CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761085Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Clinical Review and Evaluation Memorandum
Resubmission of BLA 761085

Supporting Document Number	**33**, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46
Sponsor:	Evolus, Inc.
Drug:	**JEUVEAU (prabotulinumtoxin A)**
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:	2-AUG-2018
Review Date:	28-JAN-2019
Reviewer:	Gary T Chiang MD, MPH, DDDP
Team Lead:	David Kettl MD, DDDP
Project Manager:	Matthew White

1. Introduction

1.1. Executive Summary

This application is a resubmission of the BLA in response to the Agency's Complete Response (CR) letter dated 15-MAY-2018 for JEUVEAU (prabotulinumtoxin A), designated DWP-450, manufactured by Daewoong Pharmaceuticals (Evolus Inc.) for the treatment of temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults.

The Agency CR letter list many deficiencies, all related to product quality and manufacturing issues:

Drug Substance:

1. *The Clostridium botulinum culture purity* (b) (4) (b) (4) (b) (4) *Provide the* (b) (4) *bacterial purity data from three batches. In addition, provide the* (b) (4) *limit and a description of the new test method.*
2. *You did not provide data to demonstrate that the DWP-450 drug substance (DS) is free of Clostridium botulinum spores. Provide spore monitoring data* (b) (4) (b) (4)

3. *You provided insufficient data to demonstrate that DWP-450 DS is free of Clostridium botulinum vegetative cells. Provide monitoring data of Clostridium botulinum* (b) (4) [redacted] (b) (4)
4. *You provided no in-process bioburden and endotoxin data to demonstrate adequate microbial control of the DWP-450 DS* (b) (4) *. Provide bioburden data* (b) (4) [redacted] (b) (4) *. In addition, provide the qualification data for the bioburden and endotoxin test methods* [redacted] (b) (4) *. Furthermore, establish and provide* (b) (4) *limits for these bioburden and endotoxin samples.*
5. *You provided no bioburden and endotoxin data* [redacted] (b) (4) *to demonstrate adequate microbial control* (b) (4) *. Provide microbiology validation data at commercial scale to demonstrate effective microbial control* (b) (4) [redacted] (b) (4) *.*
6. *You provided no microbiology validation data* (b) (4) *of the DWP450 DS* (b) (4) *to ensure adequate microbial control* (b) (4) [redacted] (b) (4) *. Provide microbiology validation data* (b) (4) [redacted] (b) (4) *.*
7. *You did not establish endotoxin limits for the DWP450 DS* (b) (4) *. Establish and provide endotoxin limits for the DWP450 DS* (b) (4) *.*
8. *The current test volume for DS total aerobic microbial count (TAMC) is low and thus, the bioburden release test may not have sufficient sensitivity.* (b) (4) [redacted] (b) (4) (b) (4) *. Provide bioburden qualification data of the DS* (b) (4) [redacted] (b) (4) *and DS bioburden release data from three lots. Update the BLA with a description of the test method and the new DS bioburden specification.*

Drug Product:

9. *You performed validation* (b) (4) [redacted] *using* (b) (4) [redacted] (b) (4) *the DWP-450 DP vials. No information was provided to assess* (b) (4) *. Demonstrate that* (b) (4) *DWP-450 commercial DP vials* (b) (4) [redacted] *effectively reduces endotoxin by a minimum of 3 logs and provide summary data and the validation report in the BLA resubmission.*
10. *You did not perform validation of the worst-case* (b) (4) [redacted] *parameters on the DWP-450 DP vials to ensure that commercial vials are sealed appropriately, and that container closure is integral. The vials used in the commercial manufacture of DWP-450 DP were not used to validate the* (b) (4) [redacted] *process. In addition, worst-case* (b) (4) [redacted] *parameters were not used during validation. Submit container closure integrity data to support the proposed parameters in the BLA resubmission.*
11. *You performed the* (b) (4) [redacted] *validation study with* (b) (4) [redacted] (b) (4) *the DWP-450 DP vials. No information was provided to assess* (b) (4) [redacted] (b) (4) *. Demonstrate that* (b) (4) [redacted] (b) (4) *DWP-450 DP vials is effective* (b) (4) [redacted]

[redacted] (b) (4) and provide summary data and the validation report in the BLA resubmission.

12. *The maximum sterile hold [redacted] (b) (4) for DWP-450 DP is not supported [redacted] (b) (4). Provide data [redacted] (b) (4) to support the sterile hold of [redacted] (b) (4) for DWP-450 DP [redacted] (b) (4). Include a summary of the [redacted] (b) (4) environmental monitoring data in the BLA resubmission.*
13. *You did not demonstrate that the container closure integrity test detects breaches that may allow for bacterial ingress. You did not include positive controls in the method validation. Submit information to demonstrate that the container closure integrity testing can detect breaches ≤ [redacted] (b) (4) and include positive controls during routine testing.*
14. *You did not perform low endotoxin recovery testing of DWP-450 DP to assess whether the bacterial endotoxin test method can consistently detect endotoxin in the drug product. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> Bacterial Endotoxin Test (BET). Evaluate the effect of hold time on endotoxin detection by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted DP and test for recoverable endotoxin over time [redacted] (b) (4) [redacted] (b) (4). Submit the report in the BLA resubmission.*
15. *You did not routinely monitor bioburden [redacted] (b) (4) to verify continued microbial control of the drug product [redacted] (b) (4). Implement routine bioburden monitoring [redacted] (b) (4). In addition, provide a description of the bioburden test method and provide method qualification, summary data, and the qualification report.*

Product Quality: Drug Substance and Drug Product:

16. *Reference materials play a critical role in confirming the suitability of analytical tests and the quality of the product during release and stability testing. The information you provided in the BLA suggests that your DS reference material management program does not generate sufficient quantities of a given reference material lot to support all the required testing. Revise your reference material qualification procedures to ensure that you generate sufficient quantities of reference material to support all the necessary testing, including qualification of future reference materials. In addition, revise the DS reference material qualification and requalification protocol to include adequate stability monitoring of the reference materials.*
17. *In your December 1, 2017 response to the November 13, 2017 information request to update the DP stability testing protocols to include DP reconstitution time, it appears that additional changes were made to the post-approval stability protocol originally submitted in the BLA to remove the testing points at 3, 6, 9, and 18 months. You did not provide sufficient stability data to support a reduced stability testing program. Therefore, the updated annual post-approval stability protocol in section 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (Table 3.2.P.8.2-2) received on December 1, 2017 is not adequate to ensure that potential changes to commercial DP during storage are detected in a timely manner. Revise your annual stability protocol to include testing at 3, 6, 9, and 18 months as recommended by ICH Q5C guidelines.*
18. *In your March 9, 2018 response to the March 2, 2018 information request to describe Evolus' role in DWP-450 lot release, you stated that some of Evolus' quality responsibilities will be delegated via quality agreements and standard operating procedures (SOPs) to your "soon to be established distributor". Your response indicates that the distributor may be responsible for: visual inspection for shipping or water damage; verification of release certifications (Certificate of Analysis) from Daewoong Pharmaceuticals Co., Ltd.; verification of shipment quantity and lots numbers; and*

> *verification that appropriate temperature was maintained during shipment. You also state that you will rely on the distributor's SOPs and Quality Assurance unit for these activities. If your distributor is responsible for performing release operations for Evolus then they appear to fit the definition of a manufacturer rather than a distributor per 21 CFR 600.3 (t), (u), and (aa) and should be listed as a manufacturer in the license application.*

The applicant provided a response to the CR letter deficiencies in their resubmission. The deficiencies have been remedied. There is no new safety or efficacy issues with the application. The completed biostatistical and clinical review has been finalized in the multi-review format and identified no issues which would preclude approval. No new clinical data was submitted as part of the current applicant response to the Complete Response letter.

This BLA application 761085, for JEUVEAU (botulinum toxin, Type A) is approvable from the clinical perspective.

1.2. Scientific and Regulatory Background

JEUVEAU (prabotulinumtoxin A) is manufactured by Daewoong Pharmacuetical Co., Ltd. of Seoul, South Korea and is a 900 kDa botulinum toxin produced by *Clostridium botulinum* that has the same structural characteristics, and physiochemical and biological properties as Botulinum toxin, Type A. This drug product, given the designation DWP-450 DP, has the same mechanism of action as other botulinum toxins in its class. When injected intramuscularly at therapeutic doses, botulinum toxin produces chemical denervation of the muscle resulting in localized reduction of muscle activity.

The proposed indication for this product is for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults. Glabellar lines, or also known as frown lines, occur naturally with facial animation because of the impact on the skin from underlying facial musculature, predominantly the procerus and the corrugator supercilii muscles. [1] Other approved uses for the botulinum toxin include: treatment of urinary incontinence, prophylaxis of headaches in patients with chronic migraine, treatment of upper limb spasticity, cervical dystonia and primary axillary hyperhidrosis in adults, blepharospasm, strabismus in patients 12 years of age and above, temporary improvement of lateral canthal lines, and temporary improvement in the appearance of moderate to severe glabellar lines.

Botulinum toxin, Type A was first approved for the use in glabellar lines in 2002[2], since first approval, the use of botulinum toxin has become a common treatment option for glabellar lines resulting from underlying hyper-functional facial musculature. The pharmacological mechanism by which botulinum toxin, type A works is by blocking the release of the neurotransmitter acetylcholine into the neuromuscular junction, thereby decreasing muscle contractions.[3]

This product was given the name JEUVEAU (prabotulinumtoxin A) and was designated with the suffix -xvfs. Reviews of both the proprietary name and suffix was deemed acceptable by the Agency review teams.

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[1] Pierard GE, Lapiere CM. The microanatomical bases of facial frown lines. *Arch Dermatol*. 1989; 125:1090-2.
[2] Product Approval: Botulinum toxin, Type A (BOTOX); FDA BLA 103000/5000; April 12, 2002.
[3] Simpson LL. Current concepts on the mechanism of action of clostridial neurotoxins. In: DasGutpta BR, editor. Botulinum and tetanus neurotoxins. New York: Plenum Press;1993. p. 5-15.

2. Re-Submission

2.1. CMC

- **Product Quality (Drug Product):**

We recommend approval of BLA 761085 from OBP's product quality perspective. The complete response (CR) review issues regarding the product quality of the drug product (DP) manufacturing process and control strategy have been adequately addressed.

- **Product Quality Microbiology:**

The drug product portion of this BLA was reviewed from a sterility assurance and product quality microbiology standpoint and is recommended for approval.

Reviewers Comment:
See OBP and Microbiology review for details. The issues outlined in the CR letter have been resolved. The recommendation is for approval.

2.2. Preclinical Findings

Please see non-clinical review for details. No nonclinical information was included in the current submission.

3. Clinical Summary

3.1. Efficacy

The efficacy of DWP-450 DP was demonstrated in two pivotal clinical trials (EV-001 and EV-002), a 330-subject Phase 3 and a 324-subject Phase 3 clinical trial completed in the US. These two trials provide the primary supporting evidence for the safety and effectiveness of DWP-450 DP for the treatment of temporary improvement in the appearance of moderate to severe glabellar lines in adults. The studies were double-blind and randomized, comparing 20 units (U) of DWP-450 DP with 20 U BOTOX®, injected as 4 U/0.1 mL into each of 5 target sites in the glabellar region of adult subjects with moderate to severe glabellar lines. The primary endpoint was a composite of investigator and patient response on the Glabellar Line Score (GLS) at maximum frown. In addition, an EU pivotal Phase 3 safety and efficacy clinical trial was completed and submitted as supporting evidence. EV-003 represents foreign data with consideration to ICH-E5 regarding the appropriateness of extrapolating foreign data to the US population. Specifically, ethnic factors that impact the drug's safety, efficacy, dosage, or dosing regimen in specific ethnic populations such as, Europeans, Japanese, African Americans, and Koreans. EV-003 also included an active comparator arm for BOTOX®.

The sponsor also completed 2 open-label, multiple-dose, long-term Phase 2 studies (EV-004 and EV-006) of 1-year duration in over 2100 adult male and female subjects with moderate to severe glabellar lines at maximum frown.

In the US pivotal EV-001 and EV-002 studies, the primary efficacy endpoint was defined as the proportion of subjects classified as responders on Day 30. This was a composite endpoint in which a responder was a subject with a ≥2-point improvement on the GLS from Day 0 to Day 30 at maximum frown, only if independently agreed by both Investigator and subject assessment.

The percentages of responders in the ITT Population for the composite primary endpoint (a two-point composite) in each of the US controlled single dose studies were:

- EV-001: 1.2% Placebo, 67.5% DWP-450 DP; Absolute difference 66.3%, 95% CI (59.0, 72.4)
- EV-002: 1.3% Placebo, 70.4% DWP-450 DP; Absolute difference 69.1%, 95% CI (61.5, 75.1)

The primary efficacy endpoint in the EU pivotal EVB-003 study was defined as the proportion of subjects classified as responders on Day 30, where a responder was a subject with a GLS score of 0 or 1, by Investigator assessment at maximum frown.

> ***Reviewer comment:*** *The efficacy of the drug product was demonstrated in the clinical trials for this product. The full Biostatistical review is documented in the already completed multidiscipline-review.*

3.2. Safety

The adverse events characteristics for botulinum toxin, Type A are well understood. The safety considerations are recommended by the Agency's draft guidance documents entitled "*Guidance for Industry. Upper Facial Lines: Developing Botulinum Toxin Drug Products*". The adverse events in the clinical trials were collected, including adverse events of special interest, treatment related adverse events, and possible hypersensitivity reactions. The safety population (any exposed to DWP-450 DP) totaled 2116 subjects who participated in the US/EU clinical development program (EV-001, EV-002, EV-003, EV-004, and EV-006). In all, 1659 received treatment with DWP-450 DP, 246 received treatment with BOTOX® (only in EV-003), and 211 received treatment with Placebo. In addition, 192/2116 (9.1%) subjects who were ≥65 years of age, including 154/1659 (9.3%) DWP-450 DP subjects, 19/246 (7.7%) BOTOX® subjects, and 19/211 (9.0%) Placebo subjects. Of the 1659 subjects treated with DWP-450 DP, 816 received a single treatment of 20 U (737 were in the three-controlled single-dose studies), 150 received a total of 2 treatments (i.e., 40 U), 325 received a total of 3 treatments (i.e., 60 U) and 368 received a total of 4 treatments (i.e., 80 U). All 737 subjects randomized to DWP-450 DP in the three-controlled single dose EV-001, EV-002 and EVB-003 studies received 20 U. The 922 subjects in the open-label multiple doses EV-004 and EV-006 studies received a mean total dose of 61.3 ± 18.98 U of DWP-450 DP; the median dose was 60 U – i.e., 3 treatments.

Headache was the most common adverse event and the only adverse event that occurred in ≥5% of DWP-450 DP subjects. Headache was also the most common adverse event assessed as related to study drug. The only other adverse events assessed as drug related that were reported in ≥1% of subjects were two eye disorders: eyelid ptosis reported by 1.0% (17/1659) of All DWP-450 DP subjects and eyelid sensory disorder reported by 1.6% (4/246) of BOTOX® subjects. A single subject died during the conduct of the five studies in the DWP-450 DP US/EU clinical development program. A serious adverse event reported as a drug overdose resulted in death. Altogether, 3 serious adverse events resulted in study discontinuation. One BOTOX® subject (1/246, 0.4%) discontinued the study due to cardiac valve fibroelastoma and the two DWP-450 DP subjects (2/1659, 0.1%) who discontinued the study due to a serious adverse event included one due to a transient ischemic attack (also considered to be an adverse event of special interest) and the other due to the previously noted unrelated drug overdose that resulted in the subject's death. Adverse events of special interest were reported in 2.8%

(47/1659) of All DWP-450 DP subjects and 1.6% (4/246) of BOTOX® subjects, compared with 0.5% (1/211) of pooled Placebo subjects. Eye disorders were the only system organ class with ≥1% of subjects with an adverse event of special interest: 1.9% (32/1659) of All DWP-450 DP subjects, 1.6% (4/246) of BOTOX® subjects, and no Placebo subjects. Eyelid ptosis was the only preferred term with ≥1% of subjects with an adverse event of special interest: 1.4% (24/1659) of All DWP-450 DP subjects and no Control subjects. None of the 25 events of eyelid ptosis reported in DWP-450 DP subjects were severe; 3 were moderate and the rest were mild. Eyelid ptosis is a complication that is known to occur as a result of treatment of glabellar lines with botulinum toxin. A total of 34 adverse events identified as possible hypersensitivity reactions were reported by 1.8% (30/1659) of subjects in the DWP-450 DP Pooled All group. A comparable 2.0% (5/246) of BOTOX® subjects reported 6 events and 1.4% (3/211) of Placebo subjects reported 3 events. None of the adverse events identified as possible hypersensitivity reactions were serious and none led to study discontinuation.

Most subjects were less than 65 years of age; 9.0% of all Placebo and 9.5% of all DWP-450 DP subjects were ≥65 years. Compared with those less than 65, the absolute difference in the percentages of responders between all DWP-450 DP and all Placebo subjects was 13.7% less for subjects 65 years of age and older (52.9% vs. 66.6%).

> ***Reviewer comment:*** *The relatively low risk profile of DWP-450 DP for the treatment of glabellar lines is supported by the safety data in the two US clinical trials, the EU clinical trial, and the long-term open-label studies. It is the opinion of this reviewer; the benefits of this product outweigh the risk for the temporary treatment of glabellar lines in adults.*

3.3. Labeling

- Labeling negotiations with the applicant is ongoing.
- Final Physicians Insert and Patient Labeling will be available in the approval letter.

3.4. Pediatrics

- A full waiver is acceptable for children and adolescents under 18 years of age. See multidisciplinary review for details of the pediatric waiver request.

4. Summary and Conclusions

- The applicant has addressed all the manufacturing and drug product concerns. It is this reviewer's opinion that JEUVEAU (**prabotulinumtoxin A**) should be approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults pending final agreement on product labeling.
- No PMC/PMR is recommended from clinical.

