly related to study drug and study procedure. Headache and Injection site pain were the most common treatment-related TEAEs (3.4% and 1.7% in ISS group 1, resp.). Their incidence was higher in placebo groups.

The majority of **injection site reaction** TEAEs were considered to be related to study treatment (study drug and/or study drug administration procedure) by the investigator. Treatment-related TEAEs Injection site bruising, Injection site haematoma and Injection site haemorrhage were slightly higher in AGN-151586 groups than placebo groups in ISS group 1 (resp. 0.7%, 0.3% and 0.6% vs. 0.4%, 0.0% and 0.4%) and ISS group 2 (resp. 0.6%, 0.3% and 0.5% vs. 0.3%, 0.0% and 0.3%). These risks are correctly reflected in Section 4.4 of the SmPC.

Possible distant spread of toxin (PDSOT) can be considered as a class effect of botulinum toxins. Across all studies, 14 PDSOT TEAEs were reported and the Applicant considered these events to be local rather than distant. The following PDSOT TEAEs were considered as treatment-related in AGN-151586 by the investigator: Eyelid ptosis and Dry mouth (see clinical safety discussion for details of dry mouth TEAE). Onset day of these treatment-related PDSOT TEAEs since most recent AGN-151586 treatment ranged from Day 2 to Day 7, with duration ranging from 2 to 15 days. Although considered as local event, 4 TEAEs Brow ptosis were reported and considered as treatment related by the investigator. The time to onset for Brow ptosis were between 2 and 3 days for all the TEAEs and lasted up to 7 days for 3 TEAEs. One subject has ongoing Brow ptosis at the end of study date which suggest that the TEAE lasted > 40 days. Treatment-related TEAEs Mephisto sign which is a known ADRs in other botulinum toxins (type A) were also observed with AGN-151586 700 U. Eyelid ptosis, brow ptosis and Mephisto sign are mentioned as ADR in the SmPC. A warning regarding possible distant spread of toxin is mentioned in the Section 4.4 of the SmPC

Among the 19 **neurological** assessment-associated TEAEs, 4 were related to AGN-151586 700 U: Eyelid ptosis (1), Brow ptosis (2), Visual acuity reduced (1). The onset day of these treatment-related events since the most recent AGN-151586 treatment ranged from Day 3 to Day 8, with duration ranging from 6 days to ongoing at time of study end. A warning is mentioned in the sections 4.4 and 4.7 of the SmPC.

No serious treatment-related was reported in AGN-151586 groups.

9.4.1. Uncertainties and limitations about unfavourable effects

The duration of exposure falls somewhat short of the ICH E1 requirement. Efficacy and safety of repeat injections beyond 18 weeks (3 treatment cycles) has not been evaluated. However, taking into account that other botulinum toxin serotype (i.e. type A) has been marketed for over decades, that AGN-151586 has short duration of effect and is intended for occasional use in patients with GL, the duration of exposure and number of cycles is considered sufficient. The number of subjects exposed to AGN-151586 is also considered sufficient (947 subjects in the pivotal subjects and 846 subjects who received 3 doses).

Administration of AGN-151586 700 U with another botulinum toxin at the same time has not been investigated and could increase risks of overdose or spread of toxin. Therefore, this should be prohibited. Administration of AGN-151586 700 U followed by a 30-days post-injection Botox 20 U (botulinum toxin type A) was studied in a phase 1 study. Although safety data from this study were reassuring, they are based on a low number of subjects in each group (85 subjects at second

treatment period in any Botox groups). However, taking into account the mechanism of action of botulinum toxin type E, it is not expected that injecting a botulinum toxin type A after the injection of a botulinum toxin type E will increase the risks.

