CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761225Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Clinical Reviewer/Cross-Discipline Team Leader/Associate Director for Therapeutic Review /Office Director Memorandum

BLA 761225

Date	February 28, 2024
From	Tong Li-Masters, MD, PhD (clinical reviewer, DDD) Snezana Trajkovic, MD (CDTL, DDD) Division signatory: Gordana Diglisic, MD (ADTR, DDD) Office signatory: Nikolay Nikolov, M.D., Acting Director, Office of Immunology and Inflammation
BLA #	(b) (4)
Applicant	Hugel, Inc.
Date of Submission	August 31, 2023
PDUFA Goal Date	February 29, 2024
Established/Proper Name	LetibotulinumtoxinA
(Proposed) Trade Name	Letybo
Pharmacologic Class	Acetylcholine release inhibitor and neuromuscular blocking agent
Dosage Form	Sterile powder for injection, 50 units/vial and 100 units/vial
Applicant proposed Dosing Regimen	0.1mL (4 units) by intramuscular injection into each of five sites, for a total dose of 20 units
Applicant Proposed Indication(s)/Population(s)	For the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients
Recommendation on Regulatory Action	Approval

This memorandum is in regard to the resubmission of the BLA 761225 in response to the Agency's Complete Response (CR) letter dated April 12, 2023, for LETYBO (letibotulinumtoxinA) for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults.

The CR letter listed several deficiencies that were all related to drug substance and drug product manufacturing facilities. The Applicant resubmitted the BLA 761225 on August 31, 2023. This resubmission is considered a complete response to the FDA deficiencies stated in the CR letter on April 12, 2023. This resubmission does not contain any new clinical efficacy or safety information.

The efficacy and safety of LETYBO was established following the review of clinical data during the first review cycle (refer to Unireview dated March 31, 2022). Respectively, no new clinical information was necessary for the resubmission of BLA 761225 on August 31, 2023.

In the original submission, the Applicant provided substantial evidence of effectiveness from three adequate and well-controlled studies that evaluated LETYBO for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults. These three identically designed trials were randomized, double-blinded, placebo-controlled phase 3 trials (Study CPH-301-201030 [BLESS I], Study CPH-302- 201030 [BLESS II]), and Study CPH-303-201400 [BLESS III]) that enrolled a combined total of 1272 subjects with moderate to severe glabellar lines. Adult subjects were treated with LETYBO at a dose of 4 Units (0.1 mL) by intramuscular injection into each of 5 sites, for a total dose of 20 Units, or placebo. The primary efficacy endpoint was the proportion of subjects with a Facial Wrinkle Scale (FWS) score of 0 or 1 and an improvement of ≥2 points on FWS score (at maximum frown) at the Week 4 visit relative to baseline, based on both the investigator's and the subject's in-clinic assessments. The proportion of subjects with treatment success at Week 4 was 46.5% in LETYBO group versus 0% in the placebo group in Study BLESS I, 48.8% in LETYBO group versus 1.9% in the placebo group in Study BLESS II , and 64.7% in LETYBO group versus 0% in the placebo group in Study BLESS III.

The Applicant adequately characterized the safety profile of LETYBO through analyses of data from the safety database of 1272 subjects. The numbers of subjects with LETYBO exposures at relevant doses exceeded those recommended in the International Conference on Harmonization (ICH) E1A guideline. The safety profile of LETYBO was consistent with that of other botulinumtoxin A products licensed for the same indication. LETYBO was generally well tolerated. No death was reported. No serious adverse event was considered treatment related. Most reported adverse reactions were either mild or moderate in severity and resolved spontaneously without treatment. The most frequently reported adverse reactions in LETYBO treatment groups were headache 1.9% and injection site reaction 0.7%. The safety analysis did not identify any new safety signals for this botulinumtoxin A product.

During the open-label period of the phase 3 trials (BLESS I, BLESS II, and BLESS III) which evaluated safety of LETYBO with repeated treatments, the safety profile of LETYBO did not change with repeated product administration.

Following the review of submitted data and re-inspection of manufacturing facilities, the product quality team has recommended Approval. In addition, the product quality team recommended a PMC 761225-01: To investigate the development and implementation of a non-animal-based potency assay for drug substance and drug product release and stability testing with the final report submission in 12/2028.

Labeling has been agreed upon with the Applicant during the current review cycle.

Summary and Recommendation:
The risk/benefit profile of LETYBO has not changed since the previous review cycle. The deficiencies discovered during the preapproval inspection of the drug substance and drug product manufacturing and testing facility during the last review cycle have been satisfactorily resolved. For details regarding preapproval inspection of drug substance and drug product manufacturing and testing facility, please refer to the integrated quality assessment by Hailin Wang dated 2/27/2024. This review team recommends Approval of this application. The designated signatory agrees with the assessment and recommendations by the review team. The regulatory action is Approval, with a PMC 761225-01: To investigate the development and implementation of a non-animal-based potency assay for drug substance and drug product release and stability testing with the final report submission in 12/2028.

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/s/

TONG LI-MASTERS
02/28/2024 03:31:26 PM

SNEZANA TRAJKOVIC
02/28/2024 03:33:44 PM

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02/28/2024 03:41:10 PM

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02/28/2024 03:44:01 PM

Clinical Review and Evaluation
Memorandum
Resubmission of BLA 761127

Supporting Document Number: 22
Sponsor: Hugel, Inc.
Drug: letibotulinumtoxinA for intramuscular injection, 50U and 100U
Proposed Indication: For the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.
Correspondence Date: 10/06/2022
Review Date: 4/4/2023
Primary Reviewer: Tong Li-Masters MD, PhD, DDD
Team Lead: Snezana Trajkovic, MD, DDD
Project Manager: H. F. Van Horn III, PharmD, MBA

This memorandum is in regard to the resubmission of the BLA 761225 in response to the Agency's Complete Response (CR) letter dated March 31, 2022, for LETYBO (letibotulinumtoxinA) for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults.

The CR letter listed several deficiencies that were all related to drug substance and drug product manufacturing facilities. The Applicant resubmitted the BLA 761225 on October 6, 2022. As per the Applicant, this resubmission is considered a complete response to the FDA deficiencies stated in the CR letter on March 31, 2022. This resubmission does not contain any new clinical efficacy or safety data.

The efficacy and safety of LETYBO was established following the review of clinical data during the first review cycle.

The Applicant provided substantial evidence of effectiveness from three adequate and well-controlled studies that evaluated LETYBO for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults. These three identically designed studies were randomized, double-blinded, placebo-controlled Phase 3 studies (Study CPH-301-201030 [BLESS I], Study CPH-302-201030 [BLESS II]), and Study CPH-303-201400 [BLESS III]) that enrolled a combined total of 1272 subjects with moderate to severe glabellar lines. Adult subjects were treated with LETYBO at a dose of 4 Units (0.1 mL) by intramuscular injection into each of 5 sites, for a total dose of 20 Units, or placebo. The primary efficacy endpoint was the proportion of subjects with a Facial Wrinkle Scale (FWS) score of 0 or 1 and an improvement of ≥2 points on FWS score (at maximum frown) at the Week 4 visit relative to baseline, based on both the investigator's and the subject's in-clinic assessments. The proportion of subjects with treatment success at Week 4 was 46.5% in LETYBO group versus 0% in the placebo group in BLESS I Study, 48.8% in LETYBO group versus 1.9% in the placebo group in BLESS II Study, and 64.7% in LETYBO group versus 0% in the placebo group in BLESS III Study.

The Applicant adequately characterized the safety profile of LETYBO through analyses of data from the safety database of 1272 subjects. The numbers of subjects with LETYBO exposures at relevant doses exceeded those recommended in the International Conference on Harmonization (ICH) E1A guideline. The safety profile of LETYBO was similar to that of other botulinumtoxin A products licensed for the same indication. LETYBO was generally well tolerated. No death was reported. No serious adverse event was considered treatment related. Most reported adverse reactions were either mild or moderate in severity and resolved spontaneously without treatment. The most frequently reported adverse reactions in LETYBO treatment groups were headache

1.9% and injection site reaction 0.7%. The safety analysis did not identify any new safety signals for this botulinum toxin A product.

During the open-label period of the Phase 3 studies (BLESS I, BLESS II, and BLESS III) which evaluated safety of LETYBO with repeated treatments, the safety profile of LETYBO did not change with repeated product administration.

Labeling negotiation with the applicant was not completed during the second review cycle as this application received Complete Response due to deficiencies discovered during the preapproval inspection of the drug substance and drug product manufacturing and testing facility.

Following the review of submitted data and re-inspection of manufacturing facilities, the product quality team has recommended Complete Response.

Summary and Recommendation:
The risk/benefit profile of LETYBO has not changed since the previous review cycle. However, there were deficiencies discovered during the preapproval inspection of the drug substance and drug product manufacturing and testing facility. Satisfactory resolution of these deficiencies is required before this application may be approved. This reviewer recommends Complete Response of this application.

Tong Li-Masters, MD, PhD
Medical Officer
Division of Dermatology and Dentistry (DDD)
Office of Immunology and Inflammation (OII)
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)

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/s/

TONG LI-MASTERS
04/10/2023 03:26:45 PM

SNEZANA TRAJKOVIC
04/10/2023 03:55:20 PM

Clinical Pharmacology Memorandum

NDA:	761225
SDN:	22
Submission Date:	10/06/2022
Drug product:	letibotulinumtoxinA for intramuscular injection, 50U and 100U
Applicant:	Hugel, Inc.
Indication:	Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients
Primary Reviewer:	Soo Hyeon Shin, Pharm.D., Ph.D.
Team Leader:	Chinmay Shukla, Ph.D.

Background: The original submission of BLA 761225 received a Complete Response Letter on 03/31/2022 due to deficiencies found in facility inspection, microbiology and product quality. In addition to these approvability issues, the Complete Response Letter also included additional comments and recommendations that were not approvability issues including the one shown below regarding immunogenicity:

> [redacted] (b) (4) The 2019 *FDA Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection*, recommends a 1% false positive rate for calculation of the CPP. [redacted] (b) (4) Re-analyze your immunogenicity data using a CCP based on a 1% false positive rate or provide summary data to support that the clinical ADA incidence are comparable using CCPs based [redacted] (b) (4) 1% false positive rates."
>
> "Submit an Integrated Summary of Immunogenicity (ISI) that describes the totality of your immunogenicity program supporting the proposed indication, as recommended in Section VIII Documentation of the 2019 FDA Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection. Submit this ISI report in eCTD Section 5.3.5.3 Reports of Analysis of Data from More than One Study."

In the current Resubmission of BLA 761225, the Applicant submitted a reanalysis of immunogenicity data per the Agency's recommendation.

Immunogenicity assessment from the original submission: The clinical pharmacology review included immunogenicity data that was completed during the original submission of BLA 761225 (Unireview dated 3/31/2022 in DARRTS). Among 1,129 subjects in three phase 3

pivotal studies, five subjects tested positive for ADA. Among these five subjects, three subject had preexisting ADA at screening and only two subjects (0.2%) developed ADA following treatment with the study product. All titer values were zero and no neutralizing ADA were found.

Updated immunogenicity data submitted in the current resubmission: The Applicant reanalyzed immunogenicity data using a revised cut-point of 1.0% for false positives. The reanalysis identified four additional subjects with positive ADA. Among the four additional subjects, one subject had preexisting ADA at screening and three subjects tested positive for the end-of-study sample (i.e. following treatment). For these four additional subjects with positive ADA, the Applicant did not further evaluate for titer and neutralizing ADA, stating that the low risk for immunogenicity does not warrant further evaluations given the logistical challenges of additional assay evaluations.

Reviewer's comment: *Even with the additional subjects identified with positive ADA based on the revised cut-point of 1.0%, the immunogenicity potential for this product appears to be low. In addition, this reviewer consulted with Dr. Hailin Wang from the Office of Biotechnology Products who agreed with the Applicant's rationale that further testing for neutralizing ADA in the newly identified positive samples is not needed.*

Conclusion: Among 1,129 subjects in three phase 3 pivotal studies, five subjects (0.4%) developed antibodies to letibotulinumtoxinA following treatment with the proposed drug product. In the selected samples that were further tested, no neutralizing ADAs were detected.

Recommendation: The resubmission application for BLA 761255 is approvable from Clinical Pharmacology perspective.

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/s/

SOO HYEON SHIN
01/19/2023 11:02:05 AM

CHINMAY SHUKLA
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BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761225
Priority or Standard	Standard
Submit Date(s)	March 31, 2021
Received Date(s)	March 31, 2021
PDUFA Goal Date	March 31, 2022
Division/Office	Division of Dermatology and Dentistry (DDD)
Review Completion Date	January 7, 2022
Established/Proper Name	letibotulinumtoxinA
(Proposed) Trade Name	Letybo
Pharmacologic Class	Acetylcholine release inhibitor and neuromuscular blocking agent
Code name	
Applicant	Hugel Inc
Dosage form	Sterile powder for injection, 50 units/vial and 100 units/vial
Applicant proposed Dosing Regimen	0.1mL (4 units) by intramuscular injection into each of five sites, for a total dose of 20 units
Applicant Proposed Indication(s)/Population(s)	For the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adults.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	For the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adults.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	20 Units per treatment session, divided into 5 equal intramuscular injections of 4 Units each of 5 sites; the inferomedial and superior middle of each *corrugator supercilii* and 1 in the mid-line of the *procerus* muscle).

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	H. F. Van Horn III
Nonclinical Reviewer	Cindy Xinguang Li
Nonclinical Team Leader	Barbara Hill
Office of Clinical Pharmacology Reviewer(s)	Soo Hyeon Shin
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla
Clinical Reviewer	Tong Li-Masters
Clinical Team Leader	Snezana Trajkovic
Statistical Reviewer	Lingjie Zhou, Kathleen Fritsch
Statistical Team Leader	Wanjie Sun, Mohamed Alosh
Cross-Disciplinary Team Leader	Snezana Trajkovic
Division Director (DDD)	Kendall Marcus
Office Director	Julie Beitz

Additional Reviewers of Application

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• Application Technical Lead	Zhenzhen Liu
• OBP Reviewer	Asha Hewarathna
• OBP Review Team Leader	Zhenzhen Liu
• OBP Labeling Reviewer	Vicky Borders-Hemphill
• OBP PLI Inspection	Mekonnen LemmaDechassa
• OPMA Drug Product Micro and Facility Reviewer	Michael Shanks
• OPMA Drug Substance Micro and Facility Reviewer	Candace Gomez-Broughton
• OPMA Team Leader	Madu Dharmasena
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OMP/DMPP	
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• DEPI Reviewer	Joel Weissfeld
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• Safety Regulatory Project Manager	Tri Bui Nguyen
• DMEPA Team Leader	Sevan Kolejian
OSE/DRISK	
• Risk Management Analyst	Sukminder Sandhu
• Acting Team Leader	Jacqueline Sheppard
Other	

DAPR2 = Division of Advertising and Promotion Review 2
DB=Division of Biopharmaceutics
DB III = Division of Biometrics III
DBRR I = Division of Biotechnology Research and Review 1
DDD = Division of Dermatology and Dentistry
DIIP = Division of Inflammation and Immune Pharmacology
DMA=Division of Microbiology Assessment
DMPP = Division of Medical Policy
OB = Office of Biostatistics
OCP = Office of Clinical Pharmacology
ODE III = Office of Drug Evaluation III
ODE IV = Office of Drug Evaluation IV
OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OPRO = Office of Program and Regulatory Operations
OSE= Office of Surveillance and Epidemiology
PLT = Patient Labeling Team
PMS = Project Management Staff
RBPMBI = Regulatory and Business Process Management Branch I

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Cindy Xinguang Li	OII/DPT-II	5, 19.3	Select one: _X__ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Nonclinical Supervisor	Barbara Hill	OII/DPT-II	5, 19.3	Select one: ___ Authored __X_ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Pharmacology Reviewer	Soo Hyeon Shin	OCP/DIIP	Section: 6	Select one: _X_ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Chinmay Shukla	OCP/DIIP	Section: 6	Select one: ___ Authored _X_ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Pharmacology Division Director	Suresh Doddapaneni	OCP/DIIP	Section: 6	Select one: ___ Authored _X_ Approved
	Signature: *{See appended electronic signature page}*			
	Signature:			
Clinical Reviewer	Signature:	Tong Li-Masters, MD, PhD	Sections: 1; 2; 3; 4.1; 7; 8.2; 8.4; 9; 10; 11; 13; 19.2	Select one: _x__ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Snezana Trajkovic	OND/DDD	Sections: 1; 2; 3; 4.1; 7; 8.2; 8.4; 9; 10; 11; 13; 19.2	Select one: ___ Authored __X_ Approved
	Signature: *{See appended electronic signature page}*			
Division Director (Clinical)	Kendall Marcus	OND/DDD	Sections: All	Select one: ___ Authored __X_ Approved
	Signature: *{See appended electronic signature page*			
Statistical Reviewer	Lingjie Zhou, PhD	OTS/OB/DBVIII	Sections: 8.1, 8.3, 19.5	Select one: _X_ Authored ___ Approved
	Signature: *{See appended electronic signature page*			
Statistical Reviewer	Wanjie Sun, PhD	OTS/OB/DBVIII	Sections: 8.1, 8.3, 19.5	Select one: ___ Authored ___ Approved
	Signature:			
Statistical Reviewer	Kathleen Fritsch, PhD	OTS/OB/DBIII	Sections: 8.1, 8.3, 19.5	Select one: ___ Authored ___ Approved
	Signature:			
Statistical Team Leader	Mohamed Alosh, PhD	OTS/OB/DBIII	Sections: 8.1, 8.3, 19.5	Select one: ___ Authored __X_ Approved
	Signature: *{See appended electronic signature page*			

Office Director (Clinical)	Julie Beitz	OND/OII	Sections: ALL	Select one: ___ Authored _X__ Approved
	Signature: *{See appended electronic signature page}*			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

LetibotulinumtoxinA is a Botulinum Neurotoxin Type A Drug Product (BoNT/A-DP) developed by Hugel Inc. BoNT/A-DP is based on a new isolate of a bacterium *Clostridium botulinum* strain "CBFC26", (b) (4) The structure of the BoNT/A-DS is a 900 kiloDalton (kDa) (b) (4)

LetibotulinumtoxinA, is an acetylcholine release inhibitor. BoNT/A-DP blocks cholinergic transmission at the neuromuscular junction. The mechanism of nerve terminal toxicity by the botulinum toxins can be divided into five major steps: 1) binding to nerve terminals, 2) internalization within an endocytic compartment, 3) low pH driven translocation of the light chain across the vesicle membrane, 4) release of the light chain in the cytosol by reduction of the interchain disulfide bond, and 5) cleavage of SNARE proteins with ensuing blockade of neurotransmitter release. This process produces partial chemical denervation of the muscles, inhibits muscle contraction that leads to reversible muscle atrophy. Recovery of impulse transmission is established by the formation of new nerve endings.

The proposed indication is for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adults.

The proposed dosing regimen is 20 Units per treatment session divided into 5 equal intramuscular injections of 4 Units each (2 injections in each *corrugator supercilii* muscle and 1 injection in the *procerus* muscle) with an injection volume of 0.1 mL (4 Units) into each site.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness from 3 adequate and well-controlled studies that evaluated BoNT/A-DP for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults. These 3 identically designed studies were randomized, double-blinded, placebo-controlled Phase 3 studies (Study CPH-301-201030 [BLESS I], Study CPH-302-201030 [BLESS II]), and Study CPH-303-201400 [BLESS III]) that enrolled a combined total of 1272 subjects with moderate to severe glabellar lines. Adult subjects were treated with BoNT/A-DP at a dose of 4 Units (0.1 mL) by intramuscular injection into each of 5 sites, for a total dose of 20 Units, or placebo. The primary efficacy endpoint was the proportion of subjects with a Facial Wrinkle Scale (FWS) score of 0 or 1 and an improvement of ≥2 points on FWS score

(at maximum frown) at the Week 4 visit relative to baseline, based on both the investigator's and the subject's in-clinic assessments.

The proportion of subjects with treatment success at Week 4 were:

- Study CPH-301-201030 [BLESS I]: 0% placebo vs 46.5% BoNT/A-DP
- Study CPH-302-201030 [BLESS II]: 1.9% placebo vs 48.8% BoNT/A-DP
- Study CPH-303-201400 [BLESS III]: 0% placebo vs 64.7% BoNT/A-DP

1.3. Benefit-Risk Assessment

[Do not insert text here. Use the table]

Benefit-Risk Summary and Assessment

LetibotulinumtoxinA is a Botulinum Neurotoxin Type A Drug Product (BoNT/A-DP) developed by Hugel Inc. The proposed indication for BoNT/A-DP is for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adults.