5. Recommended Regulatory Action

Approval

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GARY T CHIANG
01/28/2019 09:24:07 AM

DAVID L KETTL
01/28/2019 10:33:07 AM

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Biological Licensing Application
Application Number(s)	761085
Priority or Standard	Standard
Submit Date(s)	12-MAY-2017
Received Date(s)	15-MAY-2017
PDUFA Goal Date	15-MAY-2018
Division/Office	DDDP/ODE3
Review Completion Date	See DARRTS electronic signature page
Established Name	Botulinum toxin, type A
(Proposed) Trade Name	JEUVEAU
Pharmacologic Class	Neuromuscular inhibitor
Code name	NA – Complete Response
Applicant	Evolus, Inc. by Daewoong Pharmaceutical Co., Ltd.
Formulation(s)	For injection: 100 Units vacuum-dried powder in a single use vial for reconstitution
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	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	For the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients

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Reviewers Team and Signature Approval Section

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Product Quality Team Lead	Frances Namuswe, PhD	DBRIII/OBP/OPQ	4.2	**Select one:** ✓ Authored ____ Acknowledged ____ Approved
	Signature: Frances Namuswe -S Digitally signed by Frances Namuswe -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0014299619, cn=Frances Namuswe -S Date: 2018.05.11 10:12:50 -04'00'			Frances Namuswe -S Digital y signed by Frances Namuswe S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=00 14299619 cn=Frances Namuswe S Date: 2018 05 14 17 54:37 04'00'
Nonclinical Reviewer	Jianyong Wang, PhD	ODE III/DDDP	Sections 5 and 13.4	**Select one:** ✓ Authored ____ Acknowledged ____ Approved
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Nonclinical Supervisor	Barbara Hill, PhD	ODE III/DDDP	Sections 5 and 13.4	**Select one:** ____ Authored ____ Acknowledged ✓ Approved
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Clinical Pharmacology Reviewer	Jie Wang, PhD	OCP/DCP III	Section 6	**Select one:** ✓ Authored ____ Acknowledged ____ Approved

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
	Signature: Jie Wang -S		Digitally signed by Jie Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jie Wang -S, 0.9.2342.19200300.100.1.1=2000739081 Date: 2018.05.11 12:38:46 -04'00'	
Clinical Pharmacology Team Leader/ Division Director (DCP III)	Chandrahas G Sahajwalla, PhD	OCP/DCP III	Section 6	**Select one:** ____ Authored ____ Acknowledged ✓ Approved
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Biostatistics Reviewer	Matthew Guerra, PhD	OB/DB III	Sections: 7.1, 7.2, 7.4, and 13.3.	**Select one:** ____ Authored ____ Acknowledged ✓ Approved
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Biostatistics Reviewer	Marilena Flouri, PhD	OB/DB III	Sections: 7.1, 7.2, 7.4, and 13.3.	**Select one:** ✓ Authored ____ Acknowledged ____ Approved
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Biostatistics Team Leader	Mohamed Alosh, PhD	OB/DB III	Sections: 7.1, 7.2, 7.4, and 13.3.	**Select one:** ____ Authored ____ Acknowledged ✓ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Acting Division Director (DB III)	Laura Lee Johnson, PhD	OB/DB III	Sections: 7.1, 7.2, 7.4, and 13.3.	**Select one:** ____ Authored ____ Acknowledged ✓ Approved
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Clinical Reviewer	Gary T. Chiang, MD, MPH	ODE III/DDDP	Sections: 1, 2, 3, 7.3, 8, 9, 10, 11, 12, 13.1	**Select one:** ✓ Authored ____ Acknowledged ____ Approved
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Clinical Team Leader	David Kettl, MD	ODE III/DDDP	Sections: 1, 2, 3, 7.3, 8, 9, 10, 11, 12, 13.1	**Select one:** ✓ Authored ____ Acknowledged ✓ Approved
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Deputy Director	Jill A. Lindstrom, MD	ODE III/DDDP	Entire Document (Approved)	**Select one:** ____ Authored ____ Acknowledged ✓ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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Additional Reviewers of Application

OPQ	Ennan Guan (Drug Substance) Davinna Ligons (Drug Product and Immunogenicity) Aimee Cunningham (Micro) Bo Chi (Micro) Viviana Matta (Facilities) Kelly Ballard (OPRO RPM)
OPDP	Jina Kwak, PharmD
OSI	Bei Yu, PhD
OSE/DEPI	Michelle R. Iannacone, PhD
OSE/DMEPA	Carlos Mena-Grillasca, BSPharm
OSE/DRISK	Charlotte Jones, MD, PhD, MSPH

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BCA	best case scenario
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
CMH	Cochran-Mantel-Haenszel
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
DDDP	Division of Dermatology and Dental Products
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
GLS	Glabellar Line Scale
GRMP	Good Review Management Practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
NRI	non-responder imputation
OCS	Office of Computational Science
ODE	Office of Drug Evaluation
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
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
SPA	Special Protocol Assessment
TEAE	treatment emergent adverse event
WCS	worst case scenario

1 Executive Summary

1.1. Product Introduction

Botulinum toxin type A manufactured by Daewoong Pharmaceutical Co., Ltd. of Seoul, South Korea is a 900 kDa botulinum toxin produced by Clostridium botulinum and is claimed to have the same structural characteristics, and physiochemical and biological properties as botulinum toxin, type A. This drug product, given the designation DWP-450 or JEUVEAU (botulinum toxin type A), has the same mechanism of action as other botulinum toxins in its class. When injected intramuscularly at therapeutic doses, botulinum toxins produce chemical denervation of the muscle resulting in localized reduction of muscle activity.

The proposed indication for this product is for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults. Glabellar lines, or also known as frown lines, occur naturally with facial animation because of the impact on the skin from underlying facial musculature, predominantly the procerus and the corrugator supercilii muscles.

Other approved uses for the botulinum toxin include: treatment of urinary incontinence, prophylaxis of headaches in patients with chronic migraine, treatment of upper limb spasticity, cervical dystonia and primary axillary hyperhidrosis in adults, blepharospasm, strabismus in patients 12 years of age and above, temporary improvement of lateral canthal lines, and temporary improvement in the appearance of moderate to severe glabellar lines.

Botulinum toxin type A was first approved for the use in glabellar lines in 2002; since first approval, the use of botulinum toxin has become a common treatment option for glabellar lines resulting from underlying hyper-functional facial musculature. The pharmacological mechanism by which botulinum toxin type A works is by blocking the release of the neurotransmitter acetylcholine into the neuromuscular junction, thereby decreasing muscle contractions.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy of JEUVEAU (botulinum toxin type A) was demonstrated in two pivotal clinical trials (EV-001 and EV-002), a 330-subject and a 324-subject Phase 3 clinical trial completed in the US. These two trials provide the primary supporting evidence for the safety and effectiveness of JEUVEAU for the treatment of temporary improvement in the appearance of moderate to severe glabellar lines in adults.

The trials were double-blind and randomized, comparing 20 units (U) of JEUVEAU with placebo, injected as 4 U/0.1 mL into each of 5 target sites in the glabellar region of adult subjects with moderate to severe glabellar lines. The primary endpoint was a composite of investigator and subject response on the Glabellar Line Score (GLS) at maximum frown. In addition, an EU pivotal Phase 3 safety, efficacy, and comparison to an active arm (Botox®) clinical trial was completed and submitted as supporting evidence.

EV-003 represents foreign data with consideration to ICH-E5 regarding the appropriateness of extrapolating foreign data to the US population, specifically, ethnic factors that impact the drug's safety, efficacy, dosage, or dosing regimen in specific ethnic populations such as, Europeans, Japanese, African Americans, and Koreans. EV-003 also included an active comparator arm for Botox® (onabotulinumtoxinA) approved by the FDA for glabellar lines in October 2017.

The sponsor also completed two open-label, multiple-dose, long-term Phase 2 studies (EV-004 and EV-006) of 1-year duration in over 2100 adult male and female subjects with moderate to severe glabellar lines at maximum frown.

In the US pivotal EV-001 and EV-002 clinical trials, the primary efficacy endpoint was defined as the proportion of subjects classified as responders on Day 30. This was a composite endpoint in which a responder was a subject with a ≥ 2-point improvement on the GLS from Day 0 to Day 30 at maximum frown, only if independently agreed by both Investigator and subject assessment. The percentages of responders in the ITT Population for the composite primary endpoint (a two-point composite) in each of the US controlled single dose studies were:

- EV-001: 1.2% Placebo, 67.5% JEUVEAU (botulinum toxin type A); Absolute difference 66.3%, 95% CI (59.0, 72.4)
- EV-002: 1.3% Placebo, 70.4% JEUVEAU (botulinum toxin type A); Absolute difference 69.1%, 95% CI (61.5, 75.1)

The primary efficacy endpoint in the EU pivotal EVB-003 study was defined as the proportion of subjects classified as responders on Day 30, where a responder was a subject with a GLS score of 0 or 1, by Investigator assessment at maximum frown.

From a Clinical perspective, the BLA for JEUVEAU (botulinum toxin type A) is approvable for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult

patients at a dose of 0.1 mL (4 Units) by intramuscular injector into each of five sites, for a total dose of 20 Units. However, the Office of Pharmaceutical Quality (OPQ) recommends a Complete Response (CR) due to the lack of information required to ensure product quality.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

JEUVEAU (botulinum toxin type A) is a botulinum toxin type A manufactured by Daewoong Pharmaceutical Co., Ltd. of Seoul, South Korea that has the same structural characteristics and physicochemical and biological properties as botulinum toxin type A. When injected intramuscularly at therapeutic doses, botulinum toxin produces chemical denervation of the muscle resulting in localized reduction of muscle activity. The indication sought for this product is for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults. The efficacy of JEUVEAU was demonstrated in two pivotal, double-blind, randomized clinical trials (EV-001 and EV-002), a 330-subject Phase 3 and a 324-subject Phase 3 clinical trial completed in the US. The Phase 3 clinical trials used a composite endpoint in which a responder was a subject with a ≥ 2-point improvement on the GLS from Day 0 to Day 30 at maximum frown, only if independently agreed by both Investigator and subject assessment. The absolute difference of responders in the ITT Population for the composite primary endpoint (a two-point composite) in each of the US controlled single dose trials were 66.3% (95%CI 59.0, 72.4) for EV-001 and 69.1% (95%CI 61.5, 75.1) for EV-002. In addition, an EU study was conducted and submitted (EV-003) as supporting safety and efficacy for JEUVEAU.

The adverse event characteristics for botulinum toxin type A are well understood. The safety considerations are recommended by the Agency's draft guidance documents entitled "*Guidance for Industry. Upper Facial Lines: Developing Botulinum Toxin Drug Products*". The adverse events in the clinical trials were collected, including adverse events of special interest, treatment related adverse events, and possible hypersensitivity reactions. The safety population (any exposed to JEUVEAU) totaled 2116 subjects who participated in the US/EU clinical development program (EV-001, EV-002, EV-003, EV-004, and EV-006). In all, 1659 received treatment with JEUVEAU, 246 received treatment with Botox® (only in EV-003), and 211 received treatment with Placebo. In addition, 192/2116 (9.1%) subjects who were ≥ 65 years of age, including 154/1659 (9.3%) JEUVEAU subjects, 19/246 (7.7%) Botox® subjects, and 19/211 (9.0%) Placebo subjects. Of the 1659 subjects treated with JEUVEAU, 816 received a single treatment of 20 U (737 were in the 3-controlled single-dose studies), 150 received a total of 2 treatments (i.e., 40 U), 325 received a total of 3 treatments (i.e., 60 U) and 368 received a total of 4 treatments (i.e., 80 U). All 737 subjects randomized to JEUVEAU in the 3-controlled single dose EV-001, EV-002 and EVB-003 studies received 20 U. The 922 subjects in the open-label multiple doses EV-004 and EV-006 studies received a mean total dose of 61.3 ± 18.98 U of JEUVEAU; the median dose was 60 U – i.e., 3 treatments.

Headache was the most common adverse event and the only adverse event that occurred in ≥ 5% of JEUVEAU subjects. Headache was also the most common adverse event assessed as related to study drug. The only other adverse events assessed as drug related that were reported in ≥ 1% of subjects were two eye disorders: eyelid ptosis reported by 1.0% (17/1659) of All JEUVEAU subjects and eyelid sensory disorder reported by 1.6% (4/246) of BOTOX® subjects. A single subject died during the conduct of the five studies in the JEUVEAU US/EU clinical development program. A serious adverse event reported as a drug overdose resulted in death. Altogether, 3 serious adverse events resulted in study discontinuation. One Botox® subject (1/246, 0.4%) discontinued the study due to cardiac valve fibroelastoma and the two JEUVEAU

subjects (2/1659, 0.1%) who discontinued the study due to a serious adverse event included one due to a transient ischemic attack (also considered to be an adverse event of special interest) and the other due to the previously noted unrelated drug overdose that resulted in the subject's death. Adverse events of special interest were reported in 2.8% (47/1659) of All JEUVEAU subjects and 1.6% (4/246) of Botox® subjects, compared with 0.5% (1/211) of pooled Placebo subjects. Eye disorders were the only system organ class with ≥ 1% of subjects with an adverse event of special interest: 1.9% (32/1659) of All JEUVEAU subjects, 1.6% (4/246) of Botox® subjects, and no Placebo subjects. Eyelid ptosis was the only preferred term with ≥ 1% of subjects with an adverse event of special interest: 1.4% (24/1659) of All JEUVEAU subjects and no Control subjects. None of the 25 events of eyelid ptosis reported in JEUVEAU subjects were severe; 3 were moderate and the rest were mild. Eyelid ptosis is a complication that is known to occur because of treatment of glabellar lines with botulinum toxin. A total of 34 adverse events identified as possible hypersensitivity reactions were reported by 1.8% (30/1659) of subjects in the JEUVEAU pooled All group. A comparable 2.0% (5/246) of Botox® subjects reported 6 events and 1.4% (3/211) of Placebo subjects reported 3 events. None of the adverse events identified as possible hypersensitivity reactions were serious and none led to study discontinuation.

The majority of subjects were less than 65 years of age; 9.0% of all Placebo and 9.5% of all JEUVEAU subjects were ≥65 years. Compared with those less than 65, the absolute difference in the percentages of responders between all JEUVEAU and all Placebo subjects was 13.7% less for subjects 65 years of age and older (52.9% vs. 66.6%).

In summary, the relatively tolerable safety profile of JEUVEAU for the treatment of glabellar lines is supported by the safety data in the two US clinical trials, the EU clinical study, and the long-term open-label studies. The clinical studies conducted support the conclusion that the clinical benefits of this product outweigh the identified risks of treatment of glabellar lines in adults. However, product quality and microbiology deficiencies preclude marketing approval at this time. A Complete Response letter will be issued describing these deficiencies in detail.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Glabellar lines, or frown lines, occur naturally with facial animation because of the impact on the skin from underlying facial musculature, predominantly the procerus and the corrugator supercilii muscles. Temporary denervation of these muscles results in localized reduction of muscle activity and therefore reduction of the glabellar lines.	Reduction of glabellar lines by botulinum toxin injections, for aesthetic purposes, has become a common treatment option since 2002 when the first botulinum toxin was approved for this indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are several potential treatments for glabellar lines. Surgical release of the muscles is possible; however, it is invasive, can cause scaring and is non-reversible. Nonsurgical treatments are less invasive, but do not address the underlying musculature responsible for the facial lines. Collagen, hyaluronic acid and fat implants can temporarily fill the line or plump the glabellar area; however, this is a dangerous area to inject any type of filler or bulk agent since the underlying vasculature is connected to the retinal blood supply, and embolic damage to the retina and optic nerve resulting in blindness has been reported after fat injections.	Botulinum toxin injections produce chemical denervation of the muscles resulting in localized reduction of muscle activity that in temporary. This allows the physician to tailor the use of botulinum toxin to the clinical presentation and desired outcomes of the patient.
Benefit	• The key benefit of JEUVEAU 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 product is a temporary effect and can be discontinued if adverse reactions occur. Other treatments, such as surgical intervention, are more invasive.
Risk	• Most of the adverse events observed in the clinical studies were not assessed by either the applicant or the review team to be drug related and most were either minor or moderate in severity. There were no serious adverse events related to the drug and drop outs due to drug related adverse events were very low. There were only two drug related adverse events with a frequency of 1% or greater, headache and eyelid ptosis. Labeling will incorporate all relevant warnings and precautions established from the historical use of botulinum toxin. • Numerous product quality and microbiology deficiencies have been identified that preclude marketing approval at this time.	The Agency has established that distant spread of toxin is a risk that requires a Box Warning, although no events were observed in this development program. Section 5 Warnings and Precautions will contain all relevant safety issues.
Risk Management	• Product labeling is sufficient to manage the identified risks, if approved.	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 pertaining and submitted with this application are outlined in Table 2.

Table 1: Patient Experience Data Relevant to this Application

x	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	Studies EV-001, EV-002
		□	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	Studies Ev-001, EV-002
		□	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		
	x	Observational survey studies designed to capture patient experience data		
	x	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, also known as frown lines, occur naturally with facial animation because of the impact on the skin from underlying facial musculature, predominantly the procerus and the corrugator supercilii muscles.[1] There are a few potential treatments for glabellar lines. Surgical release of the muscles is possible; however, it is invasive, can cause scaring and is non-reversible. Nonsurgical treatments are less invasive, but do not address the underlying musculature responsible for the facial lines. Since 2002 when first approved by the FDA for this use, botulinum toxin type A has become a common aesthetic treatment option for glabellar lines resulting from underlying hyper-functional facial musculature.

2.2. Analysis of Current Treatment Options

The FDA originally approved botulinum toxin type A, marketed under the trade name Botox®, in December 1989 for the treatment of blepharospasm associated with dystonia and for the treatment of strabismus. In April 2002, the FDA approved a supplement to the BLA for the indication of the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients < 65 years of age. Under this approval, the product was marketed and labeled as Botox® Cosmetic.

Table 2: FDA-Approved Treatment for Glabellar Lines

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Dysport AbobotulinumtoxinA	Moderate to severe glabellar lines	2009	50 Units IM injection in five 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 five equal aliquots of 4 Units	GL1 (60%) GL2 (48%)	Spread of toxin, dysphagia and breathing difficulties
Botox Cosmetic OnabotulinumtoxinA	Moderate to severe glabellar lines	2002	20 Units IM injection in five equal aliquots of 4 Units	Study 1 (61%) Study 2 (46%)	Spread of toxin, dysphagia and breathing difficulties

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

[1] Pierard GE, Lapiere CM. The microanatomical bases of facial frown lines. *Arch Dermatol*. 1989;125:1090-2.

Following the original Botox® approval, the FDA approved one type B botulinum toxin (BT-B) and two other BT-A products. These differ in potency from each other and from the Botox® products, and are not interchangeable and unit strength is not consistent. To reinforce the differences between the products, the FDA and the United States Adopted Names Council (USAN) revised the established names for the botulinum toxins in 2009. The established name for the Botox® products was changed to onabotulinumtoxinA.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This drug product is not marketed in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

Evolus Inc. proposed the initial development program for JEUVEAU (DWP-450), a botulinum toxin type A for the treatment of moderate-to-severe glabellar lines, during a Pre-IND meeting on 12-MAR-2014 under IND 121493. During the teleconference, the Agency provided extensive responses to the sponsor's questions regarding the CMC, non-clinical, and clinical development program. The sponsor planned to conduct two studies (EV-001 and EV-002) in the US and one European Study (EV-003). In September of 2014, the sponsor received a "Study May Proceed" letter following the review of their Phase 2, open-label, multiple-dose, safety study, EV-004. This study was submitted to open the IND and was reviewed as a 30-Day safety IND. The sponsor subsequently followed their Phase 2 study with a Special Protocol Assessment (SPA) request for review of two identical Phase 3 protocols EV-001 and V-002 in moderate-to-severe glabellar lines. This SPA was withdrawn due to a lack of agreement with the population proposed for the Phase 3 trials. The SPA was resubmitted in November of 2014 and reviewed. An Agency letter for SPA agreement was sent in December of 2014. The sponsor requested a Pre-BLA meeting which was held October 12, 2016. Evolus Inc. was provided with extensive responses to their BLA submission questions.

The Korean MFDS approved DWP-450 for marketing on November 29, 2013. In October 2013, Daewoong Pharmaceuticals reached a licensing agreement with the US-based company Evolus Inc. to supply and distribute DWP-450 in the US and EU following product registration in those regions.

