Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Letybo

Active ingredient: LetibotulinumtoxinA

Sponsor: CROMA Australia Pty Ltd

November 2023

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
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Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event(s)
AESI	Adverse events of special interest
AU	Australia
CI	Confidence interval
CMI	Consumer Medicines Information
DLP	Data lock point
EU	European Union
FAS	Full analysis set
FDA	United States Food and Drug Administration
FWS	Facial wrinkle scale
GMP	Good Manufacturing Practice
MFAS	Modified full analysis set
PI	Product Information
PPS	Per protocol set
RMP	Risk management plan
SAE	Serious adverse event(s)
TEAE	Treatment-emergent adverse event(s)
TGA	Therapeutic Goods Administration
PK	Pharmacokinetic(s)
SD	Standard deviation

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Letybo
Active ingredient:	LetibotulinumtoxinA
Decision:	Approved
Date of decision:	23 November 2022
Date of entry onto ARTG:	28 November 2022
ARTG numbers:	370012 and 370011
, *Black Triangle Scheme*	Yes
for the current submission:	This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	CROMA Australia Pty Ltd Level 26, 1 Bligh Street Sydney NSW 2000 Australia
Dose form:	Powder for injection
Strengths:	50 and 100 units
Container:	Vial
Pack size:	One vial
Approved therapeutic use for the current submission:	*Letybo is indicated for the temporary improvement in the appearance of moderate to severe glabellar frown lines in adults.*
Route of administration:	Intramuscular injection
Dosage:	Letybo should only be administered by medical practitioners with suitable qualifications and proven experience in the application of botulinum toxin and in the use of the necessary equipment. The optimum dose and number of injection sites in the treated muscles should be individualised for each patient and determined by the treating doctor. The dose per injection site is 4 units into each of the five injection sites, two injections in each corrugator muscle and one injection in the procerus muscle. The standard dose is 20 units. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	B3 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an

increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by CROMA Australia Pty Ltd (the sponsor) to register Letybo (letibotulinumtoxinA) 50 U and 100 U, powder for injection, vial, for the following proposed indication:[1]

Letybo is indicated in adults for the treatment of glabellar frown lines.

Hyperfunctional facial lines are common aesthetic deformities involving the forehead, glabellar area, nasolabial creases, and the lateral orbital area.[2, 3] While fine wrinkling on the upper lip and cheeks, and crow's feet, as well as the deeper lines in the nasolabial area are commonly considered signs of ageing, wrinkling in the glabellar area is associated with the expression of frowning.[2]

Glabellar lines, which appear as vertical lines between the eyebrows (vertical glabellar frown lines) are largely the result of overactivity of the corrugator supercilii muscles with contribution from both the procerus and orbicularis oculi muscles.

The glabellar frown lines often become more prominent with age and can project negative emotions unintentionally. In addition, the persistent presence of glabellar frown lines can be suggestive of an older than actual age, affecting an individual's self-perception, emotional wellbeing, and perception by others, in some cases contributing to depression.[4, 5] These effects can be experienced in terms of the individual's emotional wellbeing, social and psychological functioning, self-esteem and self-confidence.[6, 7]

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

[2] Yu, M. et al. Anatomy, Head and Neck, Eye Corrugator Muscle, *StatPearls publishing*, 2022.

[3] Abramo, A.C., et al., Anatomy of Forehead, Glabellar, Nasal and Orbital Muscles, and Their Correlation with Distinctive Patterns of Skin Lines on the Upper Third of the Face: Reviewing Concepts. *Aesthetic Plastic Surgery*, 2016; 40(6): 962-971.

[4] Lewis, M.B, et al. Botulinum toxin cosmetic therapy correlates with a more positive mood, *Journal of Cosmetic Dermatology*, 2009; 8: 24-26.

[5] Wollmer M.A, et al. Facing depression with botulinum toxin: A randomized controlled trial, *Journal of Psychiatric Research*, 2012; 46: 574-581.

[6] Finn, J.C. et al. Social Implications of Hyperfunctional Facial Lines, *Dermatologic Surgery,* 2003; 29: 450-455.

[7] De Boulle, K. et al. Treating glabellar lines with botulinum toxin type A-hemagglutinin complex: A review of the science, the clinical data, and patient satisfaction, *Clinical Interventions in Aging*, 2010; 5: 101-118.

The three currently available botulinum toxin products available in Australia are all derived from the identical Hall strain of Clostridium botulinum type A (strain Hall A, ATCC 350219). In contrast, LetibotulinumtoxinA (BoNT-DP) is derived from a new Clostridium strain CBFC26 isolated from canned soybeans in 2001. The isolation and purification procedures also differ. The molecular weight of Letybo is 900 kDa compared with Botox (900 kDa),[8] Dysport (500 kDa),[9] and Xeomin (150 kDa).[10] Even though Letybo is most similar to Botox based on molecular weight it is not considered a biosimilar.

Current treatment options

There are currently three marketed botulinum toxin products in Australia, Botox,[8] Dysport,[9] and Xeomin.[10] All are approved for a range of conditions. In regard to the indication requested in this submission the wording of the indications of the three products differ as follows:

Table 1: Botulinum Toxin products approved in Australia

Trade name	Year of approval	Name of medicine (in PI)	Approved indication
Botox	1999	Botulinum toxin type A purified neurotoxin complex Also called OnabotulinumtoxinA	Temporary improvement in the appearance of upper facial rhytides (glabellar lines, crow's feet and forehead lines) in adults
Dysport	2000	*Clostridium botulinum* type A toxin – haemagglutinin complex Also called abobotulinumtoxinA	Treatment of moderate to severe glabellar line and lateral canthal lines (crow's feet)
Xeomin	2014	IncobotulinumtoxinA, purified Botulinum toxin type A, free from complexing proteins	Treatment of upper facial line (glabellar frown lines, lateral periorbital lines and horizontal forehead lines

Regulatory status

This product is considered as a new biological entity for Australian regulatory purposes.

At the time the TGA considered this submission, a similar submission had been approved in Canada on 14 June 2022.

The following table summarises these submissions and provides the indications where approved.

[8] Botox was first registered in Australia on 9 July 1999. ARTG number: 67311.

[9] Dysport was first registered in Australia on 16 June 2000. ARTG number: 74124.

[10] Xeomin was first registered in Australia on 21 March 2014. ARTG number: 205507.

Table 2: International regulatory status of selected countries

Region	Submission date	Status	Approved indications
Canada	30 June 2021	Approved on 14 June 2022	*LETYBO is indicated for: The temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients < 65 years of age.*

LetibotulinumtoxinA, the active ingredient in Letybo, is approved in 53 countries under different brand names by different sponsors and manufactured by Hugel Inc.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 3: Timeline for Submission PM-2021-02698-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	2 August 2021
First round evaluation completed	4 January 2022
Sponsor provides responses on questions raised in first round evaluation	4 March 2022
Second round evaluation completed	1 August 2022
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	6 September 2022
Sponsor's pre-Advisory Committee response	15 September 2022
Advisory Committee meeting	6 and 7 October 2022
Registration decision (Outcome)	23 November 2022
Administrative activities and registration on the ARTG completed	28 November 2022
Number of working days from submission dossier acceptance to registration decision*	222

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Quality

Letybo is derived from a newly isolated Clostridium botulinum strain CBFC26 isolated from Korean food sources. The protein complex has a molecular weight of approximately 900 kDa and is composed of a 150 kDa neurotoxin and of four non-toxic haemagglutinins and one non-haemagglutinating protein.

The drug substance is a Clostridium botulinum neurotoxin type A (BoNT/A), purified from anaerobic culture of Clostridium botulinum type A CBFC26 strain. LetibotulinumtoxinA is a multimeric complex of noncovalently associated auxiliary proteins to the covalently linked neurotoxin protein.

An evaluation was conducted to evaluate endotoxin content of the drug substance and drug product. Based on the evaluation conducted, there are no concerns with regard to endotoxin testing.

An evaluation was conducted to evaluate the infectious disease safety of the drug substance and drug product. It was concluded that sufficient evidence has been provided to demonstrate that the risks related to the presence of adventitious agents in the manufacturing of Letybo have been controlled to an acceptable level.

An evaluation was conducted to evaluate sterility aspects. Based on the evaluation conducted, there are no objections from a microbiological perspective for approval of the application for Letybo (letibotulinumtoxinA) 50 U and 100 U powder for injection.

Quality related proposed conditions of registration

- Good Manufacturing Practice (GMP) clearance for listed manufacturers: All GMP clearances must be approved prior to registration and supply of product to Australia. A commitment is required from the sponsor that they maintain the validity of all manufacturer GMP clearances for the duration of product supply to Australia. Additionally, that adherence to the conditions of GMP clearance approval is upheld.
- All batches of Letybo supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs index and periodically in testing reports on the TGA website.

The quality evaluation had no objections for the approval of this application.

Nonclinical

- No dedicated safety pharmacology studies were conducted. Electrocardiogram readings were monitored in the dog repeat dose toxicity study, which revealed no abnormal cardiovascular effects at any dose level (up to 75-fold the clinical dose in U/kg).
- No pharmacokinetic studies were conducted since the anticipated measurable systemic concentration of Letybo was likely to be below the lower limit of quantification given low initial dose and route of administration. A published study with labelled Botox, indicated intact protein remained largely at the injection site and any drug related material distant from the active site or in the systemic circulation were the result of proteolytic degradation.
  - The evaluation considered the lack of safety pharmacology and pharmacokinetic studies as acceptable.
- Repeat dose toxicity studies by the intramuscular route were conducted in rats (up to 6 months) and dogs (up to 4 weeks). No systemic toxicities were identified. Findings were restricted to the injection site and appeared to be related to the pharmacological activity of Letybo, such as muscle atrophy (reduced fibre number and diameter), fatty infiltration, and inflammation of the injection site at all tested doses (greater than or equal to 28-fold clinical dose based on U/kg). Similar findings have been reported in animal studies conducted with other botulinum toxin A products.
- No genotoxicity or carcinogenicity studies were conducted with Letybo. The nonclinical evaluation considered this as consistent with the guideline for a product of this nature.
- One embryofetal developmental toxicity study conducted in Sprague Dawley rats revealed no test article related changes in litter values. Maternal toxicity was noted in all dose groups and largely encompassed reduced body weight and paralysis (related to the pharmacology of Letybo). Small fetuses and lower fetal weights with an increased incidence of minor skeletal and visceral alterations were seen secondary to maternotoxicity. The proposed PI states pregnancy category B3.[11]

The nonclinical evaluation recommended approval.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- Four Phase III studies
  - Study CPH-301-201030 (BLESS I), a Phase III study to evaluate efficacy and safety in subjects with moderate to severe glabellar lines. The first treatment is randomised, placebo controlled. Second to fourth treatments are open label, single arm.
  - Study CPH-302-201030 (BLESS II), a Phase III study to evaluate the efficacy and safety in subjects with moderate to severe glabellar lines. The first treatment is randomised, placebo controlled. Second to fourth treatments are open label, single arm.

[11] **Pregnancy category B3**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

  - Study CPH-303-201400 (BLESS III), a Phase III study to evaluate efficacy and safety in subjects with moderate to severe glabellar lines. The first treatment is randomised, placebo controlled. Open label data is not yet available.
  - Study HG-11-01, a randomised, active controlled study to evaluate efficacy and safety in subjects with moderate to severe glabellar lines.

