EU Risk Management Plan for TrenibotulinumtoxinE

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Administrative Information on the RMP

Part Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
Part 1: Product Overview	Not applicable	Not applicable
Part II: Safety Specification	Not applicable	Not applicable
Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)	Not applicable	Not applicable
Part IV: Plan for Post-Authorization Efficacy Studies	Not applicable	Not applicable
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	Not applicable	Not applicable
Part VI: Summary of the Risk Management Plan	Not applicable	Not applicable
Part VII: Annexes		
Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	Not applicable	Not applicable
Annex 3 – Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	Not applicable	Not applicable
Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms	Not applicable	Not applicable
Annex 5 – Protocols for Proposed and Ongoing Studies in RMP Part IV	Not applicable	Not applicable
Annex 6 – Details of Proposed Additional Risk Minimization Activities (If Applicable)	Not applicable	Not applicable
Annex 7 – Other Supporting Data (Including Referenced Material)	Not applicable	Not applicable
Annex 8 – Summary of Changes to the Risk Management Plan Over Time	Not applicable	Not applicable

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QPPV oversight declaration: The content of the RMP has been reviewed and approved by the marketing authorization holder QPPV through an electronic document system per company standard operating procedure.

Table of Contents

Part I: Product(s) Overview 7
Part II: Safety Specification 8
Module SI Epidemiology of the Indication and Target Populations 8
Module SII Non-Clinical Part of the Safety Specification 10
Module SIII Clinical Trial Exposure 12
Module SIV Populations Not Studied in Clinical Trials 15
SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Clinical Development Program 15
SIV.2 Limitations to Detect Adverse Reactions in the Clinical Development Program 17
SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Development Program 18
Module SV Post-Authorization Experience 19
SV.1 Post-Authorization Exposure 20
SV.1.1 Method Used to Calculate Exposure 20
SV.1.2 Exposure 20
Module SVI Additional EU Requirements for the Safety Specification 20
Module SVII Identified and Potential Risks 20
SVII.1 Identification of Safety Concerns in the Initial RMP Submission 20
SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP 20
SVII.1.2 Risks/Missing Information Considered Important for Inclusion in the RMP 21
SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP 21
SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information 21
SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks 21
SVII.3.2 Presentation of the Missing Information 21
Module SVIII Summary of the Safety Concerns 21
Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies) 21

III.1 Routine Pharmacovigilance Activities 21
III.2 Additional Pharmacovigilance Activities 21
III.3 Summary Table of Additional Pharmacovigilance Activities 22
Part IV: Plans for Post-Authorization Efficacy Studies 22
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities) 22
V.1 Routine Risk Minimization Measures 22
V.2 Additional Risk Minimization Measures 22
V.3 Summary of Risk Minimization Measures and Pharmacovigilance Activities 22
Part VI: Summary of the Risk Management Plan 22
I The Medicine and What it Is Used For 23
II Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks 23
II.A List of Important Risks and Missing Information 24
II.B Summary of Important Risks 24
II.C Post-Authorization Development Plan 24
II.C.1 Studies Which are Conditions of the Marketing Authorization 24
II.C.2 Other Studies in Post-Authorization Development Plan 24
Part VII: Annexes 25

List of Tables

Table 1. Product Overview 7
Table 2. Duration of Exposure to AGN-151586 (Indication GL) – All Treated Subjects 12
Table 3. Exposure by Age Group and Gender (Indication: GL) – All Treated Subjects 13
Table 4. Exposure to AGN-151586 by Dose (Indication: GL) – All Treated Subjects 14
Table 5. Exposure by Ethnic Origin (Indication: GL) – All Treated Subjects 15
Table 6. Exposure for Special Populations 15

Table 7. Exposure of Special Populations Included or Not in the Clinical Development Program 18
Table 8. Summary of Safety Concerns 21

List of Annexes

Annex 1. EudraVigilance Interface 26
Annex 2. Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program 27
Annex 3. Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan 28
Annex 4. Specific Adverse Drug Reaction Follow-Up Forms 31
Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV 32
Annex 6. Details of Proposed Additional Risk Minimization Activities (If Applicable) 33
Annex 7. Other Supporting Data (Including Referenced Material) 34
Annex 8. Summary of Changes to the Risk Management Plan Over Time 36