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

4.1. Office of Scientific Investigations (OSI)

Two clinical study sites were referred to OSI for site inspections. Site 107 from study EV-001 and site 204 in study EV-002 were selected due to high enrollment, high site efficacy effect, and low reported AEs. Neither site had been the subject of a recent inspection, and both principal investigators are involved in several different IND's.

The clinical sites of Drs. Jones and Lorenc were inspected in support of this BLA. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The preliminary classification of the inspection of Dr. Jones' site was No Action Indicated (NAI). The final classification of the inspection of Dr. Lorenc's site was NAI.

4.2. Product Quality

4.2.1. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of STN 761085 for JEUVEAU manufactured by Daewoong Pharmaceutical Co., Ltd. for Evolus, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of JEUVEAU is well-controlled and will lead to a product that is safe, pure and potent for the duration of the shelf-life. From a CMC standpoint, OPQ recommends a Complete Response letter be issued to Evolus, Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

From an immunogenicity assay perspective, this BLA is recommended for approval. However, we note that the applicant did a suboptimal job in some aspects of assay validation. Specifically, they used fewer than the recommended number of samples for establishing the cut point, and they did not robustly assess assay precision. However, we do not recommend repeating the validation exercise because the assay showed adequate sensitivity, 60 ng/ml, the in-study false positive rate ranged from 4.6% - 11.3%, which is consistent with the FDA recommendation of at least 5%, and the low positive control was 200 ng/ml, which is within the FDA recommended sensitivity of ADA assays.

4.2.2. Summary of Complete Response Issues

The following general deficiencies were identified:

1. Insufficient method and [redacted] (b) (4) controls to ensure *Clostridium botulinum* culture purity [redacted] (b) (4).

2. Insufficient data to demonstrate that DWP-450 drug substance (DS) is free of *Clostridium botulinum* spores and vegetative cells.

3. Insufficient data to demonstrate adequate microbial control of the DWP-450 DS manufacturing process, [redacted] (b) (4).

4. Inadequate drug substance bioburden release test method to support the current bioburden specification.

5. Various validation studies to support microbial control during drug product (DP) manufacture and storage were conducted with vials that are not representative of the vials intended for DWP-450 DP commercial use.

6. No data to support the maximum sterile hold [redacted] (b) (4) for DWP-450 DP [redacted] (b) (4) [redacted] (b) (4).

7. Insufficient data to demonstrate that the DP container closure integrity and endotoxin tests are suitable for intended use.

8. No routine bioburden monitoring [redacted] (b) (4) to verify continued microbial control of the drug product manufacturing process.

9. The DS reference material program is deficient.

10. Insufficient DP post-approval annual stability protocol.

11. Unsolicited information submitted inappropriately to the BLA.

4.2.3. Complete Response Letter Language

General

1. We received unsolicited information in various amendments submitted during the BLA review cycle. We have not fully determined the extent of the unsolicited changes made to the BLA at this time. Examples of these changes include 1) process validation data from three new drug product (DP) lots manufactured with an

updated commercial DP manufacturing process in an amendment received on December 15, 2017, and 2) changes to the drug product post approval stability protocol to eliminate testing time points in an amendment received on December 1, 2017. To facilitate assessment of the impact of these changes made to the BLA on the approvability of the BLA, the applicant will need to provide a list of all the unsolicited information and changes added to the BLA after the initial BLA receipt on May 15, 2017.

Microbiology: Drug Substance

2. The *Clostridium botulinum* culture purity (b) (4) (b) (4) (b) (4) The applicant will need to provide the (b) (4) bacterial purity data from three batches, the (b) (4) limits and a description of the new test method.

3. The applicant did not provide data to demonstrate that DWP-450 drug substance (DS) is free of *Clostridium botulinum* spores. Spore monitoring data (b) (4) (b) (4) (b) (4) will need to be provided. (b) (4) (b) (4)

4. The applicant provided insufficient data to demonstrate that DWP-450 DS is free of *Clostridium botulinum* vegetative cells. Monitoring data of *Clostridium botulinum* (b) (4) (b) (4) will be needed. (b) (4) (b) (4)

5. The applicant provided no in-process bioburden and endotoxin data to demonstrate adequate microbial control of the DWP-450 DS (b) (4). Bioburden data (b) (4) (b) (4), and bioburden and endotoxin data (b) (4) (b) (4) will need to be provided. In addition, the qualification data for the bioburden and endotoxin test methods (b) (4)

(b) (4) will be needed. Furthermore, the applicant will need to establish and provide in-process limits for these bioburden and endotoxin samples.

6. The applicant provided no bioburden and endotoxin data (b) (4) (b) (4) to demonstrate adequate microbial control (b) (4). Microbiology validation data at commercial scale to demonstrate effective microbial control (b) (4) will be needed.

7. The applicant provided no microbiology validation data for the maximum hold times of the DWP450 DS (b) (4) to ensure adequate microbial control (b) (4) (b) (4). Microbiology validation data for the maximum hold times (b) (4) (b) (4) will be needed.

8. The applicant did not establish endotoxin limits for the DWP450 DS (b) (4) (b) (4). Endotoxin limits for the DWP450 DS (b) (4) will need to be established and provided.

9. The current test volume for DS total aerobic microbial count (TAMC) is low and thus, the bioburden release test may not have sufficient sensitivity. (b) (4) (b) (4) (b) (4). Bioburden qualification data of the DS (b) (4) and DS bioburden release data (b) (4) (b) (4) will be needed. The BLA will need to be updated with a description of the test method and the new DS bioburden specification.

Microbiology: Drug Product

10. The applicant performed validation (b) (4) using (b) (4) (b) (4) DWP-450 drug product (DP) vials. No information was provided to assess (b) (4) (b) (4). The applicant will need to demonstrate that (b) (4) DWP-450 commercial DP vials (b) (4) effectively reduces endotoxin by a minimum of 3 logs and provide summary data and the validation report in the BLA resubmission.

11. The applicant did not perform validation of the worst-case (b) (4) parameters on the DWP-450 DP vials to ensure that commercial vials are sealed appropriately and that container closure is integral. The vials used in the commercial manufacture of DWP-450 DP were not used to validate the (b) (4) process. In addition, worst-case (b) (4) parameters were not used during validation. The applicant will need to submit container closure integrity data to support the proposed parameters in the BLA resubmission.

12. The applicant performed the (b) (4) validation study with (b) (4) (b) (4) DWP-450 DP vials. No information was

provided to assess [redacted] (b) (4) [redacted] (b) (4). The applicant will need to demonstrate that [redacted] (b) (4) the DWP-450 DP vials is effective [redacted] (b) (4) and provide summary data and the validation report in the BLA resubmission.

13. The maximum sterile hold of [redacted] (b) (4) for DWP-450 DP is not supported by [redacted] (b) (4) data. The applicant will need to provide data [redacted] (b) (4) to support the sterile hold of [redacted] (b) (4) for DWP-450 DP [redacted] (b) (4) [redacted] (b) (4) and include a summary of the [redacted] (b) (4) environmental monitoring data in the BLA resubmission.

14. The applicant did not demonstrate that the container closure integrity test detects breaches that may allow for bacterial ingress, and did not include positive controls in the method validation. The applicant will need to submit information to demonstrate that the container closure integrity testing can detect breaches ≤ [redacted] (b) (4) µm and include positive controls during routine testing.

15. The applicant did not perform low endotoxin recovery testing of DWP-450 DP to assess whether the bacterial endotoxin test method can consistently detect endotoxin in the drug product. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The applicant will need to evaluate the effect of hold time on endotoxin detection by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and test for recoverable endotoxin over time [redacted] (b) (4) [redacted] (b) (4).

16. The applicant did not routinely monitor bioburden [redacted] (b) (4) to verify continued microbial control of the drug product [redacted] (b) (4). The applicant will need to implement routine bioburden monitoring [redacted] (b) (4) [redacted] (b) (4), provide a description of the bioburden test method and provide method qualification, summary data, and the qualification report.

Product Quality: Drug Substance and Drug Product

17. Reference materials play a critical role in confirming the suitability of analytical tests and the quality of the product during release and stability testing. The information provided in the BLA suggests that the DS reference material management program does not generate sufficient quantities of a given reference material lot to support all the required testing. The applicant will need to revise the reference material qualification procedures to ensure that sufficient quantities of reference material are generated to support all the necessary testing, including qualification of future reference materials. In addition, the DS reference material qualification and requalification protocol will need to be revised to include adequate stability monitoring of the reference materials.

18. In response to a November 13, 2017 information request to update the DP stability testing protocols to include DP reconstitution time, it appears that additional changes were made to the post-approval stability protocol originally submitted in the BLA to remove the testing points at 3, 6, 9, and 18 months. Sufficient stability data to support a reduced stability testing program were not provided. Therefore, the updated annual post-approval stability protocol in section *3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment* (Table 3.2.P.8.2-2) submitted on 12/01/2017 is not adequate to ensure that potential changes to commercial DP during storage are detected in a timely manner. The applicant will need to revise the annual stability protocol to include testing at 3, 6, 9, and 18 months as recommended by ICH Q5C guidelines.

19. In response to the March 2, 2018 information request to describe Evolus' role in DWP-450 lot release, the applicant stated that some of Evolus' quality responsibilities will be delegated via quality agreements and SOPs to the "soon to be established distributor". The applicant's response indicated that the distributor may be responsible for: visual inspection for shipping or water damage; verification of release certifications (C of A) from Daewoong Pharmaceuticals Co., Ltd.; verification of shipment quantity and lot numbers; and verification that appropriate temperature was maintained during shipment. The applicant also stated that they will rely on the distributor's standard operating procedures and Quality Assurance unit for these activities. If the distributor is responsible for performing release operations for Evolus then they appear to fit the definition of a manufacturer rather than a distributor per 21 CFR 600.3 (t), (u), and (aa) and should be listed as a manufacturer in the license application.

Additional comments/recommendations that are not approvability issues will be included in the Complete Response letter.

4.2.4. Benefit/Risk Considerations

JEUVEAU is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines in adult patients. It blocks neuromuscular transmission by binding to receptor sites on motor nerve terminals and inhibiting acetylcholine release. The therapeutic benefits include improved physical appearance. Potential life-threatening side effects include but are not limited to problems swallowing and breathing due to spread of the toxin away from the injection site and weakening of associated muscles.

The data submitted in this application are not sufficient to demonstrate that the manufacture of JEUVEAU is well-controlled and will lead to a product that is safe, pure and potent. Specifically, the applicant has not demonstrated that they have adequate microbial control over the DS and DP during manufacture and release. With respect to the DS, there are insufficient data to demonstrate adequate control over the purity of *Clostridium botulinum* culture (b) (4) (b) (4) in the DS, and overall microbial control (b) (4)

[redacted] (b) (4). For the DP, various validation studies to support microbial control [redacted] (b) (4) are inadequate because they were conducted with vials that are not the vials intended for DWP-450 DP commercial use. In addition, bioburden is not routinely monitored [redacted] (b) (4) to verify continued microbial control of the DP [redacted] (b) (4), and there are no data to support the proposed maximum sterile hold of the DP. Furthermore, the data provided are not sufficient to demonstrate that the container closure integrity and endotoxin tests are suitable for intended use. Other deficiencies identified in the submission include an insufficient DS reference material program, an inadequate post-approval DP annual stability program, and incomplete information on all the manufacturers that will be involved in the release of the product.

JEUVEAU does not address an unmet medical need because there are approved products on the US market for a similar indication. Based on the manufacturing deficiencies listed above and the presence of other products approved for the same indication, the risk of administering JEUVEAU to patients currently outweighs the benefits of the product.

4.3. Clinical Microbiology

Not applicable as no clinical microbiology claims were asserted or assessed.

4.4. Devices and Companion Diagnostic Issues

Not applicable to this application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

JEUVEAU (botulinum toxin type A) is a toxin known to cause muscle relaxation by blocking the transmission of acetylcholine. In a compound muscle action potential assay conducted in rats, JEUVEAU induced a significant decrease in action potential amplitude and its potency was similar to BOTOX®.

In a 6-month repeat-dose toxicity study, intramuscular (IM) doses of 0 (vehicle), 4, 8, and 16 unit/kg JEUVEAU were administered to SD rats once per month for 6 months, followed by 2-month and 3-month recovery periods. Impaired limb function was observed in all dose groups. At the end of treatment, a decrease in body weight was noted mainly in mid dose and high dose males and in high dose females. At terminal necropsy, minimal to severe myofiber atrophy in the left biceps femoris (injection site) was observed in all animals in all dose groups. The severity of myofiber atrophy increased with dose. Minimal to moderate myofiber atrophy in the right biceps femoris was also observed in males at all doses and in mid dose and high dose females. No obvious reversibility of myofiber atrophy was noted in the left biceps femoris after the recovery periods; while partial recovery was noted in the right biceps femoris. Considering that the local effects of JEUVEAU on skeletal muscles are intended pharmacological effects and reversibility was noted in the right biceps femoris after recovery periods, the NOAEL was identified as the low dose, 4 unit/kg, based on body weight decrease and more severe muscle atrophy noted at mid dose and high dose. The NOAEL is 12 times the maximum recommended human dose (MRHD), based on unit/kg dose comparison.

In an embryofetal development study, IM doses of 0 (vehicle), 0.5, 1, and 4 unit/kg JEUVEAU were administered to pregnant SD rats once daily from gestation Day 6 to Day 16. No mortality was observed in maternal animals. Paralytic gait was evident in most animals at all doses, which was an expected pharmacological effect. No significant adverse effects on body weight or food consumption were noted. No significant embryofetal toxicity was noted in this study. The NOAEL for both maternal toxicity and embryofetal toxicity was identified as the high dose, 4 unit/kg (12 times the MRHD).

In 4-week repeat-dose toxicity studies in rats, JEUVEAU administered intramuscularly at 32 unit/kg/week induced degeneration/atrophy of seminiferous tubules in testis. This finding has been known as an adverse effect of botulinum toxin in male rats. However, this effect has not been observed in other species and it is likely a species-specific effect of botulinum toxin.

During drug development, [redacted] (b) (4) the manufacturing process was changed and subsequently a new facility was built and used for the manufacture of JEUVEAU. Single dose and repeat-dose toxicity studies were conducted to compare

the toxicity of JEUVEAU produced via the old or new (b) (4) method and manufactured at the original or new facility. The toxicity of JEUVEAU was generally comparable whether produced via different (b) (4) methods or manufactured at different facilities. In addition, single dose and repeat-dose toxicity studies were conducted to compare the toxicity of JEUVEAU and BOTOX®. Their toxicity profiles were generally comparable.

Genetic toxicology or carcinogenicity studies are not needed for the development of JEUVEAU.

This BLA is approvable from a Pharmacology/Toxicology perspective. There is no recommended nonclinical PMC/PMR for this BLA.

5.2. Referenced NDAs, BLAs, DMFs

For studies that have been reviewed under IND 121493, summary pharmacology/toxicology information is provided in this review. The code name used for JEUVEAU (botulinum toxin type A) is DWP-450.

5.3. Pharmacology

Primary pharmacology

Botulinum toxin type A is a toxin known to cause muscle relaxation by blocking the transmission of acetylcholine and is widely used as a muscle relaxant. The mechanism of action of botulinum toxins is known and has been described as a 3-step process: 1) binding to the presynaptic cholinergic neurons; 2) entry into the nerve terminal; and 3) inhibition of the release of acetylcholine. While the target proteins vary with toxin serotype, botulinum toxin type A specifically cleaves SNAP-25 (synaptosomal-associated protein 25) in the cholinergic nerve terminal, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings.

When injected intramuscularly at therapeutic doses, botulinum toxin type A produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by botulinum toxin type A.

A pharmacology study was conducted using a compound muscle action potential (CMAP) assay in male SD rats to compare the pharmacological effect of DWP-450 and BOTOX® (from Allergan). Both botulinum toxins were injected into the anterior tibialis muscle of hind legs (DWP-450 injected into the left leg and BOTOX injected into the right leg of each animal) of SD rats (6/group) at doses of 2, 4 and 8 units (100 unit/ml, dissolved in saline). A vehicle control group was injected with saline only. Rats were anesthetized for electrophysiology evaluation. CMAP amplitude and latency

measurements were conducted predose, at Day 3 and 1, 2, 3 and 4 weeks postdose. A significant decrease in CMAP amplitude was noted in both DWP-450 and BOTOX groups postdose, compared to the predose values or to the concurrent vehicle control. No significant differences in the decrease of CMAP amplitude were noted among different dose levels. No significant differences in CMAP amplitudes were noted between the DWP-450 and BOTOX dose groups. No significant effects on CMAP latency were noted in this study, either with DWP-450 or BOTOX treatment. The results indicated that both DWP-450 and BOTOX induced muscle paralysis but had no significant effects on the velocity of nerve conduction. The potency of DWP-450 and BOTOX in inducing muscle paralysis was similar, judged by this CMAP assay.

In another CMAP assay, DWP-450 manufactured at two facilities [DWP-450 OF (original facility) and DWP-450 NF (new facility)] and the reference product BOTOX were compared. Test articles were injected into the gastrocnemius muscle of the left hindlimb of SD rats (4/group) at doses of 1, 4 and 8 units (50 µl per injection, dissolved in saline). Each animal received a single injection. CMAP amplitude and latency were measured on Days 3, 7, 14, 21, and 28 postdose. The reference product generated CMAP effects that were consistent with historical control data, demonstrating assay validity. Generally, the CMAP effects (reduction in amplitude) induced by DWP-450 OF and DWP-450 NF were comparable, demonstrating that the potency of the two products was similar. This pharmacology study was conducted to support the change of manufacturing facility.

Secondary Pharmacology

No secondary pharmacology studies were conducted as the pharmacologic properties of botulinum toxin type A are well known.

Safety Pharmacology

No safety pharmacology studies were conducted as DWP-450 is intended as a local treatment.

5.4. ADME/PK

DWP-450 is intended as a local treatment and systemic exposure is unlikely at the proposed doses. In addition, there are no sensitive bio-analytical methods available for evaluating the PK/TK of botulinum toxin type A. The Division has agreed with the sponsor that no PK/TK studies are needed for the development of DWP-450.

5.5. Toxicology

5.5.1. General Toxicology

Study 1 Single intramuscular dose toxicity study of DWP-450 in SD rats (Study# B11192, GLP)

Single IM doses of 0 (vehicle: saline), 5, 50, 200 and 500 unit/kg DWP-450 were administered to SD rats (5/sex/group, injected into the gastrocnemius muscle of left hindlimb). Necropsy was conducted at the end of a 14-day observation period.

Five males and four females were found dead in the 500 unit/kg group during Days 3-7. No mortality was noted in other groups. Paralytic gait and abdominal distension of injection side were major clinical signs evident in all dose groups. In addition, abnormal gait, reddish tears, decrease in food intake, decrease in fecal volume, emaciation, decrease and/or loss in locomotor activity, hypothermia, no stool, soiled perineal region, lacrimation, refusal to feed and/or staining around mouth were noted in the 200 and 500 unit/kg groups. A decrease in body weight was noted in males and females in the 50, 200 and 500 unit/kg groups on Days 3, 7 and/or 14. At necropsy, bilateral small testes were evident in one male in the 200 unit/kg group. Decreased gastrocnemius muscle size was seen in all males and females at doses of 50 unit/kg and above. Histopathological findings included atrophy of gastrocnemius muscle in all males and females at doses of 50 unit/kg and above, and atrophy of seminiferous tubules in the testis in one male in the 200 unit/kg group.