- One Phase IV study
  - Study HG-13-02, a post marketing surveillance study to evaluate safety and efficacy in subjects with glabellar lines according to the approved product labelling in Korea.

Pharmacology

The drug substance is purified from anaerobic culture of Clostridium botulinum type A, strain CBFC26, derived from canned soybeans. The active substance is a multimeric complex of noncovalently associated auxiliary proteins to the covalently linked neurotoxin protein.

Botulinum neurotoxin type A is a multimeric complex consisting of six proteins. The toxin complex, as released by bacteria, weighs approximately 900 kDa and is comprised of a 150 kDa neurotoxin, a 130 kDa nontoxic non-haemagglutinin protein and four haemagglutinins of 17, 22, 34 and 48 kDa size. The 150 kDa neurotoxin exhibits the actual biological activity while nontoxic non-haemagglutinin and the haemagglutinins may have a stabilising effect on the neurotoxin.[12, 13]

Pharmacokinetics

No pharmacokinetic (PK) studies were conducted by the sponsor. The sponsor's rationale was:

> *The clinical pharmacokinetics of BoNT/A have not been evaluated by the applicant since the administered doses of BoNT/A are systemically too low to be detected by the use of the most sensitive conventional methods. For this reason, regulatory agencies have generally exempted this class of product from having to conduct such testing.*

The Delegate noted that the sponsor's rationale for not conducting PK studies is that the PK of botulinum toxin type A is well known, and the doses are too low to be detected to conduct PK studies. It is noted that the three other botulinum toxin type A products also contain very limited PK data.

This approach is considered acceptable, as per the relevant United States Food and Drug Administration (FDA) guidance document.[14]

Pharmacodynamics

Mechanism of action

LetibotulinumtoxinA blocks the release of acetylcholine. As a consequence, nerve endings of the neuromuscular junction no longer respond to nerve impulses and secretion of the chemo-transmitter is prevented (chemical denervation). Re-establishment of impulse transmission occurs by newly formed nerve endings and motor end plates and recovery of

[12] Inoue, K. et al. Molecular composition of Clostridium botulinum type A progenitor toxins, *Infection and Immunity*, 1996; 64 (5): 1589-1594.

[13] Chen, F. et al. Biophysical Characterization of the Stability of the 150-Kilodalton Botulinum Toxin, the Nontoxic component, and the 900-Kilodalton Botulinum Toxin Complex Species, *Infection and Immunity*, 1998; 66 (6): 2420-2425.

[14] FDA, Centre for Drug Evaluation and Research, Upper Facial Lines: Developing Botulinum Toxin Drug Products, August 2014. Available from FDA website.

affected nerve endings. This is considered the basis for the transient nature of letibotulinumtoxinA's treatment effect.

The indicated clinical condition (glabellar lines) is chronic in nature and the botulinum toxin effect typically lasts only a few months (function is typically recovered by the sprouting of nerve terminals and formation of new synaptic contacts, which usually takes two to three months), hence subjects need to be injected repeatedly to maintain the effect.

No information was provided on the pharmacodynamic effects of letibotulinumtoxinA in humans. The lack of pharmacodynamic studies is in line with the currently approved botulinum products.

Efficacy

No dose finding studies were submitted.

Study HG-11-01 was conducted in South Korea comparing letibotulinumtoxinA with the Botox that is approved for use in South Korea.

The dose chosen for Study HG-11-01 was the same as that approved for Botox, 20 U per treatment applied to five injection sites (4 U per site). The results of this study suggested that the clinical efficacy of 20 U letibotulinumtoxinA is non-inferior to 20 U of Botox, 20 U was therefore chosen for pivotal studies.

Pivotal efficacy studies

Study CPH-301-201030 (BLESS I)

The primary objective of this Phase III randomised controlled trial was to assess the efficacy and safety of letibotulinumtoxinA compared with placebo in reducing the glabellar frown lines based on investigator and subject assessment.

The secondary objectives were to assess the proportion of responders at maximum frown and at rest at various time points after each treatment. Other study objectives were to assess the onset of effect and the duration of effect (at maximum frown) after a single treatment with letibotulinumtoxinA compared with placebo (first treatment cycle) and to assess the psychological impact of letibotulinumtoxinA treatment.

Facial wrinkle scale as the composite primary endpoint

The composite primary endpoint efficacy scale, facial wrinkle scale (FWS), utilised the glabellar line scale for subjects and the glabellar line scale for investigators. The FWS is a 4 point scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe lines. The sponsor initially attempted to validate the scale including line length. During the validation it became apparent that the scale was more clinically appropriate without the line length and the corresponding revised FWS was used in all BLESS studies. Prior to this, the revised FWS was validated with regards to test-retest reliability of the glabellar line scale for subjects and the glabellar line scale for investigators, inter-rater reliability of the glabellar line scale for investigators, and agreement between live assessments and photo ratings on the glabellar line scale for investigators. The sponsor concluded that the revised FWS is valid and suitable to use in BLESS studies.

Adults with moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on FWS as determined by in clinic assessment by both the investigator and the subject and score

greater than 0 on either the emotional or social functioning subscale of the modified Skindex-16 Glabellar Lines Quality of Life scale were recruited.[15]

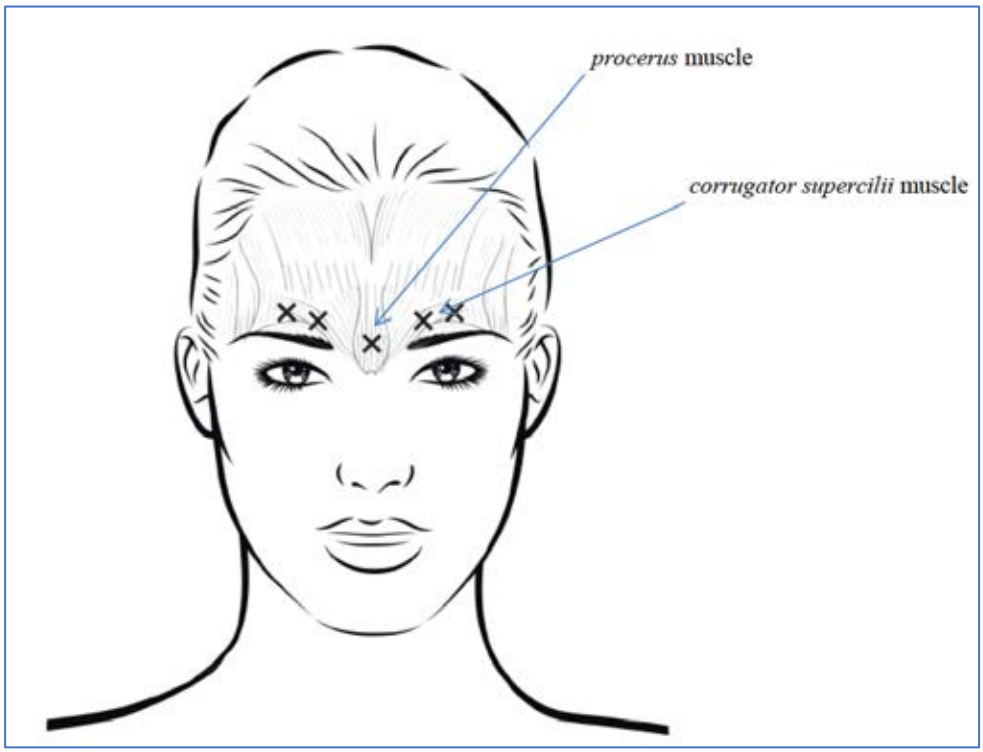
Individuals who have received any previous treatment with any serotype of botulinum toxin for any indication within the 12 months prior to screening or during the study were excluded.

Subjects were randomised 3:1 to either of the following treatments:

- letibotulinumtoxinA 4 U/0.1 mL per injection site, total dose of 20 U, 0.5 mL at a minimum interval of 12 weeks for a maximum of four treatments per study.
- Placebo

Each subject received five injections per treatment visit. Each subject received two injections in each corrugator supercilii muscle and one injection in the procerus muscle (see Figure 1).

Figure 1: Injection sites per treatment visit



The first treatment cycle was a double blind cycle followed by up to three open label treatment cycles. Each cycle was at least 12 weeks and could be prolonged in 4 week increments, depending on treatment effect. Retreatment was possible until Week 48.

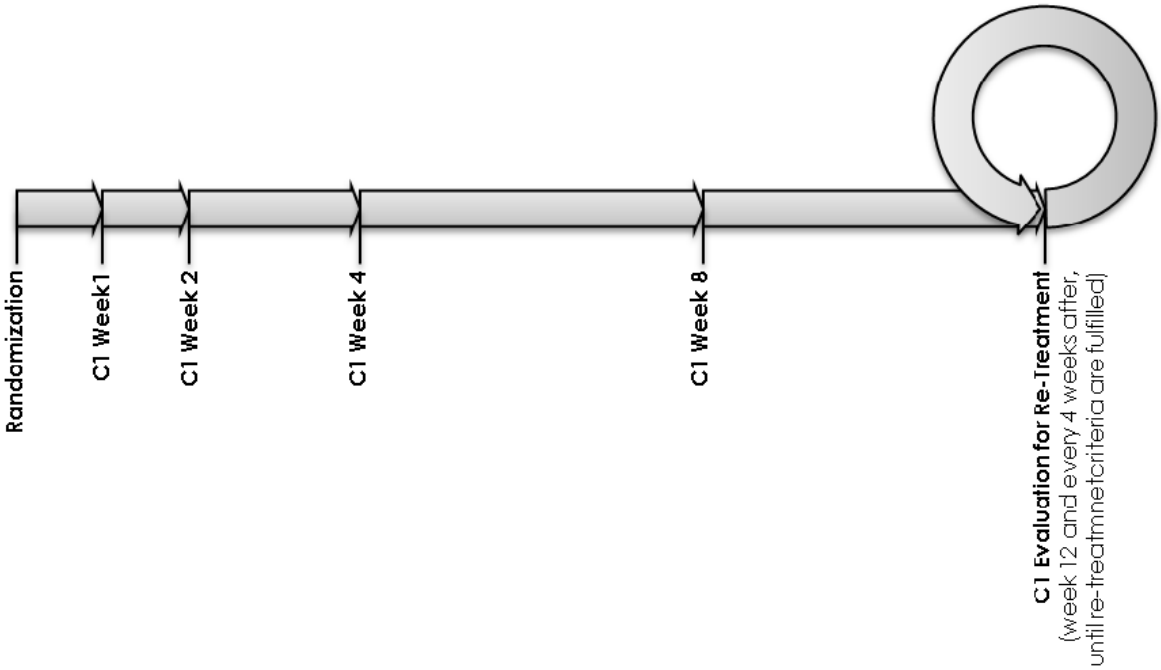
The following were the key eligibility criteria for retreatment:

- A minimum of 12 weeks must have elapsed since the previous study treatment.
- The subject's glabellar lines at maximum frown must have relapsed to a FWS score of 2 or 3 as determined by both the investigator and the subject.
- The subject must have received fewer than four study treatments.

[15] The Skindex-16 was developed to measure the impact of skin diseases on health related quality of life, it has been translated and validated in several languages and it is the most commonly used instrument to measure health related quality of life in patients with skin diseases. The Skindex-16 consists of 16 items which are scored on a seven point Likert scale (a rating scale used to measure opinions, attitudes, or behaviours), from 0 (never bothered) to 6 (always bothered). The range of possible scores was from 0 to 96, where lower scores indicate higher levels of quality of life.