List of Abbreviations

AE	adverse event
ALS	amyotrophic lateral sclerosis
ATC	anatomical therapeutic chemical
BoNT/A	botulinum toxin type A
BoNT/E	botulinum toxin type E
CHMP	Committee for Human Medicinal Products
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FWS	Facial Wrinkle Scale
GL	glabellar lines
IM	intramuscular
INN	International Nonproprietary Name
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NA	not applicable
PBRER	Periodic Benefit-Risk Evaluation Reports
PDO	polydiaxone
PL	Package Leaflet
PSUR	Periodic Safety Update Report
PT	preferred term
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event

Part I: Product(s) Overview

Table 1. Product Overview

Active substance(s) (INN or common name)	trenibotulinumtoxinE
Pharmacotherapeutic group(s) (ATC Code)	Muscle relaxants, peripherally acting agents ATC code: pending (submission made to the WHO to request a new ATC code)
Marketing Authorization	AbbVie Limited
Medicinal products to which this RMP refers	trenibotulinumtoxinE (AGN-151586[a])
Invented name(s) in the European Economic Area (EEA)	TBD
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Muscle relaxants, peripherally acting agents
	Summary of mode of action: TrenibotulinumtoxinE, like all botulinum toxin type E products, blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine from the terminals. This inhibition occurs as the neurotoxin cleaves SNAP-25, a pre-synaptic protein integral to the successful docking of vesicles situated within nerve terminals, fusion of the vesicles to the cell membrane and the subsequent release of acetylcholine from those vesicles. When injected intramuscularly at therapeutic doses, trenibotulinumtoxinE produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity within hours. Botulinum toxin type E (*Clostridium botulinum* neurotoxin type E) has been shown to prevent acetylcholine release from presynaptic nerve terminals and, as a result, inhibits muscle contraction. BoNT/E inhibits neuromuscular transmission by cleaving SNAP-25. It is believed that BoNT/E differentially affects the replenishment of SNAP-25 (Foran 2003, Meunier 2003) and the ability of SNAP-25 to bind the plasma membrane syntaxins (Bajohrs 2004). This differential replacement of SNAP-25, in addition to the subcellular, cytoplasmic location of the BoNT/E light chain, is believed to contribute to the shorter neuroparalytic duration of BoNT/E relative to BoNT/A (Fernández-Salas 2004). Results from epidemiologic studies also support the earlier onset of the BoNT/E effect compared with BoNT/A.

	Important information about its composition: The origin of the active substance (trenibotulinumtoxinE) is *Clostridium botulinum* type E organism.
Hyperlink to the Product Information	*[PLACEHOLDER]*
Indication(s) in the EEA	Current (if applicable): 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
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current (if applicable): 700 U/dose Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): single use [redacted] U/vial containing sterile lyophilized powder for solution for injection
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

a. Reference to AGN-151586 in this report will refer to AGN-151586 drug product (trenibotulinumtoxinE).

Part II: Safety Specification

Module SI Epidemiology of the Indication and Target Populations

Indication #1:

Temporary improvement in the appearance of moderate to severe lines between the eyebrows seen at maximum frown (GL) when these have an important psychological impact in adult patients.

The GL, also referred to as wrinkles of the glabella or frown lines, are creases located on the glabellar region of the forehead, usually between the eyes and above the nose. Contraction of procerus and corrugator supercilli, the muscles that draw the eyebrows downward and medially, can produce GL. With the decrease in skin elasticity, repeated facial expressions can become permanent lines (American Academy of Dermatology 2010).

Incidence: To our knowledge, the incidence of GL has not been reported in the literature.