Based on the study results, the LD_{50} of DWP-450 was greater than 200 unit/kg and less than 500 unit/kg in male and female SD rats.

Study 2 An acute and maximum tolerated dose (MTD) intramuscular comparative botulinum toxin study in rats (Study# 2242-001, GLP)

This study was conducted to compare the acute toxicity of DWP-450 and BOTOX, and establish the MTD for these two compounds when administered by IM injection to SD rats (injected into the left biceps femoris muscle). Single IM doses of 0 (vehicle: saline), 5, 50, 200 and 300/100 unit/kg DWP-450 or BOTOX were administered to SD rats (10/sex/group except the high dose groups). For the high dose groups 3 animals/sex were dosed at 300 unit/kg. Due to noted mortality the next 3 animals/sex received a dose of 100 unit/kg.

Animals were examined for mortality, clinical signs, body weight, food consumption, ophthalmology, clinical pathology and histopathology (only the testis, injection site, and gross lesions were examined microscopically). No treatment-related ophthalmology findings were noted. A total of 62 animals were euthanized or found dead during Days 2-4. All animals dosed with 300 unit/kg BOTOX and 300 unit/kg DWP-450, all animals dosed with 200 unit/kg BOTOX and all males and 9/10 females dosed with 200 unit/kg DWP-450, all animals dosed with 100 unit/kg BOTOX, and all females and 2/3 males dosed with 100 unit/kg DWP-450 were euthanized in extremis or died while on study. The cause of euthanasia or death for these animals was decreased mobility and inability to access food and/or water. Impaired limb function was observed in all DWP-450 and BOTOX dose groups; decreased activity was noted at doses ≥ 50 unit/kg DWP-450 or BOTOX; impaired or lost righting reflex was noted at doses ≥ 100 unit/kg DWP-450 or BOTOX; and dehydration was noted at doses ≥ 50 unit/kg DWP-450 or BOTOX. A decrease in mean body weight was noted in all groups administered DWP-

450 or BOTOX compared with the control group. Small testes were noted in one male dosed with 50 unit/kg DWP-450 and one male dosed with 50 unit/kg BOTOX. Microscopically, degeneration/atrophy of seminiferous tubules in the testis was noted at 5 and 50 unit/kg (both DWP-450 and BOTOX).

Based on the study results, the LD50 values of DWP-450 and BOTOX were all between 50 and 100 unit/kg in SD rats. The toxicity profiles of DWP-450 and BOTOX were similar and their potency was comparable in this study.

Study 3 A single dose comparative study of DWP450 (b) (4), DWP450 (V), and BOTOX Cosmetic (Study# 2242-005, GLP)

During the drug development, (b) (4) the manufacturing process was changed (b) (4) to vacuum drying. This study was conducted to serve as a bridging study for the DWP-450 products produced via (b) (4) [DWP-450 (b) (4)] and vacuum drying [DWP-450 (V)].

Single IM doses of 0 (vehicle: saline), 4, 8, and 32 unit/kg DWP-450 (b) (4) DWP-450 (V), or BOTOX were administered to SD rats (6 females/group, injected into the left biceps femoris muscle). No mortality was seen in this study. Impaired limb function was observed in all dose groups. At the end of the study (Day 15) a decrease in body weight gain was noted in the three mid dose groups when compared with controls: DWP-450 (b) (4) -29%, DWP-450 (V) -13% and BOTOX -54%. Body weight loss was noted in all the three high dose groups. By Day 15 the weight loss was ~23 g in the DWP-450 (b) (4) high dose group and ~22 g in the DWP-450 (V) high dose group. In the BOTOX high dose group, weight loss was ~10 g on Day 9, ~8 g on Day 14, and ~1 g on Day 15. A decrease in food consumption was noted mainly in the DWP-450 (b) (4) high dose group (in all postdose days) and DWP-450 (V) high dose group (in 5 postdose days). The decrease appeared to be more severe in the DWP-450 (b) (4) high dose group. In the BOTOX high dose group, a minor decrease in food consumption was noted in two postdose days.

At the end of treatment, a decrease in the size of the left biceps femoris (injection site) was noted in all dose groups. A decrease in the muscle weight of both left and right biceps femoris was noted at all doses, compared with control. The muscle weight decrease was more severe in the left side. The effects on muscle weight were generally comparable among the three test articles. Microscopically, minimal to moderate atrophy of muscle fiber in the left biceps femoris was observed in almost all animals in all dose groups. Minimal to mild myofiber degeneration/necrosis and inflammation were seen intermittently. Minimal to mild atrophy of muscle fiber in the right biceps femoris was also observed in 1/6, 4/6 and 2/6 animals in the high dose groups of DWP-450 (b) (4) DWP-450 (V), and BOTOX, respectively.

The adverse effects on body weight and food consumption appeared to be more severe in the DWP-450 (b) (4) and DWP-450 (V) high dose groups than the BOTOX high dose group. If judged by the muscle atrophy effects noted both macroscopically and

microscopically, the three test articles were comparable. Overall the toxicities of DWP-450 (b) (4) and DWP-450 (V) noted in this study were comparable.

Study 4 A single dose comparative bridging study of DWP450-O and DWP450-N in Sprague Dawley rats with a 14-day observation period (Study# 2242-006, GLP)

During drug development, a new facility was built and used for the manufacture of the DWP-450 product. This study was conducted to serve as a bridging study for the DWP-450 products manufactured at the original facility (DWP450-O) and the new facility (DWP450-N).

Single IM doses of 0 (vehicle: saline), 4, 8, and 32 unit/kg DWP450-O and DWP450-N were administered to SD rats (6 females/group, injected into the left biceps femoris muscle). No mortality was seen in this study. Impaired limb function was observed in all dose groups. The impaired limb function was considered adverse at the high dose of both DWP450-O and DWP450-N as it correlated with body weight effects and decreased food consumption. At the end of the study (Day 15), a significant decrease in body weight was noted at the high dose (DWP450-O: -11.7%; DWP450-N: -18.2%), compared to concurrent control. Mean food consumption was significantly lower than control group values at the high dose (DWP450-O: -57.6%; DWP450-N: -77.1%).

At the end of treatment, a decrease in the size of left biceps femoris (injection site) was noted in all dose groups. Decreases in muscle weight were noted for both left and right biceps femoris at all doses, compared with control. The muscle weight decrease was more severe on the left side. Overall, the magnitude of the decrease was slightly greater with DWP450-N but there were no statistically significant differences in the left biceps femoris muscle weights between the DWP450-N and DWP450-O dose groups.

Microscopically, minimal to mild atrophy of the left biceps femoris muscle was seen in all animals dosed with DWP450-O or DWP450-N. The severity of muscle atrophy was slightly higher in the DWP450-N groups than the DWP450-O groups. Atrophy of the right biceps femoris skeletal muscle was seen in one animal treated with high dose DWP450-O, one animal treated with mid dose DWP450-N, and 6 animals treated with high dose DWP540-N.

Generally, the toxicity profile of DWP450-O and DWP450-N was comparable. However, it appeared that the toxicity of DWP450-N was slightly higher than that of DWP-450-O, under the study conditions.

Study 5 An acute and maximum tolerated dose (MTD) intramuscular comparative botulinum toxin study in Beagle dogs (Study# 2242-002, GLP)

This study was conducted to compare the acute toxicity of DWP-450 and BOTOX, and to establish the MTD for these two compounds when administered by IM injection to

Beagle dogs (10 injection sites for each animal). Single IM doses of 0 (vehicle: saline), 5, 50, 200 and 500 unit/kg DWP-450 or BOTOX were administered to dogs [3/sex/group except the high dose groups (1/sex/group)].

Animals were examined for mortality, clinical signs, body weight, food consumption, ophthalmology, clinical pathology and histopathology (only the testis, injection sites, and gross lesions were examined microscopically). No mortality was noted in this study. No DWP-450 or BOTOX-related effects were observed on body weight, food consumption, ophthalmoscopy observations, hematology, coagulation, clinical chemistry, macroscopic observations or organ weight findings. Vocalization was the only significant clinical observation. Due to increased severity, it was considered adverse at 500 unit/kg (both DWP-450 and BOTOX). Microscopically, minimal to mild inflammation at the injection site was noted in males receiving ≥ 5 unit/kg of both DWP-450 and BOTOX and in females receiving ≥ 5 unit/kg of DWP-450, and ≥ 50 unit/kg of BOTOX. The NOAEL was identified as 200 unit/kg for both DWP-450 and BOTOX in this study. The toxicity of DWP-450 and BOTOX was comparable under the study conditions.

Reviewer's comments:
It has been known that dogs and pigs are comparatively resistant to all types of botulinum toxin. It is expected that the toxicity profile of DWP-450 is quite different in rats and dogs. Due to their insensitivity to the toxicity of botulinum toxin, dogs and pigs are not ideal animal species for toxicology studies of botulinum toxin.

Study 6 Four-week repeated (1 time/week) intramuscular toxicity study with 2-week recovery of DWP-450 in SD rats (Study# B11193, GLP)

IM doses of 0 (vehicle: saline), 4, 12, and 32 unit/kg DWP-450 were administered to SD rats (10/sex/group, injected into the gastrocnemius muscle of left hindlimb) once per week for 4 weeks. No mortality was noted in this study. Paralytic gait of the left hindlimb, left abdominal distention and curling of the left hind toes of the left hindlimb were noted at all dose levels. At the end of treatment, a decrease in body weight was noted at the mid dose (-12.4% in males and -13.7% in females) and high dose (-23.9% in males and -16.8% in females), compared with control. After the recovery period, the body weight decrease was still evident in high dose males (-24%) but not statistically significant in females. A decrease in food consumption was noted in the high dose group (up to -20%), compared with control. Such decrease was not seen in the recovery animals. No treatment-related effects on ophthalmology, hematology, clinical chemistry, or urinalysis were noted. A decrease in muscle weight of both left (injection site) and right gastrocnemius muscle was noted at all doses, compared with control. The muscle weight decrease was more severe on the left side. No recovery was noted in the high dose group after the recovery period.

Microscopically, at the end of treatment, atrophy of muscle fiber and inflammatory cell infiltration were observed in the left gastrocnemius muscle in all animals in all dose groups. Atrophy of muscle fiber in the left thigh muscle was noted in almost all animals in all dose groups. Atrophy of muscle fiber in gastrocnemius muscle and thigh muscle

on the right side was less severe, noted in some mid dose and high dose animals. Mild atrophy of seminiferous tubules in testis was seen in one high dose male; minimal to mild inhibited spermiation was seen in 5/10 high dose males; and minimal to mild increased cell debris in epididymis was observed in 6/10 high dose males. At the end of recovery period, atrophy of muscle fiber in gastrocnemius muscle (left and right) and thigh muscle (left) was still evident in high dose animals. Atrophy of seminiferous tubules, inhibited spermiation in testis and increased cell debris in epididymis were still evident in high dose animals.

The local effects on muscles are expected and intended pharmacological effects of DWP-450 and therefore not considered adverse. Body weight decrease and food consumption decrease were probably secondary effects of muscle paralysis. However, significant body weight decreases at doses ≥ 12 unit/kg/week were considered adverse. The histopathological findings in testes and epididymis noted at the high dose were also considered adverse.

Based on significant body weight decreases noted at the mid dose and high dose, the NOAEL was identified as the low dose, 4 unit/kg/week, under the study conditions.

Reviewer's comments:
Testicular degeneration has been known as an adverse effect of botulinum toxin in rats. However, the effect has not been observed in other species and is likely a species-specific effect of botulinum toxin.

Study 7

Study title: DWP450: a 4-week intramuscular toxicity study in rats with a 2-week recovery period (Study# 2242-003)

Key Study Findings

- Mortality was noted at the high dose. Muscle paralysis and atrophy were noted at all doses and still evident after the recovery period. The local effects on muscles are expected and intended pharmacological effects of DWP-450 and therefore not considered adverse. Significant body weight decreases noted at the mid dose and high dose were considered adverse.
- Degeneration/atrophy of seminiferous tubules noted at the high dose were considered adverse.
- The NOAEL was identified as the low dose, 4 unit/kg/week, under the study conditions. The study results were similar to those of Study B11193.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

<u>Methods</u>

Dose and frequency of dosing:	0 (vehicle), 4, 8 and 32 unit/kg/dose, once per week, 4 doses in total
Route of administration:	IM injection into the left biceps femoris muscle
Formulation/Vehicle:	Saline
Species/Strain:	SD rats
Number/Sex/Group:	15/sex/group
Age:	6 weeks
Satellite groups/ unique design:	Recovery animals: 5/sex/group
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	Two males and four females at HD were euthanized in extremis.
Clinical Signs	Impaired limb function was noted in all dose groups. Additional clinical observations at HD included red or black material around the eyes, hunched posture, splayed limbs, and loss of skin elasticity.
Body Weights	Body weight decreases at the end of treatment (compared with control): LD: -9% in males and -6% in females MD: -14% in males and -14% in females HD: -37% in males and -27% in females Body weight decreases at the end of the recovery period: LD: -6% in males and -13% in females MD: -14% in males and -13% in females HD: -27% in males and -25% in females
Ophthalmoscopy	No significant treatment-related effects
Hematology	No significant treatment-related effects
Clinical Chemistry	No significant adverse treatment-related effects
Urinalysis	No significant treatment-related effects
Gross Pathology	At the end of treatment, reduction in muscle mass was noted for the left biceps femoris (injection site) and right biceps femoris (less severe than the left side) at all doses.
Organ Weights	A dose-related decrease in muscle weight was noted for both left and right biceps femoris at all doses (left: -73% – -82%; right: -27% – -65%). The muscle weight decrease was more severe on the left side. No significant recovery was noted after the recovery period. A decrease in testis weight was noted in HD males (-28%). There was also no obvious recovery after the recovery period.
Histopathology	At the end of treatment:

Adequate battery: Yes	Minimal to severe dose-related muscle atrophy was observed in left biceps femoris in all animals in all dose groups. Similar findings were present in the muscles around the injection site and in the right biceps femoris, but at a lower severity. In HD males, mild to moderate unilateral degeneration/atrophy of seminiferous tubules in the testis was noted. Due to the unilateral nature of this finding and its occurrence in animals with greater severity of muscle atrophy, it was likely an indirect effect related to dysfunctional muscles and/or altered thermoregulation. Mild to severe unilateral oligospermia/germ cell debris was noted in epididymides (which rarely involved the contralateral epididymis). This finding was likely a reflection of degeneration/atrophy of the seminiferous tubules. At the end of the recovery period: No significant recovery was noted for the microscopic findings described above.

LD: low dose; MD: mid dose; HD: high dose.

Study 8

During the drug development, a new facility was built and used for the manufacture of DWP-450 product. The DWP-450 product manufactured at the new facility was tested in this study.

Study title: DWP450-N (test article manufactured in the new facility): a 4-week intramuscular toxicity study in Sprague Dawley rats with a 2-week recovery period (Study# 2242-007)

Key Study Findings

- Muscle paralysis and atrophy, as expected and intended pharmacological effects, were noted at all doses and still evident after the recovery period. Significant body weight decreases noted at the mid dose and high dose were considered adverse.
- Degeneration/atrophy of seminiferous tubules noted at the high dose were considered adverse.
- The NOAEL was identified as the low dose, 4 unit/kg/week, under the study conditions. The study findings were similar to those noted in Study 2242-003. This study demonstrated that the toxicity of the DWP-450 product manufactured at the new facility is generally comparable to that of the DWP-450 product manufactured at the original facility.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

<u>Methods</u>

Dose and frequency of dosing:	0 (vehicle), 4, 8 and 32 unit/kg/dose, once per week, 4 doses in total
Route of administration:	IM injection into the left biceps femoris muscle
Formulation/Vehicle:	Saline
Species/Strain:	SD rats
Number/Sex/Group:	16/sex/group
Age:	8 weeks
Satellite groups/ unique design:	Recovery animals: 6/sex/group
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Impaired limb function was noted in all dose groups. Additional clinical observations at the HD included hunched posture, anogenital swelling, thin body condition, and brown, red, or black material around the eyes.
Body Weights	Body weight decreases at the end of treatment (compared with control): LD: -11% in males and -9% in females MD: -16% in males and -15% in females HD: -42% in males and -32% in females Body weight decreases at the end of the recovery period: LD: -12% in males and -8% in females MD: -12% in males and -13% in females HD: -36% in males and -27% in females
Ophthalmoscopy	No significant treatment-related effects
Hematology	At the terminal necropsy: HD males: -26% in lymphocyte count, -26% in reticulocyte count At the end of recovery period: not seen
Clinical Chemistry	At the terminal necropsy: HD females: +78% in AST, +77% in ALT At the end of recovery period: not seen
Urinalysis	No significant treatment-related effects
Gross Pathology	At the end of treatment, reduction in muscle mass was noted in the left biceps femoris muscle (injection site) and right biceps femoris (less severe than the left side) at all doses.
Organ Weights	A dose-related decrease in muscle weight was noted for both left and right biceps femoris at all doses, compared with control (left: -65% – -78%; right: -12% – -62%). The muscle weight decrease was more severe on the left side. No significant recovery was noted after the recovery period.

Histopathology Adequate battery: Yes	At the end of treatment: Mild to moderate dose-related muscle atrophy was observed in left biceps femoris in all animals in all dose groups. Atrophy was also present in the right biceps femoris muscle in MD and HD dose males and in HD females, but generally at a lower severity. Minimal to moderate seminiferous tubular degeneration/atrophy in the testis was noted in HD males. This finding was unilateral in all affected animals, suggesting that it was secondary to dysfunctional muscles and/or altered thermoregulation. Minimal to moderate, unilateral or bilateral increases in germ cell debris in epididymides was noted in HD males. In the pancreas, 2 HD females had mild secretory depletion. This finding was likely related to decreases in food consumption and body weight. At the end of the recovery period: No significant recovery was noted for the muscle atrophy affecting the injection site. Seminiferous tubular degeneration/atrophy was seen in 3 HD males. The finding in the pancreas was not seen.

LD: low dose; MD: mid dose; HD: high dose.

Study 9 Four-week repeated (1 time/week) intramuscular toxicity study with 2-week recovery of DWP-450 in Beagle dogs (Study# B11195, GLP)

IM doses of 0 (vehicle: saline), 4, 12, and 32 unit/kg DWP-450 were administered to Beagle dogs (3/sex/group, injected into the gastrocnemius muscle of left hindlimb) once per week for 4 weeks. No mortality was noted in this study. There were no treatment-related effects on clinical signs, body weight, food consumption, ophthalmology, ECG, hematology, clinical chemistry, urinalysis, gross pathology, or organ weights. Microscopically, muscle atrophy at the injection sites was noted at the mid dose and high dose. This finding was no longer observed after a 2-week recovery period. The local effects on muscles are expected and intended pharmacological effects of DWP-450 and therefore not considered adverse. The NOAEL was identified as the high dose, 32 unit/kg/week, under the study conditions.

