NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
December 2024

Botulinum neurotoxin E for treating moderate to severe glabellar lines

Company/Developer	AbbVie

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 38802	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Botulinum neurotoxin E is currently in clinical development for the treatment of moderate to severe glabellar lines. Glabellar lines are short vertical lines found between the eyebrows and extending up the central forehead for about a centimetre. Glabellar lines can make the patient feel tired and angry, contribute to headaches and central forehead heaviness, and cosmetically may make the patient look cross. Exposure to high levels of sunlight, pollution, smoking, and a constant angry mood can worsen glabellar lines. The neurotoxin botulinum toxin type A (known as botox) is currently used for treating glabellar lines, however there is a need for further treatments with differing onsets/durations.

Botulinum neurotoxin E is produced by the bacterium Clostridium botulinum. The toxin reduces the release of acetylcholine, a chemical messenger that causes muscle contraction. When it is administered as an injection into the muscles above and between the eyebrows, it causes the muscles to relax, helping to make the vertical lines less noticeable. Botulinum neurotoxin E has a faster onset of action, and a shorter duration of effects compared to other available neurotoxins. Therefore, this has the potential to provide faster results, which could be particularly appealing to patients seeking quicker improvements. If licensed, botulinum neurotoxin E will offer an additional treatment option for patients with moderate to severe glabellar lines.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

Treatment of moderate to severe glabellar lines in adults.[1]

Technology

Description

Botulinum neurotoxins (BoNTs) are multi-domain proteins and are responsible for binding to gangliosides and proteins associated with nerve cell membranes, internalisation into the cell, and cleavage of one or more SNARE (soluble N-ethylmaleimide sensitive factor attachment protein receptor) proteins necessary for vesicle docking and fusion.[2] BoNTs are naturally occurring bacterial proteins (produced by *Clostridium* bacteria) that, among other actions, weaken muscles by inhibiting neurotransmitter release at neuromuscular junctions. The effect of BoNT is not permanent and upon clearance of BoNT from the neuromuscular junction, muscles will regain function.[3] BoNTs are produced as inactive single chains (150 kDa) and released as active dichains, a heavy chain (100 kDa) and a light chain (50 kDa) held together by an interchain disulfide bond and noncovalent interactions.[4] BoNTs exist as seven classical serotypes, A through G.[2] Botulinum neurotoxin E (AGN-151586, BoNTE, BoNT/E) is unique as it is released as a single chain and cleaved into active dichain by an unidentified host cell protease.[4] BoNT/E is one of the major causes of human botulism and paradoxically also a promising therapeutic agent.[5]

BoNT/E is in clinical development for the treatment of moderate to severe glabellar lines in adults. In the phase III clinical trial (NCT06308198), participants will receive either AGN-151586 or Placebo administered as 5 intramuscular injections to the glabellar complex on Day 1. Eligible participants may then receive AGN-151586 injections on Day 43 and will be followed for up to 6 weeks.[1]

Key Innovation

BoNT/E is a first-in-class, short-acting neurotoxin, with quick treatment onset in development.[6] Glabellar lines are typically treated by selectively weakening specific muscles with small quantities of botulinum toxin.[7] Botulinum neurotoxins are widely used commercially for therapeutic and cosmetic applications, and have historically belonged to serotypes A and B. Serotype E has a distinct profile with a faster onset and shorter duration of effect.[8] Structural studies have shown that in botulinum neurotoxin E, both the binding domain and the catalytic domain are located on the same side of the translocation domain, allowing for faster internalisation and quicker onset of toxic effects compared to other serotypes.[4] Aside from its role in improving scars, BoNT/E embodies a unique neurotoxin due to its quick onset of action within 24 h and its short duration of action of between 2 and 4 weeks. It would be an appealing treatment option when a shorter duration of response than that of Botulinum toxin type A (3–4 months) is required.[9]

If licensed, botulinum neurotoxin E will offer an additional treatment option for adult patients with moderate to severe glabellar lines.