Prevalence: During the fourth decade of age (thirties), GL begin to appear (Friedman 2005). During the fifth decade of age (forties), GL deepen, and during the sixth decade (fifties), GL

continue to deepen and remain noticeable when the patient is in repose (Friedman 2005). The prevalence of GL by age group was reported in a population of French (n =160) and Chinese (n = 160) women (Nouveau-Richard 2005). 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% (Nouveau-Richard 2005). 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% (Nouveau-Richard 2005).

Demographics of the target population: Race has been shown to impact the age at which GL develop, with individuals who are White or Hispanic being more likely to develop them at a younger age than individuals who are Black or Asian (Alexis 2019a, Alexis 2019b, Rossi 2017). In a globally representative survey of aesthetically conscious adults, GL were ranked 1 of the top 5 facial aesthetic concerns at every age group surveyed, excepting males 36 to 55 years of age (in this demographic, hair-related issues took precedence) (Fabi 2022). The most common response among these aesthetically conscious respondents regarding the age when individuals should first seek aesthetic treatment, among both males and females, was the fifth decade of life (forties), followed by the fourth decade of life (thirties), and then the sixth decade of life (fifties). Less than 10% responded that individuals should seek aesthetic treatment starting between the ages of 18 to 29.

Risk Factors: Both intrinsic (e.g., genetic such as age and race) and extrinsic (e.g., environmental such as solar exposure) factors impact the development of GL, with age being the primary risk factor (Alexis 2019b, McDaniel 2018, Moutraji 2023). Individuals who are white or Hispanic are more likely to develop them at a younger age than individuals who are Black or Asian; however, by the seventh decade of life (sixties), GL at rest are reported by at least 30% of individuals regardless of race (Alexis 2019b, Rossi 2017). Differences in bone mass and orbital soft tissue, which vary by race, may be associated with the age of GL onset, with individuals having greater bone mass and orbital soft tissue developing GL later in life (Alexis 2019b). When categorized by Fitzpatrick skin phototype (a categorical scale of assessment for an individual's skin reactivity to natural and therapeutic ultraviolet radiation), males with Fitzpatrick skin phototypes V and VI reported significantly fewer facial lines in the upper third of the face compared to men with Fitzpatrick skin phototype I, II, III or IV (Rossi 2017). Similarly, females with phototypes V/VI reported less severe GL compared with women with skin phototypes I/II and III/IV (Rossi 2017) (Alexis 2019b). Similarly, females with phototypes V/VI reported less severe GL compared with women with skin phototypes I/II and III/IV (Alexis 2019b).

The main treatment options: A variety of treatments such as lasers, radiofrequency, plastic surgery, toxin, and fillers have been utilized for wrinkle correction. In some cases, these effective and powerful modalities have been used in combination to achieve a better clinical outcome. In recent years, polydiaxone (PDO) has been increasingly used for lifting and tightening of facial wrinkles. Monofilament PDO thread can also be applied multiple times for single wrinkle correction. Stent-shaped multi-PDO scaffolds are another effective option for the

correction of forehead wrinkles, especially in cases of severe wrinkles (AAFPRS 2023). The presence and progressive development of facial lines is consistent with the external signs of aging, and have been associated with negative impact on self-esteem, a decrease in perceived attractiveness, body image, and communication, which are further implicated as having undesirable effects on psychological well-being and sociological sequelae (Cox 2005, Finn 2003, Khan 2001, Singh 2006). Excessively prominent lateral canthal lines around the outer sides of both eyes, deep furrows in the glabellar area, and deep FHL may be misinterpreted as anger, anxiety, fear, or fatigue, and such misinterpretation may cause considerable distress to an individual (Finn 2003).

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity: As skin ages, GL begin to appear, and deepen in severity as individuals age (Alexis 2019b, Rossi 2017). As an individual ages, facial lines, including GL, transition from dynamic lines, which convey emotion, to static lines, which are present even when an individual is at rest; for some individuals, these rhytids may negatively affect communication, societal perception of attractiveness, and an individual's self-worth (Finn 2003). Certain factors, both modifiable (e.g., level of sun protection), and non-modifiable (e.g., race), may impact the rate at which GL develop (Alexis 2019b, Rossi 2017). Although wrinkles are not considered a medical illness, intervention may be required to improve quality of life where there are concerns about changes in physical appearance related to skin aging progression. GL have not been found to be associated with increased mortality.