Study 10 Five-week repeated (1 time/week) intramuscular toxicity study with 12-week recovery of DWP-450 in SD rats (Study# B12523, GLP)

This study was conducted to compare the toxicity profile of DWP-450 and BOTOX. IM doses of 0 (vehicle: saline), 30 and 60 unit/kg DWP-450 or BOTOX were administered to SD rats (10/sex/group, injected into the gastrocnemius muscle of left hindlimb) once per week for 5 weeks. One female in the BOTOX high dose group died early. Paralytic gait of the left hindlimb, left abdominal distention, curling of the left hind toes of the left hindlimb and emaciation were noted in all dose groups (both DWP-450 and BOTOX). At the end of treatment, a decrease in body weight was noted at all dose groups when

compared with control: low dose DWP-450 (-21% in males and -29% in females), high dose DWP-450 (-37% in males and -37% in females), low dose BOTOX (-41% in males and -39% in females) and high dose BOTOX (-49% in males and -46% in females). After the recovery period, body weight decreases were still evident in the high dose DWP-450 group (-18% in males and -26% in females) and high dose BOTOX group (-19% in males and -24% in females). During the treatment period, a dose-related decrease in food consumption was noted in all dose groups (up to -20%), compared with control. The decrease appeared to be more severe in BOTOX-treated animals. Such decrease was generally recovered during the recovery period.

No treatment-related effects on ophthalmology, hematology, clinical chemistry, or urinalysis were noted. A decrease in muscle weight for both left (injection site) and right gastrocnemius muscle was noted at all doses. The muscle weight decrease was more severe on the left side. A decrease in testis weight was seen in the high dose DWP-450 group and in both low and high dose BOTOX groups. Such findings were still evident in the high dose groups after the recovery period. Microscopically, at the end of treatment, atrophy of muscle fiber was observed in the left gastrocnemius muscle in all animals in all dose groups. Atrophy of muscle fiber was noted in left and right thigh muscle in almost all animals in all dose groups. Atrophy of seminiferous tubules, inhibited spermiation in testis, oligospermia and increased cell debris and multinucleated giant cells in the epididymis were noted in males at all doses (both DWP-450 and BOTOX). The incidence of testis and epididymis findings were higher in BOTOX groups, compared to DWP-450 groups. At the end of the recovery period, atrophy of muscle fiber in gastrocnemius muscle (left and right) and thigh muscle (left) was still evident in high dose animals (both DWP-450 and BOTOX). Atrophy of seminiferous tubules, oligospermia and increased cell debris and multinucleated giant cells in the epididymis were still evident in high dose animals (both DWP-450 and BOTOX).

The NOAELs for both DWP-450 and BOTOX were less than 30 unit/kg/week. The toxicity profile of DWP-450 and BOTOX was similar. Judged by mortality, body weight and food consumption decreases, and histopathological findings, the toxicity of DWP-450 appeared to less severe than BOTOX.

Study 11 DWP-450: A 26-week intramuscular toxicity study in rats with an 8- and 12-week recovery period (Study# 2242-004, GLP)

IM doses of 0 (vehicle: saline), 4, 8, and 16 unit/kg DWP-450 were administered to SD rats (16/sex/group, injected into the left biceps femoris) once per month for 6 months (7 injections in total), followed by 2-month and 3-month recovery periods. The scheduled necropsies were conducted on Day 170 (end of treatment), Day 226 (end of 2-month recovery), and Day 254 (end of 3-month recovery). No test article-related mortality was seen. Impaired limb function and swelling in the left inguinal region were observed in all dose groups, with the highest incidence noted at the high dose. At the end of treatment, a decrease in mean body weight was noted mainly in mid dose (-9%) and high dose males (-7%) and high dose females (-6%), compared to control. The body weight decrease was generally recovered after the 3-month recovery period. Mean food

consumption tended to decrease at the mid dose and high dose in both sexes and many mid dose and high dose animals received supplemental feed. No treatment-related effects on ophthalmology or hematology were noted. At terminal collections in both sexes at all dose levels there were mild to moderate, generally dose-dependent decreases in creatinine (up to -29%) and urea nitrogen (up to -29%) levels, compared to control. Decreases in creatinine were typical of muscle atrophy. Decreases in urea nitrogen were possibly due to decreased protein metabolism. Changes in creatinine resolved in both sexes at the low dose and partially resolved in both sexes at the mid dose and high dose after the recovery periods. Changes in urea nitrogen resolved after the recovery periods. An increase in urine volume (up to +93%) was seen in mid dose and high dose males and high dose females at terminal collections. Such finding was not seen in recovery collections.

At the terminal necropsy, a decrease in the size of the left biceps femoris (injection site) was noted in all dose groups. A decrease in the size of the right biceps femoris was also noted in mid dose females and high dose males and females. No obvious recovery was noted following the recovery periods. At terminal necropsy a decrease in the muscle weight of both left and right biceps femoris was noted at all doses (left: -77% – -81%; right: -13% – -41%). The muscle weight decrease was much more severe on the left side. No obvious recovery was noted following the recovery periods. At terminal necropsy, minimal to severe dose-related myofiber atrophy in the left biceps femoris was observed in all animals in all dose groups. Minimal to moderate myofiber atrophy in the right biceps femoris was also observed in males at all doses and in mid dose and high dose females. After the recovery periods, no obvious reversibility of myofiber atrophy was noted in the left biceps femoris; while partial recovery was noted in the right biceps femoris. No myofiber atrophy in the right biceps femoris was noted at the low dose after the recovery periods. At the terminal necropsy, axonal/myelin degeneration was present in 2 high dose males at the injection site and the left sciatic nerve.

Considering that the local effects of DWP-450 on skeletal muscles are intended pharmacological effects and reversibility was noted in the right biceps femoris after recovery periods, the NOAEL was identified as the low dose, 4 unit/kg/dose, based on body weight decrease and more severe muscle atrophy noted at the mid dose and high dose.

5.5.2. Genetic Toxicology

Per the ICH S6(R1) guidance document, genetic toxicology studies are not needed for the development of DWP-450 product.

5.5.3. Carcinogenicity

Per the ICH S6(R1) guidance document, carcinogenicity studies are not needed for the development of DWP-450 product.

5.5.4. Reproductive and Developmental Toxicology

Study 12 Study for effects on embryo-fetal development by intramuscular of DWP-450 in Sprague-Dawley rats (Study# B11196, GLP)

IM doses of 0 (vehicle: saline), 0.5, 1, and 4 unit/kg DWP-450 were administered to pregnant SD rats (20-21 females/group, injected into the gastrocnemius muscle) once daily for 11 days from gestation Day 6 to Day 16. Necropsy was conducted on gestation Day 20. No mortality was observed in maternal animals. Paralytic gait was evident in most animals at all doses, which was an expected pharmacologic effect of the test article. No significant adverse effects on body weight or food consumption were noted. Implantation, early and late resorptions and dead fetuses were examined and the number of pregnancy corpus lutea was counted. Implantation index and embryofetal mortality rate were calculated. No adverse treatment-related effects were noted. Sex ratio, fetus weight, placenta weight, external findings, visceral and skeletal examination were examined for all fetuses. No significant treatment-related effects were noted.

No significant embryofetal toxicity was noted in this study. The NOAEL for both maternal toxicity and embryofetal toxicity was identified as the high dose, 4 unit/kg/day, under the study conditions.

Reviewer's comments:
The Division has agreed that additional reproductive and developmental toxicity studies are not needed for the development of DWP-450. The mechanism of action of botulinum toxin type A is well known and the secondary effects are likely to produce adverse effects on pregnancy outcomes. It is conceivable that there may be variations in the embryofetal development study results due to differences in dosing, potency of the toxin product, and sensitivity of the animal species.

5.5.5. Other Toxicology Studies

None.

5.6. Labeling

<u>Recommended revisions to the nonclinical portions of labelling</u>

Revisions to the applicant's proposed wording for the nonclinical and related sections of the labeling are provided below. It is recommended that the <u>underlined</u> wording be inserted into and the ~~strikethrough~~ wording be deleted from the JEUVEAU label proposed by the applicant. The subheadings in Section 8.1 should be in underlined format. Refer to the clinical review for recommended revisions to the clinical portions of labeling in Section 8. A clean copy of the recommended nonclinical portions of labeling is provided in Section 13.4 as an appendix to this review.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

JEUVEAU is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

8.1 Pregnancy

Risk Summary

(b) (4)

There are no available data on JEUVEAU use in pregnant women to inform a drug associated risk of adverse developmental outcomes. An embryofetal developmental study conducted with JEUVEAU in pregnant rats revealed no treatment-related effects to the developing fetus when JEUVEAU was administered intramuscularly during organogenesis at doses up to 12 times the maximum recommended human dose (MRHD) [*see Data*].

Data

Animal Data

(b) (4)

In an embryofetal developmental study, intramuscular doses up to 4 unit/kg JEUVEAU were administered to pregnant rats once daily during organogenesis (gestation days 6 to 16). No maternal or embryofetal toxicities were observed at doses up to 4 unit/kg (12 times the MRHD of 20 units, based on unit/kg comparison).

12.1 Mechanism of Action

(b) (4) JEUVEAU blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses (b) (4) (b) (4) JEUVEAU produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by (b) (4) JEUVEAU.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic, mutagenic or impairment of fertility potential of JEUVEAU.

(b) (4)

(b) (4)

6 Clinical Pharmacology

6.1. Executive Summary

JEUVEAU (or DWP-450; botulinum toxin type A) is produced from fermentation of *Clostridium botulinum*. DWP-450 inhibits acetylcholine release, blocks neuromuscular transmission, and reduces muscle activity following intramuscular injection.

- **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
- **Proposed dose**: 4 Units by intramuscular injection into each of five sites for a total of 20 Units per treatment
- **Proposed dosage form**: 100 Units vacuum-dried powder in a vial for reconstitution

The Applicant evaluated the efficacy and safety of the 20 Units dose of DWP-450 in two pivotal Phase 3 trials (EV-001 and EV-002) conducted in the US and one supporting Phase 3 trial (EVB-003) conducted in EU. The Applicant also conducted two Phase 2 trials (EV-004 and EV-006) for long-term safety evaluation of repeated treatments with the 20 Units dose of DWP-450. The Applicant has not conducted clinical pharmacology studies to characterize the bioavailability or pharmacokinetic characteristics of DWP-450 because of the limit of available analytical technology.

6.1.1. Recommendations

From a Clinical Pharmacology standpoint, the BLA is acceptable to support the approval of JEUVEAU for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling.

6.1.2. Post-Marketing Requirements and Commitments

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1. Mechanism of action and pharmacodynamics

JEUVEAU inhibits acetylcholine release, blocks neuromuscular transmission, and reduces muscle activity following intramuscular injection. JEUVEAU has the same

mechanism of action as other botulinum toxin type A products. The pharmacodynamic effects of JEUVEAU in humans has not been characterized.

6.2.1.2. Pharmacokinetics

The Applicant has not conducted clinical pharmacology studies to characterize the bioavailability or pharmacokinetics of JEUVEAU. It is not possible to detect JEUVEAU in the peripheral blood following intramuscular injection at the recommended doses using currently available bioanalytical methods.

6.2.1.3. Drug interactions

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

6.2.1.4. Immunogenicity

Among 1414 subjects who received DWP-450 treatment in pooled Phase 2/3 clinical trials, 4 subjects were found to have antibodies to DWP-450. Among the 4 antibody positive subjects, 2 subjects had pre-existing antibodies at baseline and 2 subjects had treatment-emergent antibodies. No apparent association between the development of antibodies and reduced efficacy or 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.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General dosing

The Phase 3 efficacy results overall support that the proposed 4 Units by intramuscular injection into each of five sites for a total of 20 Units per treatment is acceptable.

6.2.2.2. Therapeutic individualization

Therapeutic individualization for JEUVEAU is not necessary.

6.2.3. Outstanding Issues

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

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Immunogenicity

A summary of the general clinical pharmacology and immunogenicity of JEUVEAU is provided in **Table 4**.

Table 4: Summary of clinical pharmacology and immunogenicity of JEUVEAU.

Pharmacology	
Mechanism of action	JEUVEAU inhibits acetylcholine release, blocks neuromuscular transmission, and reduces muscle activity following intramuscular injection.
Pharmacodynamics	The pharmacodynamic effect of JEUVEAU in humans has not been characterized.
Pharmacokinetics	
ADME	The absorption, distribution, metabolism, and excretion of JEUVEAU have not been characterized. It is not possible to detect JEUVEAU in the peripheral blood following intramuscular injection at the recommended doses using currently available bioanalytical methods.
Immunogenicity	
Incidence	Among 1414 subjects who received DWP-450 treatment in pooled Phase 2/3 clinical trials, 4 subjects (<1%) were found to have antibodies to DWP-450. Among the 4 antibody positive subjects, 2 subjects had pre-existing antibodies at baseline and 2 subjects had treatment-emergent antibodies.
Impact on PK	The evaluation of the impact of immunogenicity on PK is not feasible because no human PK data is available for DWP-450.
Impact on efficacy and safety	Three out of the four antibody positive subjects experienced clinical response and both the two treatment-emergent antibody positive subjects achieved clinical response. 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

6.3.2.1 **Does the clinical pharmacology information provide supportive evidence of effectiveness?**

The efficacy of JEUVEAU for the treatment of glabellar lines has been established in the two pivotal Phase 3 trials EV-001 and EV-002. See section 7 of this multi-disciplinary review for evaluation of the efficacy results of the Phase 3 trials. No pharmacodynamic or dose-/exposure-response data are available to provide supportive evidence of effectiveness from a clinical pharmacology perspective.

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

Yes, the Phase 3 efficacy results overall support that the proposed 4 Units by intramuscular injection into each of five sites for a total of 20 Units per treatment is appropriate.

All five Phase 2/3 clinical studies in the BLA evaluated the efficacy and safety of the 20 Units dose of DWP-450 per treatment. The Applicant did not conduct dose-ranging clinical studies to facilitate Phase 3 dose selection. The Applicant selected the Phase 3 dose based on nonclinical studies that explored the comparative potency between DWP-450 and the approved product BOTOX Cosmetic. See Section 5 of this multi-discipline review for more information on the potency assessment. Note that the Applicant selected the same Phase 3 dose for DWP-450 as the dose approved for BOTOX Cosmetic for the glabellar lines indication.

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

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

DWP-450 is administered by direct injection into the target muscle and acts locally. The effectiveness of DWP-450 to treat glabellar lines is not dependent on the systemic exposure of DWP-450; therefore, systemic exposure-response (E-R) analysis for efficacy is not needed for further assessment of dosing regimens in subpopulations. While systemic exposure of DWP-450 may be pertinent to its safe use, it is not feasible to evaluate the E-R for safety in DWP-450 clinical trials because PK data are not available and likely not feasible to obtain given the current state of bioanalytical technology.

6.3.2.4 **Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?**

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

6.3.2.5 **What are the immunogenicity incidences and what are the impacts of immunogenicity on PK, efficacy and safety?**

An enzyme-linked immunosorbent assay (ELISA) was developed and validated to screen and confirm the presence of antibodies to DWP-450 in immunogenicity serum samples collected from Phase 2 and Phase 3 trials including EV-001, EV-002, EV-004, and EV-006. The antibody positive samples were further characterized for titers but the neutralizing activity was not assessed. Refer to the Product Quality review for more information of the performance of the immunogenicity assays.

Among 1414 subjects who received DWP-450 treatment, a total of 4 subjects (<1%) were found to have at least one positive antibody sample. Among the 4 antibody positive subjects, 2 subjects had pre-existing antibodies at baseline and 2 subjects had treatment-emergent antibodies (**Table 5**).

The evaluation of the impact of immunogenicity on PK is not feasible because no human PK data are available for DWP-450. Three out of the four antibody positive subjects experienced clinical response based on the Investigator's assessment. Both treatment-emergent antibody positive subjects achieved clinical response (**Table 5**). 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.

Table 5: Summary of immunogenicity results in subjects who had antibodies to DWP-450 in Phase 2 and Phase 3 clinical trials.

Study	Subject #	DWP-450 treatment	immunogenicity assessment	Antibody results		Achieved Clinical Response?
				Antibodies at Baseline?	Antibodies at post-treatment?	
EV-001	(b) (6)	Single dose	Baseline, Day 30, Day 90 and EOS	Yes (Titer of 450)	Yes (Titers of 50 to 150 post treatment)	No (GLS score of 3 at each assessment)
EV-004		Two doses	Baseline, Day 30 for the first dose, Day 0 and 30 for the second dose, and EOS	No	Yes (Titer of 50 at EOS)	Yes (GLS score of 1 at the EOS)
EV-004		Two doses	Baseline, Day 30 for the first dose, Day 0 and 30 for the second dose, and EOS	No	Yes (Titer of 50 at Day 30 after the second dose)	Yes (GLS score of 0 at Day 30 after the second dose)
EV-006		Two doses	Baseline, Day 30 and 90 for the	Yes (Titer of 50)	No	Yes

			first dose, Day 0 and 30 for the second dose, and EOS			(GLS score of 0 at Day 30 after each dose)

Immunogenicity data were collected in subjects who received DWP-450 treatment in Phase 2/3 clinical trials: EV-001 (n=246), EV-002 (n=246), EV-004 (n=352), and EV-006 (n=570). Clinical response is based on Investigator's assessment of the 4-point glabellar line scale (GLS) score at maximum frown. Subjects (b) (6) were reported to have a history of exposure to botulinum toxin prior to the current studies. EOS, end of study visit. (*Source of Data: Reviewer's summary based on* the Applicant's Integrated Summary of Safety and *individual subject's Case Narrative*.)

7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Clinical studies to establish the safety and efficacy of JEUVEAU for the treatment of moderate-to-severe glabellar lines were completed in the US, Canada, and the EU to meet regulatory requirements for the FDA and European regulatory bodies. The development program included 3 randomized, controlled, single dose Phase III studies (EV-001, EV-002, EVB-003) of 150 days' duration; and, 2 open label, multiple dose, long-term Phase II studies (EV-004, EV-006) of 1 year's duration. The studies enrolled over 2100 adult male and female subjects with moderate-to-severe glabellar lines at maximum frown.

In all 5 studies, subjects received intramuscular injections in five target sites – the midline of the procerus, the inferomedial aspect of each corrugator, and the superior middle aspect of each corrugator. Each site was injected with 0.1 mL for a total of 0.5 mL. Subjects assigned (in the open-label studies) or randomized (in the controlled studies) to JEUVEAU received a total of 20 U per treatment, administered as 4 U/0.1 mL; those randomized to placebo received 0.5 mL saline. In EVB-003 (the only study of the 5 with both a placebo and active control arm), subjects randomized to the active control received a total of 20 U of Botox® administered as 4 U/0.1 mL. In the EV-004 and EV-006 multiple dose studies, eligible subjects could receive up to four treatments of 20 U JEUVEAU each.

EV-004 and EV-006 were the two Phase II safety studies conducted in the US. Both were multicenter, open-label, repeat dose, long-term exposure studies of one year's duration. EV-004 was the first study conducted under the US Investigational New Drug application (IND); approximately 350 subjects with moderate to severe glabellar lines at maximum frown, as assessed by the Investigator on the GLS, were to be enrolled.