Glabellar lines are vertical lines that develop between the eyebrows upon frowning, and in some cases may be present at rest. Glabellar lines result from the contraction of the horizontally oriented corrugator muscles bilaterally and the vertically oriented central procerus muscles. Repeated contractions of these muscles over an extended period of time often result in skin remodeling in the area and the presence of vertical lines with contraction and at rest. Historically, treatment has been aimed at improving the cutaneous defect with soft tissue augmentation, resurfacing, or facial surgery. These treatments, however, do not address the underlying musculature that causes the facial lines and have risk of complications and prolonged recovery. Surgical release of muscles is possible; however, it is invasive, can cause scarring and is non-reversible. Botulinum toxin products have become a common treatment option for the facial lines caused by underlying hyperfunctional facial musculature.

The Applicant provided substantial evidence of effectiveness from three adequate and well-controlled studies that evaluated BoNT/A-DP for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults. Three identically designed studies were randomized, double-blinded, placebo-controlled Phase 3 studies (BLESS I, BLESS II, and BLESS III) that enrolled a combined total of 1272 adult subjects with moderate to severe glabellar lines. Subjects were treated with BoNT/A-DP at a dose of 4 Units (0.1 mL) by intramuscular injection into each of 5 sites, for a total dose of 20 Units, or with a placebo. The primary efficacy endpoint was the proportion of subjects with a Facial Wrinkle Scale (FWS) score of 0 or 1 and an improvement of ≥2 points on FWS score (at maximum frown) at the Week 4 visit relative to baseline, based on both the investigator's and the subject's in-clinic assessments. The proportion of subjects with treatment success at Week 4 was 46.5% in BoNT/A-DP group versus 0% in the placebo group in BLESS I Study, 48.8% in BoNT/A-DP group versus 1.9% in the placebo group in BLESS II Study, and 64.7% in BoNT/A-DP group versus 0% in the placebo group in BLESS III Study.

The Applicant adequately characterized the safety profile of BoNT/A-DP through analyses of data from the safety database of 1272 subjects. The numbers of subjects with BoNT/A-DP exposures at relevant doses exceeded those recommended in the ICH E1A guideline. The safety

profile of BoNT/A-DP was similar to the safety of other botulinum toxin A products licensed for the same indication. BoNT/A-DP was generally well tolerated. No death was reported. No serious adverse event was considered treatment related. Most of reported adverse reactions were either mild or moderate in severity and resolved spontaneously without treatment. The most frequently reported adverse reactions in BoNT/A-DP treatment group were headache 1.9% and injection site reaction 0.7%. The safety analysis did not identify any new safety signals for this botulinum toxin A product.

During the open-label period of the Phase 3 studies (BLESS I, BLESS II, and BLESS III) which evaluated safety of BoNT/A-DP with repeated treatments, the safety profile of BoNT/A-DP did not change with repeated product administration. At this time, BLA approval is precluded due to product quality issues that have been identified and inspectional findings. Satisfactory resolution of these deficiencies is required before this application may be approved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Glabellar lines are vertical lines that develop between the eyebrows upon frowning, and in some cases may be present at rest. Glabellar lines result from the contraction of the horizontally oriented corrugator muscles bilaterally and the vertically oriented central procerus muscles. Repeated contractions of these muscles over an extended period of time often result in skin remodeling in the area and the presence of vertical lines with contraction and at rest.	BoNTA treatment has been the standard of care for the treatment of unwanted moderate or severe dynamic glabellar lines in adults since the approval of onabotulinumtoxinA for the treatment of glabellar lines in 2002.
Current Treatment Options	• Historically, treatment has been aimed at improving the cutaneous defect with soft tissue augmentation, resurfacing, or facial surgery. These treatments, however, do not address the underlying musculature that causes the facial lines and have risk of complications and prolonged recovery. Surgical release of muscles is possible; however, it is invasive, can cause scarring and is non-reversible. Botulinum toxin products have become a common aesthetic treatment option for the glabellar lines caused by underlying	Botulinum toxin injections produce chemical denervation of the muscles resulting in localized reduction of muscle activity that is temporary. This allows the physician to tailor the use of botulinum toxin to the clinical presentation and desired outcomes of the patient.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hyperfunctional facial musculature.	
Benefit	• The key benefit of BoNT/A-DP is aesthetic (i.e., an improvement in the appearance of glabellar lines), of importance to patients who seek out this type of treatment.	The botulinum toxin produces a temporary effect and can be discontinued if adverse reactions occur. Other treatments, such as surgical intervention, are more invasive.
Risk and Risk Management	• Most of the adverse events in the submitted studies were unrelated to the study drug, and most were either mild or moderate in severity. There were no serious adverse events related to the drug treatment. The rate of drop-outs due to drug related adverse events was very low. The most frequently reported adverse reactions were headache and injection site reaction. • Labeling will incorporate all relevant warnings and precautions established from the historical use of botulinum toxin products. • Product labeling is sufficient to manage the identified risks, if approved.	BoNT/A-DP has an acceptable risk-benefit profile for the treatment of glabellar lines. The Agency has established that distant spread of toxin is a risk that requires a Boxed Warning, although no events were observed in this development program that were considered related to BoNT/A-DP treatment. Section 5 Warnings and Precautions will contain all relevant safety information. Risk management strategies beyond product labeling are not needed for this product, if approved. A REMS is not required.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Section 8.2.6
		X	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Glabellar lines are vertical lines that develop between the eyebrows upon frowning, and in some cases may be present at rest. Glabellar lines result from the contraction of the horizontally oriented corrugator muscles bilaterally and the vertically oriented central procerus muscles. Repeated contractions of these muscles over an extended period of time often result in skin remodeling in the area and the presence of vertical lines with contraction and at rest. Historically, treatment has been aimed at improving the cutaneous defect with soft tissue augmentation, resurfacing, or facial surgery. These treatments, however, do not address the underlying musculature that causes the facial lines and have risk of complications and prolonged recovery. Surgical release of muscles is possible however, it is invasive, can cause scarring and is non-reversible. Currently, botulinum toxin products are commonly used as a treatment option for glabellar lines caused by underlying hyper-functional facial musculature.

2.2. Analysis of Current Treatment Options

In the United States, there are currently several licensed botulinum toxin products available for the treatment of glabellar lines:

Table 1. FDA-Approved Treatment for Glabellar Lines

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Botox Cosmetic OnabotulinumtoxinA	Moderate to severe glabellar lines	2002	20 Units IM injection in 5 equal aliquots of 4 Units	Study 1 (61%) Study 2 (46%)	Spread of toxin, dysphagia and breathing difficulties
Dysport AbobotulinumtoxinA	Moderate to severe glabellar lines	2009	50 Units IM injection in 5 equal aliquots of 10 Units	GL1 (55%) GL2 (52%) GL3 (60%)	Spread of toxin, dysphagia and breathing difficulties
Xeomin IncobotulinumtoxinA	Moderate to severe glabellar lines	2011	20 Units IM injection in 5 equal aliquots of 4 Units	GL1 (60%) GL2 (48%)	Spread of toxin, dysphagia and breathing difficulties
Jeuveau PrabotulinumtoxinA-xvfs	Moderate to severe glabellar lines	2019	20 Units IM injection in 5 equal aliquots of 4 Units	EV-001 (67%) EV-002 (70%)	Spread of toxin, dysphagia and breathing difficulties

Source: FDA approved Physician's Inserts from Drugs@FDA

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This product is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

The development of BoNT/A-DP was conducted under an IND 123178.

- Pre-IND/End of Phase 2 meeting was held on September 10, 2014. The Agency provided recommendations on the development program for the proposed indication.

- The applicant submitted a Phase 3 study protocol (BLESS I) on October 30, 2015. A teleconference was held on November 20, 2015, during which the Agency notified the Applicant of full clinical hold on IND 123178, because this IND *"does not provide sufficient information regarding the potency methodology. Specifically, there is no assessment of parallelism between the test and reference standard*". The Applicant submitted response information to the clinical hold on December 1, 2015 and subsequently, the clinical hold was lifted on December 21, 2015.

- The Applicant submitted an initial Pediatric Study Plan on October 12, 2015, requesting a waiver of assessment pediatric age groups 0 through 17 year for the treatment of moderate to severe glabellar lines because "*Studies are impossible or highly impracticable (because, specifically, the number of pediatric patients is too small for the development)*". On December 16, 2015, the Division presented the initial Pediatric Study Plan (iPSP) to the Pediatric Review Committee (PeRC). The Division agreed with requested Full Waiver of Pediatric Studies for pediatric patients from age 0 to 17 years because studies are impossible or highly impractical due to the extremely low prevalence of glabellar lines in the pediatric population. An Agreed Initial Pediatric Study Plan-Agreement letter was issued on March 16, 2016.

- During a type C guidance meeting on October 3, 2016, the Agency provided recommendations on the size of the safety database for the studies and pointed to antidrug antibody testing issues.

- A pre-BLA meeting was held on December 20, 2018 during which content and format of the BLA application were discussed.

BoNT/A-DP has been marketed in Korea for the treatment of blepharospasm since 2010 under the name Botulax. Subsequently, BoNT/A-DP was approved for the treatment of glabellar lines based on a single Phase 3 study (Study HG-11-01) conducted in Korea.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Rationale for Site Selection

Three clinical investigator (CI) sites were chosen based on numbers of enrolled subjects, magnitude of efficacy results, protocol deviations as well as prior inspection history.

INSPECTION RESULTS

1. Joely Kaufman-Janette M.D.
Skin Research Institute LLC, 4425 Ponce De Leon Boulevard, Suite 200, Coral Gables, FL 33146
Study: CPH-303-201400 (BLESS III IA)
Site Number: B3113
Dates of Inspection: 10/18/2021 to 10/21/2021

This inspection was conducted on-site. At the time of the inspection, 61 subjects were screened, 47 enrolled and 43 subjects finished the study. Efficacy data for 22 of enrolled subjects were reviewed against source data, with no discrepancies. There was no evidence of under-reporting of protocol deviations. The inspection revealed no deficiencies with maintenance of the blind.

Two adverse events were identified by the CI but were not included in the individual patient-level data line listings submitted to the Agency. According to the AE reporting forms, both AEs were reported to the CRO prior to the data lock date (2/10/2020).

Subject/Arm	Adverse Event/ Severity	Dates	Notes
(b) (6) /placebo	Right Eyebrow Ptosis/mild	(b) (6)	Adverse Event of Significant Interest (AESI), Cycle 2, spontaneously resolved
(b) (6) /treatment	Elevated GGT/mild		Cycle 2, spontaneously resolved

Reviewer comments: The events were mild in severity and spontaneously resolved. While the elevated GGT was not reported as AE, it is appropriately captured in the lab data and was determined by the CI to not be related to the study treatment.

Except for the findings described above, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

2. Joel Schlessinger M.D.
2802 Oak View Drive Omaha, NE 68144 Study: CPH-301-201030 (BLESS I)
Site Number: B1110
Dates of Inspection: 10/04/2021 to 10/08/2021

This inspection was conducted on-site. At the time of the inspection, 52 subjects were screened and 44 enrolled into the study. There were no issues with the informed consent process. Data listings for 15 subjects were compared against source data, with no discrepancies. There was no evidence of under-reporting of adverse events or under-reported protocol deviations. The inspection revealed no deficiencies with maintenance of the blind.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

3. Sue Ellen Cox M.D.
Aesthetic Solutions P.A. Ste 101, 5821 Farrington Road, Chapel Hill, NC 27517 Study: CPH-303-201400 (BLESS III IA)
Site Number: B3111
Dates of Inspection: 10/04/2021 to 10/07/2021

This inspection was conducted on-site. At the time of the inspection, 50 subjects were screened and 44 enrolled into the study. Data listings for 14 subjects were compared against source data, with no discrepancies. There was no evidence of under-reporting of adverse events or under-reported protocol deviations. The inspection revealed no deficiencies with maintenance of the blind. There were no major issues with the informed consent process. There was one minor issue regarding the IP drug accountability record that does not impact subject safety or data integrity.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS
Hugel Inc has submitted data from three phase-3 studies to the Agency in support of a biologics license application (BLA 761225) for letibotulinumtoxin A injection, for the indication of temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adults. Three clinical investigators (Drs. Kaufman-Janette, Schlessinger, and Cox) were selected from two of the phase-3 studies for surveillance clinical inspections.

Based on these inspections, studies BLESS I and BLESS III IA appear to have been adequately conducted and the study data generated by the inspected entities appear acceptable in support of the respective indication in the BLA.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, has concluded the information and data submitted in this application are not adequate to support a conclusion that the manufacture of letibotulinumtoxinA is well-controlled and will lead to a product that is safe, pure, and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Hugel Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

The Office of Biotechnology Products (OBP) and the Office of Pharmaceutical Manufacturing Assessment (OPMA) under OPQ identified several product quality deficiencies during the review of Module 3 of BLA 761225. The deficiencies do not support that the manufacture and testing of letibotulinumtoxinA is well-controlled and will lead to a product that is safe, pure, and potent for the duration of the shelf-life. These deficiencies include, but are not limited to:

(b) (4)

In addition, following a review of the pre-license inspection (PLI) findings at Hugel Inc. (FEI #3012163998, the proposed DS and DP manufacturing facility), in support of BLA 761225, there are significant, outstanding manufacturing risks that prevent approval of this application (refer to EIR assessment memos in CMS, WA#414192). Satisfactory resolution of the deficiencies cited during the recent FDA inspections at Hugel Inc. is required before this application may be approved. Therefore, the unacceptable status of the facility is considered deficiency and will be communicated in the CR letter.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant has submitted an original BLA under section 351(a) of the Public Health Service Act for its product, letibotulinumtoxinA, for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults. The intended route of administration is intramuscular application in the corrugator supercilii muscle and procerus muscle, which are both responsible for the formation of glabellar lines.

The applicant has conducted the following nonclinical studies with letibotulinumtoxinA: single dose intramuscular toxicity studies in rats and dogs, 4-week intramuscular toxicity studies in rats and dogs, a 6-month intramuscular toxicity study in rats, and an intramuscular embryofetal development study in rats. The applicant did not provide any nonclinical pharmacokinetic data in this BLA because the systemic exposure of letibotulinumtoxinA is not detectable using current bioanalytic methods.

The common toxicities noted in the nonclinical studies conducted with letibotulinumtoxinA include muscle paralysis and muscle atrophy which are typical for botulinum neurotoxin type A products. The results from the nonclinical data provided in the submission did not reveal any new or unique toxicities associated with intramuscular administration of letibotulinumtoxinA that had not been previously observed with botulinum neurotoxin type A products.

There are no safety issues associated with the excipients or impurities identified in this biologic product.

In summary, letibotulinumtoxinA is approvable from a pharmacology/toxicology perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this BLA.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

Primary Pharmacology
The mechanism of action for botulinum neurotoxin type A products, blocking the release of acetylcholine, is well known. One in vivo pharmacology study (Induction of Muscle Paralysis by Botulinum Toxin Type A Toxin in Sprague-Dawley Rats, Study No. CP-001) was conducted with letibotulinumtoxinA to evaluate its muscle paralysis induction potential in comparison with

onabotulinumtoxinA. The two toxins were administered intramuscularly to Sprague Dawley rats at single doses of 2, 4 and 8 U/animal. No significant difference was observed between the two toxins with respect to onset and duration of muscle paralysis. The extent of letibotulinumtoxinA paralysis potential was comparable to that of onabotulinumtoxinA at all time points (3, 7, 14, 21, and 28 days post dose) and doses (2, 4 and 8 U/animal) tested. There was no recovery from the muscle paralysis after the injection of both toxins within 4 weeks after treatment.

Secondary Pharmacology
No secondary pharmacodynamics studies have been performed with letibotulinumtoxinA.

Safety Pharmacology
No stand-alone safety pharmacology studies have been conducted with letibotulinumtoxinA, as per the International Conference on Harmonisation (ICH) S7A guidance, *Safety pharmacology studies for human pharmaceuticals*. LetibotulinumtoxinA is intended as a local treatment without measurable systemic concentrations.

5.4. ADME/PK

No nonclinical pharmacokinetic evaluations were performed. Systemic concentrations of letibotulinumtoxinA following intramuscular administration of clinically relevant doses are not detectable by current bioanalytical methods.

5.5. Toxicology

5.5.1. General Toxicology

The single and repeat dose toxicity studies with letibotulinumtoxinA in dogs have been conducted and submitted to this BLA, and therefore the findings of these studies are summarized in this General Toxicology section for completeness sake. However, it should be noted that dogs are not an appropriate animal species for evaluating the toxicity associated with botulinum toxin because dogs are resistant to the toxicity elicited by botulinum toxin.

Study title/ number: A Single Dose Intramuscular Toxicity Study of Botulinum Toxin Type A in Sprague-Dawley Rats (Study No. 05-RA-241-1)

A single dose of letibotulinumtoxinA was administered intramuscularly to male and female rats at doses of 6, 30 and 150 U/kg. A dose-dependent paralysis of the muscles around the injection site, decrease in body weight and increase in stress-related clinical signs were observed after letibotulinumtoxinA treatment. Mortality was observed at 150 U/kg. The calculated LD_{50} value was 129.5 U/kg letibotulinumtoxinA for both male and female rats.

Study title/ number: Single Dose Intramuscular Toxicity Study of Botulinum Toxin Type A in Beagle Dogs (Study No. 05-DA242)

A single dose of letibotulinumtoxinA was administered intramuscularly to two male and two female dogs at doses of 2.5, 10, and 40 U/kg. After 7 days, the test article was once again administered intramuscularly at 50, 100 and 200 U/kg. The minimum lethal dose of letibotulinumtoxinA was higher than 200 U/kg in Beagle dogs.

Study title/ number: A 4-Week Repeated Intramuscular Toxicity Study of Botulinum Toxin Type A in Rats Followed by A 2-Week Recovery Study (Study No. 05-RR-243)

Administration of letibotulinumtoxinA to Sprague-Dawley rats via intramuscular injection at doses of 0, 1.5 , 3, and 6 U/kg once a week for 4 weeks resulted in paralysis of the muscle at the injection site (hind leg) in all dose groups. Effects secondary to paralysis included muscle atrophy and dose dependent decreases in body weight gains and food consumption. Decreased serum creatinine was noted in high dose animals which is consistent with muscle atrophy. Histopathological findings of muscle atrophy were noted in all treated animals at ≥3 U/kg. The NOAEL was less than 1.5 U/Kg/dose based on paralysis noted in all dose groups.

Study title/ number: A 4-Week Repeated Intramuscular Toxicity Study of Botulinum Toxin Type A in Beagle Dogs Followed by A 2-Week Recovery Study (Study No. 05-DR-244)

Administration of letibotulinumtoxinA to Beagle dogs via intramuscular injection at doses of 0, 3, 10, 30 U/kg once a week for 4 weeks resulted in no significant toxicological changes. The NOAEL was defined as 30 U/kg, the highest tested dose.

Study title/ number: A 6-Month Intramuscular Repeated Dose Toxicity Study in Sprague Dawley Rats with BoNT/A-DP 50U Including a 6-Month Recovery Period (Study No. 167857)

Animals used in this study were taken from a previous 6-month intramuscular repeat dose toxicity study that was terminated early because of an unexpected issue with the formulation resulting in a low activity of the test article. The re-usage of these animals in the present study is not considered to have any impact on the integrity of the study due to use of an adequate washout period. The vehicle used in this study consisted of 0.1% human serum albumin in 0.9% sodium chloride.

Once monthly intramuscular administration of letibotulinumtoxinA (0, 0.67/3.75, 2.0/7.5 and 6.0/15 U/kg) to Sprague-Dawley rats (15/sex/group for main study and 10/sex/group for recovery animals) resulted in the characteristic pharmacologic effects of reduced size of the injected muscle correlating with the histological findings of muscle fiber atrophy and degeneration in all dose groups. Often there was an inflammatory infiltrate and less frequently fibrosis in the injected muscle. The inflammatory infiltrate was also observed in the injected muscle of vehicle control animals. The doses were increased after the first dose administration

due to no clinical signs of paralysis observed after first dose administration. Effects on muscular tissue showed some evidence of reversal after the 6-month treatment free recovery period based on special histological techniques used to identify structural changes in muscle fibers.

5.5.2. Genetic Toxicology

As per the ICH S6(R1) guidance, *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*, no genetic toxicology testing is warranted for letibotulinumtoxinA.

5.5.3. Carcinogenicity

As per ICH S6(R1) guidance, no carcinogenicity testing is warranted for letibotulinumtoxinA.