Few subjects aged ⩾ 65 years were included in the studies (n=48 subjects treated with AGN-151586 700 U in pivotal studies). Patients ≥ 65 years old could have more or serious adverse effects due to their skin and/or concomitant medications (e.g. anti-coagulants). However, among AGN-151586 treated subjects, a lower percentage of subjects ≥ 65 years old reported at least 1 TEAE compared with subjects < 65 years old (12.5% vs. 24.2%, resp.) and no treatment-related TEAE was reported in subjects ⩾ 65 years old treated with AGN-151586 700 U in the pivotal studies. It should be noted that the claimed indication for Boey does not limit the use of trenibotulinumtoxinE to patients under 65 years of age. The CHMP considers this acceptable based on the available data.

Immunogenicity has been evaluated in approximately 2000 subjects and a low incidence (1 patient, < 0.1%) of treatment-emergent binding antibody formation was observed. No safety impact was observed related to antibody formation. No hypersensitivity reactions or immune-related events were observed in the one subject who developed antibodies post AGN-151586 treatment. No subjects developed treatment emergent neutralizing antibodies post AGN-151586 treatment. However, taking into account that it cannot be ruled out that some patients will be treated for more than 3 treatment cycles (the maximum number of cycles studied in this application), it cannot be excluded that a risk of antibody formation arise with multiple injections. Immunogenicity data is mentioned in the Section 5.1 of the SmPC.

Injections of AGN-151586 has not been studies in subjects with pre-existing neuromuscular disorders (i.e. Myasthenia gravis, Lambert-Eaton syndrome, or amyotrophic lateral sclerosis) and it is known that patients with neuromuscular junction disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise with the use of botulinum toxins. Myasthenia gravis and Lambert-Eaton syndrome are contraindicated with botulinum toxin type A. Therefore, generalised disorders of muscle activity (e.g. myasthenia gravis, Eaton Lambert Syndrome) are considered as a contraindication in the SmPC and ALS is mentioned in Section 4.4 of the SmPC. The risks related to neuromuscular disorders cannot be excluded with botulinum toxin type E, thus "Unmasking of or exacerbation of neuromuscular disorders" is considered as an important potential risk in the PSUR.

Although not observed with trenibotulinumtoxinE, ophthalmic adverse reactions such as reduced blinking may occur given that the mechanism of action is similar to that of other botulinum toxins. A warning is mentioned in the section 4.4 of the SmPC.

Taking into account that 700 U is recommended for the improvement in the appearance of moderate to severe lines between the eyebrows seen at maximum frown, the risk of use of the remaining 700 units contained in a vial to other parts of the face is mitigated by clear product information, HCP education and training and postmarketing pharmacovigilance. Therefore, 1400 U/vial is acceptable as commercial presentation.

9.5. Effects table

Table 21: Effects Table for Boey (AGN-151586)

Effect (short description)	*Treatment*	*Control*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable effects				

Effect (short description)	*Treatment*	*Control*	*Uncertainties/ Strength of evidence*	*Ref*
Improvement of appearance of Glabellar Lines PE1: FWS at Maximum Frown – Subject: Number (%) of Subjects with ≥ 2-Grade Improvement from Baseline at Day 7	63.1%	0.5%	**SoE:** difference 62.6% (58.3, 66.8) p< 0.0001 **Unc:**	Pooled data from M21-500 and M21-508
PE2: FWS at Maximum Frown – Subject: Number (%) of Subjects with ≥ 2-Grade Improvement from Baseline at Day 7	72.6%	0.5%	**SoE:** difference 72.0% (68.1, 76.0) p< 0.0001 **Unc:**	Pooled data from M21-500 and M21-508
Improvement in psychological impact SE1: FLO-11: Number (%) of Subjects with ≥ 20-Point Improvement from Baseline Total Transformed Score at Day 7	65.0%	8.5%	**SoE:** difference 56.9% (51.2, 62.5) p<0.0001 **Unc:**	Pooled data from M21-500 and M21-508
Onset of effect SE: Time to first ≥ 1-grade improvement from Baseline on FWS at maximum frown (mean days) assessed by subject	4.6 days	33.0 days	**SoE:** difference -28.4 (-30.6, -26.2) p<0.0001 **Unc:**	Pooled data from M21-500 and M21-508
SE: Time to first ≥ 1-grade improvement from Baseline on FWS at maximum frown (mean days) assessed by investigator	3.8 days	30.1 days	**SoE:** difference -26.3 (-28.4, -24.1) p<0.0001 **Unc:**	Pooled data from M21-500 and M21-508
Duration of effect Time to Return to Baseline FWS Criterion After Achieving Responder Definition on Day 7 in the subgroup with psychological impact by subject	20.6 days			Pooled data from M21-500 and M21-508