Table 6: Tabular Listing of All Clinical Studies

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	Description
Controlled Studies to Support Efficacy and Safety							
EV-001	Double-Blind, Placebo and Active Controlled, Efficacy and Safety	0.1 mL injections at 5 sites; or BOTOX or Placebo	Composite endpoint based on IGA and subject assessments of glabellar lines at maximum frown on the GLS	150 Days	330	Moderate-to-severe glabellar lines in healthy adults, 18 years or older	Conducted in the US
EV-002	Double-Blind, Placebo Controlled, Efficacy and Safety	0.1 mL injections at 5 sites; or Placebo	Composite endpoint based on IGA and subject assessments of glabellar lines at maximum frown on the GLS	150 Days	324	Moderate-to-severe glabellar lines in healthy adults, 18 years or older	Conducted in the US
Studies to Support Safety							

EVB-003	Double-Blind, Placebo and Active Controlled, Efficacy and Safety	0.1 mL injections at 5 sites; or BOTOX or Placebo	GLS score of 0 or 1, as assessed by the Investigator at maximum frown on Day 30	150 Days	540	Moderate-to-severe glabellar lines in healthy adults, 18 years or older	EU and Canada Phase III study to demonstrate the efficacy and safety of DWP-450 by comparison to BOTOX® and placebo
Other studies pertinent to the review of safety							
EV-004	Non-Randomized, Open-Label Safety of Multiple Dose	Up to 4 treatments with a total of 20U (0.1 mL per injection)	Investigator's assessment of glabellar lines and subject's assessment of aesthetic improvements	365 Days	352	Moderate-to-severe glabellar lines in healthy adults, 18 years or older	Phase II, Repeat dose, long-term study for safety; conducted in the US
EV-006	Non-Randomized, Open-Label Safety of Multiple Dose	Up to 4 treatments with a total of 20U (0.1 mL per injection)	Investigator's assessment of glabellar lines and subject's assessment of aesthetic improvements	365 Days	540	Moderate-to-severe glabellar lines in healthy adults, 18 years or older	Phase II, Repeat dose, long-term study for safety; conducted in the US

7.1.2. Review Strategy

Data and Analysis Quality

Data Sources

The sources of data used for the evaluation of the efficacy and safety of JEUVEAU for the proposed indication included final study reports submitted by the applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] and literature references.

This application was submitted in eCTD format and entirely electronic. The electronic submission including protocols, statistical analysis plans (SAPs), clinical study reports, SAS transport datasets in legacy, Study Data Tabulation Modal (SDTM), and Analysis Data Model (ADaM) format are located in the following network path:

- Original submission: \\CDSESUB1\evsprod\BLA761085\0001

Data and Analysis Quality

In collaboration with the Office of Computational Science (OCS), the statistical and clinical team evaluated the data fitness. 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 data and analysis provided by the sponsor is acceptable per Agency guidance.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Pivotal Phase 3 Trials (Trials EV-001 and EV-002)

7.2.1.1. Study Design and Endpoints

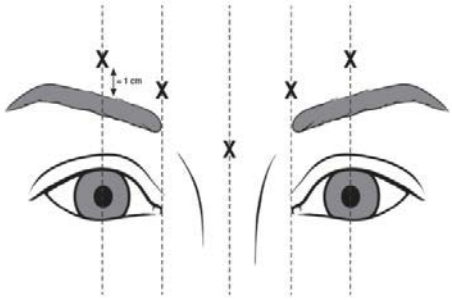
The applicant conducted two identically-designed, randomized, double-blind, multicenter, placebo-controlled, pivotal Phase 3 trials (Trials EV-001 and EV-002). For both trials, the key inclusion criteria that defined the study population were identical and are as follows:

- Male or female 18 years of age or older.
- Have moderate-to-severe glabellar lines at maximum frown as independently assessed by both the investigator and the subject using the photonumeric 4-point Glabellar Line Scale (GLS); refer to Appendix 13.3 for details on the GLS.

The trials excluded subjects who had ptosis (eyelid and/or eyebrow), deep dermal scarring, or an inability to substantially lessen glabellar lines even by physical spreading the glabellar lines apart. In addition, subjects who received previous treatment with botulinum toxin of any serotype in any area within the last 6 months were excluded.

The protocols for the two trials specified randomizing approximately 324 subjects in a 3:1 ratio to either DWP-450 (N=243) or placebo (N=81). At baseline (Day 0), the subjects were administered a single dose (20 units) of lyophilized DWP-450 (clostridium botulinum Type A) or 0.9% saline (placebo). The appearance of the 100 unit vials (DWP-450 or placebo) was identical. Subjects were injected intramuscularly into 5 sites using a 30 G needle and a 1cc syringe. The target sites were the mid-line of the procerus, the inferomedial aspect of each corrugator muscle and the superior middle aspect of each corrugator, at least 1 cm above the bony orbital rim, as shown in Figure 1. Each target site was injected with 0.1 mL (4 units), for a total of 20 units and 0.5 mL.

Figure 1: Injection Points for Trials EV-001 and EV-002



Source: Protocol for Trial EV-001.

Subjects were followed for 150 days, with site visits at screening, baseline (Day 0) and Days 2, 7, 14, 30, 90, 120, and 150 (end-of-study visit). Per the protocols, “ideally, a subject will always have the same investigator performing treatment and assessment during the entire trial”.

For both Trials EV-001 and EV-002, the protocol-specified primary efficacy endpoint was the proportion of subjects with treatment success at Day 30, where treatment

success was defined as at least a 2-point improvement at maximum frown from baseline, as assessed by both the investigator and the subject using the GLS.

The protocols for Trials EV-001 and EV-002 specified the following secondary efficacy endpoints:

1. At least a 2-point improvement at maximum frown from baseline to Day 120, as assessed by both the investigator and the subject using the GLS.
2. At least a 2-point improvement at rest from baseline to Day 30, as assessed by both the investigator and the subject using the GLS, for the subset of subjects with moderate to severe glabellar lines at baseline (as assessed by investigator and subject).
3. At least a 2-point improvement at maximum frown from baseline to Day 150, as assessed by both the investigator and the subject using the GLS.

The protocols also specified several exploratory efficacy endpoints. The results of these exploratory endpoints are not included in this review.

Glabellar Line Scale (GLS):
The assessment of glabellar lines was performed at rest and at maximum frown using a 4-point photonumeric Glabellar Line Scale (GLS); refer to Appendix 13.3 for the GLS. The instruction to the subject to elicit a maximum frown was “frown as much as possible, as if concentrating hard”. Both the investigator and the subject used the same scale for their assessments.

7.2.1.2. Statistical Methodologies

The protocol-specified primary analysis population was the intent-to-treat (ITT) population, defined as all randomized subjects. The statistical analysis plans (SAPs) specified conducting supportive analyses using the per-protocol (PP) population, which was specified to include all randomized subjects who:

- receive the protocol-required one treatment (i.e., five injections),
- receive the correct study medication according to the treatment arm the subject was randomized to,
- have a baseline primary outcome measure, and
- have the primary outcome assessed on Day 30 without any major protocol deviation.

The protocols specified randomizing the subjects using a block randomization scheme prepared by a contract research organization (CRO). Each block contained assignments of subjects to DWP-450 or placebo in a ratio of 3:1 and each vial was assigned a unique randomization number. During enrollment, site personnel assigned and dispensed investigational product in sequential order. No stratification was applied in the blocked randomization.
For the analysis of the primary efficacy endpoint (i.e., the proportion of subjects with at least a 2-point improvement at maximum frown from baseline to Day 30, as assessed

by both the investigator and the subject using the GLS), the protocols specified using the Cochran-Mantel-Haenszel (CMH) test stratified by site. After unblinding the data, the applicant discovered that response rate in the placebo arm in both trials was very small (i.e., only 1 responder in each trial). The applicant noted that the pre-specified analysis method (i.e., CMH test stratified by site) was not suitable for the given data (i.e., response rates of 0% for the placebo arm in 9 out of 10 sites) and amended the SAPs to include a *post hoc* analysis of efficacy endpoints using an exact unconditional test (unlike Fisher's exact test, which is a permutation test conditioning on the rows and columns marginal totals of a contingency table) along with its corresponding exact confidence interval by inversion of the two-sided tests using standardized statistics (Chan, I., and Zhang, Z., 1999; *Test-Based Exact Confidence Intervals for the Difference of Two Binomial Proportions*. Biometrics 55: 1202-1209).

The protocols specified analyzing the three secondary endpoints (all binary endpoints) the same manner as the primary endpoint (i.e., using the stratified CMH test); however, as mentioned above, the SAPs were amended to include a *post hoc* analysis of these efficacy endpoints using an exact unconditional test (Chan and Zhang, 1999). To control the Type I error rate, the protocols specified using a sequential gatekeeping approach. The protocols specified testing the secondary efficacy endpoints in the order listed in Section 7.2.1.1. The first secondary endpoint was to be tested only if the primary endpoint was significant at the 0.05 level, and the subsequent secondary endpoint(s) were to be tested only if the first secondary endpoint was significant at the 0.05 level.

It should be noted that two of the secondary endpoints assess treatment effect at Day 120 and Day 150; however, during the pre-BLA meeting (dated October29, 2016), the Agency commented that "after establishing treatment effect against placebo at the primary time point (Day 30), comparison against placebo would not be meaningful for assessing the duration of treatment effect".

The protocols specified that the primary efficacy analysis "will be performed on all randomized subjects who have a Day 0 and a Day 30 primary endpoint data". In the Special Protocol Assessment (SPA) agreement letter dated December 19, 2014 and the advice letter dated February 12, 2016, the Agency commented that the primary efficacy analysis should be based on the ITT, defined as all randomized subjects regardless of whether they have a post-baseline evaluation and requested the applicant to specify in their protocols a scientifically sound method as the primary imputation approach for the handling of missing data.
To assess the potential impact of missing data at Day 30, the protocols specified the following sensitivity analyses:

- Worst case scenario (WCS): missing data for the DWP-450 arm is imputed as failures and missing data for the placebo arm is imputed as successes.
- Best case scenario (BCS): missing data for the DWP-450 arm is imputed as successes and missing data for the placebo arm is imputed as failures.
- Tipping Point Analysis: this analysis consists of determining if, for subjects with a

missing Day 30 primary outcome, there is a combination of imputing DWP-450 subjects as failures and placebo as successes that results in a non-statistically significant result.

- Count as a success any subject who is missing Day 30 value and was classified as a success on Day 14 and Day 90.
- In the SAPs, the applicant stated that other methods, such as multiple imputation (MI), may be explored if the results of the tipping analysis suggest that missing outcome data are influential.

The protocols did not specify how the missing data for the secondary endpoints would be handled.

7.2.1.3. Patient Disposition, Demographics and Baseline Disease Characteristics

Trial EV-001 enrolled and randomized a total of 330 subjects (246 subjects to DWP-450 and 84 subjects to placebo) from 10 sites in the United States. Trial EV-002 enrolled and randomized a total of 324 subjects (246 subjects to DWP-450 and 78 subjects to placebo) from 10 sites in the United States. Table 7 presents the disposition of subjects for Trials EV-001 and EV-002. The discontinuation rates were low in both trials. In Trial EV-001, the discontinuation rates between the two treatment arms were the same; however, in Trial EV-002, the discontinuation rate was slightly higher in the DWP-450 arm compared to the placebo arm. The most common reason for discontinuation for both trials was 'lost to follow-up'.

Table 7: Subject Disposition for Trials EV-001 and EV-002

	Trial EV-001		Trial EV-002	
	DWP-450 (N=246)	**Placebo (N=84)**	**DWP-450 (N=246)**	**Placebo (N=78)**
Completed	236 (96%)	81 (96%)	237 (96%)	77 (99%)
Discontinued	10 (4%)	3 (4%)	9 (4%)	1 (1%)
Did not meet all selection criteria	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Lost to follow-up	5 (2%)	3 (4%)	8 (3%)	1 (1%)
AE that required intervention	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Investigator or sponsor decision	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Other	1 (<1%)	0 (0%)	0 (0%)	0 (0%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); AE = Adverse Event.

The demographics for both trials are presented in Table 8. The demographics were generally balanced between the treatment arms within each trial and were similar across the trials. Approximately 90% of the subjects were below the age of 65 years old, and approximately 91% of the subjects were females. The majority of subjects were White (approximately 84%) with smaller proportions of Blacks, Asians, or Others.

Table 8: Baseline Demographics for Trials EV-001 and EV-002 (ITT)

		Trial EV-001		Trial EV-002	
		DWP-450 (N=246)	Placebo (N=84)	DWP-450 (N=246)	Placebo (N=78)
Age	Mean (SD)	50.2 (11.8)	50.4 (11.9)	51.5 (11.5)	50.4 (10.1)
	Median	52	51	53	49
	Range	22 – 81	23 – 74	21 – 81	18 – 71
	< 65 years	220 (89%)	75 (89%)	219 (89%)	72 (92%)
	≥ 65 years	26 (11%)	9 (11%)	27 (11%)	6 (8%)
Sex	Female	227 (92%)	79 (94%)	220 (89%)	70 (90%)
	Male	19 (8%)	5 (6%)	26 (11%)	8 (10%)
Race	White	205 (83%)	63 (75%)	215 (87%)	69 (88%)
	Black or African American	18 (7%)	7 (8%)	19 (8%)	6 (8%)
	American Indian/Alaska Native	1 (<1%)	1 (1%)	0 (0%)	0 (0%)
	Native Hawaiian/Other Pacific Islander	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
	Asian	2 (1%)	4 (5%)	5 (2%)	2 (3%)
	Multiple	7 (3%)	2 (2%)	3 (1%)	1 (1%)
	Other	12 (5%)	7 (8%)	4 (2%)	0 (0%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); Intent-to-Treat (ITT) population: all randomized subjects

Table **9** presents the baseline disease characteristics. For enrollment, subjects should have had a GLS score of 2 or 3, as assessed by both the investigator and subject at maximum frown, as this was specified as an inclusion criterion in the protocols. Baseline GLS scores, as assessed by the investigator or subject at maximum frown, were generally balanced across the treatment arms in each trial.

In general, more subjects with 'severe' than 'moderate' glabellar lines were enrolled in the two trials, as assessed by each of the investigator and the subject, at maximum frown. Moreover, the percentage of subjects with 'severe' glabellar lines at maximum frown was slightly higher in Trial EV-002 compared to Trial EV-001.

Comparing the scores among the two raters, the assessments between the investigator and the subject are more consistent in Trial EV-002 compared to Trial EV-001. Section 7.2.1.8 includes additional discussion regarding the agreement between the investigator's and subject's assessments.

Table 9: Baseline Disease Severity for Trials EV-001 and EV-002 (ITT)

		Trial EV-001		Trial EV-002	
		DWP-450 (N=246)	Placebo (N=84)	DWP-450 (N=246)	Placebo (N=78)
At Max Frown					
Investigator GLS	Moderate	78 (32%)	28 (33%)	42 (17%)	12 (15%)
	Severe	168 (68%)	56 (67%)	204 (83%)	66 (85%)
Subject GLS	Moderate	56 (23%)	18 (21%)	46 (19%)	13 (17%)
	Severe	190 (77%)	66 (79%)	200 (81%)	65 (83%)
At Rest					
Investigator GLS	None	68 (28%)	30 (36%)	70 (29%)	20 (26%)
	Mild	91 (37%)	25 (30%)	94 (38%)	35 (45%)
	Moderate	37 (15%)	13 (15%)	17 (7%)	4 (5%)
	Severe	50 (20%)	16 (19%)	65 (26%)	19 (24%)
Subject GLS	None	48 (20%)	13 (15%)	33 (13%)	8 (10%)
	Mild	91 (37%)	36 (43%)	111 (45%)	40 (52%)
	Moderate	20 (8%)	8 (10%)	9 (4%)	1 (1%)
	Severe	87 (35%)	27 (32%)	93 (38%)	29 (37%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); Intent-to-Treat (ITT) population: all randomized subjects.

7.2.1.4. Results for the Primary Efficacy Endpoint

As indicated in Section 7.2.1.2, the applicant conducted efficacy analysis for the primary endpoint using observed data, defined as subjects who have Day 0 and Day 30 primary endpoint data. The reader is reminded of the Agency's comment that the primary efficacy analysis should be based on the ITT population (i.e., all randomized subjects), and that a scientifically sound method should be specified in the protocols as the primary imputation approach for handling the missing data.

Table 10 presents the number of subjects with missing data for the primary efficacy endpoint by treatment arm and trial at Day 30 (primary time point). Overall, the proportion of subjects with missing data was relatively low. The proportion of subjects with missing data at Day 30 was slightly higher in the active arm compared to the placebo arm for Trial EV-001, while the opposite direction holds for the proportion of subjects with missing data at Day 30 across the treatment arms in Trial EV-002.

Table 10: Missing Data for the Primary Efficacy Endpoint at Day 30 (Trials EV-001 and EV-002 - ITT)

	Trial EV-001		Trial EV-002	
	DWP-450 (N=246)	Placebo (N=84)	DWP-450 (N=246)	Placebo (N=78)
Day 30 (Primary Time Point)	6 (2.4%)	1 (1.2%)	6 (2.4%)	3 (3.8%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); Intent-to-Treat (ITT) population: all randomized subjects.

The statistical reviewer advocates carrying out the primary analysis using the ITT population (i.e., all randomized subjects) and the method of Multiple Imputation (MI) for the handling of missing data, which assumes missingness is at random. The MI procedure used the Markov Chain Monte Carlo (MCMC) method stratifying on treatment arm to impute missing GLS scores and generated 5 imputed datasets. The results from the statistical reviewer's analysis are presented in Table 11. DWP-450 was statistically superior to placebo for the primary efficacy endpoint in both trials (p-values < 0.001). Table 12 presents the results from the applicant's analysis (based on the observed data); the results are very similar to those based on the statistical reviewer's analysis.

Table 11: Results for the Primary Efficacy Endpoint at Day 30 (Statistical Reviewer's Analysis - MI)

	Trial EV-001			Trial EV-002		
	DWP-450 N=246	Placebo N=84	P-Value (2)	DWP-450 N=246	Placebo N=78	P-Value (2)
Primary Efficacy Endpoint (1)	67%	1%	<0.001	71%	1%	<0.001

Source: Statistical Reviewer's Analysis.
Note: Missing data was imputed using Multiple Imputation (MI). The rates displayed are the averages over the 5 imputed datasets.
(1) The primary efficacy endpoint was the proportion of subjects with at least a 2-point improvement at maximum frown from baseline to Day 30, as assessed by both the investigator and the subject using the GLS.
(2) P-value was calculated using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by site.

Table 12: Results for the Primary Efficacy Endpoint at Day 30 (Applicant's Analysis based on Observed Data)

	Trial EV-001			Trial EV-002		
	DWP-450 N=246	Placebo N=84	P-Value (3)	DWP-450 N=246	Placebo N=78	P-Value (3)
Observed Data (1)	**N=240** 68%	**N=83** 1%	<0.001	**N=240** 70%	**N=75** 1%	<0.001
PP Population (2)	**N=235** 68%	**N=82** 1%	<0.001	**N=227** 71%	**N=75** 1%	<0.001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis).
Note: The primary efficacy endpoint was the proportion of subjects with at least a 2-point improvement at maximum frown from baseline to Day 30, as assessed by both the investigator and the subject using the GLS.
(1) Observed data, defined as subjects who have Day 0 and Day 30 primary endpoint data.
(2) Per-Protocol (PP) population (see Section7.2.1.2)
(3) P-value was calculated using an exact unconditional test based on the inversion of 2 one-sided tests, as described in Section 7.2.1.2.