Regulatory & Development Status

Botulinum neurotoxin E does not currently have Marketing Authorisation in the EU/UK for any indication.

Botulinum neurotoxin E is not currently in clinical development for any other indications.[10]

Patient Group

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Disease Area and Clinical Need

Glabellar lines also known as frown lines or "11 lines," are the vertical lines that appear between the eyebrows on the forehead. They are called frown lines because they often form when a person frowns, squints, or expresses negative emotions. Over time, these repeated facial movements can lead to the formation of permanent lines or wrinkles in the area.[11] Facial lines result from a combination of intrinsic skin aging, ultraviolet damage, and repetitive action of underlying facial muscles; the onset of glabellar lines is closely related to the movements of the underlying procerus, corrugator supercilii, and orbicularis oculi muscles.[12] Glabellar lines can make the patient feel tired and angry. The effect of constantly contracting the glabella muscles contributes to headaches and central forehead heaviness. Cosmetically, the glabellar lines may make the patient look angry or cross, while also making the upper face appear heavier. This occurs as the muscles to the sides of the lines bunch up instead of looking refined, open, and relaxed.[13]

Botulinum toxin type A injection is the most widely performed nonsurgical cosmetic procedure in the United Kingdom. From February to June 2023, 457 patients (21 to 77 years) received prabotulinumtoxinA injections for glabellar line treatment.[14] However, the population in the UK likely to be eligible to receive botulinum neurotoxin E could not be estimated from available published sources.

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended pharmacological treatment options for glabellar lines. Botulinum toxin type A is approved in the UK for the temporary improvement of moderate to severe upper facial lines in adults under 65 years (specialist use only).[15]

Clinical Trial Information

Trial	NCT05248880; A Phase 3, Multicenter Study to Evaluate the Safety and Efficacy of AGN-151586 for the Treatment of Glabellar Lines in Toxin-Naïve Subjects **Phase III** – Completed **Locations:** USA and Canada **Primary completion date:** February 2023
Trial Design	Randomised, parallel assignment, double masking
Population	N= 309 (actual); participants aged 18 years and older with moderate or severe glabellar lines at maximum frown
Intervention(s)	BoNT/E administered via intramuscular injection
Comparator(s)	Placebo
Outcome(s)	**Primary outcome measures:** • Percentage of participants with ≥ 2-grade improvement from baseline on the facial wrinkle scale (FWS) according to both investigator and participant assessments (composite) of glabellar lines severity at maximum frown [time frame: day 7] • Number of participants with adverse events [time frame: up to 12 weeks] • Change from baseline in vital sign measurements [time frame: up to 12 weeks] • Change from baseline in ECG parameters [time frame: up to 12 weeks]

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	• Change from baseline in laboratory evaluations [time frame: up to 12 weeks] • Presence of binding and neutralizing antidrug antibodies [time frame: up to 12 weeks] See trial record for full list of other outcomes.
Results (efficacy)	The primary endpoints demonstrated statistical significance for improvement with BoNT/E versus placebo (p<0.0001) in glabellar line severity on the FWS from baseline at day 7 (based on both subject and investigator assessments). All tested secondary endpoints, including patient-reported outcomes on overall treatment satisfaction, demonstrated statistical significance, favouring improvement with BoNT/E versus placebo. The onset of efficacy (i.e., at least 2-grade FWS improvement from baseline) was demonstrated at 8 hours after drug administration (the earliest assessment time) and efficacy duration was observed for 2-3 weeks after drug administration.[6]
Results (safety)	Treatment-emergent adverse events for BoNT/E were similar to placebo, both as a single treatment and up to two consecutive treatments.[6]