A maximum of four retreatments were administered per subject, with the last retreatment at Week 48.

Figure 2: Study CPH-301-201030 Visit scheme for treatment cycle 1 (double blind)



Abbreviations: C1 = cycle 1

The dosage form of letibotulinumtoxinA is a lyophilizate for solution for injection. LetibotulinumtoxinA was provided in single use vials containing 50 U/vial. LetibotulinumtoxinA was reconstituted with a volume of 1.25 mL sterile physiological saline. A volume of 0.5 mL was taken from the vial for treatment. The use of product from one vial or syringe was restricted to one single subject treatment during a single session.

The primary endpoint was a composite endpoint comprising investigator and subject assessments of treatment effectiveness.

The primary efficacy endpoint was the proportion of subjects in both letibotulinumtoxinA and placebo groups with a FWS score of 0 or 1 and an improvement 2 points or greater in FWS score (at maximum frown) at Week 4 (of the first treatment cycle) relative to baseline (responders), based on both the investigators and the subject's in clinic assessments.

Responder rates at other time points in the first treatment cycle were defined as key secondary endpoints.

The FWS is a 4 point scale. Two points or greater improvement in FWS was considered as effective.

A total 708 subjects were randomised, 660 subjects completed the double blind phase and 601 subjects completed the study.

Major protocol deviations were reported for a total of 42 (7.9%) subjects in the letibotulinumtoxinA group and 15 (8.6%) subjects in the placebo group during the double blind phase, and for 50 (7.6%) subjects during the open label phase (safety analysis set).

Around 90% of subjects completed the study and entered open label phase.

At Baseline, the mean standard deviation (SD) age was 49.13 ± 11.830 years; and 88.1% of the subjects were under 65 years of age. There were 638 (90.6%) female and 66 (9.4%) male subjects.

Results

Primary composite outcome

The composite responder rate at Week 4 was 46.5% for the letibotulinumtoxinA group and 0% for the placebo group. The treatment difference was statistically significant. A 46.5% higher responder rate was reported in the letibotulinumtoxinA group, compared to placebo (95% confidence interval (CI): 41.78, 50.76, p < 0.001).

Table 4: Study CPH-301-201030 Summary of responder rates with a 2 point or greater reduction in facial wrinkle scale and facial wrinkle scale score of 0 or 1 at maximum frown at Week 4 (primary endpoint, composite investigator and subject assessment)

Composite Endpoint Treatment Response[a]	Responder Rate[b]				Risk Difference vs. Placebo	95% CI for Risk Difference vs. Placebo	CMH p-value For Responder Rate[c]
	BoNT/A-DP		Placebo				
	N	n (%)	N	n (%)			
FAS	529	246 (46.5)	175	0 (0.0)	46.50	41.78, 50.76	< 0.001
MFAS	526	246 (46.8)	173	0 (0.0)	46.77	42.02, 51.04	< 0.001
PPS	480	224 (46.7)	154	0 (0.0)	46.67	41.62, 51.14	< 0.001

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, CHM = Cochran-Mantel–Haenszel, FAS = full analysis set, FWS = facial wrinkle scale, MFAS = modified full analysis set, N = number of subjects in stratum, n (%) = number (percentage) of subjects with event, PPS = per protocol set, vs = versus.

[a] Composite endpoint treatment responder was only if both investigator and subject rated success criteria were satisfied.

[b] Response was defined as 2 point or greater reduction in FWS score at maximum frown achieving a score of 0 or 1 at Week 4 relative to baseline. Subjects with missing investigator or subject in clinic assessments with the FWS at Baseline or Week 4 were assigned as non-responders.

[c] CMH test based on 1-sided p-value for the proportion of responders in the treatment groups (BoNT/A-DP and placebo). Centre was used as stratification variable and small centres with less than three placebo subjects were combined.

Table 5: Study CPH-301-201030 Summary of responder rate with a 2 point or greater reduction in facial wrinkle scale and facial wrinkle scale score of 0 or 1 at maximum frown at Week 4, botulinum toxin treatment naïve versus non-naïve subjects (full analysis set)

Composite Endpoint Treatment Response[a]	Responder Rate[b]				Risk Difference vs. Placebo	95% CI for Risk Difference vs. Placebo	CMH p-value For Responder Rate[c]
	BoNT/A-DP		Placebo				
	N	n (%)	N	n (%)			
Previous use of Botulinum toxin	183	86 (47.0)	59	0 (0.0)	46.99	37.63, 52.21	<0.001
Naive	346	160 (46.2)	116	0 (0.0)	46.24	40.15, 51.51	<0.001

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, CI = confidence interval, FWS = facial wrinkle scale, N = number of subjects in stratum, n (%) = number (percentage) of subjects with event, vs = versus.

[a] Composite endpoint treatment responder was only if both investigator and subject rated success criteria were satisfied.

[b] Response was defined as 2 point or greater reduction in FWS score at maximum frown achieving a score of 0 or 1 at Week 4 relative to baseline. Subjects with missing investigator or subject in clinic assessments with the FWS at Baseline or Week 4 were assigned as non-responders.

[c] Pearson Chi-Square test based on 1-sided p-value for the proportion of responders in the treatment groups (BoNT/A-DP and placebo). In case of a total number of observations below 30, or in case of 1 cell or greater frequency below 5, Fisher's exact test was used instead.

In the investigator assessment, the responder rates at Week 4 were 65.8% of subjects for the letibotulinumtoxinA group and 0.6% of subjects for the placebo group. The treatment difference was 65.21% (95% CI: 60.32, 69.16); p < 0.001).

In the subject assessment, the responder rates at Week 4 were 54.8% and 0% for the letibotulinumtoxinA and placebo groups, respectively. The treatment difference was 54.82% (95% CI: 50.05, 59.01) p < 0.001. These analyses were done in the full analysis set (FAS).

The results for the modified full analysis set (MFAS) and per protocol set (PPS) for the separate investigator and subject assessment of FWS responder rate were consistent with the FAS results. Separate analyses of the investigator and subject assessments for treatment response at Week 4 were consistent with the (primary) composite endpoint.

Secondary endpoints

The responder rates were higher for the letibotulinumtoxinA arm at Weeks 12, 16 and 20. The treatment difference was statistically significant for Weeks 12 and 16 and not for Week 20.

In the Week 12 observed analysis, missing values were excluded.

Table 6: Study CPH-301-201030 Summary of responder rates with a 2 point or greater reduction in facial wrinkle scale and facial wrinkle scale score of 0 or 1 at maximum frown at Week 12, 16 and 20 (full analysis set)

Treatment Response [b]		Responder rate				Risk Difference vs. Placebo	95% CI for Risk Difference vs. Placebo	CMH p-value (vs Placebo)[c]
		BoNT/A-DP (N=529)		Placebo (N=175)				
		N	n (%)	N	n (%)			
Week 12	Composite [a]	529	67 (12.7)	175	0 (0.0)	12.67	9.32, 15.77	<0.001
	Investigator	529	131 (24.8)	175	1 (0.6)	24.19	19.85, 28.07	<0.001
	Subject	529	92 (17.4)	175	0 (0.0)	17.39	13.71, 20.85	<0.001
Week 12 Observed	Composite [a]	508	67 (13.2)	162	0 (0.0)	13.19	9.66, 16.41	<0.001
	Investigator	508	131 (25.8)	162	1 (0.6)	25.17	20.60, 29.18	<0.001
	Subject	508	92 (18.1)	162	0 (0.0)	18.11	14.24, 21.69	<0.001
Week 16 Observed	Composite [a]	501	22 (4.4)	159	0 (0.0)	4.39	1.61, 6.56	0.003
	Investigator	501	44 (8.8)	159	0 (0.0)	8.78	5.57, 11.58	<0.001
	Subject	501	36 (7.2)	159	1 (0.6)	6.56	3.11, 9.21	<0.001
Week 20 Observed	Composite [a]	503	6 (1.2)	158	0 (0.0)	1.19	-1.27, 2.58	0.084
	Investigator	503	10 (2.0)	158	0 (0.0)	1.99	-0.55, 3.62	0.037
	Subject	503	13 (2.6)	158	0 (0.0)	2.58	-0.02, 4.37	0.020

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, CI = confidence interval, CMH = Cochran–Mantel–Haenszel, FWS = facial wrinkle scale, N = number of subjects in stratum, n (%) = number (percentage) of subjects with event, vs = versus.

Observed = missing values were excluded from analysis.

[a] Composite endpoint treatment responder was only if both investigator and subject rated success criteria were satisfied.

[b] Response was defined as 2 point or greater reduction in FWS score at maximum frown achieving a score of 0 or 1 at Week 4 relative to baseline. Subjects with missing investigator or subject in clinic assessments with the FWS at Baseline or Week 4 were assigned as non-responders.

[c] CMH test based on 1-sided p-value for the proportion of responders in the treatment groups (BoNT/A-DP and placebo). Centre was used as stratification variable and small centres with less than three placebo subjects were combined.

At Weeks 12, 16 and 20, the responder rates were similar for subjects who had received previous treatment with botulinum toxin 12 months before the study compared with treatment

naïve subjects. The treatment differences at various time points remained in favour of letibotulinumtoxinA relative to placebo.

Responder rates for FWS score at rest

The rate for 1 point or greater reduction in FWS score at rest was 63.1% for the letibotulinumtoxinA group and 15.4% for the placebo group at Week 4 for the investigator assessment ($p < 0.001$); and 77.9% and 9.7% for the letibotulinumtoxinA and placebo groups, respectively for the subject assessment ($p < 0.001$)

It appears that previous treatment with botulinum toxin had no apparent effect on rates of subjects with 1 point or greater reduction in FWS at rest.

The sponsor provided an addendum to the clinical study report as it was discovered that subjects for which the FWS score at rest was less than 1 at Baseline in the ADEFF dataset (Efficacy Endpoints Occurrence Data) were not excluded from the analyses. In consequence, the response rate and related results for each group was underestimated because the denominator contained more subjects than it should. Therefore, at rest, the responder rates for 1 or greater point reduction in FWS score were 70.5% for the letibotulinumtoxinA group and 16.9% for the placebo group at Week 4 for the investigator assessment ($p < 0.001$); and 82.1% and 10.2% for the letibotulinumtoxinA and placebo groups, respectively for the subject assessment ($p < 0.001$).

Psychological impact at Week 4 after first treatment

Based on the modified Skindex-16 glabellar line quality of life scale, emotional and functional domains showed greater improvement for subjects who received letibotulinumtoxinA. The treatment differences were statistically significant.

Table 7: Study CPH-301-201030 Summary of modified Skindex-16 glabellar line quality of life scale (full analysis set)

			BoNT/A-DP (N=529)	Placebo (N=175)	p-value [a]
Absolute change from baseline to Week 4, double-blind phase	Emotional domain	n	522	168	<0.001
		Mean ± SD	-32.74 ± 31.134	0.63 ± 16.997	
		Median	-31.20	0.00	
		Minimum, maximum	-100.0, 50.0	-50,0, 50.0	
	Functioning domain	n	522	168	<0.001
		Mean ± SD	-27.44 ± 30.358	-1.14 ± 22.041	
		Median	-25.00	0.00	
		Minimum, maximum	-100.0, 83.4	-100.0, 58.3	
	Overall (emotional and functioning)	n	522	168	<0.001
		Mean ± SD	-30.47 ± 28.707	-0.14 ± 16.637	
		Median	-28.60	0.00	
		Minimum, maximum	-100.0, 46.4	-50.0, 50.0	

Abbreviations: BoNT /A-DP = Botulinum neurotoxin type A drug product, N = number of subjects randomised, n = number of subjects included in the analysis, SD = standard deviation.