5.5.4. Reproductive and Developmental Toxicology

Embryo-Fetal Development
Study title/ number: Intramuscular Embryo-Fetal Development Study of Botulinum Toxin Type A in Sprague-Dawley Rats (Study No. 08-RP-375)

An embryofetal development study was conducted in pregnant Sprague-Dawley rats (25/group) with daily intramuscular administration of letibotulinumtoxinA (0, 1, 4, 8 U/kg/dose) during the period of organogenesis (gestation days 5-16) . The vehicle used in this study was saline. Dams in all treated groups were observed with paralytic gait and had reduced body weight. No drug related malformations were observed in fetuses from treated dams. However, decreased fetal body weights were observed at all doses, with ossification delays also noted in the mid- and high dose groups. These effects are secondary to maternal toxicity and not relevant to the proposed clinical exposure.

5.5.5. Other Toxicology Studies

None.

6 Clinical Pharmacology

6.1. Executive Summary

LetibotulinumtoxinA (or BoNT/A-DP) is an acetylcholine release inhibitor and a neuromuscular blocker which induces muscle paralysis. The proposed product contains botulinum neurotoxin type A as the active pharmaceutical ingredient, is a noncovalent multimeric complex consisting of 6 proteins with a molecular weight of approximately 900 kDa.

- Proposed Indication: Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients

- Proposed dosing regimen: A total of 20 Units divided into 5 intramuscular injections of 0.1 mL each per treatment. Treatment intervals should not be more frequent than every 3 months.

The Applicant evaluated the efficacy and safety of BoNT/A-DP in three pivotal Phase 3 trials (BLESS I, II, and III). In addition, the Applicant also submitted supportive data from a Phase 3 study (HG-11-01) which was conducted to support approval in Korea and other countries and a post-marketing surveillance study (HG-13-02). The Applicant did not conduct clinical pharmacology studies to characterize the bioavailability or pharmacokinetic characteristics of BoNT/A-DP due to lack of bioanalytical techniques to measure the anticipated low systemic exposures.

6.1.1. Recommendations

From a clinical pharmacology standpoint, this BLA is acceptable to support the approval of letibotulinumtoxinA for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and/or corrugator muscle activity in adults.

6.1.1. Post-Marketing Requirement(s) and Commitments(s)

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action and Pharmacodynamics

LetibotulinumtoxinA blocks the release of the neurotransmitter acetylcholine at peripheral cholinergic nerve terminals, thus inducing muscle paralysis following intramuscular injection. The mechanism of action of letibotulinumtoxinA is the same as other botulinum toxin type A products. The pharmacodynamic effects of letibotulinumtoxinA in humans have not been characterized by the Applicant.

Pharmacokinetics

The Applicant has not conducted clinical pharmacology studies to characterize the bioavailability or pharmacokinetics of letibotulinumtoxinA because it is not possible to measure the anticipated low systemic exposures of letibotulinumtoxinA following intramuscular administration of the recommended dose using currently available bioanalytical methods.

Drug Interactions

The Applicant has not conducted clinical pharmacology studies to evaluate the drug interaction potential of letibotulinumtoxinA.

Immunogenicity

The immunogenicity potential of letibotulinumtoxinA was evaluated in the three Phase 3 pivotal studies (BLESS I, II and III). Blood samples for testing were collected at Screening/Baseline (pre-treatment) and for each cycle at Week 4 post-treatment and end-of-cycle/study. Among 1,129 subjects, 3 subjects had pre-existing antibodies at Screening/Baseline and 2 subjects developed antibodies at the end of study. For these 5 subjects who tested positive for antibodies, all titer values were zero and all tests for neutralizing antibodies were found to be negative. For information on immunogenicity assay validation, refer to the review from the Office of Biotechnology Products (OBP). No apparent association between the development of antibodies and reduced efficacy or adverse events was observed in this submission. The immunogenicity, efficacy and safety findings from these five subjects are summarized below.

Study	Subject ID	Antibody results	Clinical Response[a]	Adverse Events
BLESS I	(b) (6)	Positive at Screening	No	None
BLESS I		Positive at Screening	Yes	None
BLESS I		Positive at Screening	No	Gingivitis, not treatment-emergent
BLESS I		Positive at the end of study	Yes	None

BLESS I	(b) (6)	Positive at the end of study	Yes	None

[a]Primary efficacy endpoint; composite response at Week 4; both investigator and subject rated success criteria (a FWS score of 0 or 1 and an improvement of ≥2 points in FWS score at maximum frown relative to baseline)
Source: Listing 16.2.7.1.3, Listing 16.2.8.1

No positive antibody samples were found among 271 subjects in a supportive study conducted in South Korea (Study HG-11-01). The samples for this study were collected at Baseline and at the end of study/Week 16.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen, a total of 20 Units divided into 5 intramuscular injections of 0.1 mL each per treatment, is supported by the Phase 3 efficacy and safety results.

Therapeutic Individualization

Therapeutic individualization for letibotulinumtoxinA is not necessary and therefore not studied in this application.

Outstanding Issues

There are no outstanding issues that would preclude the approval of letibotulinumtoxinA from a Clinical Pharmacology's perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A summary of the general clinical pharmacology and immunogenicity of letibotulinumtoxinA is provided in Table 2.

Table 2. Summary of clinical pharmacology and immunogenicity of letibotulinumtoxinA.

Pharmacology	
Mechanism of action	LetibotulinumtoxinA blocks the release of the neurotransmitter acetylcholine at peripheral cholinergic nerve terminals, thus inducing muscle paralysis following intramuscular injection.
Pharmacodynamics	The pharmacodynamic effect of letibotulinumtoxinA in humans has not been characterized.

Pharmacokinetics	
ADME	The absorption, distribution, metabolism, and excretion of letibotulinumtoxinA have not been characterized. It is not possible to measure the anticipated low systemic exposures of letibotulinumtoxinA following intramuscular administration of the recommended dose using currently available bioanalytical methods.
Immunogenicity	
Incidence	Among 1,129 subjects who received letibotulinumtoxinA treatment in three Phase 3 clinical trials, 3 subjects (<1%) had pre-existing antibodies at Screening/Baseline and 2 subjects (<1%) developed antibodies at the end of study.
Impact on PK	The evaluation of the impact of immunogenicity on PK is not feasible because no human PK data is available for letibotulinumtoxinA.
Impact on efficacy and safety	No apparent association between the development of antibodies and adverse events was observed. However, the small number of antibody positive subjects limits the ability to draw definitive conclusions regarding the impact of immunogenicity on clinical efficacy or safety.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy of letibotulinumtoxinA has been established in the three pivotal Phase 3 trials, BLESS I, BLESS II and BLESS III. See section Error! Reference source not found. for evaluation of the efficacy results. No pharmacodynamic or pharmacokinetic dose-/exposure-response data are available to provide supportive evidence of effectiveness from a clinical pharmacology perspective.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the Phase 3 efficacy results support the proposed dosing regimen, which is a total of 20 Units divided into 5 intramuscular injections of 0.1 mL each per treatment.

The Applicant did not conduct a dose-ranging study to inform the Phase 3 dose selection. The Phase 3 dose was supported by the supportive study (Study HG-11-01) results which demonstrated the similar efficacy to those of the approved Botox product administered at the same dose (20 Units).

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No, a dose adjustment based on intrinsic factors is not necessary.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant has not conducted clinical studies to evaluate the drug interaction potential for letibotulinumtoxinA.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The following studies were submitted in support of current application and are listed in the table below.

Table 3. Tabular Listing of All Clinical Studies

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
BLESS I (Study CPH-301-201030)	Double-Blind, Randomized, Placebo Controlled, Efficacy and Safety Study; Followed by Long-Term, Open-Label, Extension Study	0.1 mL injections at 5 sites; or Placebo	The proportion of subjects achieving an FWS score of 0 or 1 and an improvement of ≥2 points relative to baseline in FWS score on both the investigator and subject ratings of frown wrinkle severity (IGA-FWS and PFWS) at Week 4 for the first treatment cycle	up to 60 weeks	708	Moderate-to severe Glabellar lines in healthy adults, 18-75 years of age	US, Germany, Poland – 18 centers
BLESS II (Study CPH-302-201030)	Double-Blind, Randomized, Placebo Controlled, Efficacy and Safety Study; Followed by Long-Term, Open-Label, Extension Study	0.1 mL injections at 5 sites; or Placebo	The proportion of subjects achieving an FWS score of 0 or 1 and an improvement of ≥2 points relative to baseline in FWS score on both the investigator and subject ratings of frown wrinkle severity (IGA-FWS and PFWS) at Week 4 of the first treatment cycle	up to 60 weeks	213	Moderate-to severe Glabellar lines in healthy adults, 18-75 years of age	US – 6 centers
BLESS III (Study CPH-303-201400)	Double-Blind, Randomized, Placebo Controlled, Efficacy and Safety Study; Followed by Long-Term, Open-Label, Extension Study	0.1 mL injections at 5 sites; or Placebo	The proportion of subjects achieving an FWS score of 0 or 1 and an improvement of ≥2 points relative to baseline in FWS score on both the investigator and subject ratings of frown wrinkle severity (IGA-FWS and PFWS) at Week 4 for the first treatment cycle	up to 60 weeks	355	Moderate-to severe Glabellar lines in healthy adults, 18-75 years of age	Austria and US – 7 centers

Studies to Support Safety							
HG-11-01	Double-Blind, Randomized, Active Control Comparative, Efficacy and Safety	0.1 mL injections at 5 sites; or Botox	To evaluate the safety and efficacy for improvement of glabellar lines of Botulax compared to Botox in patients with moderate to severe glabellar lines	16 week follow-up period	272	Moderate-to severe Glabellar lines in healthy adults, 18-75 years of age	Korea
HG-12-02	Post-Marketing Surveillance (PMS) Study	0.1 mL injections at 5 sites	To provides additional supportive safety data in a postmarketing setting.	4 years	815	Moderate-to severe Glabellar lines in healthy adults, 18-65 years of age	Korea

Abbreviations: IGA-FWS = Investigator Global Assessment Facial Wrinkle Scale; PFWS = Patient Facial Wrinkle Scale.
Source: Created from submitted information.

7.2. Review Strategy

Data Sources

The sources of data used for the evaluation of the efficacy and safety of BoNT/A-DP for the proposed indication included final study reports submitted by the Applicant, datasets (Study Data Tabulation Model and Analysis Data Model), and literature references.

This application was submitted in electronic common technical document format and is entirely electronic. The electronic submission, including protocols, statistical analysis plans, clinical study reports, and SAS transport datasets in legacy, Study Data Tabulation Model, and Analysis Data Model format.

Data and Analysis Quality

In collaboration with the Office of Computational Science, the statistical and clinical team evaluated the fitness of the data. This included an assessment of the compatibility of the data with the review tools and data quality metrics such as the following:

- Availability of appropriate variables
- Variables populated by expected data points
- Appropriate use of standard terminology
- Data well-described by metadata

A final statistical analysis plan (SAP) was submitted and most relevant analysis decisions (e.g., pooling of sites, analysis population membership, etc.) were made prior to unblinding.
The databases required minimal data management prior to performing analyses. The sponsor submitted statistical programs for generating the multiple imputations for missing data and the confidence interval calculations for the primary efficacy endpoint. The data and analysis provided by the sponsor is acceptable per Agency guidance.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Design for Studies BLESS I, II and III

Trial Design

Study BLESS I (Protocol CPH-301-201030), Study BLESS II (Protocol CPH-302-201030) and Study BLESS III (Protocol CPH-303-201040) were identically designed multicenter Phase 3 trials that evaluated the efficacy and safety of letibotulinumtoxinA (Letybo) for the temporary improvement in the appearance of moderate to severe glabellar lines in comparison with placebo. All three trials were comprised of two parts: the first part of the study was a randomized, double-blind, placebo-controlled phase which aimed to demonstrate the efficacy and safety of Letybo compared with placebo; the second part was an open-label extension phase to assess the long-term safety of the treatment and efficacy after repeat treatments. Subjects aged between 18 and 75 years with glabellar lines of at least moderate severity at maximum frown based on the glabellar line scale (GLS) as determined by in-clinic assessments by both the investigator and the subject were eligible for enrollment. Eligible subjects were randomized 3:1 at baseline (Day 0) to a single treatment with 20 Units of Letybo or placebo. After receiving the first treatment, subjects were evaluated at Weeks 1, 2, 4 and 8, and on the day of evaluation for retreatment visit (starting at Week 12 and at 4-weekly intervals thereafter, until they were eligible for retreatment). After the double-blind phase, subjects could enter the open-label extension phase to be dosed with 20 Units of Letybo for up to 3 subsequent retreatments. The double-blind phase and retreatment cycles lasted at least 12 weeks and ended when the subject was qualified for retreatment (in accordance with the eligibility for retreatment criteria) with the last retreatment occurring no later than Week 48, or with the End of Study visit if the subject did not qualify for retreatment within 48 weeks after the first injection visit.

Study Endpoints

Efficacy was assessed independently by both the investigator and the subject using the 4-point grading scale (0=none, 1=mild, 2=moderate, 3=severe). Both scales used the same levels and descriptors, which are presented in Table 4.

Table 4. Glabellar Line Scale for Investigator (GLS-I) and for Subject (GLS-S)

Score	Line Severity When Frowning
0	None: The area between the eyebrows is smooth, with no visible lines

1	Mild: The area between the eyebrows has one or more thin or shallow lines
2	Moderate: The area between the eyebrows has one or more lines of medium depth
3	Severe: The area between the eyebrows has one or more deep and pronounced lines

For all three studies, the primary efficacy endpoint was measured at Week 4 after the first treatment and was defined as the proportion of subjects who achieved treatment success, that is, a score of 0 or 1 (none or mild) and an improvement of at least 2 points from baseline to Week 4 at maximum frown, based concurrently on both the GLS-I and GLS-S. The Applicant refers to this endpoint as "composite responder rate" comprising investigator and subject assessments of treatment effectiveness.

Statistical Reviewers' Comment:

- *According to FDA's Multiple Endpoints in Clinical Trials Guidance (FDA 2017[1]), this primary efficacy endpoint is not a composite endpoint but a multi-component endpoint. The statistical reviewers refer to this endpoint as "multi-component responder rate" in this review.*

For Studies BLESS I and II, the protocol specified five key secondary efficacy endpoints which evaluated different definitions of success during the double-blind phase based on the GLS-I and/or GLS-S, and extent of change in psychological impact based on the modified Skindex-16 GL-QoL scale and FACE-Q scales. In this review, the statistical reviewers conducted analyses for the following four key secondary endpoints that were based on the GLS-I and/or GLS-S to be consistent with the primary endpoint.

1. Multi-component responder rate at Week 12
2. Multi-component responder rate at Week 16
3. The proportion of subjects achieving a ≥ 1-point improvement from baseline to Week 4 at rest, based separately on the GLS-I and GLS-S (applicable only for subjects who had the GLS at rest ≥ 1 at baseline)
4. Multi-component responder rate at Week 20

For Study BLESS III, the secondary endpoints were the same as those for Studies BLESS I and II but for exploratory purpose only.

Statistical Analysis Plan

The primary analysis population was the Full Analysis Set (FAS) defined as all randomized subjects who received at least one injection with study medication (independent of whether it was Letybo or placebo). Within the FAS, a subject was evaluated per the treatment assigned by

[1] Multiple Endpoints in Clinical Trials Guidance for Industry, January 2017. (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry)

randomization rather than the treatment actually received, if different, i.e., following the ITT principle.

The Per Protocol Set (PPS) was a supportive analysis population, which included all subjects in the FAS who had no significant protocol deviations and in-clinic assessments (GLS-I and GLS-S) at baseline and at Week 4 visit. Within the PPS, all subjects were evaluated per the treatment actually received.

Efficacy Analyses

The protocol/SAP specified that the primary and secondary endpoints to be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by study center using a significance level of 0.025. The one-sided p-value was derived by halving the two-sided p-value delivered by the SAS procedure Proc Freq using the General Association Statistic. Small study centers with < 3 placebo subjects were combined. The Applicant did not pre-specify in the protocol/SAP but used the Newcombe confidence limits (unstratified) to calculate the 95% confidence intervals (CIs) for the risk difference.

Statistical Reviewers' Comment:

- *The CMH test statistic has a chi-squared distribution with one degree of freedom. Due to the asymmetric nature of the chi-squared distribution, the one-sided p-value cannot be derived by simply halving the two-sided p-value. The statistical reviewers used the two-sided p-value for the CMH test with a significance level of 0.05 in this review.*
- *The Applicant did not pre-specify but used the Newcombe confidence limits (unstratified) to calculate the 95% CIs for the risk difference for all three studies. Considering that randomization was stratified by study center and there were zero-frequency rows, columns or cells (in Studies BLESS I and III, the placebo responder rate was 0%), statistical reviewers calculated the common risk difference stratified by study center based on the commonly used Mantel-Haenszel estimate (Mantel and Haenszel 1959[2]) and its variance (Sato 1989[3]).*

Multiplicity

For Studies BLESS I and II, the statistical tests for the primary and the four secondary endpoints were performed with appropriate multiplicity control based on the FAS, where the primary and the four secondary endpoints were analyzed in a hierarchical order as follows:

- Primary Endpoint: Multi-component responder rate at Week 4
- Secondary Endpoint 1: Multi-component responder rate at Week 12

[2] Mantel, N., & Haenszel, W. (1959). Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the national cancer institute, 22(4), 719-748.
[3] Sato, T. (1989). On the variance estimator for the Mantel-Haenszel risk difference. Biometrics, 45(4), 1323-1324.

- Secondary Endpoint 2: Multi-component responder rate at Week 16
- Secondary Endpoint 3:
  - 3.1: The proportion of subjects achieving a ≥ 1-point improvement from baseline to Week 4 at rest, based on the GLS-I (applicable only for subjects who had the GLS-I at rest ≥ 1 at baseline)
  - 3.2: The proportion of subjects achieving a ≥ 1-point improvement from baseline to Week 4 at rest, based on the GLS-S (applicable only for subjects who had the GLS-S at rest ≥ 1 at baseline)
- Secondary Endpoint 4: Multi-component responder rate at Week 20

The protocol/SAP specified that the results of each test were considered to be confirmative, only if the previous test in the order showed a confirmatory result at a one-sided significance level of 0.025. Otherwise, the results of the subsequent tests were considered exploratory, and not confirmatory.

Statistical Reviewers' Comment:

- *Similar to the previous concern on the halved one-sided p value for the CMH test, statistical reviewers used the two-sided p value and the two-sided significance level of 0.05 in the hierarchical testing procedure. That is, the results of each test were considered to be confirmative, only if the previous test in the order showed a confirmatory result at a two-sided significance level of 0.05.*

Handling of Missing Data

For the primary endpoint as well as secondary endpoints 1 and 3, subjects with missing in-clinic assessments (GLS-I or GLS-S) at baseline or Week 4/Week 12 were designated as non-responders. For secondary endpoints 2 and 4, analysis was conducted on observed values only, i.e., subjects with missing in-clinic assessments (GLS-I or GLS-S) at baseline or Week 16/Week 20 were excluded from analysis but not assigned as non-responders.

The Applicant pre-specified the following sensitivity analyses as additional approaches for handling of missing values for the primary endpoint:

- Analysis on observed values only, i.e., missing values were excluded from analysis (observed)
- Last observation carried forward (LOCF)
- Tipping point analysis: each missing data was assigned to either a response or non-response so that all possible combinations of replacing one or more missing values within each treatment group were analyzed.

Statistical Reviewers' Comment:

- *For the handling of missing data, the Applicant pre-specified using non-responder imputation in the primary analysis and using the observed values only, LOCF and tipping point analysis as sensitivity analyses. For Studies BLESS II and III, the Applicant conducted the*

analyses as planned. For Study BLESS I, the Applicant did all the other analyses but did not conduct the tipping point analysis stating that "the data were not compatible with this type of analysis". The statistical reviewers conducted the worst-case imputation, that is, non-responder imputation (worst outcome) for subjects in the Letybo arm with missing in-clinic assessments (GLS-I or GLS-S) at baseline or Week 4 and responder imputation (best outcome) for those in the placebo arm with missing in-clinic assessments (GLS-I or GLS-S) at baseline or Week 4. The worst-case imputation is the most extreme case of the tipping point analysis. Given that the treatment effect is relatively large and the proportion of subjects with missing data is small, the statistical reviewers do not expect that the method of handling the missing data would impact the efficacy conclusion.

Statistical Analysis Conduct

For Studies BLESS I and II, the Applicant performed statistical analysis of the double-blind phase (treatment cycle 1) and the open-label extension phase (treatment cycles 2-4) after database lock for all data up to the end of the study and final unblinding.