Trial	NCT06308198; A Phase 3, Multicentre, Randomized, Placebo-Controlled Study of AGN-151586 for the Treatment of Moderate to Severe Glabellar Lines **Phase III** - Recruiting **Locations:** China and Taiwan **Primary completion date:** March 2025
Trial Design	Randomised, sequential assignment, double masking
Population	N=160 (estimated); participants aged 18 years and older with moderate or severe glabellar lines at maximum frown
Intervention(s)	BoNT/E administered via intramuscular injection
Comparator(s)	Placebo
Outcome(s)	**Primary outcome measures:** • Percentage of participants with a >= 2-grade improvement from baseline on the FWS with Asian (FWS-A) guide according to investigator assessment of glabellar lines severity at maximum frown [time frame: day 7] • Percentage of participants with a >= 2-grade improvement from baseline on the FWS-A guide according to participant assessment of glabellar lines severity at maximum frown [time frame: day 7] • Number of participants with adverse events [time frame: up to approximately day 84] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

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Trial	NCT05248867; **EudraCT** 2021-003667-10 A Phase 3, Multicentre Study to Evaluate the Safety and Efficacy of AGN-151586 for the Treatment of Glabellar Lines **Phase III** - Completed **Locations:** Three EU countries, USA, and Canada **Primary completion date:** March 2023
Trial Design	Randomised, parallel assignment, double masking
Population	N=638 (actual); participants aged 18 years and older with moderate or severe glabellar lines at maximum frown
Intervention(s)	BoNT/E administered via intramuscular injection
Comparator(s)	Placebo
Outcome(s)	**Primary outcome measures:** • Percentage of participants with a grade 0 or 1 and a ≥ 2-grade improvement from baseline on the FWS according to both investigator and subject assessments of glabellar lines severity at maximum frown at day 7 [US FDA] • Percentage of participants with a ≥ 2-grade improvement from baseline on the FWS according to participant assessment of glabellar lines severity at maximum frown at day 7 [European Union Regulatory Agencies] • Percentage of participants with a ≥ 2-grade improvement from baseline on the FWS according to investigator assessment of glabellar lines severity at maximum frown at day 7 [European Union Regulatory Agencies] • Number of participants with adverse events from time of informed consent to end of study. See trial record for full list of other outcomes.
Results (efficacy)	The primary endpoints demonstrated statistical significance for improvement with BoNT/E versus placebo ($p<0.0001$) in glabellar line severity on the FWS from baseline at day 7 (based on both subject and investigator assessments). All tested secondary endpoints, including patient-reported outcomes on overall treatment satisfaction, demonstrated statistical significance, favouring improvement with BoNT/E versus placebo. The onset of efficacy (i.e., at least 2-grade FWS improvement from baseline) was demonstrated at 8 hours after drug administration (the earliest assessment time) and efficacy duration was observed for 2-3 weeks after drug administration.[6]
Results (safety)	Treatment-emergent adverse events for BoNT/E were similar to placebo, both as a single treatment and up to two consecutive treatments.[6]

Trial	NCT05248893; A Phase 3, Multicentre, Open-label Study to Evaluate the Safety of AGN-151586 for the Treatment of Glabellar Lines **Phase III** - Completed

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	Locations: USA and Puerto Rico **Primary completion date:** June 2023
Trial Design	Single group assignment, open label
Population	N=986 (actual); participants aged 18 years and older with moderate or severe glabellar lines at maximum frown
Intervention(s)	BoNT/E administered via intramuscular injection
Comparator(s)	No comparator
Outcome(s)	**Primary outcome measures:** • Number of participants with adverse events [time frame: day 1 to day 126] • Change in vital sign measurements [time frame: day 1 to day 126] • Change in electrocardiogram measurements [time frame: day 1 to day 126] • Presence of binding and neutralising antidrug antibodies [time frame: day 1 to Day 126] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of botulinum neurotoxin E is not yet known.

Relevant Guidance

NICE Guidance

No relevant NICE guidance was identified for this indication.

NHS England (Policy/Commissioning) Guidance

- NHS England. NHS service specification for specialised dermatology services (adults and children). A12 S/a. 2024.

Other Guidance

- Société Avancée de Médecine et Chirurgie Esthétique & Plastique (SAMCEP). SAMCEP Society consensus on the treatment of upper facial lines with botulinum neurotoxin type A: A tailored approach. 2023.[16]

Additional Information

AbbVie did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an

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essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

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