Emotional = sum of items (appearance, self-conscious/uncomfortable, annoyed/frustrated, unhappy/low mood). Functioning = sum of items (personal relationship, social interactions, work/daily activities).

[a] P-value was based on Wilcoxon Rank Sum test to compare the absolute change from Baseline between BoNT /A-DP and placebo.

Study CPH-302-201030 (BLESS II)

A Phase III randomised controlled trial with a similar study design as BLESS I.

A total 213 individuals were randomised in a 3:1 ratio to letibotulinumtoxinA (n = 160) and placebo (n = 53) arms. Across treatment groups, 84% subjects completed the study.

At Baseline, mean age was around 52 years, 87.2% of subjects were under 65 years of age, 91.5% of subjects were female.

Results

Primary composite outcome

The composite responder rate at Week 4 was 48.8% for the letibotulinumtoxinA group, and 1.9% for the placebo group (FAS). The difference in responder rates between the letibotulinumtoxinA and placebo groups at Week 4 was 46.86%, which was statistically significant (95% CI: 35.77, 54.70; p < 0.001).

Table 8: Study CPH-302-201030 Summary of composite responder rates for 2 point or greater reduction in facial wrinkle scale and facial wrinkle scale score of 0 or 1 at maximum frown at Week 4 (primary endpoint, composite investigator and subject assessment)

Composite Endpoint Treatment Response [a]	Responder Rate [b]				Risk Difference vs. Placebo	95% CI for Risk Difference vs. Placebo	CMH p-value for Responder Rate [c]
	BoNT/A-DP		Placebo				
	N	n (%)	N	n (%)			
FAS	160	78 (48.8)	53	1 (1.9)	46.86	35.77, 54.70	< 0.001
MFAS	158	78 (49.4)	52	1 (1.9)	47.44	36.21, 55.32	< 0.001
PPS	134	70 (52.2)	45	0 (0.0)	52.24	40.73, 60.52	< 0.001

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, CI = confidence interval, CMH = Cochran–Mantel–Haenszel, FAS = full analysis set, FWS = facial wrinkle scale, MFAS = modified full analysis set, N = number of subjects in stratum, n (%) = number (percentage) of subjects with event, PPS = per protocol set, vs = versus.

[a] Composite endpoint treatment responder was only if both the investigator and subject rated success criteria were satisfied.

[b] Response was defined as 2 point or greater reduction in FWS score at maximum frown achieving a score of 0 or 1 at Week 4 relative to baseline. Subjects with missing investigator or subject in clinic assessments with the FWS at Baseline or Week 4 were assigned as non-responders.

[c] CMH test based on 1-sided p-value for the proportion of responders in the treatment groups (BoNT/A-DP and placebo). Study centre was used as stratification variable and small study centres with less than three placebo subjects were combined.

Similar to BLESS I, a higher scoring by investigator, compared to subjects was noted. The sensitivity analysis results were consistent with the primary analysis and the MFAS and PPS were consistent with the FAS results.

Table 9: Study CPH-302-201030 Summary of responder rates for 2 point or greater reduction in facial wrinkle scale and facial wrinkle scale score of 0 or 1 at maximum frown at Week 4 (investigator assessment and subject assessment)

Treatment Response	Responder Rate [a]				Risk Difference vs. Placebo	95% CI for Risk Difference vs. Placebo	CMH p-value for Responder Rate [b]
	BoNT/A-DP		Placebo				
	N	n (%)	N	n (%)			
Assessment by:							
FAS							
Investigator	160	120 (75.0)	53	1 (1.9)	73.11	62.28, 79.38	<0.001
Subject	160	83 (51.9)	53	1 (1.9)	49.99	38.85, 57.75	<0.001
MFAS							
Investigator	158	120 (75.9)	52	1 (1.9)	74.03	63.10, 80.23	<0.001
Subject	158	83 (52.5)	52	1 (1.9)	50.61	39.33, 58.40	<0.001
PPS							
Investigator	134	105 (78.4)	45	0 (0.0)	78.36	67.34, 54.49	<0.001
Subject	134	75 (56.0)	45	0 (0.0)	55.97	44.42, 64.09	<0.001

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, CI = confidence interval, CMH = Cochran–Mantel–Haenszel, FAS = full analysis set, FWS = facial wrinkle scale, MFAS = modified full analysis set, N = number of subjects in stratum, n (%) = number (percentage) of subjects with event, PPS = per protocol set, vs = versus.

[a] Response was defined as 2 point or greater reduction in FWS score at maximum frown achieving a score of 0 or 1 at Week 4 relative to baseline. Subjects with missing investigator or subject in clinic assessments with the FWS at Baseline or Week 4 were assigned as non-responders.

[b] CMH test based on 1-sided p-value for the proportion of responders in the treatment groups (BoNT/A-DP and placebo).

Study centre was used as stratification variable and small study centres with less than three placebo subjects were combined.

The treatment effect for letibotulinumtoxinA versus placebo was consistent for subjects who had previous use of botulinum toxin compared with treatment naïve subjects, but with a larger effect for those who had previously used botulinum toxin.

Table 10: Study CPH-302-201030 Summary of responder rates for 2 point or greater reduction in facial wrinkle scale and facial wrinkle scale score of 0 or 1 at maximum frown at Week 4, botulinum toxin treatment naïve versus non-naïve subjects (full analysis set)

Composite Endpoint Treatment Response[a]	Responder rate [2]				Risk Difference vs Placebo	95% CI for Risk Difference vs Placebo	Pearson Chi-square p-value[c]
	BoNT/A-DP (N=160)		Placebo (N=53)				
	N	n (%)	N	n (%)			
Previous use of botulinum toxin	55	29 (52.7)	11	0 (0.0)	52.73	23.79, 65.31	<0.001
Naïve	105	49 (46.7)	42	1 (2.4)	44.29	30.70, 53.98	<0.001

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, CI = confidence interval, FWS = facial wrinkle scale, N = number of subjects in stratum, n (%) = number (percentage) of subjects with event, vs = versus.

[a] Composite endpoint treatment responder was only if both investigator and subject rated success criteria were satisfied.

[b] Response was defined as 2 point or greater reduction in FWS score at maximum frown achieving a score of 0 or 1 at Week 4 relative to baseline. Subjects with missing investigator or subject in clinic assessments with the FWS at Baseline or Week 4 were assigned as non-responders.

[c] Pearson Chi-Square test based on 1-sided p-value for the proportion of responders in the treatment groups (BoNT/A-DP and placebo). In case of a total number of observations below 30, or in case of 1 cell or greater frequency below 5, Fisher's exact test was used instead.

In the letibotulinumtoxinA group, the composite FWS rate was 51.8% for subjects under 65 years of age (N = 141) and 26.3% for those 65 years of age or older (N = 19). The composite responder rate was 51.3% for females (N = 150) and 10% for males in the letibotulinumtoxinA group. However, as only 10 participants were males, results in male subjects are inconclusive. Furthermore, as only a few subjects in the study were of racial groups other than White, responder rates by race were also inconclusive.

The low number of participants in the over 65 years age group was noted. Also, the reduced proportion of males and non-White subjects.

Secondary efficacy outcomes

This study did not achieve its secondary endpoints.

The responder rates were higher for the letibotulinumtoxinA group at Weeks 12, 16 and 20 compared to placebo. However, the 95% CI for the treatment difference included zero and it was not statistically significant.

Table 11: Study CPH-302-201030 summary of responder rates 2 point or greater reduction in facial wrinkle scale and facial wrinkle scale score of 0 or 1 at maximum frown at Weeks 12, 16, and 20 (full analysis set)

Treatment response[b]		Responder Rate				Risk Difference vs. Placebo	95% CI for Risk Difference vs. Placebo	CMH p-value (vs placebo)[c]
		BoNT/A-DP (N=160)		Placebo (N=53)				
		N	n (%)	N	n (%)			
Week 12	**Composite[a]**	160	7 (4.4)	53	0 (0.0)	4.38	-2.74, 8.75	0.087
	Investigator	160	18 (11.3)	53	0 (0.0)	11.25	3.39, 17.08	0.007
	Subject	160	15 (9.4)	53	0 (0.0)	9.38	1.71, 14.89	0.013
Week 12 (Observed)	Composite[a]	148	7 (4.7)	47	0 (0.0)	4.73	-3.20, 9.44	0.096
	Investigator	148	18 (12.2)	47	0 (0.0)	12.16	3.45, 18.41	0.008
	Subject	148	15 (10.1)	47	0 (0.0)	10.14	1.63, 16.05	0.016
Week 16 (Observed	Composite[a]	149	5 (3.4)	48	0 (0.0)	3.36	-4.30, 7.61	0.121
	Investigator	149	5 (3.4)	48	0 (0.0)	3.36	-4.30, 7.61	0.121
	Subject	149	7 (4.7)	48	0 (0.0)	4.70	-3.09, 9.38	0.071
Week 20 (Observed)	Composite[a]	148	2 (1.4)	48	0 (0.0)	1.35	-6.12, 4.79	0.218
	Investigator	148	2 (1.4)	48	0 (0.0)	1.35	-6.12, 4.79	0.218
	Subject	148	3 (2.0)	48	0 (0.0)	2.03	-5.50, 5.79	0.146

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, CI = confidence interval, CMH = Cochran–Mantel–Haenszel, FWS = facial wrinkle scale, N = number of subjects in stratum, n (%) = number (percentage) of subjects with event, vs = versus.

Observed = missing values were excluded from analysis.

[a] Composite endpoint treatment responder was only if both investigator and subject rated success criteria were satisfied.

[b] Response was defined as 2 point or greater reduction in FWS score at maximum frown achieving a score of 0 or 1 at Week 4 relative to baseline. Subjects with missing investigator or subject in clinic assessments with the FWS at Baseline or Week 4 were assigned as non-responders.

[c] CMH test based on 1-sided p-value for the proportion of responders in the treatment groups (BoNT/A-DP and placebo).

Study centre was used as stratification variable and small study centres with less than three placebo subjects were combined.

At Weeks 12, 16, and 20, the composite responder rates were similar for subjects who had received previous treatment with botulinum toxin before the study compared to treatment naïve subjects.

Psychological impact at Week 4

Despite the study not achieving the secondary endpoints, the modified Skindex-16 glabellar line quality of life scale showed a positive psychological impact in both emotional and functional domains. The treatment differences were statistically significant.

Table 12: Study CPH-302-201030 summary of modified Skindex-16 glabellar line quality of life scale (full analysis set)

Absolute Change from Baseline to Week 4, Double-blind Phase		BoNT/A-DP (N=160)	Placebo (N=53)	p-value[a]
Emotional domain	N	154	49	< 0.001
	Mean ± SD	-32.47 ± 24.410	-3.06 ± 15.772	
	Median	-35.00	0.00	
	Minimum, maximum	-80.0, 30.0	-60.0, 30.00	
Functioning domain	N	154	49	< 0.001
	Mean ± SD	-26.79 ± 26.469	-8.30 ± 16.468	

	Median	-20.00	-6.60	
	Minimum, maximum	-80.00, 40.0	-40.0, 33.3	
Overall (emotional and functioning)	N	154	49	< 0.001
	Mean ± SD	-30.04 ± 23.529	-5.31 ± 14.273	
	Median	-28.60	-5.70	
	Minimum, maximum	-80.0, 31.4	-51.4, 31.4	

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, N = number of subjects, SD = standard deviation.