For Study BLESS III, the Applicant performed the interim analysis (IA) after all subjects had completed the re-evaluation for retreatment visit at Week 16 or had completed the double-blind phase (whichever occurred earlier) (cut-off date: February 10 2020). The results of efficacy analysis supported the efficacy claim based on the IA.

Protocol Amendments

Study BLESS I

The protocol was finalized on October 13, 2015, with an amendment on January 28, 2016 (version 1.1) to address safety procedures and assessments, statistical analyses, minor change in scales, and contact details for reporting serious adverse events (SAEs) and adverse events of special interest (AESIs). An additional amendment was issued on March 11, 2016 (version 1.2) to clarify adverse event (AE) follow-up definition. Amendment v1.1 and v1.2 were implemented before the first subject was randomized on March 21, 2016.

The SAP was initially finalized on June 23, 2017. After study completion and unblinding of the database, the SAP was amended to include a post-hoc endpoint that assesses an improvement of ≥ 1-point from baseline at maximum frown, based on multi-component evaluation, as well as individual assessments, of the investigator and subject and to include additional subgroup analyses by race, by naïve versus previous use of toxin by center, and by additional age groups. The SAP was finalized on June 7, 2018.

Study BLESS II

The protocol was finalized on October 20 2015, with an amendment on January 29 2016 (version 1.1) to address safety procedures and assessments, statistical analyses in the study, minor change in scales, and contact details for reporting serious adverse events (SAEs) and adverse events of special interest (AESI), an additional amendment on May 13 2016 (version

1.2) to clarify adverse event (AE) follow-up, and a further amendment on August 25 2016 (version 1.3) to update section 2.0 and 7.1, and amend inclusion criteria bullet point 4. Amendment v1.1 was implemented before the first subject was randomized on April 12 2016. Amendment v1.2 and v1.3 were implemented after that date.

The SAP was initially finalized on August 15 2017. After study completion and unblinding of the database, the SAP was amended to include a post-hoc endpoint that assesses an improvement of ≥ 1-point from baseline at maximum frown, based on multi-component evaluation, as well as individual assessments, of the investigator and subject and to include additional subgroup analyses by race, by naïve versus previous use of toxin by center, and by additional age groups. The SAP was finalized on June 7 2018.

Study BLESS III

The protocol was finalized on January 7 2019, with an amendment on July 15 2019 (version 2) to adapt the secondary endpoints and statistical analyses and to address safety procedures and assessments according to FDA recommendations. Amendment v2 was implemented after the first subject was randomized on May 6 2019.

The SAP was initially finalized on November 19 2019. Following the Site 110 audit findings in January 2020 (an unblinded center staff performed blinded tasks on safety assessments at Site 110), the SAP was amended (dated February 21 2020) to include sensitivity analyses by excluding subjects from Site 110.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that the trials were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, Good Clinical Practice (GCP), the Code of Federal Regulation (CFR; Title 21, Part 312), and local regulatory requirements. Trial protocols were reviewed and approved by a central institutional review board (IRB) (Copernicus). A signed, IRB-approved , written informed consent was obtained from each subject prior to trial initiation.

Financial Disclosure

Please see Appendix 19.2.

Patient Disposition

Study BLESS I randomized 708 subjects, 531 to Letybo and 177 to placebo. Study BLESS II randomized 213 subjects, 160 to Letybo and 53 to placebo. Study BLESS III randomized 355 subjects, 266 to Letybo and 89 to placebo. In total, the three studies randomized 1276 subjects,

957 to Letybo and 319 to placebo. Table 5 shows details about subject disposition in each study.

Among the 1276 randomized subjects, 1272 received treatment and 1271 were included in the FAS, the primary analysis population. A total of 4 randomized subjects didn't received treatment and were excluded from the FAS. In additiona, Subject (b) (6) in Study BLESS I was randomized to the Letybo arm, but had baseline glabellar lines rated as mild at maximum frown based on the GLS-S, which did not meet the inclusion criteria of moderate to severe glabellar frown lines at maximum frown at baseline. As per the clinical reviewer (email dated January 4 2022), this subject was taken out of the FAS and primary efficacy analysis, but kept in the safety population and analysis.

The 1271 FAS subjects (954 in Letybo and 317 in placebo) included 708 in Study BLESS I (528 in Letybo and 175 in placebo), 213 in Study BLESS II (160 in Letybo and 53 in placebo), and 355 in Study BLESS III (266 in Letybo and 89 in placebo).

Approximately 92 to 94% of Letybo subjects and 90 to 94% of placebo subjects completed the double-blind phase, and approximately 85 to 86% of Letybo subjects and 81 to 90% of placebo subjects completed the entire study in the three studies. The most common reasons for discontinuation from the double-blind phase and from the entire study were withdrawal by subject and lost to follow-up.

Table 5. Subject Disposition (Studies BLESS I, II, and III)

	Study BLESS I		Study BLESS II		Study BLESS III	
	Letybo N=531	Placebo N=177	Letybo N=160	Placebo N=53	Letybo N=266	Placebo N=89
Randomized	531	177	160	53	266	89
Received treatment	529 (99.6)	175 (98.9)	160 (100)	53 (100)	266 (100)	89 (100)
Subjects included in the FAS	528 (99.4)	175 (98.9)	160 (100)	53 (100)	266 (100)	89 (100)
Completed double-blind phase	500 (94.2)	160 (90.4)	147 (91.9)	48 (90.6)	249 (93.6)	84 (94.4)
Primary reason for discontinuation from double-blind phase						
Withdrawal by subject	11 (2.1)	8 (4.5)	5 (3.1)	2 (3.8)	9 (3.4)	2 (2.2)
Lost to follow-up	11 (2.1)	7 (4.0)	8 (5.0)	3 (5.7)	4 (1.5)	3 (3.4)
Per investigator decision	2 (0.4)	--	--	--	1 (0.4)	--
Adverse event	1 (0.2)	1 (0.6)	--	--	--	--
Other	6 (1.1)	1 (0.6)	--	--	3 (1.1)	--
Completed study	456 (85.9)	145 (81.9)	136 (85.0)	43 (81.1)	227 (85.3)	80 (89.9)
Primary reason for study discontinuation						
Withdrawal by subject	37 (7.0)	18 (10.2)	8 (5.0)	4 (7.5)	20 (7.5)	3 (3.4)
Lost to follow-up	25 (4.7)	10 (5.6)	15 (9.4)	6 (11.3)	15 (5.6)	5 (5.6)
Per investigator decision	3 (0.6)	--	--	--	2 (0.8)	1 (1.1)
Adverse event	3 (0.6)	3 (1.7)	--	--	--	--
Other	7 (1.3)	1 (0.6)	1 (0.6)	--	2 (0.8)	--

Percentages were calculated using the number of subjects randomized as the denominator
Source: reviewer analysis

Protocol Violations/Deviations

Approximately 84 to 90% of Letybo subjects and 85 to 91% of placebo subjects were included in the PPS. The most common reasons for exclusion from the PPS were protocol deviations related to visit schedule and conduct of the procedures/tests (see Table 6).

Table 6. Per Protocol Set (PPS) (Studies BLESS I, II, and III)

	Study BLESS I		Study BLESS II		Study BLESS III	
	Letybo N=531	Placebo N=177	Letybo N=160	Placebo N=53	Letybo N=266	Placebo N=89
Randomized	531	177	160	53	266	89
Subjects included in the PPS	480 (90.4)	154 (87.0)	134 (83.8)	45 (84.9)	240 (90.2)	81 (91.0)
Primary reason for exclusion from the PPS						
Didn't receive treatment	2 (0.4)	2 (1.1)	--	--	--	--
Had missing in-clinic assessment at baseline or Week 4 visit	7 (1.3)	7 (4.0)	6 (3.8)	4 (7.5)	3* (1.1)	4* (4.5)
Major protocol deviations	42 (7.9)	15 (8.5)	26 (16.3)	8 (15.1)	23 (8.6)	4 (4.5)
Visit Schedule -- Visit outside protocol window	15	5	5	0	16	2
Visit Schedule -- Visit not done	1	1	2	0	0	0
Procedures/Tests -- Performed outside window	1	0	0	0	0	0
Procedures/Tests -- Procedure not done	0	0	5	4	0	0
Procedures/Tests -- GLS-I not assessed by same investigator	0	0	0	0	1	0
Procedure/Tests -- Specify in comments	24	7	2	2	0	0
Inclusion/Exclusion -- Deviations in inclusion/exclusion criteria	1	0	1	0	2	0
Inclusion/Exclusion -- Subject on excluded medication/s	2	1	0	0	0	0
Study Drug -- Stored at incorrect temperature/excursion not reported	0	0	0	0	3	1
Study Drug -- Incorrect treatment allocation or dose	0	0	0	0	1	0
Study Drug -- Specify in comments	0	0	13	2	0	0
Concomitant Medications -- Took prohibited medication	2	1	0	0	0	1

during treatment						

*Subject (b) (6) in placebo arm and Subject (b) (6) in Letybo arm were excluded from the PPS by the Applicant in Study BLESS III. They had in-clinic assessments (GLS-I and GLS-S) at baseline and at Week 4 visit, but withdrew from the study early at Week 4 visit.
Percentages were calculated using the number of subjects randomized as the denominator
Subjects may have been excluded from PPS for more than one reason.
Source: reviewer analysis

Table of Demographic Characteristics

The baseline demographics were generally balanced across treatment groups in the FAS among the three studies (see Table 7). The majority of subjects were female, white and not Hispanic or Latino. The mean age was 50 years, with 88% of subjects younger than 65 years in the three studies. Study BLESS I was conducted in 9 US sites and 9 EU sites, Study BLESS II was conducted in 6 US sites, and Study BLESS III was conducted in 6 US Sites and 1 EU site.

Table 7. Subject Demographics (Studies BLESS I, II, and III; FAS)

	Study BLESS I		Study BLESS II		Study BLESS III	
	Letybo N=528	Placebo N=175	Letybo N=160	Placebo N=53	Letybo N=266	Placebo N=89
Age (years)						
Mean	49.3	48.7	52	52.4	52.2	49.4
Median	49	49	52.5	51	53	52
Range	19-75	21-74	27-75	29-73	21-75	22-75
18-64 years	462 (87.5)	157 (89.7)	141 (88.1)	45 (84.9)	233 (87.6)	81 (91.0)
65-75 years	66 (12.5)	18 (10.3)	19 (11.9)	8 (15.1)	33 (12.4)	8 (9.0)
Gender						
Female	483 (91.5)	155 (88.6)	150 (93.8)	45 (84.9)	248 (93.2)	80 (89.9)
Male	45 (8.5)	20 (11.4)	10 (6.3)	8 (15.1)	18 (6.8)	9 (10.1)
Race						
White	482 (91.3)	153 (87.4)	153 (95.6)	50 (94.3)	236 (88.7)	79 (88.8)
Black or African American	33 (6.3)	18 (10.3)	3 (1.9)	1 (1.9)	25 (9.4)	7 (7.9)
Asian	7 (1.3)	3 (1.7)	2 (1.3)	1 (1.9)	4 (1.5)	1 (1.1)
Am. Ind. or AK Native	2 (0.4)	0	1 (0.6)	0	0	0
Native HI or Pac. Isl.	0	0	0	1 (1.9)	0	0
Other	4 (0.8)	1 (0.6)	1 (0.6)	0	1 (0.4)	2 (2.2)
Ethnicity						
Not Hispanic or Latino	497 (94.1)	166 (94.9)	126 (78.8)	45 (84.9)	200 (75.2)	67 (75.3)
Hispanic or Latino	25 (4.7)	8 (4.6)	33 (20.6)	7 (13.2)	66 (24.8)	22 (24.7)
Missing	6 (1.1)	1 (0.6)	1 (0.6)	1 (1.9)	0	0
Region						
US	268 (50.8)	95 (54.3)	160 (100)	53 (100)	225 (84.6)	79 (88.8)
EU	260 (49.2)	80 (45.7)	0	0	41 (15.4)	10 (11.2)

Am. Ind. = American Indian; AK = Alaska; HI = Hawaiian; Pac. Isl. = Pacific Islander
EU: Germany and Poland in Study BLESS I, Austria in Study BLESS III
Percentages were calculated using the number of subjects in the FAS as the denominator
Percentages may not sum to 100% due to rounding
Source: reviewer analysis

Appears this way on original

Other Baseline Characteristics

Baseline GLS-I and GLS-S at maximum frown were generally balanced across treatment groups in the FAS among the three studies (see Table 8). A higher proportion of subjects whose glabellar lines were rated as severe (74%) than moderate (26%) based on both the GLS-I and GLS-S. Proportion of subjects with previous use of botulinum toxin was balanced between treatment groups in Studies BLESS I and III, but higher in the Letybo arm (34%) than in the placebo arm (21%) in Study BLESS II (see Table 8).

Table 8. Other Baseline Characteristics (Studies BLESS I, II, and III; FAS)

	Study BLESS I		Study BLESS II		Study BLESS III	
	Letybo N=528	Placebo N=175	Letybo N=160	Placebo N=53	Letybo N=266	Placebo N=89
Previous Use of Botulinum Toxin						
No	345 (65.3)	116 (66.3)	105 (65.6)	42 (79.2)	169 (63.5)	53 (59.6)
Yes	183 (34.7)	59 (33.7)	55 (34.4)	11 (20.8)	97 (36.5)	36 (40.4)
GLS-I (at maximum frown)						
3=Severe	384 (72.7)	133 (76.0)	112 (70.0)	37 (69.8)	202 (75.9)	67 (75.3)
2=Moderate	144 (27.3)	42 (24.0)	48 (30.0)	16 (30.2)	64 (24.1)	22 (24.7)
GLS-S (at maximum frown)						
3=Severe	401 (75.9)	121 (69.1)	121 (75.6)	42 (79.2)	196 (73.7)	64 (71.9)
2=Moderate	127 (24.1)	54 (30.9)	39 (24.4)	11 (20.8)	70 (26.3)	25 (28.1)

Percentages were calculated using the number of subjects in the FAS as the denominator
Source: reviewer analysis

Efficacy Results – Primary Endpoint

Table 9 presents the statistical reviewers' analysis results for the primary efficacy endpoint among the FAS in Studies BLESS I, II and III. The proportion of subjects who achieved treatment success for the Letybo treatment was statistically superior to that for the placebo treatment in each of the three pivotal trials. The stratified common risk difference was 47.0% (42.7%, 51.4%) in Study BLESS I, 45.1% (36.0%, 54.3%) in Study BLESS II, and 65.2% (59.3%, 71.2%) in Study BLESS III. Between the two individual components, the GLS-I had responder rates that were 10 to 23% higher than the GLS-S in the Letybo arm. Similar results were also observed among the PPS, which are reported in Appendix Table 31 in Section 19.5. For Study BLESS I, a sensitivity analysis was carried out by including Subject (b) (6) (who had baseline glabellar lines rated as mild at maximum frown based on the GLS-S) also showed similar result as the primary analysis (see Appendix Table 32 in Section 19.5).

Table 9. Primary Efficacy Endpoint at Week 4 (Studies BLESS I, II and III; FAS)

	Study BLESS I		Study BLESS II		Study BLESS III	
	Letybo N = 528	Placebo N = 175	Letybo N = 160	Placebo N = 53	Letybo N = 266	Placebo N = 89
Treatment Success						

Multi-Component Assessment n (%) #	246 (46.6%)	0 (0%)	78 (48.8%)	1 (1.9%)	172 (64.7%)	0 (0%)
Treatment Difference and 95% CI *	47.0% (42.7%, 51.4%)		45.1% (36.0%, 54.3%)		65.2% (59.3%, 71.2%)	
P-value **	<0.0001		<0.0001		<0.0001	
Individual Components						
Investigator Assessment n (%) #	348 (65.9%)	1 (0.6%)	120 (75.0%)	1 (1.9%)	209 (78.6%)	1 (1.1%)
Subject Assessment n (%) #	290 (54.9%)	0 (0%)	83 (51.9%)	1 (1.9%)	183 (68.8%)	0 (0%)

Subjects with missing in-clinic assessments (GLS-I or GLS-S) at baseline or Week 4 were imputed as non-responders.
* Mantel-Haenszel estimate and confidence limits for the common risk difference by using the Mantel-Haenszel weights for study center.
** P-values are based on the CMH general association test stratified on study center.
Source: reviewer analysis

Handling of Missing Data

In the primary analysis, missing data were handled with the non-responder imputation, that is, subjects with missing in-clinic assessments (GLS-I or GLS-S) at baseline or Week 4 were imputed as non-responders. As shown in Table 10, all three studies had a small proportion of subjects with missing data (0.8 to 3.8% of Letybo subjects and 3.4 to 7.5% of placebo subjects).

Table 10. Subjects with Missing Data for the Primary Efficacy Endpoint at Week 4 (Studies BLESS I, II, and III; FAS)

	Study BLESS I		Study BLESS II		Study BLESS III	
	Letybo N=528	Placebo N=175	Letybo N=160	Placebo N=53	Letybo N=266	Placebo N=89
Subjects with Missing Data	7 (1.3)	7 (4.0)	6 (3.8)	4 (7.5)	2 (0.8)	3 (3.4)

Source: reviewer analysis

As sensitivity analyses, the statistical reviewers performed the pre-specified analyses using the observed values only and the LOCF for handling the missing data, as well as the worst-case imputation as discussed in Section 8.1.1 (Statistical Analysis Plan). All these sensitivity analyses (see Table 11, Table 12 and Table 13Table 11. Primary Efficacy Endpoint at Week 4 Using the Observed Values Only (Studies BLESS I, II and III; FAS)) showed consistent results with the primary analysis. Missing data had a limited impact on the efficacy results because of the large effect size and the small proportion of subjects with missing data.

Table 11. Primary Efficacy Endpoint at Week 4 Using the Observed Values Only (Studies BLESS I, II and III; FAS)

	Study BLESS I		Study BLESS II		Study BLESS III	
	Letybo N = 521	Placebo N = 168	Letybo N = 154	Placebo N = 49	Letybo N = 264	Placebo N = 86
Treatment Success						

Multi-Component Assessment n (%) #	246 (47.2%)	0 (0%)	78 (50.6%)	1 (2.0%)	172 (65.2%)	0 (0%)
Treatment Difference and 95% CI *	47.8% (43.4%, 52.2%)		46.8% (37.3%, 56.4%)		66.0% (60.1%, 71.9%)	
P-value **	<0.0001		<0.0001		<0.0001	
Individual Components						
Investigator Assessment n (%) #	348 (66.8%)	1 (0.6%)	120 (77.9%)	1 (2.0%)	209 (79.2%)	1 (1.2%)
Subject Assessment n (%) #	290 (55.7%)	0 (0%)	83 (53.9%)	1 (2.0%)	183 (69.3%)	0 (0%)

Subjects with missing in-clinic assessments (GLS-I or GLS-S) at baseline or Week 4 were excluded from analysis.
* Mantel-Haenszel estimate and confidence limits for the common risk difference by using the Mantel-Haenszel weights for study center.
** P-values are based on the CMH general association test stratified on study center.
Source: reviewer analysis

Table 12. Primary Efficacy Endpoint at Week 4 Using the LOCF (Studies BLESS I, II and III; FAS)

	Study BLESS I		Study BLESS II		Study BLESS III	
	Letybo N = 528	Placebo N = 175	Letybo N = 160	Placebo N = 53	Letybo N = 266	Placebo N = 89
Treatment Success						
Multi-Component Assessment n (%) #	249 (47.2%)	0 (0%)	81 (50.6%)	1 (1.9%)	172 (64.7%)	0 (0%)
Treatment Difference and 95% CI *	47.6% (43.2%, 52.0%)		46.7% (37.5%, 55.9%)		65.2% (59.3%, 71.2%)	
P-value **	<0.0001		<0.0001		<0.0001	
Individual Components						
Investigator Assessment n (%) #	352 (66.7%)	1 (0.6%)	124 (77.5%)	1 (1.9%)	209 (78.6%)	1 (1.1%)
Subject Assessment n (%) #	293 (55.5%)	0 (0%)	86 (53.8%)	1 (1.9%)	183 (68.8%)	0 (0%)

Subjects with missing in-clinic assessments (GLS-I or GLS-S) at baseline or Week 4 were imputed using the LOCF.
* Mantel-Haenszel estimate and confidence limits for the common risk difference by using the Mantel-Haenszel weights for study center.
** P-values are based on the CMH general association test stratified on study center.
Source: reviewer analysis

Table 13. Primary Efficacy Endpoint at Week 4 Using the Worst-Case Imputation (Studies BLESS I, II and III; FAS)

	Study BLESS I		Study BLESS II		Study BLESS III	
	Letybo N = 528	Placebo N = 175	Letybo N = 160	Placebo N = 53	Letybo N = 266	Placebo N = 89
Treatment Success						
Multi-Component Assessment n (%) #	246 (46.6%)	7 (4.0%)	78 (48.8%)	5 (9.4%)	172 (64.7%)	3 (3.4%)
Treatment Difference and 95% CI *	43.1% (37.8%, 48.4%)		37.4% (25.7%, 49.0%)		62.1% (55.2%, 69.1%)	
P-value **	<0.0001		<0.0001		<0.0001	
Individual Components						

Investigator Assessment n (%) #	348 (65.9%)	8 (4.6%)	120 (75.0%)	5 (9.4%)	209 (78.6%)	4 (4.5%)
Subject Assessment n (%) #	290 (54.9%)	7 (4.0%)	83 (51.9%)	5 (9.4%)	183 (68.8%)	3 (3.4%)

Subjects with missing in-clinic assessments (GLS-I or GLS-S) at baseline or Week 4 were imputed as being non-responders for the Letybo arm, and responders for the placebo arm.
* Mantel-Haenszel estimate and confidence limits for the common risk difference by using the Mantel-Haenszel weights for study center.
** P-values are based on the CMH general association test stratified on study center.
Source: reviewer analysis

Data Quality and Integrity

As mentioned in Section 8.1.1 (Protocol Amendments), a center audit conducted in January 2020 reported a protocol non-compliance in Study BLESS III: an unblinded center staff performed blinded tasks on safety assessments at Site 110. In order to assess its impact on the efficacy results, the Applicant conducted a sensitivity analysis by excluding all the subjects of Site 110 (44 Letybo subjects and 7 placebo subjects). As shown in Table 14, the resulting common risk difference at Week 4 was 66.1% (59.7%, 72.5%) in favor of Letybo, very close to that in the primary analysis: 65.2% (59.3%, 71.2%). Hence, excluding the subjects of Site 110 had a minimal impact on the overall efficacy results and did not change the efficacy conclusion of the primary analysis.