Important co-morbidities:

Wrinkles cannot be considered a medical illness requiring intervention but concerns about changes in physical appearance brought on by ageing can have a detrimental effect on quality of life. In some cases, concerns about physical appearance can affect personal interactions, occupational functioning, and self-esteem (Gupta 1996).

Module SII Non-Clinical Part of the Safety Specification

Key Safety Findings (from Non-Clinical Studies)	**Relevance To Human Usage**
Toxicity	
Single and repeat dose toxicity • Transient disuse of the injected limb, abnormal gait, body weight loss, hunched posture, decreased activity, decreased muscle tone, labored breathing, and mortality.	Adverse effects observed were consistent with those that would be anticipated from an exaggerated dose of trenibotulinumtoxinE.

Key Safety Findings (from Non-Clinical Studies)	**Relevance To Human Usage**
Reproductive toxicity Reproductive studies have not been conducted with trenibotulinumtoxinE.	Not applicable
Developmental toxicity Developmental studies have not been conducted with trenibotulinumtoxinE.	Not applicable
Nephrotoxicity No non-clinical evidence of nephrotoxicity	None
Hepatotoxicity No non-clinical evidence of hepatotoxicity	None
Genotoxicity The mutagenic and genotoxic studies have not been conducted with trenibotulinumtoxinE.	Not applicable
Carcinogenicity Carcinogenicity studies have not been conducted with trenibotulinumtoxinE in animals.	Not applicable
General Safety Pharmacology	
Cardiovascular TrenibotulinumtoxinE was tested in safety pharmacology core battery (including cardiovascular) in monkeys. There were no electrocardiographic abnormalities (quantitative and qualitative) recorded following single IM administration in this study at the doses up to 134 and 55 U/kg in male and female monkeys, respectively.	None
Nervous system There were no trenibotulinumtoxinE-related neurological changes at the doses up to 134 and 55 U/kg in male and female monkeys, respectively.	None
Other systems (dependent on the product's pharmacological activity) No respiratory insufficiencies were noted in mice up to 100 U/kg.	None
Mechanisms for drug interactions No data available.	Not applicable

Key Safety Findings (from Non-Clinical Studies)	Relevance To Human Usage
Other toxicity-related information or data Not applicable	Not applicable

Non-Clinical Safety Findings that are Included as Safety Concerns

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

Module SIII Clinical Trial Exposure

Table 2. Duration of Exposure to AGN-151586 (Indication GL) – All Treated Subjects

Dose Group	Duration of Exposure	Patients	Person-Time (Weeks)
Overall	< 6 Weeks	132	552.57
	6 to < 12 Weeks	556	3984.86
	12 to < 18 Weeks	695	9140.43
	18 to < 24 Weeks	773	14257.71
	24 to < 30 Weeks	4	103.29
	30 to < 36 Weeks	0	0
	36 to < 42 Weeks	1	38.14
	42 to < 48 Weeks	0	0
	≥ 48 Weeks	0	0
	Total	2161	28077.00

Studies included: EB001-GL201, 2034-201-008, M21-500, M21-508, M21-509, M23-365, and M24-040.

Table 3. Exposure by Age Group and Gender (Indication: GL) – All Treated Subjects

		Patients			Person-Time (Weeks)		
Dose Group	**Age Group**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
Overall	< 45	157	686	843	1995.43	8703.86	10699.29
	≥ 45 to < 65	130	1022	1152	1728.57	13322.71	15051.29
	≥ 65	19	147	166	235.57	2090.86	2326.43
	Total	306	1855	2161	3959.57	24117.43	28077.00

Studies included: EB001-GL201, 2034-201-008, M21-500, M21-508, M21-509, M23-365, and M24-040.