Emotional = sum of items (appearance, self-conscious/uncomfortable, annoyed/frustrated, unhappy/low mood).

Functioning = sum of items (personal relationship, social interactions, work/daily activities).

[a] P-value was based on Wilcoxon Rank Sum test to compare the absolute change from Baseline between BoNT/A-DP and placebo.

Of those subjects who entered the open label phase, 65.6% of subjects were retreated with study drug at Week 12; and 26.3% of subjects were retreated between Week 16 and Week 28. The mean (± SD) time to retreatment was 98.61 (± 32.408) days in the letibotulinumtoxinA group compared to 85.32 (± 31.343) days for subjects in the placebo group. The study design did not allow for treatment after Week 48.

Study CPH-303-201400 (BLESS III)

At the time of submission, this study was in progress. The submitted data were analysed at the interim analysis cut-off date of 10 February 2020.

The study design was identical to studies BLESS I and II.

This study was a Phase III randomised controlled trial to assess the efficacy and safety of letibotulinumtoxinA in the treatment of glabellar lines in comparison with placebo followed by an open label extension study. Adults with moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on the 4 point FWS) as determined by in clinic assessments by both the investigator and the subject (where: 0 = none, 1 = mild, 2 = moderate, 3 = severe) were enrolled. The study treatment was identical to BLESS I and II.

An interim analysis was performed after all subjects had completed the re-evaluation for retreatment visit at Week 16 of the first treatment cycle or had completed the double blind phase (whichever occurred earlier).

Since the primary and the key secondary efficacy endpoints belong to the first 16 weeks of the double blind phase, the final analysis of these endpoints was conducted during this interim analysis.

A total 355 subjects were randomised (266 in letibotulinumtoxinA, 89 in placebo). Major protocol deviations were reported for 23 (8.6%) subjects in the letibotulinumtoxinA group and four (4.5%) subjects in the placebo group during the double blind phase.

Overall, the mean ± SD age was 51.5 ± 11.58 years, 11.5% of subjects were 65 years of age or older, 7.6% of subjects were males.

Results

Primary composite outcome

At Week 4, the composite responder rate was 64.7% for the letibotulinumtoxinA group and 0% for the placebo group. The treatment difference was statistically significant: 64.66% (95% CI: 57.44, 70.16; p < 0.00, FAS).

Table 13: Study CPH-303-201400 Summary of composite responder rates for 2 point or greater reduction in facial wrinkle scale and facial wrinkle scale score of 0 or 1 at

maximum frown at Week 4, primary endpoint, composite investigator and subject assessment (interim analysis)

Composite Endpoint Treatment Response[a]	Responder Rate[b] BoNT/A-DP		Placebo		Risk Difference vs. Placebo	95% CI for Risk Difference vs. Placebo	CMH p-value vs. Placebo[c]
	N	n (%)	N	n (%)			
FAS	266	172 (64.7)	89	0 (0.0)	64.66	57.44, 70.16	<0.001
MFAS	264	172 (65.2)	86	0 (0.0)	65.15	57.84, 70.64	<0.001
PP	240	159 (66.3)	81	0 (0.0)	66.25	58.58, 71.93	<0.001

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, CI = confidence interval, CMH = Cochran–Mantel–Haenszel, FAS = full analysis set, FWS = facial wrinkle scale, MFAS = modified full analysis set, N = number of subjects in corresponding population and subgroup, n (%) = number (percentage) of subjects with event, PP = per protocol, vs = versus.

[a] Composite endpoint treatment responder was only applicable if both the investigator and subject rated success criteria were satisfied.

[b] Response was defined as 2 point or greater reduction in FWS score at maximum frown achieving a score of 0 or 1 at Week 4 relative to baseline. Subjects with missing investigator or subject in clinic assessments with the FWS at Baseline or Week 4 were assigned as non-responders.

[c] CMH test based on 1-sided p-value for the proportion of responders in the treatment groups (BoNT/A-DP and placebo). Study centre was used as stratification variable and small study centres with less than three placebo subjects were combined.

Psychological impact at Week 4

The modified Skindex-16 glabellar line quality of life scale showed a large positive psychological impact in both emotional and social functioning domains.

Table 14: Study CPH-303-201400 Summary of modified Skindex-16 glabellar line quality of life scale, interim analysis (full analysis set)

Absolute Change from Baseline to Week 4, Double-blind Phase		BoNT/A-DP (N=266)	Placebo (N=89)	p-value[a]
Emotional domain	n	264	86	<0.001
	Mean ± SD	-42.27 ± 34.484	0.50 ± 20.427	
	Median	-43.80	0.00	
	Minimum, maximum	-100.0, 68.8	-68.8, 68.7	
Social functioning domain	n	264	86	<0.001
	Mean ± SD	-33.14 ± 33.193	-2.23 ± 31.088	
	Median	-25.00	0.00	
	Minimum, maximum	-100.0, 100.0	-100.0, 75.0	
Overall (emotional and social functioning)	n	264	86	<0.001
	Mean ± SD	-38.35 ± 31.075	-0.67 ± 22.369	
	Median	-42.90	0.00	
	Minimum, maximum	-100.0, 60.7	-71.4, 53.6	

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, N = number of subjects, n (%) = number (percentage) of subjects with event, SD = standard deviation.

Emotional = sum of items (appearance, self-conscious/uncomfortable, annoyed/frustrated, unhappy/low mood).

Social functioning = sum of items (personal relationship, social interactions, work/daily activities).

[a] P-value was based on Wilcoxon Rank Sum test to compare the absolute change from Baseline between BoNT/A-DP and placebo.

Table 15: Study CPH-303-201400 Psychological impact of modified Skindex-16 glabellar line quality of life scale at Baseline and Week 4 of double blind phase, interim analysis (full analysis set)

Psychological Impact		BoNT/A-DP (N=266)		Placebo (N=89)	
		N	n (%)	N	n (%)
Baseline	Mild (overall score at baseline: 0-9 points)	266	31 (11.7)	89	13 (14.6)
	Moderate (overall score at baseline: 10-18	266	127 (47.7)	89	36 (40.4)
	Severe (overall score at baseline: 19-28 points)	266	108 (40.6)	89	40 (44.9)
Week 4	Mild (overall score at baseline: 0-9 points)	266	187 (70.3)	89	17 (19.1)
	Moderate (overall score at baseline: 10-18	266	49 (18.4)	89	31 (34.8)
	Severe (overall score at baseline: 19-28 points)	266	28 (10.5)	89	38 (42.7)

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, N = number of subjects in corresponding population and subgroup, n (%) = number (percentage) of subjects with event.

Other efficacy studies

Studies HG-11-01 and HG-13-02 were supportive efficacy studies.

Study HG-11-01

Study HG-11-01 was a double blind, non-inferiority study conducted in 271 subjects in Korea. In the study letibotulinumtoxinA (tradename in Korea 'Botulax Inj') was compared with the approved botulinum toxin A (Botox) in South Korea.

The dose of letibotulinumtoxinA was the same as the approved dose of Botox, that is, 20 U given as five intramuscular injections of 4 U per injection site.

The primary efficacy objective was to evaluate the responder rate by physician's rating line severity at maximum frown at 4 weeks post treatment. The study was designed as a non-inferiority study.

The results demonstrated non-inferiority of letibotulinumtoxinA compared with Botox. The responder rate of 89.34% for the letibotulinumtoxinA group was greater than that of 81.89% for the Botox Inj group. The lower end of the 95% CI for the between group difference in the responder rate was -1.24 which was greater than the non-inferiority margin (-14.57) demonstrating non-inferiority of letibotulinumtoxinA to Botox.

The primary outcome was supported by the secondary endpoints which all showed a greater or similar response between letibotulinumtoxinA and Botox Inj.

Study HG-13-02

Study HG-13-02 was an open label, post marketing study required to meet regulatory requirements in Korea.

The objective of this study was to assess the safety of Letybo, when used in clinical practise, according to the indication approved in Korea. This product is marketed in Korea with the trade name 'Botulax'.

Botulinum toxin type A (Botulax) is indicated for the temporary improvement of upper facial rhytids (glabellar lines and crow's feet) in adults.

Efficacy was also assessed from the responder rate by physician rating of line severity at maximum frown that were collated at Week 4 post treatment.

Adults between 18 and 65 years of age with moderate to severe glabellar lines were included.

A total 815 subjects were included in the safety set. Around 85% of subjects were females. Majority of subjects were below 60 years of age (around 98%). Almost all of the subjects had

grade 2 to 3 (moderate to severe) line severity at maximum frown. Around 66% of subjects had received prior treatment with botulinum toxin.

LetibotulinumtoxinA achieved FWS scores for clinical effectiveness in 276 out of 289 (95.5%) physician assessment of glabellar line severity at maximum frown and 96 out of 100 (96%) physician assessment of glabellar line severity at rest. Subject assessment at Week 4 was considered effective in 685 out of 814 subjects (84.15%).

Pooled and meta-analyses of efficacy studies

A greater proportion of subjects in the Letybo group achieved the composite endpoint. The higher investigator compared to subject rating is evident across studies.

Table 16: Results of the pivotal studies for primary outcome measure, composite, investigator, and subject responder rate at Week 4

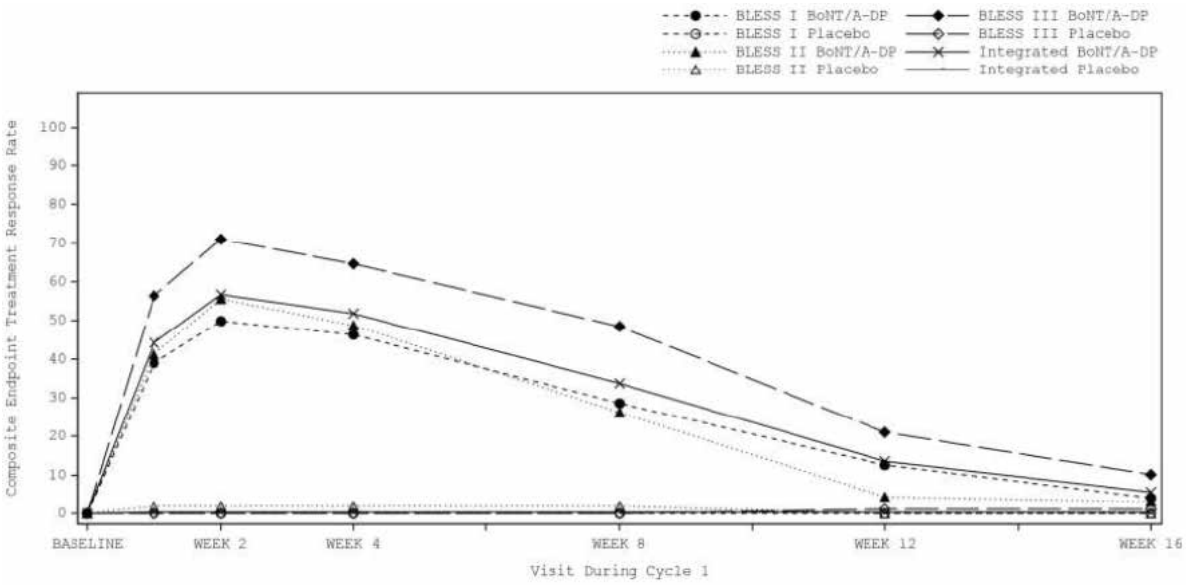
Primary Outcome measure	Study CPH-301-201030 BLESS I		Study CPH-302-201030 BLESS II		Study CPH-303-201400 BLESS III		Overall	
	BoNT/A-DP N=529	Placebo N=175	BoNT/A-D N=160	Placebo N=53	BoNT/A-DP N=266	Placebo N=89	BoNT/A-DP N=957	Placebo N=319
Composite	246 46.5%	0 0%	78 48.8%	1 1.9%	172 64.7%	0 0%	496 51.8%	1 0.3%
Investigator	348 65.8%	1 0.6%	120 75.0%	1 1.9%	209 78.6%	1 1.1%	677 70.7%	3 0.9%
Subject	290 54.8%	0 0%	83 51.9%	1 1.9%	183 68.8%	0 0%	556 58.1%	1 0.3%

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, N = number of subjects in corresponding population and subgroup.