Table 14. Primary Efficacy Endpoint at Week 4 Excluding Site 110 (Study BLESS III; FAS)

	Study BLESS III (Excluding Site 110)	
	Letybo N = 222	Placebo N = 82
Treatment Success		
Multi-Component Assessment n (%) #	147 (66.2%)	0 (0%)
Treatment Difference and 95% CI *	66.1% (59.7%, 72.5%)	
P-value **	<0.0001	
Individual Components		
Investigator Assessment n (%) #	182 (82.0%)	1 (1.2%)
Subject Assessment n (%) #	153 (68.9%)	0 (0%)

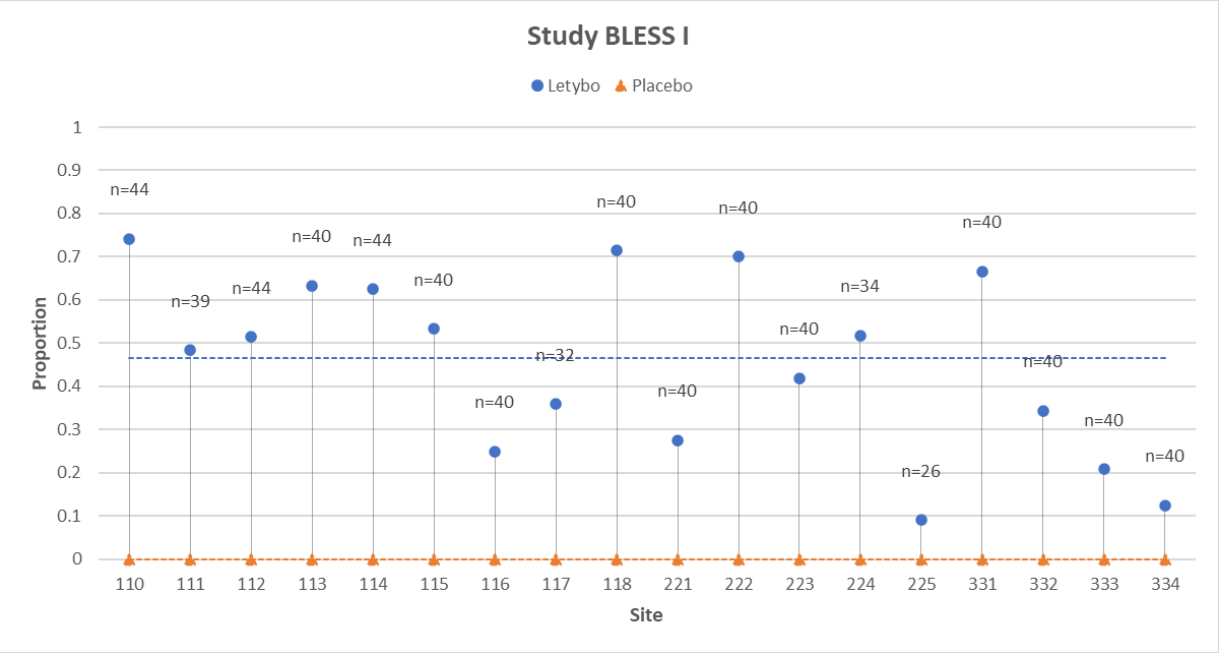
Subjects with missing in-clinic assessments (GLS-I or GLS-S) at baseline or Week 4 were imputed as non-responders.
* Mantel-Haenszel estimate and confidence limits for the common risk difference by using the Mantel-Haenszel weights for study center.
** P-values are based on the CMH general association test stratified on study center.
Source: reviewer analysis

Efficacy by Center

Study BLESS I enrolled subjects from 18 sites, Study BLESS II enrolled subjects from 6 sites, and

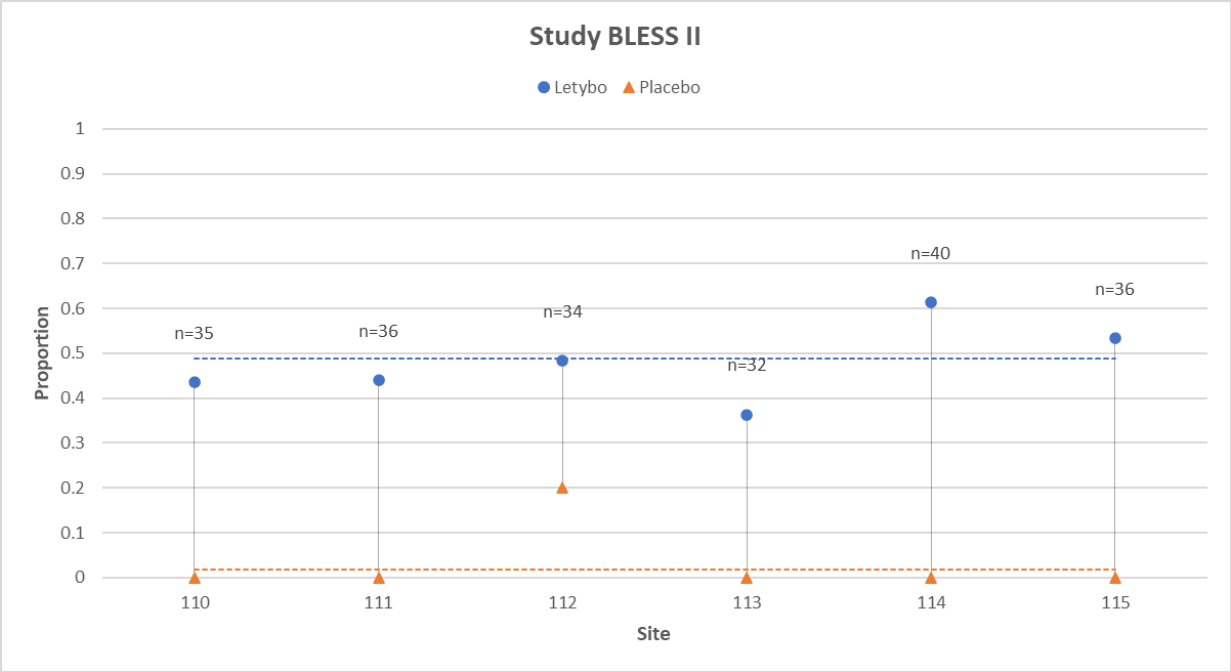
Study BLESS III enrolled subjects from 7 sites. No sites were combined as all sites had more than 3 placebo subjects. Results were generally consistent across sites for the primary endpoint (see Figure 1, Figure 2 and Figure 3). Study BLESS I (18 sites: 9 in US, 5 in Germany and 4 in Poland) had more variation than Study BLESS II (6 US sites) and Study BLESS III (7 sites: 6 in US and 1 in Austria), likely due to a larger number of sites, different countries (US, Germany and Poland), and being the first study conducted.

Figure 1. Primary Efficacy Endpoint by Site (Study BLESS I; FAS)



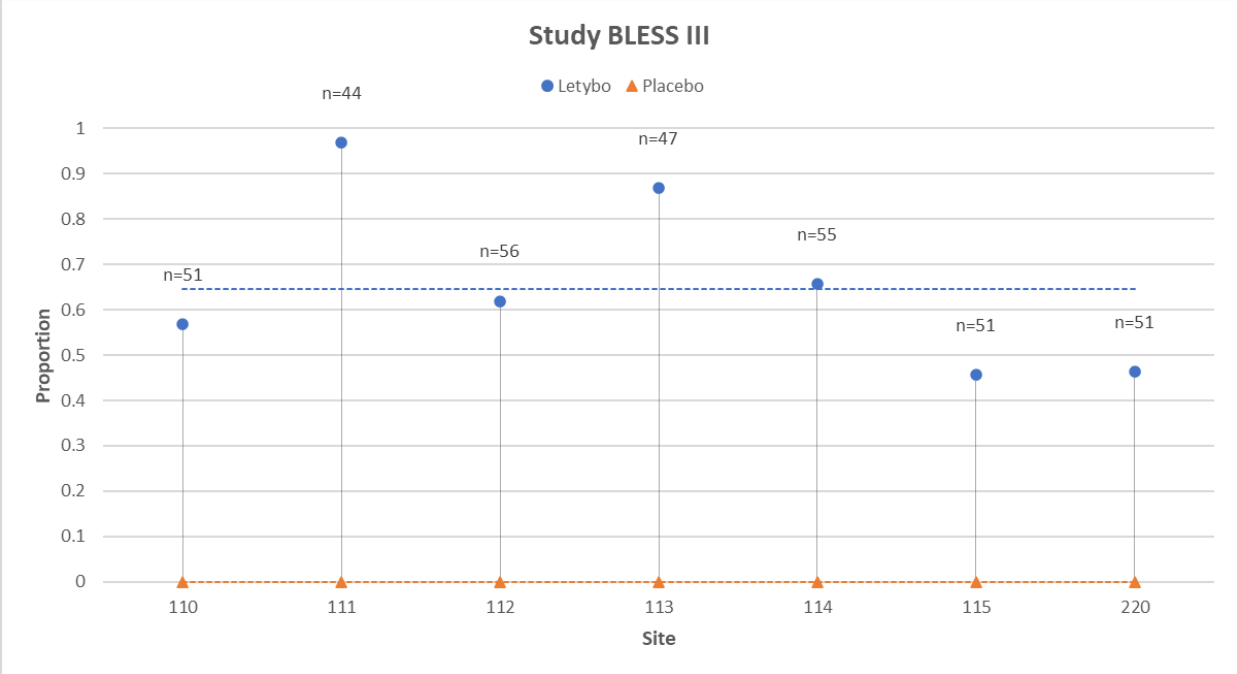
The total sample size (n) is presented for each site.
The dashed line represents the overall responder rate in each treatment arm for Study BLESS I.
Source: reviewer analysis

Figure 2. Primary Efficacy Endpoint by Site (Study BLESS II; FAS)



The total sample size (n) is presented for each site.
The dashed line represents the overall responder rate in each treatment arm for Study BLESS II.
Source: reviewer analysis

Figure 3. Primary Efficacy Endpoint by Site (Study BLESS III; FAS)



The total sample size (n) is presented for each site.
The dashed line represents the overall responder rate in each treatment arm for Study BLESS III.
Source: reviewer analysis

Efficacy Results – Secondary Endpoints

For Studies BLESS I and II, a pre-specified hierarchical testing procedure of the secondary endpoints was implemented. For Study BLESS III, the results of each test were considered to be exploratory. Table 15 presents the statistical reviewers' analysis results for the secondary efficacy endpoints among the FAS in Studies BLESS I, II and III. For Study BLESS I, the hierarchical testing procedure did not stop until secondary endpoint 4 (i.e., multi-component responder rate at Week 20), where the two-sided p-value was 0.169 > 0.05. For Study BLESS II, the hierarchical testing procedure stopped right after secondary endpoint 1 (i.e., multi-component responder rate at Week 12), where the two-sided p-value was 0.173 > 0.05.

Therefore, the difference between Letybo and placebo in multi-component responder rate (≥ 2-point improvement from baseline at maximum frown) was maintained and statistically significant (at level of 0.05) up to 16 weeks following the first treatment for Study BLESS I, and up to 4 weeks following the first treatment for Study BLESS II. In addition, efficacy in responder rate for ≥ 1-point improvement from baseline to Week 4 at rest was also demonstrated based separately on the GLS-I and GLS-S for Study BLESS I.

Table 15. Secodary Efficacy Endpoints (Studies BLESS I, II, and III; FAS)

	Study BLESS I ^		Study BLESS II ^		Study BLESS III ~	
	Letybo	Placebo	Letybo	Placebo	Letybo	Placebo
Secondary Endpoint 1 at Week 12 #						
Multi-Component Assessment n/N (%)	67/528 (12.7%)	0/175 (0%)	7/160 (4.4%)	0/53 (0%)	56/266 (21.1%)	1/89 (1.1%)
Treatment Difference and 95% CI *	12.2% (9.3%, 15.0%)		3.6% (0.6%, 6.6%)		19.4% (13.8%, 25.0%)	
P-value **	<0.0001		0.173 > 0.05 (Stop)			
Secondary Endpoint 2 at Week 16 $						
Multi-Component Assessment n/N (%)	22/501 (4.4%)	0/159 (0%)	5/149 (3.4%)	0/48 (0%)	27/254 (10.6%)	1/84 (1.2%)
Treatment Difference and 95% CI *	4.5% (2.6%, 6.3%)		2.9% (-0.0%, 5.7%)		8.6% (4.1%, 13.2%)	
P-value **	0.006					
Secondary Endpoint 3 at Week 4 #						
3.1 Investigator Assessment n/N (%)	333/473 (70.4%)	27/160 (16.9%)	95/141 (67.4%)	3/47 (6.4%)	163/215 (75.8%)	8/66 (12.1%)
Treatment Difference and 95% CI *	54.8% (47.7%, 61.9%)		58.5% (47.4%, 69.6%)		62.4% (52.8%, 72.0%)	
P-value **	<0.0001					
3.2 Subject Assessment n/N (%)	412/502 (82.1%)	17/167 (10.2%)	113/148 (76.4%)	9/52 (17.3%)	214/255 (83.9%)	11/82 (13.4%)
Treatment Difference and 95% CI *	72.5% (66.7%, 78.2%)		57.7% (44.7%, 70.7%)		69.4% (60.6%, 78.1%)	
P-value **	<0.0001					
Secondary Endpoint 4 at Week 20 $						
Multi-Component Assessment n/N (%)	6/503 (1.2%)	0/158 (0%)	2/148 (1.4%)	0/48 (0%)	NA	

Treatment Difference and 95% CI *	1.2% (0.2%, 2.2%)	1.3% (-0.7%, 3.2%)	
P-value **	0.169 > 0.05 (Stop)		

* Mantel-Haenszel estimate and confidence limits for the common risk difference by using the Mantel-Haenszel weights for study center.
** P-values are based on the CMH general association test stratified on study center.
# For secondary endpoints 1 and 3 (3.1 and 3.2), non-responder imputation was used for handling of missing data.
$ For secondary endpoints 2 and 4, analysis was conducted on observed values only.
^ For Studies BLESS I and II, a pre-specified hierarchical testing procedure of secondary endpoints was implemented.
~ For Study BLESS III, the results of each test (based on the IA) were considered to be exploratory. P values are not provided for exploratory results.
Source: reviewer analysis

Findings in Special/Subgroup Populations

Subgroup analyses were conducted for the primary endpoint by age groups (< 65 years, ≥ 65 years), gender, race, ethnicity and whether there was previous use of botulinum toxin treatment. Treatment effects were generally consistent across most of the subgroups (see Table 16). The treatment effect for females was higher than that for males and the treatment effect for subjects below age 65 was higher than that for subjects above age 65 in all three studies. However, due to the small sample size in male subjects (6-15%) and subjects of ≥ 65 years of age (9-15%), the treatment effect may not be reliably estimated in these subgroups.

Table 16. Primary Efficacy Endpoint at Week 4 by Subgroup (Studies BLESS I, II and III; FAS)

	Study BLESS I		Study BLESS II		Study BLESS III	
	Letybo N=528	Placebo N=175	Letybo N=160	Placebo N=53	Letybo N=266	Placebo N=89
Age (years)						
18-64 years	222/462 (48.1%)	0/157 (0%)	73/141 (51.8%)	1/45 (2.2%)	155/233 (66.5%)	0/81 (0%)
65-75 years	24/66 (36.4%)	0/18 (0%)	5/19 (26.3%)	0/8 (0%)	17/33 (51.5%)	0/8 (0%)
Gender						
Female	230/483 (47.6%)	0/155 (0%)	77/150 (51.3%)	1/45 (2.2%)	166/248 (66.9%)	0/80 (0%)
Male	16/45 (35.6%)	0/20 (0%)	1/10 (10.0%)	0/8 (0%)	6/18 (33.3%)	0/9 (0%)
Race						
White	216/482 (44.8%)	0/153 (0%)	75/153 (49.0%)	1/50 (2.0%)	157/236 (66.5%)	0/79 (0%)
Black or Afric. Amer.	22/33 (66.7%)	0/18 (0%)	2/3 (66.7%)	0/1 (0%)	12/25 (48.0%)	0/7 (0%)
Asian	5/7 (71.4%)	0/3 (0%)	0/2 (0%)	0/1 (0%)	2/4 (50.0%)	0/1 (0%)
Am. Ind. or AK Native	1/2 (50.0%)	--	1/1 (100%)	--	--	--
Native HI or Pac. Isl.	--	--	--	0/1 (0%)	--	--

Other	2/4 (50.0%)	0/1 (0%)	0/1 (0%)	--	1/1 (100%)	0/2 (0%)
Ethnicity						
Not Hispanic or Latino	233/497 (46.9%)	0/166 (0%)	60/126 (47.6%)	0/45 (0%)	121/200 (60.5%)	0/67 (0%)
Hispanic or Latino	10/25 (40.0%)	0/8 (0%)	18/33 (54.5%)	1/7 (14.3%)	51/66 (77.3%)	0/22 (0%)
Region						
US	146/268 (54.5%)	0/95 (0%)	78/160 (48.8%)	1/53 (1.9%)	153/225 (68.0%)	0/79 (0%)
EU	100/260 (38.5%)	0/80 (0%)	--	--	19/41 (46.3%)	0/10 (0%)
Previous Use of Botulinum Toxin						
No	160/345 (46.4%)	0/116 (0%)	49/105 (46.7%)	1/42 (2.4%)	106/169 (62.7%)	0/53 (0%)
Yes	86/183 (47.0%)	0/59 (0%)	29/55 (52.7%)	0/11 (0%)	66/97 (68.0%)	0/36 (0%)

Am. Ind. = American Indian; AK = Alaska; HI = Hawaiian; Pac. Isl. = Pacific Islander
EU: Germany and Poland in Study BLESS I, Austria in Study BLESS III
Source: reviewer analysis

8.1.3. Assessment of Efficacy Across Trials

The results for the primary efficacy endpoint were consistent across Studies BLESS I, II and III. Given the evidence from the three studies, Letybo showed superiority to placebo for the primary efficacy endpoint of the proportion of subjects who achieved treatment success (see Table 9). The results for the sensitivity analyses, secondary efficacy endpoints and subgroup analyses were supportive of the primary efficacy endpoint.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary focus of the safety review is the data obtained from three Phase 3 studies, BLESS I, II and III. Data from these 3 studies will be pooled together to compare incidences of adverse events (AEs). These studies were chosen as the focus of the safety review because they were of placebo-control design, enrolled similar study populations, and studied the dose that reflects anticipated use. Data obtained from these studies will allow the direct comparison of AE rates in BoNT/A-DP treated subjects to those in placebo treated subjects.