The protocols specified the following sensitivity analyses for the handling of missing data: (i) worst case scenario (WCS), (ii) best case scenario (BCS), and (iii) counting as success any subject who is missing Day 30 value and was classified as a success on Day 14 and Day 90. The statistical reviewer conducted an additional sensitivity analysis using the non-responder imputation (NRI) method.
Table 13 presents the results for the primary efficacy endpoints in both trials by the various imputation methods. Note that with such a low occurrence of missing data, the results were similar across the various imputation methods. In the extreme case (i.e., worst case scenario), DWP-450 remained statistically superior to placebo in both trials (p-values < 0.001).

Table 13: Results of the Primary Endpoint at Day 30 with Different Approaches for Handling Missing Data (Trials EV-001 and EV-002 – ITT)

	Trial EV-001			Trial EV-002		
	DWP-450	**Placebo**	**P-Value (4)**	**DWP-450**	**Placebo**	**P-Value (4)**
Applicant's Sensitivity Analysis						
Worst Case Scenario (WCS) (1)	**N=246** 66%	**N=84** 2%	<0.001	**N=246** 69%	**N=78** 1%	<0.001
Best Case Scenario (BCS) (2)	**N=246** 68%	**N=84** 1%	<0.001	**N=246** 71%	**N=78** 1%	<0.001
Day 14/Day 90 Imputation (3)	**N=240** 68%	**N=83** 1%	<0.001	**N=240** 70%	**N=77** 1%	<0.001
Reviewer's Additional Analysis						
Non-responder Imputation	**N=246** 66%	**N=84** 1%	<0.001	**N=246** 69%	**N=78** 1%	<0.001

Source: Statistical Reviewer's Analysis (WCS, BCS and Day 14/Day 90 imputation same as Applicant's Analysis); Intent-to-Treat (ITT) population: all randomized subjects.
Note: The primary efficacy endpoint was the proportion of subjects with at least a 2-point improvement at maximum frown from baseline to Day 30, as assessed by both the investigator and the subject using the GLS.
(1) Missing data for the DWP-450 and placebo was imputed as failures and successes, respectively.
(2) Missing data for the DWP-450 and placebo was imputed as successes and failures, respectively.
(3) Missing data was imputed as successes for the subjects classified as successes on Day 14 and Day 90.
(4) P-value was calculated using an exact unconditional test based on the inversion of 2 one-sided tests, as described in Section 7.2.1.2.

7.2.1.5. Results for the Secondary Efficacy Endpoints

This section discusses the analysis of the secondary efficacy endpoints listed in Section 7.2.1.1. As already discussed in Section 7.2.1.2, two of the secondary endpoints assess treatment effect at Day 120 and Day 150. At this point the statistical reviewer reiterates the Agency's comment that comparison against placebo after the primary time point of Day 30 is not meaningful and therefore, results from the analysis of the secondary efficacy endpoints are not presented in this review.

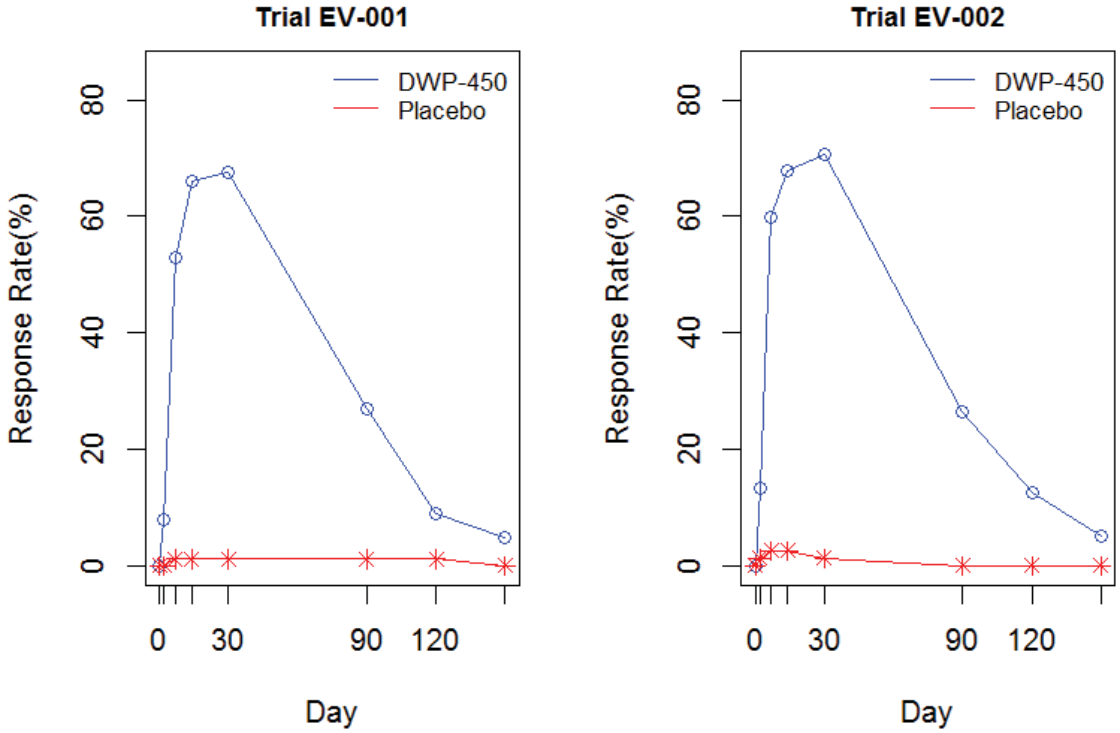
7.2.1.6. Patient Reported Outcomes (PROs)

In addition to the GLS assessed by the subject, the protocols for Trials EV-001 and EV-002 included assessment of the following two patient reported outcomes (PROs): 1) Global Aesthetic Improvement Scale and 2) Subject Satisfaction Scale. As the endpoints based on these PROs were designated as 'exploratory' endpoints and were not included in the multiplicity testing strategy, the efficacy results for these endpoints are not presented in this review.

7.2.1.7. Efficacy Over Time

Figure 2 presents the treatment success rates over time for the two Phase 3 trials, where treatment success was defined as achieving at least a 2-point improvement at maximum frown from baseline, as assessed by both the investigator and the subject using the GLS. From the plots, it appears that the treatment success rates reached their peak between Days 14 and 30, and decreased thereafter, until the end of the trials (Day 150). In addition, the results for the treatment success over time were very similar across the two trials.

Figure 2: Treatment Success Rates over Time for Trials EV-001 and EV-002



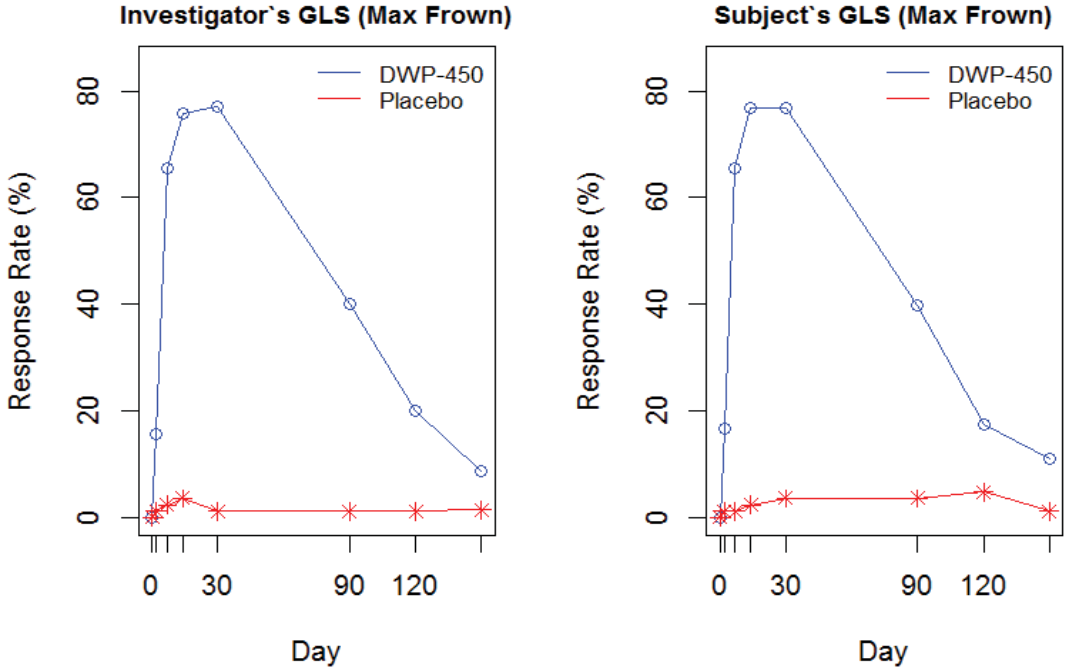
Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population: all randomized subjects; Missing data was imputed using multiple imputation (MI).
Note: Treatment success was defined as the proportion of subjects achieving at least a 2-point improvement at maximum frown from baseline, as assessed by both the investigator and the subject using the GLS.

Figure 3 presents the success rates over time for Trial EV-001 and
Figure 4 presents the success rates over time for Trial EV-002, where success was defined as achieving at least a 2-point improvement at maximum frown from baseline, as assessed by the individual rater (investigator and subject, separately) using the GLS. The results are comparable across the investigator's and subject's assessments in both trials. In addition, comparing the two trials, the plots in .

Figure 3 and APPEARS THIS WAY ON ORIGINAL

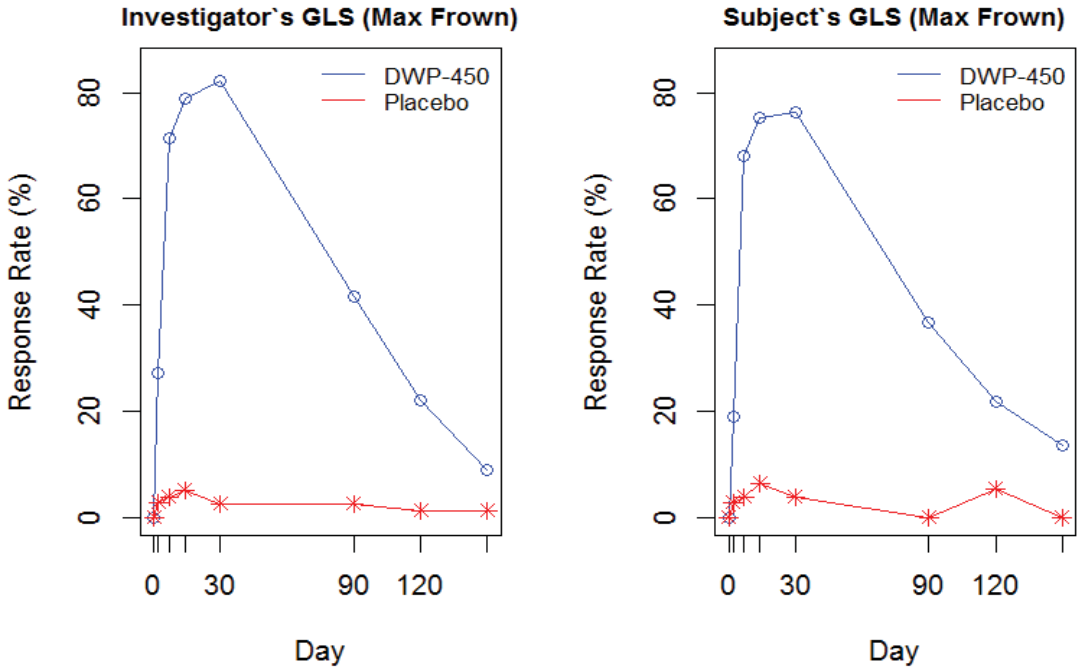
Figure 4 show similar success rates over time across the two trials, based on each of the individual rater's assessments.

Figure 3: Success Rates on the Individual Assessment over Time (Trial EV-001)



Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population: all randomized subjects; Missing data was imputed using multiple imputation (MI).
Note: Success was defined as at least a 2-grade of improvements from baseline on the investigator's assessment at maximum frown using the GLS.

Figure 4: Success Rates on the Individual Assessment over Time (Trial EV-002)



Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population: all randomized subjects; Missing data was imputed using multiple imputation (MI).
Note: Success was defined as at least a 2-grade of improvements from baseline on the investigator's assessment at maximum frown using the GLS.

7.2.1.8. Agreement between Investigator's and Subject's Assessments

As establishing efficacy was based on achieving success on both the investigator's and subject's assessment, it is of interest to examine the agreement between the two raters. For this, the statistical reviewer considered cross-tabulation of the investigator and subject GLS ratings at baseline (see Table 14), as well as at the primary timepoint Day 30 (see Table 15).

At baseline, although there were only two possible categories of glabellar lines severity (2-moderate and 3-severe), many subjects were discordant between the investigator's and the subject's assessments at maximum frown; see off-diagonal elements of Table 14. In addition, it is noted that subjects rated themselves more severe than the investigator in Trial EV-001; however, this is not the case for Trial EV-002.

At Day 30, there were less discordant subjects compared to baseline and most of them were within 1 grade of each other; see off-diagonal elements of Table 15. The percentages of agreement/disagreement between the investigator and the subject ratings are presented in Table 16.

Table 14: Cross-tabulation of Investigator and Subject GLS Ratings at Maximum Frown at Baseline for Trials EV-001 and EV-002

Trial EV-001		Subject GLS			Trial EV-002		Subject GLS		
		2	3	Total			2	3	Total
Investigator GLS	2	57	49	106	Investigator GLS	2	26	28	54
	3	17	207	224		3	33	237	270
	Total	74	256	330		Total	59	265	324

Source: Statistical Reviewer's analysis.
2-moderate; 3-severe.

Table 15: Cross-tabulation of Investigator and Subject GLS Ratings at Maximum Frown at Day 30 for Trials EV-001 and EV-002 (Observed Data)

Trial EV-001		Subject GLS					Trial EV-002		Subject GLS				
		0	1	2	3	Total			0	1	2	3	Total
Investigator GLS	0	91	24	6	1	122	Investigator GLS	0	75	35	2	0	112
	1	21	58	6	1	86		1	18	59	19	4	100
	2	1	8	29	19	57		2	0	9	15	9	33
	3	0	0	7	51	58		3	0	1	11	58	70
	Total	113	90	48	72	323		Total	93	104	47	71	315

Source: Statistical Reviewer's analysis.
0-none; 1-mild; 2-moderate; 3-severe.

Table 16: Percentages of agreement/disagreement between Investigator and Subject GLS Ratings at Maximum Frown at Day 30 for Trials EV-001 and EV-002 (Observed Data)

	Absolute agreement	1-grade disagreement	2-grade disagreement	3-grade disagreement
Trial EV-001	71%	26%	2%	<1%
Trial EV-002	66%	32%	2%	0%

Source: Statistical Reviewer's analysis.

The statistical reviewer also considered the Kappa statistic to measure the degree of agreement between the two raters for the subjects treated with DWP-450 at Day 30. The values of Kappa range from -1 to +1 with -1 indicating perfect disagreement and +1 indicating perfect agreement between raters. Landis and Koch (1977) categorized the values of Kappa to indicate the strength of agreement as shown below.

Kappa	Strength of Agreement
<0	Poor
0 - 0.20	Slight
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Substantial
0.81 - 1.00	Almost perfect

Source: Landis, J. R., Koch, G. G. (1977). *The measurement of observer agreement for categorical data*. Biometrics 33:159-174.

Table 17 presents the agreements in the success rates (i.e. the proportion of subjects with at least a 2-grade improvement in the GLS from baseline to Day 30) based on the investigator and subject ratings at maximum frown in both trials. The diagonal cells are the "agreements". The Kappa statistic was computed based on the magnitude of such agreement as well as on the 'non-agreements' (i.e., off-diagonals) along with the number of subjects. In both studies, the Kappa at maximum eyebrow elevation suggested 'moderate' strength of agreement.

Table 17: Agreement in Success based on the Investigator and Subject assessment at Day 30 at Maximum Frown (DWP-450 Subjects) for Trials EV-001 and EV-002 (ITT -MI)

Trial EV-001		Subject GLS		
		Success	Failure	Total
Investigator GLS	Success	166 (68%)	25 (10%)	191
	Failure	23 (9%)	32 (13%)	55
	Total	189	57	246
κ=0.4481 (moderate strength of agreement)				

Trial EV-002		Subject GLS		
		Success	Failure	Total
Investigator GLS	Success	174 (71%)	30 (12%)	204
	Failure	14 (6%)	28 (11%)	42
	Total	188	58	246
κ=0.4526 (moderate strength of agreement)				

Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population: all randomized subjects; Missing data imputed using multiple imputation (MI).

7.2.1.9. Findings in Special/Subgroup Populations

7.2.1.9.1. Sex, Race, Age and Baseline Disease Severity

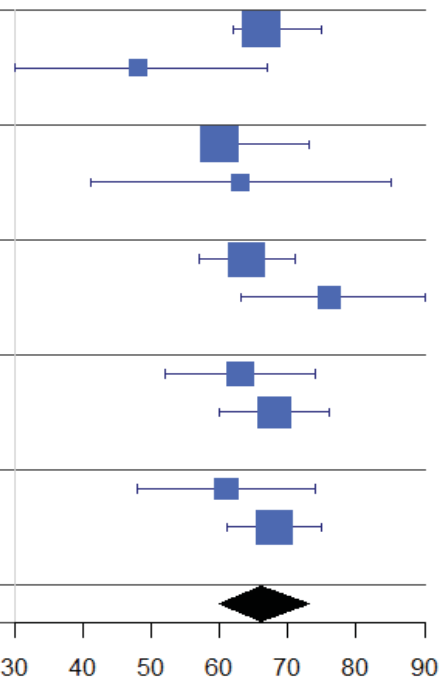
Figure 5 and Figure 6 present the efficacy results for the primary efficacy endpoint (i.e., at least a 2-point improvement at maximum frown from baseline to Day 30, as assessed by both the investigator and the subject using the GLS) by age (<65 and ≥65), sex, race and baseline GLS score at maximum frown (moderate and severe), for Trial EV-001 and Trial EV-002, respectively. The forest plots in these figures contain 95% confidence

intervals for the difference in proportions between DWP-450 arm and placebo arm using the ITT population and the multiple imputation (MI) approach for handling the missing data.
It should be noted that subgroup analyses by age, sex and race are not meaningful due to the small number of subjects in the subgroups of ≥65 years of age, male, and Non-White, in both trials.

For baseline disease severity at maximum frown, subjects with 'severe' glabellar lines, as assessed by each of the investigator and the subject, had a higher treatment effect compared to those with 'moderate' glabellar lines. However, more than twice as many subjects had 'severe' glabellar lines at baseline compared to 'moderate' glabellar lines, in the two trials.