Time course for primary efficacy

The treatment effect appears to be at maximum at two weeks post treatment and declining over the 4 to 16 week period.

Figure 3: Time course of composite endpoint treatment response (observed values) at maximum frown by visit during Cycle 1, integrated analysis/summary of efficacy for BLESS I, II, and III interim analysis



Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product.

Safety

Study HG-13-02

Study HG-13-02 was a post market surveillance study that assessed safety as the primary outcome. This study was conducted in South Korea.

Adults aged between 18 and 65 years with moderate to severe glabellar lines associated with corrugator muscle and/or procerus muscle activities were included.

The mean total dose of Botulax lnj was 15.78 ± 6.83 U (minimum 6 U, maximum 45 U, median 14 U).

The clinical evaluation highlighted that the dose regimen and administration recommended in the Korean PI is the same as described in the pivotal studies and the proposed Australian PI. It was also noted that the maximum dose used in this study was more than twice the recommended maximum dose in the proposed Australian PI.

A total 815 subjects were included in the safety analysis, 85.15% of subjects were females. Mean age was 36.45 ± 11.20 years. Around 6% of subjects reported adverse events (AEs). The most common AEs were injection site reaction, injection site bruising, eyelid sensory disorder, and headache.

Around 2% of subjects reported unexpected AEs. The most common unexpected AEs were injection site bruising, periorbital oedema, body aches, injection site redness, injection site pressure and allergic dermatitis.

Around 5% subjects reported treatment-emergent adverse events (TEAEs). The most common TEAEs were headache, injection site itching, periorbital oedema, injection site pressure, injection site redness, ptosis and injection site swelling.

No serious adverse evets (SAEs) or deaths were reported.

Study HG-11-01

Study HG-11-01 compared the safety profile of letibotulinumtoxinA with Botox, approved in South Korea.

Overall, a lower proportion of subjects in the letibotulinumtoxinA group experienced TEAEs, compared to the Botox group (28.4% versus 32.8%). A greater proportion of subjects in the letibotulinumtoxinA group experienced eye disorders, compared to the Botox group (7.5% versus 5.1%). Incidence of eyelid ptosis was two times higher in the letibotulinumtoxinA group, compared to the Botox group (4.5% versus 2.2%). Headache was more commonly reported in the Botox, compared to the letibotulinumtoxinA group (2.9% versus 0.7%).

Discontinuations were comparable across treatment groups. Nine subjects discontinued the study, four in the letibotulinumtoxinA group and five in the Botox group. Five subjects were lost to follow-up (two subjects in the letibotulinumtoxinA group and three in the Botox group). Three subjects (one subject in the letibotulinumtoxinA group and two in the Botox group) withdrew informed consent (one subject experiencing sudden hearing loss in the Botox group, which was reported as an SAE). One further discontinuation was due to an SAE (cellulitis in the letibotulinumtoxinA group).

Two SAEs were reported in one subject in each treatment group. One event of cellulitis in the letibotulinumtoxinA group and one event of sudden hearing loss in the Botox group. Neither was classified as a treatment related SAE.

Table 17: Study HG-11-01 Frequency (n and %) of treatment-emergent adverse events occurring in 1% or less of subjects in any treatment group by system organ class and preferred term (safety population)

System Organ Class **Preferred Term**	**BoNT/A-DP (N=134)**	**Botox® (N=137)**
Subjects with TEAEs	**38 (28.4)**	**45 (32.8)**
Infections and infestations	*10 (7.5)*	*9 (6.6)*
Influenza	2 (1.5)	1 (0.7)
Cystitis	2 (1.5)	*0*
Nasopharyngitis	0	2 (1.5)
General disorders and administration site conditions	*6 (4.5)*	*12 (8.8)*
Injection site reaction	4 (3.0)	11 (8.0)
Eye disorders	*10 (7.5)*	*7 (5.1)*
Eyelid ptosis	6 (4.5)	3 (2.2)
Conjunctivitis	2 (1.5)	1 (0.7)
Nervous system disorders	*2 (1.5)*	*6 (4.4)*
Headache	1 (0.7)	4 (2.9)
Respiratory, thoracic and mediastinal disorders	*2 (1.5)*	*6 (4.4)*
Cough	1 (0.7)	2 (1.5)
Skin and subcutaneous tissue disorders	*6 (4.5)*	*2 (1.5)*
Dermatitis contact	2 (1.5)	*0*
Injury, poisoning and procedural complications	*5 (3.7)*	*2 (1.5)*
Joint sprain	2 (1.5)	*0*
Musculoskeletal and connective tissue disorders	*2 (1.5)*	*5 (3.6)*
Back pain	2 (1.5)	0
Pain in extremity	0	2 (1.5)
Gastrointestinal disorders	*2 (1.5)*	*2 (1.5)*
Vomiting	0	2 (1.5)

Abbreviations: BoNT/A-DP = Botulinum neurotoxin type A drug product, N = number of subjects treated, n (%) = number (percentage) of subjects with event, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event.

Table 18: Treatment exposure across pivotal studies

	Double-blind Part		**Open-label Part**	**Overall**
Study Treatment	**BoNT/A-DP n (%)**	**Placebo n (%)**	**BoNT/A-DP n (%)**	**n (%)**
Study BLESS I	**N=529**	**N=175**	**N=659**	**N=704**
First study treatment	529 (100.0)	175 (100.0)		704 (100.0)
Second study treatment			659 (100.0)	
Third study treatment			616 (93.5)	
Fourth study treatment			464 (70.4)	
Study BLESS II	**N=160**	**N=53**	**N=195**	**N=213**
First study treatment	160 (100.0)	53 (100.0)		213 (100.0)
Second study treatment			195 (100.0)	
Third study treatment			181 (92.8)	
Fourth study treatment			149 (76.4)	
Study BLESS III (IA)	**N=266**	**N=89**	**N=0**	**N=355**
First treatment	266 (100.0)	89 (100.0)	-	355 (100.0
BLESS I, II, and III (ISS Population)	**N=955**	**N=317**	**N=854[a]**	**N=1272**

First study treatment	955 (100.0)	317 (100.0)		1272 (100.0)
Second study treatment			854 (100.0)[a]	854 (67.1)[a]
Third study treatment			797 (93.3)[a]	797 (62.7)[a]
Fourth study treatment			613 (71.8)[a]	613 (48.2)[a]

Abbreviations: BoNT/A-DP = botulinum neurotoxin type A drug product, IA = interim analysis, N = number of subjects randomised, n (%) = number (percentage) of subjects with event.

Overall = sum of subjects in double blind part.

[a] BLESS I and BLESS II only.

Overall, the treatment exposure was around 70% for the second and third treatment and around 50% for the fourth treatment.

Across the pivotal studies, the most commonly reported AE was headache. Other AEs were upper respiratory tract infections and procedural pain.

Treatment-emergent adverse events

The most common treatment emergent adverse events (TEAE) were headache, injection site pain, contusion, eyelid ptosis, blepharospasm and haematoma.

A higher incidence of headache in the letibotulinumtoxinA, compared to placebo group was noted. Eyelid ptosis was reported in around 0.2% of subjects in letibotulinumtoxinA group.

Table 19: Treatment-emergent adverse events

System Organ Class **Preferred Term**	**Double-blind**		**Open-label[a] BoNT/A-DP (N=854)**	**Both parts[b]**
	Treatment Cycle 1 BoNT/A-DP (N=955)	**Placebo (N=317)**		**BoNT/A-DP only (N=1162)**
Subjects with any TEAE[c]	**33 (3.5)**	**8 (2.5)**	**46 (5.4)**	**70 (6.0)**
Nervous system disorders	*19 (2.0)*	*2 (0.6)*	*20(2.3)*	*33 (2.3)*
Headache	16 (1.7)	1 (0.3)	16 (1.9)	27 (2.3)
Head discomfort	2 (0.2)	0	1 (0.1)	3 (0.3)
Migraine	0	1 (0.3)	1 (0.1)	1 (0.1)
Dizziness	1 (0.1)	0	0	1 (0.1)
Paraesthesia	1 (0.1)	0	1 (0.1)	1 (0.1)
Sinus headache[d]	0	0	1 (0.1)	1 (0.1)
Tension headache[e]	0	0	1 (0.1)	1 (0.1)
Visual field defect	1 (0.1)	0	0	1 (0.1)
General disorders and administration site conditions	*7 (0.7)*	*4 (1.3)*	*6 (0.7)*	*4 (0.5)*
Injection site pain	3 (0.3)	1 (0.3)	0	3 (0.3)
Injection site bruising	1 (0.1)	1 (0.3)	1 (0.1)	2 (0.2)
Facial pain[d]	0	1 (0.3)	1 (0.1)	1 (0.1)
Injection site haematoma[d]	1 (0.1)	0	0	1 (0.1)
Swelling	1 (0.1)	1 (0.3)	0	1 (0.1)
Administration site swelling[d]	0	0	1 (0.1)	1 (0.1)
Discomfit	0	0	1 (0.1)	1 (0.1)
Influenza line illness	0	0	1 (0.1)	1 (0.1)
Injection site mass	0	0	1 (0.1)	1 (0.1)
Injection site nodule	0	0	1 (0.1)	1 (0.1)
Injection site reaction[d]	1 (0.1)	0	1 (0.1)	1 (0.1)
Pain[e]	0	0	1 (0.1)	1 (0.1)
Pyrexia[e]	0	0	1 (0.1)	1 (0.1)
Eye disorders	*5 (0.5)*	*0*	*4 (0.5)*	*4 (0.5)*