Table 4. Exposure to AGN-151586 by Dose (Indication: GL) – All Treated Subjects

Dose Group	Patients	Person-Time (Weeks)
AGN-151586 [redacted]U	5	22.57
AGN-151586 [redacted]U	5	24.43
AGN-151586 [redacted]U	5	22.29
AGN-151586 [redacted]U	5	19.57
AGN-151586 [redacted]U	5	21.14
AGN-151586 [redacted]U	32	197.57
AGN-151586 [redacted]U	5	21.86
AGN-151586 [redacted]U	5	21.00
AGN-151586 [redacted]U	28	172.29
AGN-151586 [redacted]U	6	37.00
AGN-151586 [redacted]U	27	160.86
AGN-151586 [redacted]U	6	36.86
AGN-151586 [redacted]U	30	187.29
AGN-151586 700U	1966	26941.57
AGN-151586 [redacted]U	31	190.71
Total	2161	28077.00

Studies included: EB001-GL201, 2034-201-008, M21-500, M21-508, M21-509, M23-365 and M24-040.

AGN-151586 700U is derived from AGN-151586 [redacted]U for Studies M21-500, M21-508, M21-509, M23-365 and M24-040.

AGN-151586 [redacted]U and [redacted]U are derived from Study M24-040 AGN-151586 [redacted]U and [redacted]U, respectively.

Source: Table 1 [Risk Management Plan 1]

Table 5. Exposure by Ethnic Origin (Indication: GL) – All Treated Subjects

Dose Group	Ethnic Origin	Patients	Person-Time (Weeks)
Overall	White	1885	24644.14
	Asian	90	939.29
	Black or African American	121	1682.00
	American Indian or Alaska Native	18	289.71
	Native Hawaiian or Other Pacific Islander	13	118.43
	Multiple	33	397.14
	Missing	1	6.29
	Total	2161	28077.00

Studies included: EB001-GL201, 2034-201-008, M21-500, M21-508, M21-509, M23-365, and M24-040.

Note: At the time of the data lock point for this RMP, Study M24-040 had undergone database lock and treatment assignments had been unblinded but was still ongoing without a completed CSR. Therefore, data from this study was included in the exposure data (Table 2, Table 3, Table 4, and Table 5 above) and, for completeness, used in the adverse drug reaction (ADR) assessment, but not included elsewhere in the document.

Table 6. Exposure for Special Populations

Not applicable.

Module SIV Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Clinical Development Program

Criterion 1: Presence of infection at the proposed injection site
Reason for exclusion: Patients who have an infection at the proposed injection site(s) should not receive trenibotulinumtoxinE injections as this could potentially exacerbate the already existing infection.
Is it considered to be included as missing information?: No
Rationale: TrenibotulinumtoxinE is contraindicated in the presence of infection at the proposed injection site(s).

Criterion 2: Known allergy or sensitivity to treatment or its components
Reason for exclusion: In order to ensure accurate interpretation of any safety findings observed during a clinical study, it is considered appropriate to exclude any patients who may present confounding factors.
Is it considered to be included as missing information?: No
Rationale: TrenibotulinumtoxinE is contraindicated in individuals with known hypersensitivity to any Botulinum toxin preparation or to any of the components in the formulation

Criterion 3: Mild severity of GL as indicated on the FWS
Reason for exclusion: There are no adequate and well-controlled studies in patients with mild GL as indicated by FWS
Is it considered to be included as missing information?: No
Rationale: TrenibotulinumtoxinE is not recommended for use in this population as the indication for use is moderate or severe GL as indicated on the FWS

Criterion 4: Pregnant and lactating patients
Reason for exclusion: There are no adequate and well-controlled studies in pregnant or lactating patients
Is it considered to be included as missing information?: No
Rationale: TrenibotulinumtoxinE is not recommended for use in this population

Criterion 5: Age < 18 years old
Reason for exclusion: The disease or condition does not occur in the specified subsets of the pediatric population
Is it considered to be included as missing information?: No
Rationale: EMA granted a product-specific waiver for all subsets of the pediatric population on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified subsets of the pediatric population

Criterion 6: Any medical or neurological condition that may put the patient at increased risk with exposure to trenibotulinumtoxinE including diagnosed myasthenia gravis, Lambert-Eaton Syndrome, amyotrophic lateral sclerosis (ALS), or any other significant diseases or concomitant medications that might interfere with neuromuscular function
Reason for exclusion: To avoid confounding safety and efficacy data
Is it considered to be included as missing information?: No
Rationale: Sufficient warning is included in the label regarding use of AGN-151586 in this population: Extreme caution, including close monitoring, should be exercised when administering trenibotulinumtoxinE to individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy) or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular junction disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise. Included as an Important Potential Risk (SVII.1.2).