Data from the repeat-dose, open-label period of the three Phase 3 studies will be used to assess potential safety signals that may occur following repeated administration of BoNT/A-DP. However, these data may be difficult to interpret due to lack of a comparison arm.

Phase 3 study (HG-11-01) will be analyzed separately because of different study design. Botox was included as an active comparator in Study HG-11-01.

8.2.2. Review of the Safety Database

Overall Exposure

The development program for BoNT/A-DP included a total of 1272 subjects in three BLESS studies and 271 subjects in Study HG-11-01 with 134 subjects receiving one dose BoNT/A-DP and 137 subjects receiving one dose Botox control. Of these, 1380 subjects were exposed to at least one dose BoNT/A-DP at the to-be-marketed dose of 20 U (1246 subjects in the 3 BLESS studies and 134 subjects in Study HG-11-01). Of these subjects, 546 subjects received a total of 4 BoNT/A-DP treatments, 994 subjects received at least 3 BoNT/A-DP treatments, and 1160 subjects received at least 2 BoNT/A-DP treatments.

The overall extent of exposure in the 3 BLESS studies is summarized in the table below. Data in this table refer to study treatment cycles, not cycles of active BoNT/A-DP treatment as subjects, who received placebo at study cycle 1, then received their first active (BoNT/A-DP) treatment with study cycle 2 which was the first open-label cycle. As the number of study cycles was limited to 4 study cycles, subjects in the placebo group could only receive up to 3 active treatment cycles.

Table 17. Subject Drug Exposure in the 3 BLESS Studies for the Indication Glabellar Lines

	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)		
Second study treatment			659 (100.0)	704 (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)		
Second study treatment			195 (100.0)	213 (100.0)
Third study treatment			181 (92.8)	
Fourth study treatment			149 (76.4)	
Study BLESS III	**N = 266**	**N = 89**	**N = 323**	**N = 355**
First treatment	266 (100.0)	89 (100.0)	-	
Second study treatment			323 (100.0)	355 (100.0)
Third study treatment			265 (82.0)	
Fourth study treatment			139 (43.0)	
BLESS I, II, and III (ISS Population)	**N = 955**	**N = 317**	**N = 1177**	**N = 1272**
First study treatment	955 (100.0)	317 (100.0)		1272 (100.0)
Second study treatment			1177 (100.0)	1177 (92.5)
Third study treatment			1062 (90.2)	1062 (83.5)
Fourth study treatment			752 (63.9)	752 (59.1)

Overall = sum of subjects in double-blind part.

Abbreviations:BoNT/A-DP: Botulinum neurotoxin type A drug product; N: number of subjects randomized; n (%): number (percentage) of subjects with event. ISS: Integrated Summary of Safety.
Source: Day 120 SUR Clinical Summary of Safety (CSS) Table 1.

Adequacy of the safety database:

The safety database submitted by the applicant is sufficient to characterize the safety profile of BoNT/A-DP.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of BoNT/A-DP.

The Applicant reported that "A site audit conducted in January 2020 identified a critical finding for protocol non-compliance for Study BLESS III Site 110. A member of the unblinded site staff performed blinded tasks on safety assessments". Therefore, the safety data analyses were performed excluding subjects from BLESS III site 110 (44 subjects in the BoNT/A-DP group and 7 subjects in the placebo group).

Categorization of Adverse Events

The adverse events (AEs) were categorized as follows:

- Deaths
- Other Serious Adverse Events (SAEs)
- Adverse events that led to study discontinuation
- Other significant adverse events, including
  - Adverse Events of Special Interest (AESI) including AEs of local and potential distant spread of toxin (PDSOT)
  - Hypersensitivity reactions
- Treatment Emergent Adverse Events and Adverse Reactions
  - Severe Treatment Emergent Adverse Events (TEAEs)
  - Common Treatment Emergent Adverse Events
  - Adverse Reactions (ARs): study medication or injection procedure-related TEAEs

Adverse Event
An AE was defined as any untoward medical occurrence in a subject administered study treatment that did not necessarily have a causal relationship with the treatment. An AE was therefore any unfavorable and unintended sign (including an abnormal laboratory finding),

symptom, or disease temporally associated with study treatment, whether or not related to study treatment.

Treatment Emergent Adverse Event
A TEAE was defined as any AE not present prior to the initiation of the treatment, or any AE already present that worsened in terms of severity, duration, or frequency following exposure to the treatment.

TEAEs were recorded between first dose and EOS visit. All AEs, AESIs, and SAEs were recorded, irrespective of whether they were considered related to study treatment.

Adverse Reaction
An AR is defined as an AE that is definitely, possibly, or probably caused by the study treatment, or if causality assessment is missing.

The Relationship of an AE to the Study Medication or Injection Procedure
The classification of TEAEs as medication-related or injection procedure related was based on investigator assessments. Investigators could report a single TEAE as both medication-related and injection procedure-related. Related TEAEs were events with definite, probable, possible relationship to study medication and/or injection procedure or missing assessment of relationship to study medication and/or injection procedure. Analyses were performed overall (including events related to medication and/or injection procedure), and separately for medication-related and injection procedure related TEAEs.

Adverse Events of Special Interest
All botulinum toxin products have the potential to spread beyond the site of injection and induce pharmacological effects of botulinum toxin adjacent to the sites of injection (local spread) or disseminate widely and affect tissues remote to the sites of injection (distant spread). The potential for local and distant toxin spread was reported as AESI.

Adverse events suggestive of spread of BoNT/A are listed in the FDA guideline on facial lines - FDA Draft Guidance for Industry: *Upper Facial Lines Developing Botulinum Toxin Drug Products* (2014). These terms are included in the overall AESI analyses within the integrated Summary of Safety (ISS) based on investigator-reported events.

Serious Adverse Events
An SAE was defined as an untoward medical occurrence that at any dose met 1 or more of the following criteria:

- Resulted in death.
- Was life threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it did not refer to an event that hypothetically might have caused death had it been more severe.
- Required subject hospitalization or resulted in prolongation of existing hospitalization.

- Resulted in persistent or significant disability/incapacity.
- Was a congenital anomaly/birth defect.
- Was an important medical event.

Medical or scientific judgment was to be exercised in deciding whether reporting was appropriate in other situations, such as important medical events that were not immediately life threatening or resulted in death or required hospitalization but might have jeopardized the subject or might have required medical or surgical intervention to prevent one of the other outcomes listed in the definitions above.

Severity of Adverse Event

The following definitions for rating severity were used:

- Mild: The AE is easily tolerated and does not interfere with daily activity.
- Moderate: The AE interferes with daily activity, but the subject is still able to function.
- Severe: The AE is incapacitating and/or requires medical intervention.

Routine Clinical Tests

During the placebo-controlled and open label studies, the investigators performed safety assessments. The safety results in BLESS I, II, and III were pooled for analysis.

Adverse events were assessed in Cycle 1 at baseline and Weeks 1, 2, 4, 8, and 12 (and at 4-week intervals thereafter until eligible for re-treatment or discontinued). For the subsequent open-label cycles, subjects were evaluated for AEs before each re-treatment, at Weeks 1, 2, 4, 8, and 12 of Cycles 2 to 4 (and at 4-week intervals thereafter until eligible for re-treatment or discontinued), and at the end of study (EOS) visit.

ECG was assessed at screening, Week 4, and the end of the double-blind part of the study.

Vital signs were assessed at screening, the day of first treatment, Week 1, and Week 4 of each treatment cycle, at the end of each cycle visit, and at the EOS visit.

Clinical laboratory assessments (serum chemistry and hematology) and anti-drug-antibody (ADA) tests were performed at screening, Week 4 following each treatment, and the End of Cycle and EOS visits.

The pooled safety analyses of studies BLESS I, II, and III include the following:

- study drug exposure
- subject disposition
- demographics and baseline characteristics
- medical history

- prior and concomitant medications
- analyses of treatment-emergent adverse events (TEAEs)
- clinical laboratory data
- electrocardiography (ECG) data
- anti-drug antibody (ADA) testing
- physical examination data
- vital sign data

Overall, the safety assessments allowed adequate characterization of safety of this product.

8.2.4. Safety Results

8.2.4.1. Deaths

There were no deaths during the studies.

8.2.4.2. Other Serious Adverse Events

In the Phase 3 studies (BLESS I, II and III), a total of 10 (1.1%) subjects experienced one or more SAEs in the BoNT/A-DP group (N = 911) while 1 (0.3%) subject experienced an SAE in the placebo group (N=310) during the double-blind period of the studies.

During open-label period of the studies, 21 subjects (1.9%) overall experienced at least one SAE (N=1129). The reporting rate for SAEs generally decreased with subsequent treatment cycles. In BoNT/A-DP treatment cycles 1, 2, 3, and 4, 10/911 (1.1%) subjects, 12/1129 (1.1%) subjects, 7/1020 (0.7%) subjects, and 3/722 (0.4%) subjects, respectively, experienced SAEs.

All SAEs by PT were reported for 1 (0.1%) subject, except for cholecystitis, osteoarthritis and coronary artery disease, which were reported for 2 (0.2%) subjects each. None of these SAEs was judged by the investigator to be related to treatment.

Table 18. Serious Adverse Events in Double-Blinded Period (BLESS I, II, and III)

Subject	Dosing Group	Adverse Event	Outcome
(b) (6)	BoNT/A-DP	Bowel perforation with pneumotosis coli	Recovered/Resolved
		Biliary colic	Recovered/Resolved
		Cholecystitis	Recovered/Resolved
(b) (6)	BoNT/A-DP	Ovarian cancer recurrent	Recovered/Resolved

(b) (6)	BoNT/A-DP	Worsening of depression	Recovered/Resolved
	BoNT/A-DP	Meniscus injury	Recovered/Resolved
	BoNT/A-DP	Thyroid cancer	Recovered/Resolved
	BoNT/A-DP	Breast cancer	Recovered/Resolved
	BoNT/A-DP	Low Back pain	Recovered/Resolved
	BoNT/A-DP	Gastric ulcer	Recovered/Resolved
		Gastritis erosive	Recovered/Resolved
		Helicobacter pylori infection	Recovered/Resolved
	BoNT/A-DP	Burn of right hand	Recovered/Resolved
	BoNT/A-DP	Worsening of right hallux valgus	Recovered/Resolved
	Placebo	Syncope	Recovered/Resolved

Source: Day 120 Safety Update Report (SUR) ISS Listing 5.3.

During open-label treatment, 17 subjects (2.0%) experienced at least one SAE.

Table 19. Serious Adverse Events in Open-Label Period (BLESS I, II, and III)

Subject	DB Period Dosing Group	Onset Cycle	Adverse Event	Outcome
(b) (6)	BoNT/A-DP	2	Worsening of right knee osteoarthritis	Recovered/Resolved
	BoNT/A-DP	4	Colon adenoma	Recovered/Resolved
		4	Right hemicolectomy	Recovered/Resolved
	Placebo	2	Ovarian adenoma	Recovered/Resolved
		2	Uterine leiomyoma	Recovered/Resolved
		2	Worsening of chronic cervicitis of cervix	Recovered/Resolved
		2	Worsening of secretory endometrium of uterus	Recovered/Resolved
	BoNT/A-DP	2	Arrhythmia	Recovered/Resolved
	BoNT/A-DP	2	Left hip osteoarthritis	Recovered/Resolved
	Placebo	2	Squamous cell carcinoma of skin	Recovered/Resolved
	BoNT/A-DP	3	Colon cancer	Recovered/Resolved
	BoNT/A-DP	4	Hypersomnia	Not Recovered/Not Resolved
	BoNT/A-DP	3	Angina unstable	Recovered/Resolved
		3	Multivessel coronary artery disease	Recovered/Resolved
	Placebo	3	Large intestine polyp	Recovered/Resolved
	BoNT/A-DP	2	Bilious attack with surgery	Recovered/Resolved with sequelae
	Placebo	3	Fall	Recovered/Resolved
		3	Traumatic Haematoma right hip after fall	Recovered/Resolved
		3	Wound back of the head after fall	Recovered/Resolved with sequelae
	BoNT/A-DP	3	Left distal humerus fracture	Recovered/Resolved
		3	Left distal radius fracture	Recovered/Resolved
	Placebo	2	Right upper colic abdominal pain	Recovered/Resolved
	BoNT/A-DP	2	Coronary artery disease	Recovered/Resolved

(b) (6)	BoNT/A-DP	3	Adenomyosis	Recovered/Resolved
		3	Vaginal haemorrhage	Recovered/Resolved
	BoNT/A-DP	2	Chest pain	Recovered/Resolved
		4	Vitreous detachment	Not Recovered/Not Resolved
	BoNT/A-DP	2	Worsening of goiter	Recovered/Resolved
	BoNT/A-DP	2	Cholecystitis	Recovered/Resolved
	Placebo	3	Acute myocardial infarction	Recovered/Resolved
		3	Pulmonary embolism	Recovered/Resolved
	BoNT/A-DP	2	Cholelithiasis	Recovered/Resolved

Source: Day 120 SUR ISS Listing 5.3.

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

As shown in the table below, adverse events leading to study discontinuation occurred only in Study BLESS I. One subject each in the BoNT/A-DP group (exposure during pregnancy) and the placebo group (injection site bruising) had a TEAE leading to withdrawal during the double-blind period.

Table 20. Subjects with TEAEs Leading to Study Discontinuation (BLESS I, II, and III)

Subject No.	Age/ Sex/ Race	MedDRA Preferred Term	Treatment Part	Causality (study drug)	Severity	Injection Procedure-related	SAE	Out-come
Original treatment group: BoNT/A-DP								
(b) (6)	31/F/W	Exposure during pregnancy	DB	Not related	n.d.	Not related	No	R
	42/F/W	Headache	OL	Definitely	Moderate	Not related	No	R
	39/F/W	Lyme disease	OL	Not related	Moderate	Not related	No	R
	34/F/W	Exposure during pregnancy	OL	Not related	Mild	Not related	No	NR
	28/F/W	Exposure during pregnancy	DB	Not related	Mild	Not related	No	R
Original treatment group: Placebo								
(b) (6)	61/F/W	Injection site bruising	DB	Unlikely	Mild	Possibly	No	R
	71/F/W	Actinic keratosis	OL	Not related	Mild	Not related	No	NR
	36/F/W	Exposure during pregnancy	OL	Not related	Mild	Not related	No	NR

Abbreviations:BoNT/A-DP: Botulinum neurotoxin type A drug product; DB: double-blind; F: female; IA: interim analysis; MedDRA: Medical Dictionary for Regulatory Activities; n.d.: 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 23.1).
Source: Day 120 SUR CSS Table 15.

A total of 8 subjects experienced TEAEs that led to study discontinuation (7 subjects who received BoNT/A-DP during the double-blind or open-label parts of studies and one who received placebo). None of these TEAEs were severe in intensity. Four of the TEAEs that led to study drug discontinuation were pregnancies. All 4 subjects received treatment with BoNT/A-DP. All 4 subjects discontinued the study drug as a result of the pregnancy and subsequently delivered healthy babies.

Of the 4 other TEAEs leading to withdrawal, two were not considered related to study treatment (lyme disease and actinic keratosis), one was considered related to study-mediation (headache), and one was considered related to injection procedures (injection site bruising).

TEAEs leading to discontinuation after BoNT/A-DP treatment:

• Subject (b) (6) a 42 year old female, who experienced moderate headache on Day 2 of her third BoNT/A-DP treatment and the study drug was permanently discontinued due to this event. The AE was considered definitely related to the study drug but not to be related to the injection procedure and resolved on Day 4. The subject completed 3 cycles of BoNT/A-DP treatment before discontinuation from study.

• Subject (b) (6) a 71-year-old female with a history of squamous cell skin carcinoma had actinic keratosis 41 days after second BoNT/A-DP treatment during Cycle 3. This was considered not related to study medication or injection procedure and had not resolved by the time of the last follow-up. The subject did not complete the third treatment cycle before discontinuation from the study, due to the event of actinic keratosis.

• Subject (b) (6) a 39-year-old female, who had Lyme disease 98 days after her third BoNT/A-DP treatment. The study drug was permanently discontinued due to this event. The AE was considered not to be related to study drug or injection procedure and resolved. The subject completed 3 cycles of BoNT/A-DP treatment before discontinuation from study.

TEAE leading to discontinuation after placebo treatment:

• Subject (b) (6) a 61 year old female, who had mild injection site bruising on Day 3 after placebo administration which resolved. The AE was considered possibly related to injection-site procedures. The subject was permanently discontinued form study treatment due to the event.

In addition, this reviewer considers the following subject discontinuations to likely be due to adverse reactions:

Subject (b) (6) a 48-year-old female, had mild eye pain on Day 2 – 4 of her second injection (first BoNT/A-DP injection) and periorbital haematoma on Day 3 – 11, which were considered to be related to the injection procedure. She then experienced moderate right eyelid ptosis on Day 9 which was treated with apraclonidine (Day 14 – 28), and resolved on Day

66. Eyelid ptosis was considered to be definitely related to the study treatment and to the injection procedure. The subject did not receive any further injections as she withdrew consent and was discontinued from the study on Day 92.

Subject (b) (6), a 72-year-old female, experienced mild eyelid ptosis and mild diplopia 8 days and 10 days after her third injection (second BoNT/A-DP injection), respectively. No action was reported for either events. Both events were considered to be possibly related to the study treatment and possibly related to the injection procedure. Diplopia resolved after 3 days, and eyelid ptosis resolved after 134 days. No further injections were done. The subject was discontinued the study 28 days after resolution of eyelid ptosis due to investigator decision.

Subject (b) (6) a 58-year-old male, experienced mild blurred vision 2 days after his second BoNT/A-DP injection, which resolved 7 months later. No action was reported for the event. The event was considered not to be related to the study treatment or the injection procedure. No further injections were done. The subject was discontinued the study on 30 days after the onset of blurred vision because investigator decision.

Considering the temporal relationship of this AE to the BoNT/A-DP treatment, this reviewer cannot to rule out the blurred vision was related to the study treatment

8.2.4.4. Other Significant Adverse Events

8.2.4.4.1. Adverse Events of Special Interest

The potential for spread of botulinum toxin into tissues adjacent to the target muscle or more remotely via tissue planes or into the blood stream is the primary concern with the use of botulinum toxin products. Because botulinum toxin is a small biologic protein, it is reasonable to raise the concern that diffusion to distant sites may be possible. The potential for local and distant toxin spread was reported as AESI.

A total of 24 AESIs were reported in the studies, based on investigator assessments (excluding one subject from BLESS III, Site 110), of which 12 occurred during the double-blind treatment period (10 after BoNT/A-DP treatment and two after placebo treatment). Three of the events in the double-blind period (2 x eyelid ptosis and 1 x facial discomfort), all after BoNT/A-DP treatment, were considered possibly or probably related to study medication and two of these (1 x eyelid ptosis and 1 x facial discomfort) also possibly or probably related to injection procedures.

The other 12 AESIs were reported during the open-label treatment period, 7 of them (5 x eyelid ptosis, 1 x brow ptosis, 1 x diplopia) were considered definitely related to study medication and 6 (5 x eyelid ptosis, 1 x diplopia) were considered related to injection procedures. For an

additional AESI of constipation after open-label treatment, no information as to relationship was available.

None of the AESIs were considered serious or severe.

Table 21. Subjects with TEAEs of Local or Distant Spread of Toxin (BLESS I, II, and III)

		Double-Blind	Open-Label
	BoNT/A-DP (N=911)	Placebo (N=310)	BoNT/A-DP (N=1129)
Local spread of toxin			
Eyelid ptosis	3 (0.3)	0	6 (0.5)
Brow ptosis and heaviness	3 (0.3)	0	1 (0.1)
Vision blurred	1 (0.1)	0	1 (0.1)
Photophobia	0	0	1 (0.1)
Diplopia	0	0	1 (0.1)
Distant spread of Toxin			
Bradycardia	1 (0.1)	0	0
Dysarthria	1 (0.1)	0	0
Constipation	1 (0.1)	0	1 (0.1)
Dyspnoea	0	0	1 (0.1)
Muscular weakness	0	1 (0.3)	0
Dysphagia	0	1 (0.3)	0

Source: Created with the submitted data.

Events indicative of local spread of toxin

A total of 15 subjects experienced 17 TEAEs that are indicative of local spread of toxin in the three Phase 3 studies (excluding one subject from BLESS III, Site 110).