System Organ Class Preferred Term	Double-blind		Open-label[a] BoNT/A-DP (N=854)	Both parts[b]
	Treatment Cycle 1 BoNT/A-DP (N=955)	Placebo (N=317)		BoNT/A-DP only (N=1162)
Eyelid ptosis	2 (0.2)	0	2 (0.2)	2 (0.3)
Blepharospasm	2 (0.2)	0	1 (0.1)	1 (0.1)
Conjunctivial haemorrhage[d]	0	0	1 (0.1)	1 (0.1)
Dry eye[d]	1 (0.1)	0	0	1 (0.1)
Eye pain[d]	0	0	1 (0.1)	1 (0.1)
Eyelid oedema[d]	0	0	1 (0.1)	1 (0.1)
Infections and infestations	*1 (0.1)*	*2 (0.6)*	*5 (0.6)*	*3 (0.4)*
Nasopharyngitis	0	1 (0.3)	2 (0.2)	1 (0.1)
Oral herpes	0	1 (0.3)	1 (0.1)	1 (0.1)
Bronchitis	0	0	1 (0.1)	1 (0.1)
Folliculitis[d]	1 (0.1)	0	0	1 (0.1)
Pharyngitis streptococcal	0	0	1 (0.1)	1 (0.1)
Pneumonia	0	0	1 (0.1)	1 (0.1)
sinusitis	0	0	1 (0.1)	1 (0.1)
Injury, poisoning and procedural complications	*2 (0.2)*	*1 (0.3)*	*3 (0.4)*	*5 (0.4)*
Contusion	2 (0.2)	1 (0.3)	1 (0.1)	3 (0.3)
Periorbital haematoma[d]	0	0	1 (0.1)	1 (0.1)
Procedural pain	0	0	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders	*2 (02)*	*0*	*1 (0.1)*	*3 (03)*
Brow ptosis	1 (0.1)	0	0	1 (0.1)
Dry skin[e]	1 (0.1)0	0	0	1 (0.1)
Urticaria[e]	00		1 (0.1)	1 (0.1)
Gastrointestinal disorders	*0*	*0*	*2 (02)*	*2 (02)*
Constipation	0	0	1 (0.1)	1 (0.1)
Nausea[e]	0	0	1 (0.1)	1 (0.1)
Vascular disorders	*1 (0.1)*	*1 (0.3)*	*0*	*1 (0.1)*
Haematoma[d]	1 (0.1)	1 (0.3)	0	1 (0.1)
Investigations	*0*	*0*	*1 (0.1)*	*1 (0.1)*
Blood potassium increased[e]	0	0	1 (0.1)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	*1 (0.1)*	*0*	*0*	*1 (0.1)*
Pharyngeal hypoaesthesia	1 (0.1)	0	0	1 (0.1)

Abbreviations: AE = adverse event, BoNT/A-DP = botulinum neurotoxin type A drug product, IA = interim analysis, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects randomised, n (%) = number (percentage) of subjects with event, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event.

Classifications of AEs based on MedDRA (version 22.1).

Percentage (%) based on number of subjects in the row category/N within the column category. A TEAE was defined as any event with onset or worsening (increase in severity) after receiving first dose of study (independent of whether it was BoNT/A-DP or placebo).

[a] Open label BoNT/A-DP with any retreatment (first, second, and third retreatment); restricted to studies BLESS I and II.

[b] Double blind BoNT/A-DP (first treatment) and open label BoNT/A-DP with any retreatment (first, second and third retreatment).

[c] Definite, probable, possible relationship to study medication and/or injection procedure or missing assessment of relationship to study medication and/or injection procedure.

[d] Events were only reported as injection procedure related NOT as related to study medication.

[e] Events were only reported as study medication related NOT as related to injection procedure.

Serious adverse events

The incidence of serious adverse events (SAEs) was 1% during double blind phase of the studies and 2% during open label extension phase. Osteoarthritis and coronary artery disease were reported for two (0.2%) subjects each.

Discontinuations

Across pivotal studies, seven subjects experienced TEAEs that led to study discontinuation (six subjects who received letibotulinumtoxinA during the double blind or open label parts of studies and one who received placebo (injection site bruising).

Three of the TEAEs that led to study drug discontinuation were pregnancies. In all three cases (all receiving letibotulinumtoxinA) healthy babies were born and no safety concerns were detected.

Of the four further TEAEs leading to withdrawal, two were not considered related to study treatment, one was considered related to study medication (headache), and one was considered related to injection procedures (injection site bruising).

The SAE of sudden hearing loss was reported by one subject 49 days after the administration of 50 U of letibotulinumtoxinA. It was classified as an SAE as it required treatment with steroids (dose not provided). The severity was reported as moderate. The subject had not fully recovered at the time of study termination but was reported as recovering. The event was considered 'probably not related' to the study drug but the subject was withdrawn from the study.

Adverse events of special interest

Adverse events of special interest (AESIs) were defined as events potentially related to local and/or distant spread of toxin effect.

Seventeen AESIs were reported by 16 patients. Twelve occurred during the double blind treatment phase (10 after receiving letibotulinumtoxinA and two after receiving placebo) and five in the open label phase.

Three of the events in the double blind treatment part (two eyelid ptosis and one brow ptosis), all after receiving letibotulinumtoxinA were considered possibly or probably related to study medication and two of these (eyelid ptosis and brow ptosis) also possibly or probably related to injection procedures.

The five AESI reported during the open label treatment comprised three eyelid ptosis which were considered drug related and three eyelid ptosis which were considered related to injection procedures.

Table 20: Adverse events of special interest indicative of spread of toxin in BLESS I, II, and III (integrated analysis) by subject, integrated summary of safety (safety analysis set)

Subject No.	Age/ Sex/ Race	MedDRA Preferred Term	Treat-ment Part	Causality (study drug)	Severity	Injection Procedure-related	SAE/ Disc	Out-come
Original treatment group: BoNT/A-DP								
1	40/F/W	Bradycardia	DB	Not related	Mild	No	No/No	R
2	40/F/W	Brow ptosis[a]	DB	Probably	Mild	Yes	No/No	R
3	63/F/W	Brow ptosis[a]	DB	Not related	Mild	No	No/No	NR
4	49/F/W	Eyelid ptosis	DB	Not related	Mild	No	No/No	R
5	47/F/W	Dysarthria	DB	Unlikely	Mild	No	No/No	R
6	59/F/W	Constipation	DB	Unlikely	Mild	No	No/No	NR
7	35/F/W	Eyelid ptosis	DB	Possibly	Mild	Yes	No/No	R

Subject No.	Age/ Sex/ Race	MedDRA Preferred Term	Treat-ment Part	Causality (study drug)	Severity	Injection Procedure-related	SAE/ Disc	Out-come
		Brow ptosis[a]	DB	Unlikely	Mild	No	No/No	R
8	70/F/W	Eyelid ptosis	DB	Possibly	Mild	No	No/No	R
9	45/F/B	Vision blurred	DB	Not related	Mild	No	No/No	R
10	46/F/W	Constipation	OL	nd	Mild	nd	No/No	NR
11	56/F/W	Eyelid ptosis	OL	Definitely	Mild	No	No/No	R
Original treatment group: Placebo								
12	38/F/W	Dysphagia	DB	Not related	Moderate	No	No/No	R
13	55/F/W	Muscular weakness	DB	Not related	Mild	No	No/No	R
14	59/F/B	Eyelid ptosis	OL	Definitely	Mild	Yes	No/No	R
15	48/F/B	Eyelid ptosis	OL	Definitely	Moderate	Yes	No/No	R
16	58/F/W	Eyelid ptosis	OL	Not related	Mild	Yes	No/No	R

Abbreviations: AESI = adverse event of special interest, BoNT/A-DP = botulinum neurotoxin type A drug product, B = Black or African American, DB = double blind, Disc = discontinuation of study drug, F = female, IA = interim analysis, MedDRA = Medical Dictionary for Regulatory Activities, nd = information not available, NR = not recovered/ not resolved, OL = open label, R = recovered/ resolved, SAE = serious adverse event, W = White.

Classifications of AEs based on MedDRA (version 22.1).

[a] Brow ptosis was not listed in the protocol to be reported as an AESI. Nevertheless, this event was reported as an AESI for one subject. The other events of brow ptosis in two subjects were not reported as an AESI by the investigator.

A total of six subjects reported TEAEs indicative of local spread of toxin during the double blind parts of the studies, all after receiving letibotulinumtoxinA. The AEs were brow ptosis in two subjects, eyelid ptosis in three subjects, and blurred vision in one subject. One event of brow ptosis and two events of eyelid ptosis were considered related to study medication while the two additional ptosis cases and the event of vision blurred were considered non-related.

A total of five subjects reported TEAEs indicative of distant spread of toxin during the double blind parts of the studies, three subjects after receiving letibotulinumtoxinA (bradycardia, dysarthria, and constipation) and two subjects after receiving placebo (muscular weakness, dysphagia). None of the events were considered related to study medication or injection procedures.

Hypersensitivity reactions

A total of three subjects in the letibotulinumtoxinA group reported TEAEs indicative of hypersensitivity during the double blind parts of the studies (hypersensitivity in two subjects and urticaria in one subject).

Immunogenicity and immunological events

At Baseline, 68 of 917 subjects (7.4%) and at end of study 67 of 854 subjects (7.8%) showed antidrug antibody reactivity. No neutralising anti-drug antibodies were detected in subjects receiving up to 4 treatments with letibotulinumtoxinA in the Phase III clinical studies.

Deaths

No deaths were reported during studies with letibotulinumtoxinA.

Recommendation following the clinical evaluation

The clinical evaluation has recommended approval of this application.

Risk management plan

The sponsor has submitted an Australian (AU) risk management plan (RMP) version 0.1 (dated 20 May 2021; data lock point (DLP) 1 September 2020). With the response to TGA questions, the sponsor has submitted AU-RMP version 0.2 (20 February 2022, DLP 1 September 2020).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 21. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 21: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Local and distant spread of toxin	ü	–	ü	–
	Exacerbation of pre-existing or subclinical neuromuscular disorders	ü	–	ü	–
Missing information	Use in pregnancy and lactation	ü	–	ü	–

The summary of safety concerns is acceptable and similar to other botulinum products.

Routine pharmacovigilance activities only are proposed which is acceptable as the product has been available overseas for a considerable length of time.

Routine risk minimisation activities only have been proposed and are considered acceptable. The sponsor has satisfactorily addressed matters raised in the initial report and is advised to monitor and report on off-label use through routine pharmacovigilance, given the lack of interchangeability of Letybo with other approved botulinum products currently in the Australian market.

Risk-benefit analysis

Delegate's considerations

The broader approach, in terms of dose selection and study design during the clinical development programme of Letybo was based on the already approved product Botox. In consideration of the minimal systemic absorption, from a mechanistic perspective, the lack of pharmacokinetic (PK) studies is considered acceptable. This approach is similar to previously approved products with botulinum toxin type A as the active ingredient and in line with the relevant FDA guideline.[14] A comparison of efficacy between Letybo and Botox at the proposed dose was performed prior to the conduct of pivotal studies.

The sponsor has proposed registration of two strengths at 50 U and 100 U. The proposed maximum dosage is 20 U and the presentation is a single use vial. The rationale for the 50 U, which has more than twice the amount of the maximum dose and the 100 U vial which has an even higher amount of the medication is not clear. The extra dose increases the chances of medication error, particularly when considering that the post market Study HG-13-02 data suggests that the physicians in South Korea were using a maximum dose of up to 45 U that was

more than twice higher than the recommended maximum dose of 20 U. This practice also reflects the evidence to suggest a dose dependent increase in the treatment benefit with botulinum toxin type A.[16,17] In addition, an event of sudden hearing loss was reported in a subject who received 50 U of Letybo, which is more than double the recommended dose. The Delegate has also noted that the previously approved products with botulinum toxin type A have single use vials with strengths of botulinum toxin type A from 50 U to 200 U. However, they are approved for multiple indications other than for the treatment of glabellar lines, where a higher dose might be required.