Criterion 7: Concurrent or previous botulinum toxin treatment of any serotype within 6 months of trenibotulinumtoxinE treatment
Reason for exclusion: In order to ensure accurate interpretation of any safety findings observed during a clinical study, it is considered appropriate to exclude any patients who may present confounding factors. The effect of administering different botulinum neurotoxin serotypes at the same time is currently unknown.
Is it considered to be included as missing information?: No
Rationale: Timing of trenibotulinumtoxinE treatment (including retreatment) is to be determined by the healthcare provider assessment of wrinkle severity. Patients are eligible for treatment as long as their GL severity is moderate or severe, irrespective of last toxin use.

SIV.2 Limitations to Detect Adverse Reactions in the Clinical Development Program

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Development Program

Table 7. Exposure of Special Populations Included or Not in the Clinical Development Program

Type of special population	Exposure	Implications
Pregnant women	Excluded from clinical trials. However, there were 3 reported pregnancies during the trenibotulinumtoxinE clinical trial program, 2 with outcomes of live birth, no reported defects or anomalies and 1 outcome unknown.	There are no adequate data from the use of trenibotulinumtoxinE in pregnant women. The potential risk for humans is unknown. TrenibotulinumtoxinE is not recommended for use during pregnancy.
Breastfeeding women	Not included in the clinical development program.	There is no adequate data from the use of trenibotulinumtoxinE in lactating patients. The potential risk for humans is unknown. TrenibotulinumtoxinE is not recommended for use in lactating patients.
Patients with relevant comorbidities: • Patients with preexisting neuromuscular disorders	Patients with preexisting neuromuscular disorders were excluded from the clinical trials program.	Based on mechanism of action, there is a theoretical potential risk of increased adverse reactions in this population with the use of trenibotulinumtoxinE. Extreme caution should be exercised when administering trenibotulinumtoxinE to patients with preexisting neuromuscular disorders.

Type of special population	Exposure	Implications
Patients with relevant comorbidities (continued): • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients	There have been no specific studies performed to evaluate the use of trenibotulinumtoxinE in patients with hepatic, renal, or cardiovascular impairment or in immunocompromised patients.	It is believed that there is little systemic distribution of trenibotulinumtoxinE. Since trenibotulinumtoxinE is administered by local injection directly into the intended sites of clinical effects, the renal or hepatic clearance function is not expected to affect the pharmacologic effects from trenibotulinumtoxinE. TrenibotulinumtoxinE is most likely metabolized by proteases and its degraded components recycled through normal metabolic pathways of proteins. Patients with cardiovascular impairment and immunocompromised patients have not been studied.
Population with relevant different ethnic origin	See Table 5.	The available data does not indicate a different safety profile for trenibotulinumtoxinE based on patient's ethnic origin.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program	There are no known relevant genetic polymorphisms that affect the metabolism, degradation, or pharmacological effects of trenibotulinumtoxinE.
Patients younger than 18 years of age	Not included in the clinical development program	TrenibotulinumtoxinE is not recommended for use in patients less than 18 years old
Elderly (patients 65 years of age and older)	In the clinical development program, a total of 162 subjects aged 65 years old and older have been exposed to at least 1 treatment cycle of trenibotulinumtoxinE 700 U.	Based on the available data and analysis of AEs reported, there were no new safety concerns for trenibotulinumtoxinE in the population aged 65 or older.

Module SV Post-Authorization Experience

This module is not applicable since the MAH has never marketed trenibotulinumtoxinE.