Double-Blinded Period

In the DB period of the studies, a total of 6 subjects experienced 7 TEAEs that are indicative of local spread of toxin, all of whom were treated with BoNT/A-DP.

This reviewer disagrees with the investigators' assessments on the causality of the following AEs:

Subject (b) (6) a 63-year-old female, experienced mild left eyebrow ptosis on Day 48 of her first BoNT/A-DP injection, for which no action was taken. The event was considered not to be related to the study treatment or the injection procedure. The subject completed 4 cycles of treatment. The event of brow ptosis had not resolved at the time of the last contact.

Considering the temporal relationship of this AE to the BoNT/A-DP treatment, this reviewer cannot to rule out the eyelid ptosis was related to the study treatment

Subject (b) (6) a 49-year old female, had mild left eyelid ptosis on Day 8 of her first BoNT/A-DP treatment. No action was taken for the event. The event was considered not to be

related to the study treatment or the injection procedure, and eyelid ptosis resolved on Day 14 without treatment. The subject completed 4 cycles of treatment.

Considering the temporal relationship of this AE to the BoNT/A-DP treatment, this reviewer cannot to rule out the eyelid ptosis was related to the study treatment.

Subject (b) (6) a 35-year old female, had mild eyelid ptosis (eyelid drooping) and mild brow ptosis (feeling of heaviness in brow) on Day 1 of her first BoNT/A-DP treatment. No action was taken for the events. The event of eyelid ptosis was considered to be possibly related to study treatment and the injection procedure. The event of brow ptosis was considered to be unlikely related to study treatment and unrelated to the injection procedure. Both events resolved on Day 12. The subject completed 3 cycles of treatment.

Considering the temporal relationship of this AE to the BoNT/A-DP treatment, this reviewer cannot to rule out the brow ptosis was related to the study treatment.

Open-Label Period
In the OL period of the studies, 9 subjects experienced 10 TEAEs that are indicative of local spread of toxin (excluding one subject from BLESS III, Site 110), all of whom were treated with BoNT/A-DP.

This reviewer disagrees with the investigators' assessments on the causality of the following AEs:

Subject (b) (6) a 58-year old female, experienced mild eyelid ptosis (unilateral eyelid droop) on Day 3 of her third injection (second BoNT/A-DP injection), which resolved on Day 6. This event was considered not to be related to study treatment but related to the injection procedure. The subject completed 4 cycles of treatment (3 BoNT/A-DP injections).

Considering the temporal relationship of this AE to the BoNT/A-DP treatment, this reviewer cannot to rule out the eyelid ptosis was related to the study treatment.

Subject (b) (6) a 58-year-old male, experienced mild blurred vision 2 days after his second BoNT/A-DP injection, which resolved 7 months later. No action was reported for the event. The event was considered not to be related to the study treatment or the injection procedure. No further injections were done. The subject was discontinued the study on 30 days after the onset of blurred vision because investigator decision.

Considering the temporal relationship of this AE to the BoNT/A-DP treatment, this reviewer cannot to rule out the blurred vision was related to the study treatment.

<u>Events indicative of distant spread of toxin</u>

A total of 5 subjects reported 5 TEAEs indicative of distant spread of toxin during the double-blind period of the studies, 3 of them after receiving BoNT/A-DP, and 2 subjects after receiving placebo. None of the events potentially indicative of distant spread of toxin was considered related to study medication or injection procedures.

During the open-label period of the studies, one subject reported constipation with no information on causality available in Study BLESS I, and another subject reported dyspnoea in Study BLESS III. Following a worst-case scenario, the case of constipation is considered related both to study medication and to injection procedures.

This reviewer agrees with the investigators assessment of causality that none of these TEAEs was related to study medication or injection procedures.

8.2.4.4.2. Hypersensitivity

During the double-blind period of the studies, 3 subjects reported 3 TEAEs that were potentially indicative of hypersensitivity (2 x hypersensitivity and 1 x urticaria), all of which occurred after BoNT/A-DP treatment. The 3 events were considered not related to study medication or injection procedures.

During the open-label period of the studies, 7 subjects reported 7 TEAEs that were potentially indicative of hypersensitivity; only one of these events (investigator reported: forehead hives/urticaria) was considered possibly related to study medication and none were considered related to injection procedures by the investigator.

Subject (b) (6) a 65-year old male, had forehead hives on Day 2 of his fourth BoNT/A-DP injection, which resolved on Day 5. No action was taken for the event. The event was considered to be possibly related to study treatment and not related to the injection procedure. The subject completed 4 cycles of treatment.

Table 22. Treatment Emergent Adverse Events of Hypersensitivity (BLESS I, II, and III)

Subject No.	Age/ Sex/ Race	MedDRA Preferred Term	Treat-ment Part	Causality (study drug)	Severity	Injection Procedure - related	SAE/ Disc	Out-come
(b) (6)	52/F/W	Hyper-sensitivity	DB	Not related	Mild	No	No/No	R
	35/F/W	Hyper-sensitivity	DB	Not related	Moderate	No	No/No	R
	57/F/W	Urticaria	DB	Not related	Mild	No	No/No	R
	65/M/W	Urticaria	OL	Possibly	Mild	No	No/No	R
	50/F/W	Drug hyper-sensitivity	OL	Unlikely	Mild	Unlikely	No/No	R
	65/F/W	Seasonal allergy	OL	Not related	Mild	No	No/No	NR

(b) (6)								
	42/F/B	Urticaria	OL	Not related	Mild	No	No/No	R
	54/F/B	Allergy to animal	OL	Not related	Mild	No	No/No	R
	69/F/W	Seasonal allergy	OL	Not related	Mild	No	No/No	R
	65/F/W	Drug hyper-sensitivity	OL	Not related	Mild	No	No/No	R

Abbreviations: BoNT/A-DP: Botulinum neurotoxin type A drug product; B: black or African American; DB: double-blind; Disc: discontinuation of study drug; F: female; M: male; MedDRA: Medical Dictionary for Regulatory Activities; NR: not recovered / not resolved; OL:open-label; R: recovered / resolved; SAE: serious adverse event; W: white
Classifications of AEs based on MedDRA (version 23.1).
Source: Day 120 SUR CSS Table 19.

8.2.4.4.3. Events of Vision and Ocular Neuromuscular Disorders

According to the Applicant, the 9 events of eyelid ptosis (excluding one subject from BLESS III Site 110), the 2 events of vision blurred, and the event of diplopia identified as indicative of spread of toxin during were also identified in a search for events indicative of vision and ocular neuromuscular disorders (see Section 8.2.4.4.1 - Treatment Emergent Adverse Events Indicative of Local Spread of Toxin).

8.2.4.4.4. Events of Exacerbation of Pre-existing or Subclinical Neuromuscular Disorders

No such events were identified.

8.2.4.4.5. Cardiac Events

As shown in the table below, during the double-blind period, cardiac disorders were reported for 4 subjects treated with BoNT/ADP and 1 subject treated with placebo. None of these were considered serious. Additional AEs considered relevant for the assessment of cardiac safety during the double-blind period were hypertension in 2 subjects treated with BoNT/A-DP, and carotid artery stenosis in one subject treated with placebo.

During the open-label period, 4 subjects reported 5 events of cardiac disorders - 2 cases of coronary artery disease and 1 case each of arrythmia, acute myocardial infarction, and angina unstable which were considered serious. There were also 10 cases of hypertension which were non-serious. The event of chest pain was also considered serious.

According to the Applicant, none of the above cardiac events was judged to be treatment related and none of them was consistent with a major adverse cardiovascular event (MACE).

Table 23. Incidence of Cardiovascular Adverse Events (BLESS I, II, and III)

	Double-blind	**Open-label[a]**	**Both Parts[b]**

System Organ Class	BoNT/A-DP	Placebo	BoNT/A-DP	BoNT/A-DP Only
Preferred Term	(N = 955)	(N = 317)	(N = 1177)	(N = 12722)
Cardiac disorders	*4 (0.4)*	*1 (0.3)*	*4 (0.3)*	*8 (0.6)*
Arrhythmia	1 (0.1)	0	1 (0.1)	2 (0.2)
Atrioventricular block first degree	1 (0.1)	1 (0.3)	0	1 (0.1)
Coronary artery disease	0	0	2 (0.2)	2 (0.2)
Acute myocardial infarction	0	0	1 (0.1)	1 (0.1)
Angina unstable	0	0	1 (0.1)	1 (0.1)
Bradycardia	1 (0.1)	0	0	1 (0.1)
Palpitations	1 (0.1)	0	0	1 (0.1)
Nervous system				
Carotid artery stenosis	0	1 (0.3)	0	0
Vascular disorders				
Hypertension	2 (0.2)	0	10 (0.8)	12 (1.0)
General disorders and administration site conditions				
Chest pain	0	0	1 (0.1)	1 (0.1)

Abbreviations: AE: adverse event; BoNT/A-DP: Botulinum neurotoxin type A drug product; MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects randomized; n (%): number (percentage) of subjects with event; PT: MedDRA Preferred Term; SOC: MedDRA System Organ Class; TEAE: treatment emergent adverse event. Classifications of AEs based on MedDRA (version 23.1).
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 drug (independent of whether it was BoNT/A-DP or placebo).
a Open-label BoNT/A-DP with any retreatment (first, second, and third retreatment).
b Double-blind BoNT/A-DP (first treatment) and open-label BoNT/A-DP with any retreatment (first, second and third retreatment).
Source: Day 120 SUR CSS Table 20.

The assessment of ECG data did not suggest any concerns for cardiac safety of study treatment (see Section 8.2.4.8).

8.2.4.5. Treatment Emergent Adverse Events and Adverse Reactions

8.2.4.5.1. Severe Treatment Emergent Adverse Events

The severe AEs that occurred during the double-blind period of the studies are listed in the table below.

Table 24. Incidence of Severe TEAEs in BLESS I, II, and III (Double-Blind Period)

Preferred Term	BoNT/A-DP (N==911) n (%)	Placebo (N=310) n (%)
Any TEAE	14 (1.5)	3 (1)
Upper respiratory tract infection[a]	3 (0.3)	1 (0.3)
Headache	2 (0.2)	0
Abdominal pain	1 (0.1)	0

Asthma	1 (0.1)	0
Back pain	0	1 (0.3)
Biliary colic	1 (0.1)	0
Breast cancer	1 (0.1)	0
Cholecystitis	1 (0.1)	0
Conjunctivitis	1 (0.1)	0
Diarrhoea	0	1 (0.3)
Intestinal perforation	1 (0.1)	0
Ligament sprain	1 (0.1)	0
Neck pain	1 (0.1)	0
Ovarian cancer recurrent	1 (0.1)	0
Pneumatosis intestinalis	1 (0.1)	0
Tendon injury	1 (0.1)	0
Thyroid cancer	1 (0.1)	0

Source: Information Request (IR) Response on 8/23/2021.
a Includes nasopharyngitis, pharyngitis, and tonsillitis.

The severe AEs that occurred during the open-label period of the studies are listed in the table below.

Table 25. Incidence of Severe TEAEs in BLESS I, II, and III (Open-Label Period)

Preferred Term	**CYCLE 2 (N=1129) n (%)**	**CYCLE 3 (N=1020) n (%)**	**CYCLE 4 (N=722) n (%)**	**Total (N=1129) n (%)**
Any TEAE	10 (0.9)	6 (0.6)	5 (0.7)	21 (1.9)
Back pain	1 (0.1)	1 (0.1)	0	2 (0.2)
Coronary artery disease	1 (0.1)	1 (0.1)	0	2 (0.2)
Upper respiratory tract infection[a]	1 (0.1)	1 (0.1)	0	2 (0.2)
Acute myocardial infarction	0	1 (0.1)	0	1 (0.1)
Angina unstable	0	1 (0.1)	0	1 (0.1)
Arthralgia	1 (0.1)	0	0	1 (0.1)
Arthropod bite	0	0	1 (0.1)	1 (0.1)
Bronchitis	1 (0.1)	0	0	1 (0.1)
Cervicitis cystic	1 (0.1)	0	0	1 (0.1)
Cholecystitis	1 (0.1)	0	0	1 (0.1)
Colectomy	0	0	1	1 (0.1)
Colon cancer	0	1 (0.1)	0	1 (0.1)
Conjunctivitis	1 (0.1)	0	0	1 (0.1)
Diverticulitis	0	0	1 (0.1)	1 (0.1)
Endometrial disorder	1 (0.1)	0	0	1 (0.1)
Fall	0	1 (0.1)	0	1 (0.1)
Fuchs' syndrome	1 (0.1)	0	0	1 (0.1)
Gastroenteritis	1 (0.1)	0	0	1 (0.1)
Goiter	1 (0.1)	0	0	1 (0.1)
Hypersomnia	0	0	1 (0.1)	1 (0.1)
Osteoarthritis	1 (0.1)	0	0	1 (0.1)
Ovarian adenoma	1 (0.1)	0	0	1 (0.1)
Pneumonia	1 (0.1)	0	0	1 (0.1)
Pulmonary embolism	0	1 (0.1)	0	1 (0.1)
Sciatica	0	0	1 (0.1)	1 (0.1)
Traumatic haematoma	0	1 (0.1)	0	1 (0.1)
Uterine leiomyoma	1 (0.1)	0	0	1 (0.1)
Vitreous detachment	0	0	1 (0.1)	1 (0.1)

Wound	0	1 (0.1)	0	1 (0.1)

Source: IR Response on 8/23/2021.
a Includes nasopharyngitis and pharyngitis streptococcal.

Two subjects (both in BLESS I) who received BoNT/A-DP experienced severe study medication-related TEAEs (neither was considered SAEs).

- Subject (b) (6) experienced severe medication-related headache during the double-blind study period of the study.

- Subject (b) (6) experienced severe pharyngitis streptococcal, pneumonia, and bronchitis during open-label period of the study for which the relationship to study drug was not reported so the relationship automatically defaulted to "related".

No subjects experienced placebo-related severe TEAEs.

8.2.4.5.2. Common Treatment Emergent Adverse Events

The common TEAEs that occurred during the double-blind period of the studies are listed in the table below. The most common TEAEs were upper respiratory tract infection and headache for both treatment groups, and they occurred more frequently in the BoNT/A-DP group than the placebo group.

Table 26. Incidence of TEAEs Occurring in ≥ 1% of Subjects in BLESS I, II, and III (Double-Blind Period)

Preferred Term	BoNT/A-DP (N=911) n (%)	Placebo (N=310) n (%)
Any TEAE	215 (23.6)	60 (19.4)
Upper respiratory tract infection[a]	47 (5.2)	12 (3.9)
Headache[b]	31 (4.3)	5 (1.6)
Injection site reaction[c]	11 (1.2}	6 (1.9)
Urinary tract infection	9 (1)	0

Source: Created from the submitted data.
a. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, laryngitis, tonsillitis, pharyngitis, and pharyngitis streptococcal.
b. Includes headache, head discomfort, migraine, and procedural headache.
c. Includes contusion, facial pain, folliculitis, haematoma, injection site pain, injection site bruising, injection site hematoma, injection site pruritus, and swelling.

The common TEAEs that occurred during the open-label period of the studies are listed in the table below. Overall, the frequency of TEAE declined with increased treatment cycles.

Table 27. Incidence of TEAEs Occurring in ≥ 1% of Subjects in BLESS I, II, and III (Open-Label Period)

Preferred Term	CYCLE 2	CYCLE 3	CYCLE 4	Total

	(N=1129) n (%)	(N=1020) n (%)	(N=722) n (%)	(N=1129) n (%)
Any TEAE	240 (21.3)	185 (18.1)	87 (12)	397 (35.2)
Upper respiratory tract infection[a]	84 (7.4)	49 (4.8)	20 (2.8)	141 (12.5)
Headache[b]	25 (2.2)	13 (1.3)	4 (0.6)	39 (3.5)
Influenza	7 (0.6)	11 (1.1)	2 (0.3)	20 (1.8)
Liver function test increased[c]	8 (0.7)	5 (0.5)	4 (0.6)	17 (1.5)
Bronchitis	7 (0.6)	4 (0.4)	1 (0.1)	12 (1.1)
Injection site reaction[d]	5 (0.4)	4 (0.4)	3 (0.4)	12 (1.1)

Source: Created from the submitted data.
a Includes nasopharyngitis, upper respiratory tract infection, sinusitis, pharyngitis, pharyngitis streptococcal, rhinitis, viral upper respiratory tract infection, acute sinusitis, chronic sinusitis, and tonsilitis.
b. Includes headache, head discomfort, migraine, sinus headache, and tension headache.
c. Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, gamma-glutamyl transferase abnormal, gamma-glutamyl transferase increased, and liver function test increased.
d. Includes contusion, facial pain, injection site reaction, administration site swelling, injection site bruising, injection site hematoma, injection site mass, injection site nodule, skin swelling, and periorbital hematoma.

8.2.4.5.3. Adverse Reactions

The adverse reactions that occurred during the double-blind period of the studies are listed in the table below. Headache and injection site reaction were the only ARs that occurred in >1% of the subjects in either treatment group. It occurred at a higher rate in the BoNT/A-DP group than in the placebo group.

Table 28. Incidence of Adverse Reactions Occurring in ≥ 1% of Subjects in BLESS I, II, and III (Double-Blind Period)

Preferred Term	BoNT/A-DP (N=911) n (%)	Placebo (N=310) n (%)
Any TEAE	33 (3.6)	8 (2.6)
Headache[a]	17 (1.9)	2 (0.6)
Injection site reaction[b]	11 (1.2)	6 (1.9)

Source: Created from the submitted data.
a. Includes headache, head discomfort, migraine, and procedural headache.
b. Includes contusion, facial pain, folliculitis, haematoma, injection site pain, injection site bruising, injection site hematoma, injection site pruritus, and swelling.

The table below listed the ARs that are included in Injection Site Reactions.

Table 29. Incidence of Injection Site Reactions in BLESS I, II, and III (Double-Blind Period)

Preferred Term	BoNT/A-DP (N=911) n (%)	Placebo (N=310) n (%)
Any injection site reaction	6 (0.7)	2 (0.6)
Injection site pain	3 (0.3)	1 (0.3)
Contusion (bruising)	2 (0.2)	1 (0.3)
Haematoma	1 (0.1)	1 (0.3)
Swelling	1 (0.1)	1 (0.3)
Injection site bruising	1 (0.1)	1 (0.3)

Facial pain	0	1 (0.3)
Folliculitis	1 (0.1)	0
Injection site haematoma	1 (0.1)	0
Injection site pruritus	1 (0.1)	0

Source: Created from the submitted data.

The adverse reactions that occurred during the open-label period of the studies are listed in the table below. Headache was the only AR that occurred in ≥ 1% of the study subjects.

Table 30. Incidence of Adverse Reactions Occurring in ≥ 1% of Subjects in BLESS I, II, and III (Open-Label Period)

Preferred Term	CYCLE 2 (N=1129) n (%)	CYCLE 3 (N=1020) n (%)	CYCLE 4 (N=722) n (%)	Total (N=1129) n (%)
Any TEAE	28 (2.5)	23 (2.3)	7 (1)	55 (4.9)
Headache[a]	15 (1.3)	8 (0.8)	2 (0.3)	23 (2)

Source: Created from the submitted data.
a. Includes headache, head discomfort, migraine, sinus headache, and tension headache.

For the most common AR, headache, differences in frequencies were seen in subgroups by age and by previous botulinum toxin treatment. ARs of headache were more frequent in younger subjects and in treatment naive subjects. A total of 47 subjects (4.6%) aged <65 years reported headache at some time during active treatment while only 2 older subjects (1.4%) reported headache. A total of 39 treatment naive subjects (5.1%) reported headache while only 10 pre-treated subjects (2.5%) reported headache.

Summaries of related TEAEs by SOC and PT and by age group, gender, ethnicity, race group, baseline FWS, or previous botulinum toxin treatment generally did not show any meaningful differences between the subgroups.

All related TEAEs (with the exception of 1 event of constipation) resolved, mostly within a short period of time.

8.2.4.6. Laboratory Findings

After reviewing the submitted laboratory information, this reviewer agrees that the laboratory hematology and chemistry test results were generally similar between the 2 treatment groups in the placebo-controlled period of the Phase 3 studies (BLESS I, II and III). No clinically significant changes were observed from baseline to Week 4 and the end of each treatment cycle for either the BoNT/A-DP or the placebo groups.

During the open-label period, re-treatment with BoNT/A-DP for Cycles 2, 3, and 4 did not indicate any clinically relevant changes from baseline to Week 4 in laboratory parameters.

No clinically meaningful differences in laboratory test results were observed among the subgroups of age group, gender, ethnicity, race group, baseline FWS, or previous botulinum toxin treatment.