The pivotal studies included subjects that are the targeted patient population in the proposed indication. The sponsor's study design and endpoints were largely in line with the relevant FDA guideline. Across the studies, at 4 weeks post treatment, Letybo group achieved a greater treatment benefit, compared to placebo. The treatment difference was statistically significant.

In BLESS I, at Week 4 post treatment, a greater proportion of subjects in the Letybo group (46.5%) achieved a FWS score of 0 or 1 and an improvement 2 points or greater in FWS score (at maximum frown). The treatment difference at Weeks 12 and 16 were also statistically significant. However, compared to Week 4, around 40% reduction in the proportion of responders was noted at Week 12 (13.19%), Week 16 (8.78%) and Week 20 (1.19%). The improvement in clinical endpoints was supported by the improvement in the patient reported outcomes that measured quality of life.

Study BLESS II achieved its primary endpoint at Week 4. However, it was not supported by a statistically significant treatment difference for the key secondary endpoints measured at Week 16 and 20. There was a positive trend towards the Letybo group for greater treatment benefit, compared to placebo.

A considerably higher investigator rating, compared to subject rating for both primary and secondary endpoints was noted for all the studies with Letybo. At Week 4, it was around 10% in BLESS I and around 40% higher in BLESS II. The disparity was higher at Weeks 12, 16 and 20 post treatment in BLESS I. In addition, the magnitude of treatment benefit at Week 4 does not appear to be sustained. The treatment difference between the Letybo and placebo group declined after Week 4 in both studies BLESS I and BLESS II. It was more marked in study BLESS II, compared to BLESS I. This finding reflects the transient action of botulinum toxin on the facial muscles. A similar trend was also noted with previously approved products with botulinum toxin type A as the active ingredient. Glabellar frown lines are a chronic condition and the changes that have occurred to the facial muscles are permanent. The long term treatment benefit with Letybo that has a transient effect is unclear.

The maximum treatment benefit appears to be at around 2 weeks after treatment and the duration of treatment benefit appears to be around 12 to 16 weeks. The comparative data for the mean duration of treatment effect after the retreatments, compared to the initial treatment is not clear.

The supportive efficacy studies provide evidence to suggest non-inferiority of Letybo to Botox. The responder ratings were only performed by the investigators and the lack of a composite responder rating is a limitation of this study. It should be noted that the comparative data is with the Botox that is approved in South Korea. It is not clear whether this product is the same as the Botox that TGA has approved for use in Australia.

[16] Frampton, J.E. et al. Botulinum toxin A (Botox Cosmetic): a review of its use in the treatment of glabellar frown lines, *Am J Clin Dermatol,* 2003; 4(10): 709-25.

[17] Kaufman-Janette, J. et al. Botulinum Toxin Type A for Glabellar Frown Lines: What Impact of Higher Doses on Outcomes? *Toxins (Basel)*, 2021; 13(7).

Majority (91%) of the subjects required retreatment between Week 12 and Week 28 for a sustained treatment benefit. A mean number of three retreatments were administered during the study period. The maximum number of retreatments was four. It was also noted that around 50% of subjects received the fourth retreatment. Considering the waning of treatment effect beyond 12 weeks, the reason for the subjects for not having the fourth retreatment is not clear. Based on the efficacy data, it is understood that the treatment effect only last for around 12 weeks. There is no data related to efficacy and safety of retreatments with Letybo after 48 weeks.

Overall, 22% of subjects in the Letybo and 19% of subjects in the placebo group in the pivotal studies reported adverse events. The Delegate has considered that the safety aspects of this treatment is heavily dependent on the expertise of the healthcare professional administering the injections. In clinical studies the procedure related AEs were low (3%). Headache was the commonest adverse event reported and a higher incidence was reported in the Letybo, compared to placebo group. Majority of the events were mild to moderate in severity and resolved during the study period. One event of headache lead to discontinuation from the study. Injection site reaction, injection site bruising, eyelid and brow ptosis had a greater incidence in the Letybo, compared to placebo group.

Adverse events due to local and distant spread of toxin were not frequent in the Letybo group. A greater incidence of eyelid ptosis was reported in Letybo, compared to placebo group. Eyelid ptosis is a known adverse event of products with botulinum toxin as active ingredient and approved for the treatment of glabellar lines.[16,18] In studies with Letybo, eyelid ptosis could be attributed to both as a result of administration error and/or the botulinum toxin. Eyelid ptosis was twice more common in Letybo, compared to the Botox arm (4.5% versus 2.2%). Adverse events due to distant spread of toxin was not frequently reported. No trends were noted.

One event of sudden hearing loss was reported after administration of 50 U of Letybo. The study investigator considered this event as 'probably not related' to the study treatment. The Advisory Committee on Medicines (ACM) opinion on this matter was requested.

No apparent evidence of immunogenicity was noted. The safety data did not suggest cumulative toxicity with repeated doses of Letybo.

Proposed action

Treatment of glabellar frown lines with Letybo achieved greater treatment benefits compared to placebo and was non-inferior to Botox that is approved for use in South Korea. Treatment benefit appears to be transient with study BLESS II not achieving secondary end points and the decline in treatment benefit over Weeks 8, 12, 16 and not achieving significant treatment benefit at Week 20 in BLESS I. There is a lack of long term efficacy data for greater than 48 weeks and/or four retreatments with Letybo. Improvement in FWS was associated with improvement in quality of life measures.

Overall, the type of adverse events due to local and distant spread are known with previously approved botulinum toxin type A products.18 No apparent trend of events was noted to suggest cumulative toxicity with repeated doses of Letybo. However, safety data for more than four retreatments is lacking.

In consideration of the above facts, the Delegate recommends the following indication:

[18] Ahsanuddin, S. et al. Adverse Events Associated with Botox as Reported in a Food and Drug Administration Database, 2021; 45(3): 1201-1209.

Letybo is indicated in adults for the temporary improvement in the appearance of moderate to severe glabellar frown lines.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***The proposed strengths of Letybo (50 U and 100 U) could provide a dose that will be much higher than the recommended maximum dose of 20 U. From a clinical perspective, please comment on the safety aspects of providing a much higher surplus of the product than what is required for treatment and the need for 50 U and 100 U vials in a clinical setting.***

The ACM noted that this reflects current clinical practice and is consistent with other forms of botulinum toxin A. The ACM commented that Letybo will be used by specialists who are familiar with these medications and did not express concern about safety issues regarding Letybo being supplied in a larger quantity than what is required for the recommended maximum dose for the currently applied indication. The ACM also advised that there is limited risk of overdose noting that other forms of approved botulinum toxin A agents are used in preparation which exceed the indicated dosage for this application. The ACM however highlighted that these other indications are currently not applicable to Letybo.

In view of the '*single use in one patient only*' specification of Letybo, the ACM was concerned with the potential wastage of medicine that could happen. The ACM also considered that the sponsor may apply for other indications in future that may require a larger dose.

2. ***Please comment on the adequacy of the efficacy data to support the proposed indication.***

The ACM considered that the pivotal efficacy study design for this indication for Letybo is comparable to and has similar magnitude of effect as the Australian approved Xeomin. The efficacy study for Letybo shows zero placebo effect, is adequately powered and has a larger (nearly double) sample size compared to the other efficacy studies for this indication. Therefore, the ACM considered the efficacy data for Letybo acceptable.

3. ***Long term efficacy and safety data of Letybo is limited to 48 weeks and/or not more than four retreatments. The use of Letybo is not restricted to 48 weeks and/or to four retreatments in the proposed PI. What is the committee's opinion about the potential long term use of Letybo for greater than 48 weeks and/or more than four retreatments?***

The ACM was of the view that long term use of Letybo is reasonable. The ACM advised that it is reasonable to extrapolate from and reflect the contemporary use of currently available forms of botulinum toxin A, as Letybo has similar characteristics as these agents. Thus, it is reasonable to assume that Letybo will have similar uses and behaviours.

The ACM noted that the Product Information is not phrased in a way that limits use to 48 weeks, as some patients may need additional retreatments. The ACM advised that based on expected changes at the neuromuscular junction, the effect of the agent could be lost overtime. From a neurological perceptive, indefinite treatment is common for patients with dystonia, migraine and/or limb spasticity often with much higher doses.

4. ***An event of sudden hearing loss was reported in a subject treated with 50 U of Letybo. The investigator determined this event as 'probably not related' to treatment with***

Letybo. Based on the evidence, please comment on the relationship between this event and treatment with Letybo.

From a causality point of view, the ACM agreed there is no conclusive evidence to date of any causal relationship for hearing loss with any form of botulinum toxin A.

The ACM noted that a sudden onset of loss of hearing is common in the middle age population universally treated with corticosteroid. Further noting that treatment with botulinum toxin A might improve hearing. It is suggested in the literature that the auditory disturbances accompanying hemifacial spasm could be caused by eustachian tube dysfunction, which are improved after treatment with botulinum toxin A.[19]

5. Please comment on any other aspects of this submission that need to be considered.

Advice regarding indications:

The original indication proposed by the sponsor is:

> *Letybo is indicated in adults for the treatment of glabellar frown lines.*

The Delegate suggested to revise and include severity in the indication:

> *Letybo is indicated for the temporary improvement in the appearance of moderate to severe glabellar frown lines in adults.*

The ACM discussed the wording of the indication and noted differences in the wording for products with a glabellar frown lines indication. The ACM noted the Delegate's proposal to include 'moderate to severe' within the indication for this product and commented that the definition of moderate to severe could be subjective. However, on balance the ACM was of the view that the inclusion of the moderate to severe wording is beneficial from a consumer perspective as it may assist with determining treatment usage and need.

The Delegate sought advice on any concern regarding the non-Australian approved Botox used in the comparative study.

The ACM advised that in practice, titration is usually required to determine dosage prior to the use of Botox. For example, in the treatment of dystonia clinicians usually start with a lower dose, observe effect over a period of time, and then review before prescribing a higher dose.

The ACM was of the opinion that it is reasonable to expect comparable efficacy and safety between the preparation manufactured overseas and the Australian preparation. The ACM did not express major clinical concern regarding use of an approved product manufactured overseas within the comparative study.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Letybo is indicated for the temporary improvement in the appearance of moderate to severe glabellar frown lines in adults.*

[19] Rudzińska, M. et al. The Influence of Botulinum Toxin on Auditory Disturbances in Hemifacial Spasm, *Neurol Neurochir Pol*, 2012; 46(1): 29-36.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Letybo (letibotulinumtoxinA) 50 U and 100 U, powder for injection, vial, indicated for:

> *LETYBO is indicated for the temporary improvement in the appearance of moderate to severe glabellar frown lines in adults.*

Specific conditions of registration applying to these goods

- Letybo (letibotulinumtoxinA) is to be included in the Black Triangle Scheme. The PI and CMI [Consumer Medicines Information] for Letybo must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The LetibotulinumtoxinA (Letybo) AU-Risk Management Plan (RMP) (version 0.2, dated 20 February 2022, data lock point 1 September 2020), included with submission PM-2021-02698-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  If the product is approved in the EU [European Union] during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- Good Manufacturing Practice (GMP) clearance for listed manufacturers: All GMP Clearances must be approved prior to registration and supply of product to Australia. A commitment is required from the sponsor that they maintain the validity of all manufacturer GMP Clearances for the duration of product supply to Australia. Additionally, that adherence to the conditions of GMP Clearance approval is upheld.

  All batches of Letybo supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually

in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs index and periodically in testing reports on the TGA website.

Attachment 1. Product Information

The PI for Letybo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

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Reference/Publication #