Effect (short description)	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Time to Return to Baseline FWS Criterion After Achieving Responder Definition on Day 7 in the subgroup with psychological impact by investigator	20.6 days			Pooled data from M21-500 and M21-508
Unfavourable effects				
Injections site reactions	117/1960 (6.0%)		**SoE**: Treatment-related TEAE reported, mechanistic plausibility, known risk with other toxins.	
Brow ptosis	3/1960 (0.2%)		**SoE:** Treatment-related TEAE reported, mechanistic plausibility, known risk with other toxins	
Eyelid ptosis	3/1960 (0.2%)		**SoE:** Treatment-related TEAE reported, mechanistic plausibility, known risk with other toxins	
Mephisto signs	1/2320 (0.04%)		**SoE:** Treatment-related TEAE reported, mechanistic plausibility, known risk with other toxins	

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; PE: primary endpoint; SE: secondary endpoint

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

Favourable effect

It is overall agreed that the efficacy of the product in the proposed indication has been demonstrated, statistically significant difference between AGN-151586 and placebo was achieved in the conducted clinical studies.

The results are presented in the subgroup of subjects with a psychological impact (with FLO ≤ 50 at baseline) which is in line with the claimed indication.

The co-primary endpoints results from pooled data showed a response rate as assessed by investigator of 72.1% vs 0.8% [difference 71.4%, (95%CI 66.5,76.2)] and by subject [61.0% vs 0.8% [difference 60.2% (95%CI 54.9, 65.4)].

Through secondary endpoints, the patient-reported outcomes showed an emotional and appearance-related impact with more than 20-point change from baseline (FLO-11 questionnaire) and a satisfaction of the subject (FLSQ questionnaire).

Indeed at all timepoints, the proportion of subjects who were *Mostly satisfied* or *Very satisfied* with the appearance of their GL based on the FLSQ follow-up version Item 5 (overall satisfaction) was greater for the trenibotulinumtoxinE group compared to the placebo group during the double-blind period.

The response rates of the repeated administration done at Day 43 were similar compared to the 1st injections.

Unfavourable effect

Overall, the treatment-related TEAEs reported with AGN-151586 were known adverse reactions of other botulinum toxins, were not serious and were generally mild in severity. None led to study treatment discontinuation. Injection site reactions and possible distant spread of toxin are known risks of botulinum toxin type A and therefore are mentioned as a warning in the SmPC of trenibotulinumtoxinE. Administration of trenibotulinumtoxinE700 U with another botulinum toxin at the same time should be prohibited. Safety profile of trenibotulinumtoxinE following multiple injections is unknown and could theoretically increase the risk of antibody formation. Immunogenicity data is mentioned in the Section 5.1 of the SmPC. The risks related to neuromuscular disorders cannot be excluded with trenibotulinumtoxinE so generalised disorders of muscle activity (e.g. myasthenia gravis, Eaton Lambert Syndrome) are contraindicated in the SmPC).

9.6.2. Balance of benefits and risks

The superiority of trenibotulinumtoxinE to treat moderate to severe Glabellar Lines in a single treatment was demonstrated over placebo at Day 7 in both pivotal phase 3 studies.

The benefit/risk of trenibotulinumtoxinE is considered positive in the only situation of occasional use as the benefit lasts about 5 days with a peak effect at Day 7 and with a similar safety profile as botulinum toxin A products.