8.2.4.7. Vital Signs

After reviewing the submitted vital sign information, this reviewer agrees with the assessment that no clinically meaningful changes or trends were noted in systolic/diastolic blood pressure or heart rate between treatment groups, or from baseline throughout the studies (BLESS I, II and III).

8.2.4.8. Electrocardiograms (ECGs)

This reviewer agrees with the Applicant that no clinically meaningful differences were noted in ECG parameters between BoNT/A-DP and placebo treatment groups, and no clinically meaningful differences in ECG test results were observed among the subgroups of age group, gender, ethnicity, race group, baseline FWS, or previous botulinum toxin treatment.

8.2.4.9. QT

No significant QT prolongation was detected in the Phase 3 studies.

8.2.4.10. Immunogenicity

Please see Clinical Pharmacology review on immunogenicity in Section 6.2.1.

8.2.5. Analysis of Submission-Specific Safety Issues

No submission-specific safety issues were identified.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There was no COA analysis informing safety/tolerability.

8.2.7. Safety Analyses by Demographic Subgroups

After reviewing the submitted information, this reviewer agrees with the Applicant that no meaningful differences in the rates of TEAEs or laboratory test results were observed among

the subgroups of age group, gender, ethnicity, race group, baseline FWS, or previous botulinum toxin treatment during double-blind treatment, or for active treatment overall.

8.2.8. Specific Safety Studies/Clinical Trials

There was no specific safety study.

8.2.9. Additional Safety Explorations

8.2.9.1. Human Carcinogenicity or Tumor Development

No genotoxicity, carcinogenicity, or pre- and postnatal development studies are warranted for letibotulinumtoxinA (see Section Error! Reference source not found.).

8.2.9.2. Human Reproduction and Pregnancy

Four pregnancies were reported as adverse events ("exposure during pregnancy"), of which one was reported during the double-blind phase and three during the open-label phase. These 4 pregnancies were the only pregnancies during the study. All 4 subjects discontinued the study drug as a result of the pregnancy. The narratives below also indicate the pregnancy outcomes; all ended in live births of healthy babies.

- Subject (b) (6) (a 34-year-old female) was found pregnant by blood serum pregnancy test at the EOS visit after her second BoNT/A-DP treatment. Her previous pregnancy test on the day of her second BoNT/A-DP treatment was negative. The pregnancy was reported as an AE ("exposure during pregnancy"), and led to discontinuation from the study drug and the study. The subject reported a healthy pregnancy and delivered a healthy female baby.

- Subject (b) (6) (a 31-year-old female) was found pregnant by blood serum pregnancy test at the EOS visit after her first BoNT/A-DP treatment. Her previous pregnancy test on the day of her BoNT/A-DP treatment was negative. The pregnancy was reported as an AE ("exposure during pregnancy"), and led to discontinuation from the study drug and the study. The subject delivered a healthy male baby via cesarean section.

- Subject (b) (6) (a 28-year-old female) was found pregnant by blood serum pregnancy test at the EOS visit after her first BoNT/A-DP treatment. Her previous pregnancy test on the day of her BoNT/A-DP treatment was negative. The pregnancy was reported as an AE ("exposure during pregnancy"), and the subject withdrew consent for participation in the study. The subject delivered a healthy male baby.

- Subject (b) (6) (a 36-year-old female), was found pregnant by home urine serum pregnancy test 3.5 months after her third BoNT/A-DP treatment. Her previous pregnancy test on the day of her BoNT/A-DP treatment was negative. The pregnancy was reported as an AE ("exposure during pregnancy"), and led to discontinuation from the study. The subject delivered a healthy female baby.

8.2.9.3. Pediatrics and Assessment of Effects on Growth

The Applicant conducted studies in adult subjects (18 years of age and older) only, which is the relevant population for treatment of glabellar lines, and for whom the Applicant seeks labeling.

8.2.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
The Applicant stated that no case of systemic toxicity resulting from accidental injection of BoNT/A-DP has been reported; and that no cases of oral ingestion of BoNT/A-DP have been reported.

This reviewer considers that because doses of BoNT/A-DP in the clinical studies were prepared and administered under the direct supervision of a qualified healthcare provider, overdose is considered unlikely.

Drug Abuse Potential
The Applicant stated that this is not applicable.

BoNT/A-DP is not expected to be present in the peripheral blood at detectable levels following IM injection at the intended clinical doses, and there is lack of overlap between botulinum toxin's mechanism of action and known abuse mechanisms.

This reviewer considers that no dependence or abuse potential for BoNT/A-DP is foreseen.

Withdrawal and Rebound
The Applicant stated that an evaluation of withdrawal effects or rebound effects regarding safety have not been systematically evaluated for BoNT/A-DP.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability
The Applicant reported that no studies on the effects of BoNT/A-DP on the ability to drive and use machines have been performed.

This reviewer agrees with the Applicant that some observed TEAEs could affect the ability to drive or to operate machines (e.g., visual disturbance, dizziness, asthenia, and muscle weakness).

8.2.9.5. Drug-Drug Interactions

The Applicant reported that drug interactions have not been evaluated by the sponsor in this BLA.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

According to the Applicant, BoNT/A-DP has been available in Korea since 2010 under the name Botulax® and is also licensed in 22 other countries.

Overall an estimated 16,709,837 vials (50 U, 100 U, 150U or 200 U) of BoNT/A-DP have been distributed during the period between 13 March 2009 and 01 Sep 2020 globally for the various indications including blepharospasm, glabellar lines, cervical dystonia, urinary incontinence, chronic migraine, paediatric cerebral palsy, equinus foot deformity, strabismus, axillar hyperhidrosis, focal spasticity, spasmodic dystonia, upper limb spasticity, post stroke spasticity, muscle spasticity, correction of facial wrinkles, latheral canthal lines.

A post-marketing safety study (HG-13-02) was conducted in Korea to investigate the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugators muscle and/or procerus muscle activity in 815 adults between 18 and 65 years of age.

The safety profile of botulinum toxin products are well characterized and no new safety signals were identified in the reported post-marketing safety data from Korea for BoNT/A-DP.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the safety data for BoNT/A-DP identified no new safety signals. There are no safety concerns that are expected to change the favorable risk/benefit assessment or lead to increased risk with administration of BoNT/A-DP in the postmarket setting.

8.2.11. Integrated Assessment of Safety

The intended use of BoNT/A-DP for the indication of treatment of glabellar lines in adults is an aesthetic indication. The clinical studies showed that BoNT/A-DP was effective and has an expected safety profile. The performance of BoNT/A-DP is similar to that of the currently marketed botulinum toxin products for the same indication. Most of the adverse events in the submitted studies were unrelated to the study drug, and were either mild or moderate in severity. There were no serious adverse events related to the drug treatment. The rate of drop-

outs due to drug related adverse events was low. There were two drug related adverse events with a frequency of 1% or greater (headache and injection site reaction). Most of these events were either mild or moderate in severity and resolved spontaneously without treatment. In summary, BoNT/A-DP has an acceptable risk-benefit profile for the treatment of glabellar lines in adults.

8.3. Statistical Issues

No significant statistical issues were identified.

Subject (b) (6) in Study BLESS I was randomized to the Letybo arm, but had baseline glabellar lines rated as mild rather than moderate or severe (as required by the inclusion criteria) at maximum frown based on the GLS-S. This subject was taken out of the FAS and efficacy analysis, as per the clinical reviewer.

The statistical method used to calculate CIs for the risk difference in the primary and secondary efficacy endpoints had to be modified because the Applicant used the unstratified Newcombe confidence limits without considering the stratification of study center. It was not appropriate for data with 0% responder rates, which was the case for the placebo arm in Studies BLESS I and III. Therefore, the Mantel-Haenszel method was used to calculate the common risk difference and its CIs stratified by study center, which can be applied to zero-frequency rows, columns or cells.

The Applicant used the one-sided p value by halving the two-sided p value and the one-sided significance level of 0.025 for the CMH test and the hierarchical testing procedure. Due to the asymmetric nature of the chi-squared distribution, the one-sided p-value cannot be derived by simply halving the two-sided p-value. The statistical reviewers used the two-sided p-value with a significance level of 0.05 for the CMH test and the hierarchical testing procedure.

None of these statistical issues affected the efficacy conclusion.

8.4. Conclusions and Recommendations

To establish the efficacy and safety of BoNT/A-DP, the Applicant submitted data from 3 identical, randomized, double-blinded, placebo-controlled Phase 3 studies (Study CPH-301-201030 referred to as BLESS I, Study CPH-302-201030 referred to as BLESS II, and Study CPH-303-201400 referred to as BLESS III). The studies enrolled subjects 18 years of age and older with moderate-to-severe glabellar lines at maximum frown as assessed independently by both investigator and subject using the Frown Wrinkle Severity scale. The primary efficacy endpoint was the proportion of subjects with a Facial Wrinkle Scale (FWS) score of 0 or 1 and an improvement of ≥2 points on FWS score (at maximum frown) at the Week 4 visit relative to baseline, based on both the investigator's and the subject's in-clinic assessments, with a single

dose of the 20 U of BoNT/A-DP against placebo. In all 3 studies, BoNT/A-DP was statistically superior to placebo for the primary endpoint at Week 4.

The safety profile of BoNT/A-DP was similar to the safety of other botulinum toxin A products licensed for the same indication. BoNT/A-DP was generally well tolerated. No death was reported. No serious adverse event was considered treatment related. Most of reported adverse reactions were either mild or moderate in severity and resolved spontaneously without treatment. The most frequently reported adverse reactions in BoNT/A-DP treatment groups were headache 1.9% and injection site reaction 0.7%. The safety analysis did not identify any new safety signals for this botulinum toxin A product. The safety profile of botulinum toxins in general are well characterized and this product will carry class labeling for the uncommon and potentially serious adverse events.

Based on safety and efficacy data provided by the applicant, this reviewer recommends to Division and Office leadership that BoNT/A-DP be approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients at a dose of 0.1 mL (4 Units) by intramuscular injection into each of 5 sites, for a total dose of 20 Units.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was convened. The review team determined that this product for the treatment of glabellar lines presented no novel or complex issues that required input from an advisory committee.

10 Pediatrics

The applicant submitted an initial pediatric study plan (iPSP) on October 12, 2015, requesting a waiver from conducting studies in patients 17 years of age and younger based on the rationale that trials are "impossible or highly impractical'. This full waiver request was made in accordance with FDA *draft* Guidance for Industry *Upper Facial Lines: Developing Botulinum Toxin Drug Products (August 2014)*, "Because upper facial lines are uncommon in the pediatric population, the sponsor may request a waiver for the requirement to submit a pediatric assessment in the pediatric study plan."

On December 16, 2015, the Division presented the initial Pediatric Study Plan (iPSP) to the Pediatric Review Committee (PeRC). The Division agreed with the requested Full Waiver of Pediatric Studies for pediatric patients from age 0 to 17 years because studies are impossible or highly impractical due to the extremely low prevalence of glabellar lines in the pediatric population. The full waiver was granted on March 16, 2016 for subjects less than 18 years of age.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The medical officer has reviewed all labeling. Labeling negotiations were placed on hold at the time of closure of this review as product quality issues and inspectional findings preclude approval at this time. Refer to discussions in the sections on the corresponding product quality review.

12 Risk Evaluation and Mitigation Strategies (REMS)

REMS will not be required for this application.

13 Postmarketing Requirements and Commitment

No postmarketing requirements or commitments are recommended.

14 Division Director (DPT-II) Comments

Not applicable.

15 Division Director (OCP) Comments

16 Division Director (OB) Comments

17 Division Director (Clinical) Comments

18 Office Director Comments

I concur with the recommendation of the Division of Dermatology and Dentistry to not approve BLA 761225 for letibotulinumtoxinA lyophilized powder for reconstitution for injection (Letybo) for the treatment of moderate-to-severe facial lines. Product quality issues and inspectional findings preclude approval of the application at this time. Satisfactory resolution of these deficiencies is required before this application may be approved. No other approvability issues have been identified.

Like other botulinumtoxinA products, Letybo is an acetylcholine release inhibitor and neuromuscular blocking agent; it is injected intramuscularly in corrugator and procerus muscles to temporarily improve the appearance of moderate-to-severe glabellar lines.

The efficacy of Letybo was demonstrated in three identically-designed, randomized, double-blinded, placebo-controlled trials that enrolled adult subjects with moderate-to-severe glabellar lines at maximum frown as assessed using the Frown Wrinkle Severity (FWS) scale. In all three trials, a 20 U dose of Letybo was superior to placebo for the primary efficacy endpoint (the proportion of subjects with a FWS score of 0 or 1 and an improvement of ≥2 points at maximum frown) at Week 4 relative to baseline, as assessed by both the investigator and the subject.

Letybo clinical trials assessed the safety of up to four treatments. Like other botulinumtoxinA

products used for glabellar lines, Letybo administration was generally well-tolerated and did not raise any new safety concerns. If approved, product labeling for Letybo will carry class labeling for the uncommon but potentially serious adverse events that have been reported with intramuscular injections of botulinumtoxinA products.

19 Appendices

19.1. References

None.

19.2. Financial Disclosure

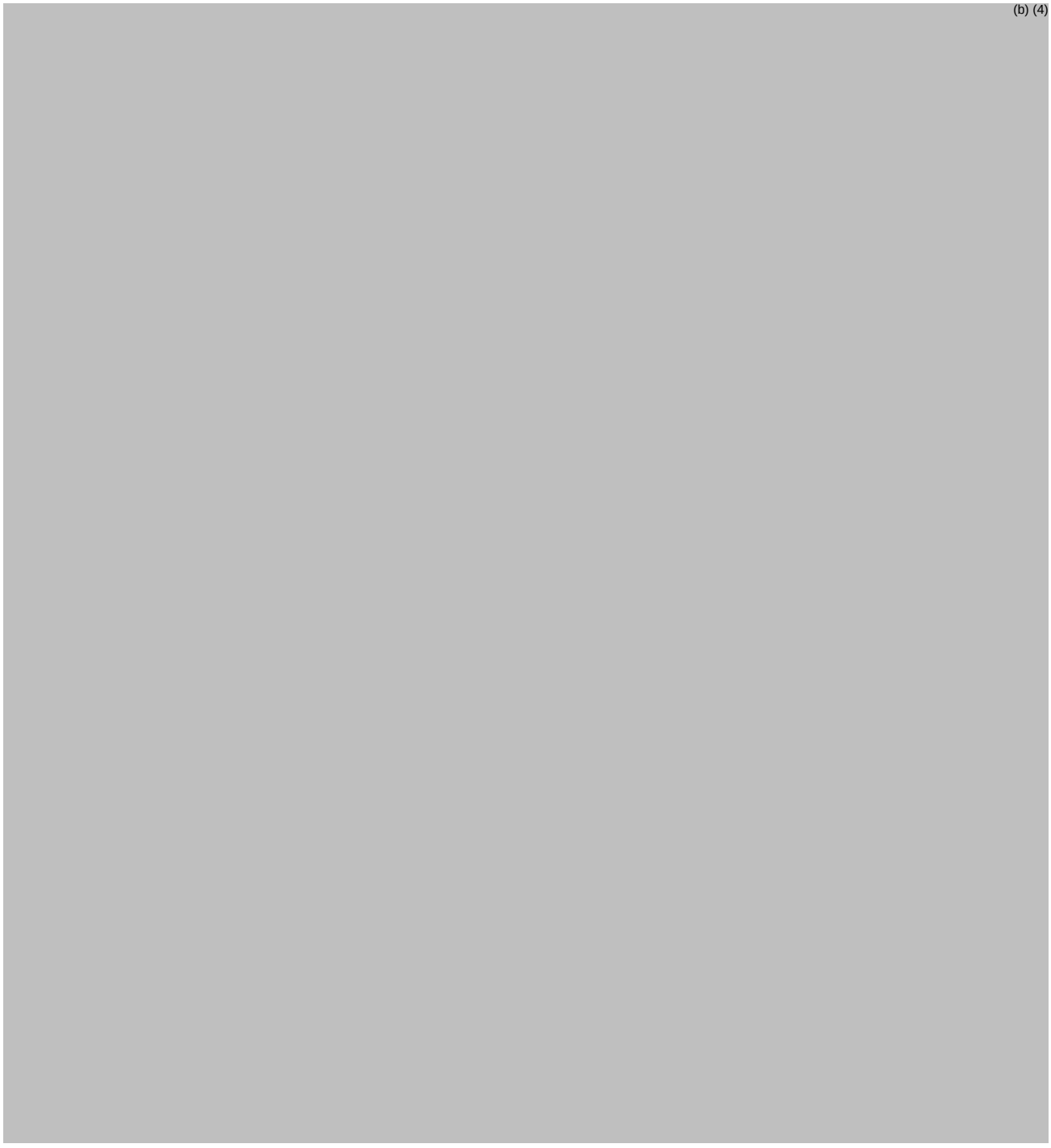
Covered Clinical Study (Name and/or Number): Study CPH-301-201030 [BLESS I], Study CPH-302-201030 [BLESS II], and Study CPH-303-201400 [BLESS III]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 101		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

Revisions to the applicant's proposed wording for the nonclinical and related sections of the label are provided below. It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted from the product label proposed by the applicant. The subheadings in Section 8.1 should be in underlined format.

(b) (4)



(b) (4)

[redacted]

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

Not applicable.

19.5. Additional Statistical Analyses

Assessment of efficacy in the primary endpoint was conducted among the PPS to verify the results from the primary analysis among the FAS. Table 31 shows the statistical reviewers' analysis results for the primary efficacy endpoint among the PPS in Studies BLESS I, II and III. The analysis results among the PPS were consistent with the primary analysis results among the FAS. Additional analysis for Study BLESS III by including the two subjects (b) (6) [redacted] to the PPS shows that including/excluding the two subjects did not impact the analysis result.

Table 31. Primary Efficacy Endpoint at Week 4 (Studies BELSS I, II, and III; PPS)

	Study BLESS I		Study BLESS II		Study BLESS III	
	Letybo N = 480	Placebo N = 154	Letybo N = 134	Placebo N = 45	Letybo N = 240	Placebo N = 81
Treatment Success						
Multi-Component Assessment n (%) #	224 (46.7%)	0 (0%)	70 (52.2%)	0 (0%)	159 (66.3%)	0 (0%)
Treatment Difference and 95% CI *	47.8% (43.3%, 52.4%)		50.8% (41.8%, 59.8%)		67.8% (61.7%, 73.8%)	
P-value **	<0.0001		<0.0001		<0.0001	
Individual Components						
Investigator Assessment n (%) #	318 (66.3%)	1 (0.6%)	105 (78.4%)	0 (0%)	192 (80.0%)	1 (1.2%)
Subject Assessment n (%) #	264 (55.0%)	0 (0%)	75 (56.0%)	0 (0%)	167 (69.6%)	0 (0%)

Subjects with missing in-clinic assessments (GLS-I or GLS-S) at baseline or Week 4 were imputed as non-responders.
* Mantel-Haenszel estimate and confidence limits for the common risk difference by using the Mantel-Haenszel weights for study center.
** P-values are based on the CMH general association test stratified on study center.
Source: reviewer analysis

As mentioned in Section 8.1.2 (Patient Disposition), Subject (b) (6) in Study BLESS I had baseline glabellar lines rated as mild at maximum frown based on the GLS-S, which violated the inclusion criteria. This subject was taken out of the FAS and primary efficacy analysis. In order to assess its impact on the efficacy results, the statistical reviewers conducted a sensitivity analysis by repeating the primary analysis but including Subject (b) (6) in the FAS. This subject was randomized to the Letybo arm and did not respond at Week 4. The sensitivity analysis result (see Table 32) was consistent with the primary analysis result.

Table 32. Primary Efficacy Endpoint at Week 4 Including Subject (b) (6) (Study BLESS I; FAS)

	Study BLESS I (Including Subject (b) (6))	
	Letybo N = 529	Placebo N = 175
Treatment Success		
Multi-Component Assessment n (%) #	246 (46.5%)	0 (0%)
Treatment Difference and 95% CI *	46.9% (42.6%, 51.3%)	
P-value **	<0.0001	
Individual Components		
Investigator Assessment n (%) #	348 (65.8%)	1 (0.6%)
Subject Assessment n (%) #	290 (54.8%)	0 (0%)

Subjects with missing in-clinic assessments (GLS-I or GLS-S) at baseline or Week 4 were imputed as non-responders.

* Mantel-Haenszel estimate and confidence limits for the common risk difference by using the Mantel-Haenszel weights for study center.
** P-values are based on the CMH general association test stratified on study center.
Source: reviewer analysis

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/s/

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