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

Not applicable

SV.1.2 Exposure

Not applicable

Module SVI Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

There is no evidence to suggest that trenibotulinumtoxinE will be used for illegal purposes. However, as with any medicinal product, the potential for counterfeiting is real and AbbVie will be manufacturing and distributing TrenibotulinumtoxinE in vials specifically designed with easily recognizable labelling and holographic marking to help ensure authenticity.

Module SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Known risks that require no further characterization beyond routine pharmacovigilance, for which the risk minimization messages are described in the product information and that are followed through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered to by prescribers:

- Eyelid ptosis
- Brow ptosis
- Mephisto sign

Known risks that do not impact the risk-benefit profile:

- Injection site reactions

SVII.1.2 Risks/Missing Information Considered Important for Inclusion in the RMP

This section is not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

This section is not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

This section is not applicable.

SVII.3.2 Presentation of the Missing Information

This section is not applicable.

Module SVIII Summary of the Safety Concerns

Table 8. Summary of Safety Concerns

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

Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)

III.1 Routine Pharmacovigilance Activities

Adverse drug reaction reporting, aggregate safety reporting via PSUR/PBRER, and signal detection.

III.2 Additional Pharmacovigilance Activities

AbbVie has no additional pharmacovigilance activities planned or ongoing.

III.3 Summary Table of Additional Pharmacovigilance Activities

This section is not applicable.

Part IV: Plans for Post-Authorization Efficacy Studies

No efficacy studies have been imposed by competent authorities as a condition of marketing authorization or are Specific Obligations in the context of the conditional marketing authorization or marketing authorization under exceptional circumstances.

Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

This section is not applicable.

V.2 Additional Risk Minimization Measures

This section is not applicable.

V.3 Summary of Risk Minimization Measures and Pharmacovigilance Activities

This section is not applicable.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for TrenibotulinumtoxinE

This is a summary of the risk management plan (RMP) for trenibotulinumtoxinE (AGN-151586). The RMP details important risks of trenibotulinumtoxinE, how these risks can be minimized, and how more information will be obtained about trenibotulinumtoxinE's risks.

TrenibotulinumtoxinE summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how trenibotulinumtoxinE should be used.

This summary of the RMP for trenibotulinumtoxinE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of trenibotulinumtoxinE's RMP.

I The Medicine and What it Is Used For

TrenibotulinumtoxinE is authorized for the temporary improvement in the appearance of moderate to severe lines between the eyebrows seen at maximum frown (glabellar lines) (see SmPC section 4.1), when these have an important psychological impact in adult patients.

It is given by injection.

Further information about the evaluation of trenibotulinumtoxinE benefits can be found in trenibotulinumtoxinE EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage [PLACEHOLDER]<< link to the EPAR summary landing page >>.

II Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of trenibotulinumtoxinE (AGN-151586) together with measures to minimize such risks and the proposed studies for learning more about trenibotulinumtoxinE's risks, are outlined below.

TrenibotulinumtoxinE (AGN-151586) does not currently have risks designated as 'important identified risks' or 'important potential risks.'

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions will be collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Important risks of trenibotulinumtoxinE are risks that need special risk management activities to further investigate or minimize the risk so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of trenibotulinumtoxinE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

This section is not applicable.

II.C Post-Authorization Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of trenibotulinumtoxinE.

II.C.2 Other Studies in Post-Authorization Development Plan

There are no studies required for trenibotulinumtoxinE.

Part VII: Annexes

Annex 1	EudraVigilance Interface
Annex 2	Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program
Annex 3	Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan
Annex 4	Specific Adverse Drug Reaction Follow-Up Forms
Annex 5	Protocols for Proposed and Ongoing Studies in RMP Part IV
Annex 6	Details of Proposed Additional Risk Minimization Activities (If Applicable)
Annex 7	Other Supporting Data (Including Referenced Material)
Annex 8	Summary of Changes to the Risk Management Plan Over Time

Annex 4. Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 6. Details of Proposed Additional Risk Minimization Activities (If Applicable)

Not applicable.

Annex 7. Other Supporting Data (Including Referenced Material)

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