Figure 5: Forest Plot for the Composite Success at Day Center by Age, Gender, Race and Baseline GLS Score for Trial EV-001 (ITT - MI)

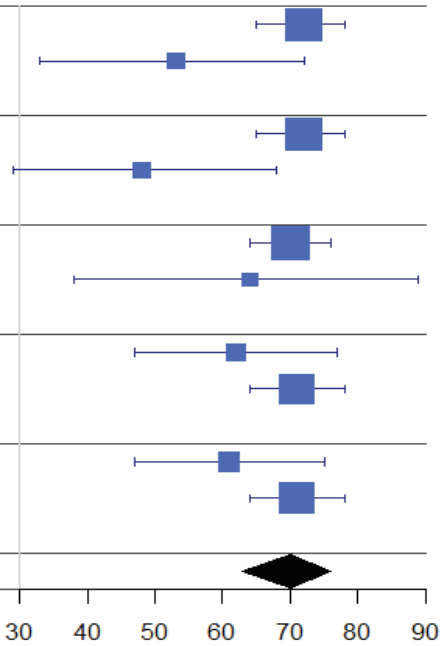
Subgroups (n[D], n[P])	DWP-450 (N=246)	Placebo (N=84)	Differences in Proportions
Age			
<65 (220, 75)	70%	1%	66%
>=65 (26, 9)	48%	0%	48%
Sex			
Females (227, 79)	67%	1%	66%
Males (19, 5)	63%	0%	63%
Race			
White (205, 63)	66%	2%	64%
Non-White (41, 21)	76%	0%	76%
Inv_Max			
Moderate (78, 28)	63%	0%	63%
Severe (168, 56)	70%	2%	68%
Subj_Max			
Moderate (56, 18)	61%	0%	61%
Severe (190, 66)	70%	2%	68%
Overall	**67%**	**1%**	**66%**



Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population: all randomized subjects; Missing data imputed using multiple imputation (MI).
n[D] = subgroup sample size for DWP-450 arm; n[P] = subgroup sample size in placebo arm; Inv_Max: baseline GLS score at maximum frown, as assessed by the investigator; Subj_Max: baseline GLS score at maximum frown, as assessed by the subject.
Forest Plot: 95% asymptotic confidence interval for the difference in proportions.

Figure 6: Forest Plot for the Composite Success at Day Center by Age, Gender, Race and Baseline GLS Score for Trial EV-002 (ITT - MI)

Subgroups (n[D], n[P])	DWP-450 (N=246)	Placebo (N=78)	Differences in Proportions
Age			
<65 (219, 72)	73%	1%	72%
>=65 (27, 6)	53%	0%	53%
Sex			
Females (207, 70)	73%	1%	72%
Males (26, 8)	48%	0%	48%
Race			
White (215, 69)	70%	0%	70%
Non-White (31, 9)	75%	11%	64%
Inv_Max			
Moderate (42, 12)	62%	0%	21%
Severe (204, 66)	72%	1%	71%
Subj_Max			
Moderate (46, 13)	61%	0%	61%
Severe (200, 65)	73%	2%	71%
Overall	**71%**	**1%**	**70%**

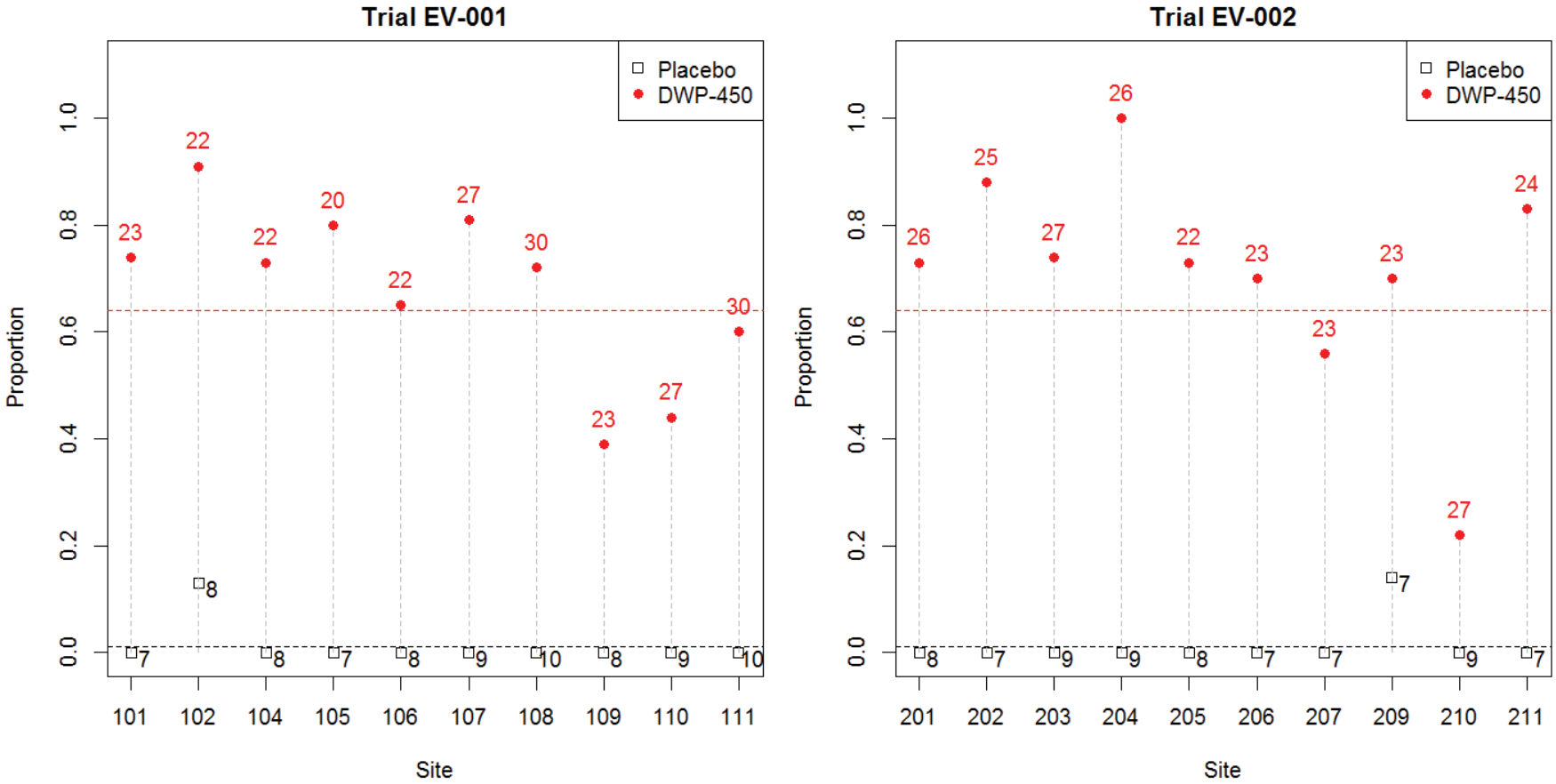


Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population: all randomized subjects; Missing data imputed using multiple imputation (MI).
n[D] = subgroup sample size for DWP-450 arm; n[P] = subgroup sample size in placebo arm; Inv_Max: baseline GLS score at maximum frown, as assessed by the investigator; Subj_Max: baseline GLS score at maximum frown, as assessed by the subject.
Forest Plot: 95% asymptotic confidence interval for the difference in proportions.

7.2.1.9.2. Study Site

Trial EV-001 enrolled 330 subjects from 10 sites and Trial EV-002 enrolled 324 patients from 10 sites. All sites were located in the United States. Figure 7 presents the results for the primary endpoint (i.e., at least a 2-grade improvement at maximum frown from baseline to Day 30, as assessed by both the investigator and the subject using the GLS) by site for both trials. Treatment effects varied somewhat across the sites, but no one site had extreme results. In addition, the treatment effect was slightly more spread out across sites in Trial EV002 (mean=0.71, SE=0.21) compared to Trial EV-001 (mean=0.68, SE=0.16).

Figure 7: Results for the Primary Efficacy Endpoint (Composite Success) by Site (ITT, MI) for Trials EV-001 and EV-002



Source: Statistical Reviewer's Analysis; Intent-to-Treat (ITT) population: all randomized subjects; Missing data imputed using multiple imputation (MI).
Note: The dotted horizontal line denotes the overall efficacy for each treatment arm.
The numbers on the plot denote the sample size of each treatment arm within each site.

7.3. Review of Safety

JEUVEAU (DWP-450) is a 900kDa botulinum toxin produced by *Clostridium botulinum* that is claimed to have the same physiochemical and biological properties as botulinum toxin type A. DWP-450 was approved by the Korean MDSA for marketing on 29-NOV-2013. IN 2014, Evolus Inc. initiated the development program for US, Canada, and the EU to meet the regulatory requirements for a BLA in the US and a MAA in the EU. The clinical program included: 3 randomized, controlled, single dose Phase III studies (EV-001, EV-002 and EVB-003) of 150-days duration; and, 2 open label, multiple dose, long-term Phase II studies (EV-004 and EV-006) of 1 year duration.

All 5 studies are complete. In total, between September 2014 and August 2016, over 2100 adult male and female subjects with moderate to severe glabellar lines at maximum frown participated in this program. Subjects received intramuscular injections in five target sites – the midline of the procerus, the inferomedial aspect of each corrugator muscle, and the superior middle aspect of each corrugator. Each site was injected with 0.1 mL for a total of 0.5 mL. Subjects assigned or randomized to JEUVEAU received a total of 20 U per treatment, administered as 4 U/0.1 mL; those randomized to placebo received 0.5 mL saline. In the EVB-003 study (the only study of the 5 with an active control arm), subjects randomized to the active control received a total of 20 U of Botox® administered as 4 U/0.1 mL. In the multiple dose studies, eligible subjects could receive up to four 20 U JEUVEAU treatments.

7.3.1. Safety Review Approach

The three clinical trials representing pivotal safety and efficacy studies for JEUVEAU include the two US clinical trials (EV-001 and EV-002) and the single EU clinical trial with an active Botox® arm (EV-003). The three clinical trials will make up the safety population for pivotal Phase 3 clinical trial analysis. The two multiple-dose, open-label studies (EV-004 and EV-006) will provide supportive safety analysis.

7.3.2. Review of the Safety Database

Overall Exposure

In the 3-controlled single-dose studies, all 1194 subjects randomized received a complete treatment of JEUVEAU, Botox® or placebo on Day 0 that included a total of 5 intramuscular injections of 0.1 mL each in the glabellar region. For JEUVEAU and Botox® subjects, the total injected volume of 0.5 mL (4 U/0.1 mL) corresponded to 20.0 U of botulinum toxin type A reconstituted with saline; for Placebo subjects, the total injected volume of 0.5 mL was comprised of saline only.

The extent of exposure only applies to multiple-dose studies (EV-004 and EV-006) since subjects in the single dose study will all have received 20 Units for treatment. In total 2116 subjects received treatment with JEUVEAU, Botox®, or placebo in the 5 clinical studies. Of these, 1659 subjects received treatment with JEUVEAU. All 737 subjects randomized to JEUVEAU in the 3-controlled single dose EV-001, EV-002 and EVB-003 studies received 20 U. The 922 subjects in the open-label multiple dose EV-004 and EV-006 studies received between 20 and 80 U of JEUVEAU; of these, 843 subjects received 1 or more repeat treatments. The mean total dose administered in these latter 2 studies was 61.3 ± 18.98 U of JEUVEAU; the median dose was 60 U (3 treatments).

Relevant characteristics of the safety population:

The demographic for the safety population are presented below.

Table 18: Baseline Demographics – Safety Population

Demographic Parameters	Controls		JEUVEAU			Total (N=1659) n (%)
	Pooled Placebo (N=211) n (%)	BOTOX® (N=246) n (%)	US Pooled Single Dose (N=492) n (%)	Pooled Single Dose (N=737) n (%)	Pooled Multiple Dose (N=922) n (%)	
Sex						
Male	21 (10.0)	31 (12.6)	45 (9.1)	70 (9.5)	81 (8.8)	151 (9.1)
Female	190 (90.0)	215 (87.4)	447 (90.9)	667 (90.5)	841 (91.2)	1508 (90.9)
Age						
Mean years (SD)	49.9 (11.04)	49.7 (10.41)	50.8 (11.65)	50.2 (11.39)	50.8 (10.65)	50.5 (10.98)
Median (years)	50.0	50.0	52.0	51.0	51.0	51.0
Min, max (years)	18,74	24,75	21,81	21,81	19,83	19,83
Age Group						
< 65 years	192 (91.0)	227 (92.3)	439 (89.2)	667 (90.5)	838 (90.9)	1505 (90.7)
≥ 65 years	19 (9.0)	19 (7.7)	53 (10.8)	70 (9.5)	84 (9.1)	154 (9.3)
Race						
White	168 (83.6)	183 (95.3)	420 (85.4)	585 (86.7)	756 (82.0)	1341 (84.0)
Black or African American	14 (7.0)	1 (0.5)	37 (7.5)	40 (5.9)	47 (5.1)	87 (5.4)
Asian	7 (3.5)	5 (2.6)	7 (1.4)	13 (1.9)	9 (1.0)	22 (1.4)
American Indian or Alaska Native	1 (0.5)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	1 (0.1)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	1 (0.1)
Other[1]	8 (4.0)	2 (1.0)	16 (3.3)	24 (3.6)	103 (11.2)	127 (8.0)
Fitzpartrick Skin Type						
I	12 (5.7)	4 (1.6)	21 (4.3)	30 (4.1)	57 (6.2)	87 (5.2)
II	64 (30.3)	84 (34.1)	144 (29.3)	228 (30.9)	273 (29.6)	501 (30.2)
III	86 (40.8)	118 (48.0)	187 (38.0)	303 (41.1)	320 (34.7)	623 (37.6)
IV	35 (16.6)	36 (14.6)	96 (19.5)	127 (17.2)	211 (22.9)	338 (20.4)
V	10 (4.7)	2 (0.8)	32 (6.5)	36 (4.9)	39 (4.2)	75 (4.5)
VI	4 (1.9)	2 (0.8)	12 (2.4)	13 (1.8)	22 (2.4)	35 (2.1)

Source: adapted from Table 14.1.1.3.3 Applicant's submission

Most subjects (90.9%) who received treatment with JEUVEAU in the 5 studies of the clinical development program were female. The mean age of all JEUVEAU subjects was 50.5 years; subjects ranged in age from 19 to 83 years. Most subjects (90.7%)

were less than 65 years of age; 9.3% were 65 years of age or older. Most (84.0%) were white; 5.4% were black and 1.4% was Asian. Most (88.1%) had Fitzpatrick skin types II, III or IV; the most common was type III; 37.6% of subjects had this skin type.

Table 19: Baseline Glabellar Line Characteristics – Safety Population

GLS Score	Controls		JEUVEAU			Total (N=1659) n (%)
	Pooled Placebo (N=211) n (%)	BOTOX® (N=246) n (%)	US Pooled Single Dose (N=492) n (%)	Pooled Single Dose (N=737) n (%)	Pooled Multiple Dose (N=922) n (%)	
Investigator Assessments At Maximum Frown						
None	0	0	0	0	0	0
Mild	0	0	0	0	0	0
Moderate	53 (25.1)	70 (28.5)	120 (24.4)	182 (24.7)	253 (27.4)	435 (26.2)
Severe	158 (74.9)	176 (71.5)	372 (75.6)	555 (75.3)	669 (72.6)	1224 (73.8)
At Rest						
None	21 (10.0)	15 (6.1)	54 (11.0)	64 (8.7)	93 (10.1)	157 (9.5)
Mild	67 (31.8)	80 (32.5)	138 (28.0)	232 (31.5)	309 (33.5)	541 (32.6)
Moderate	75 (35.5)	105 (42.7)	185 (37.6)	282 (38.3)	361 (39.2)	643 (38.8)
Severe	48 (22.7)	46 (18.7)	115 (23.4)	159 (21.6)	159 (17.2)	318 (19.2)
Subject Assessment[a] At Maximum Frown						
None	0	0	0	0	0	0
Mild	0	2 (0.8)	0	0	0	0
Moderate	40 (19.0)	44 (17.9)	102 (20.7)	146 (19.8)	107 (18.8)	253 (19.4)
Severe	171 (81.0)	200 (81.3)	390 (79.3)	591 (80.2)	463 (81.2)	1054 (80.6)
Missing	0	0	0	0	352	352
At Rest						
None	12 (5.7)	13 (5.3)	29 (5.9)	38 (5.2)	17 (3.0)	55 (4.2)
Mild	29 (13.7)	50 (20.3)	81 (16.5)	137 (18.6)	109 (19.1)	246 (18.8)
Moderate	102 (48.3)	105 (42.7)	202 (41.1)	316 (42.9)	272 (47.7)	588 (45.0)
Severe	68 (32.2)	78 (31.7)	180 (36.6)	246 (33.4)	172 (30.2)	418 (32.0)
Missing	0	0	0	0	352	352

Note: Baseline was defined as the last non-missing value collected at the time closest, but prior,

to randomization. Percentages were calculated with the number of subjects in the Safety Population as the denominator. GLS= Glabellar Line Scale.

a. Subject GLS scores were not collected in the open-label, multiple dose EV-004 study. Percentages were calculation with the number of subjects with non-missing information in the Safety Population as the denominator.

The pooled placebo subjects and pooled JEUVEAU subjects who participated in the 3 single dose studies were similar in terms of their baseline glabellar line characteristics. In total, 74.9% of placebo subjects and 75.3% of JEUVEAU subjects in these studies had severe glabellar lines at maximum frown by Investigator assessment at baseline; similarly, 75.6% of the US DWP-450 subjects had this assessment. The percentages of Placebo subjects and JEUVEAU subjects were also similar for those who had severe glabellar lines at maximum frown by subject assessment at baseline. In total, 81.0% of Placebo subjects and 80.2% of JEUVEAU subjects in these studies had severe glabellar lines at maximum frown by subject assessment at baseline; similarly, 9.3% of the US DWP-450 subjects had this assessment.

Subjects tended to provide more severe assessments of their glabellar lines than did investigators at baseline. In total, 22.7% of placebo subjects and 21.6% of JEUVEAU subjects in the single dose studies had a GLS score of severe at rest by investigator assessment at baseline; similarly, 23.4% of the US DWP-450 subjects had this assessment. By subject assessment, 32.2% of placebo subjects and 33.4% of JEUVEAU subjects had a GLS score of severe at rest at baseline; similarly, 36.6% of the US DWP-450 subjects had this assessment.

Adequacy of the safety database:

The safety database presented in this application is sufficient for a drug product that is used for a chronic condition. Pooled single-dose US studies include 492 subjects and over 900 subjects are included in the long-term multiple use studies.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

None, the data quality is acceptable.

Categorization of Adverse Events

The various types of adverse events are then reviewed as follows:

- common adverse events
- the single unrelated death that occurred
- other serious adverse events
- other significant adverse events, including

  – adverse events that led to study discontinuation
  – adverse events of special interest
  – adverse events identified as possible hypersensitivity reaction
- an analysis of adverse events by system organ class

Routine Clinical Tests

Laboratory tests were not collected in the EVB-003 study; therefore, the Pooled Placebo and Pooled JEUVEAU groups for the single dose studies are pooled from the US pivotal EV-001 and EV-002 studies only.

No significant differences were found in the laboratory testing compare to Placebo pooled subjects.

In the multiple-dose studies, only three subjects tested positive for the presence of botulinum toxin antibodies at the different times of visits. These subjects were reported to have been exposed to botulinum toxin previously. One subject in the EV-006 subsequently tested negative for the presence of anti-botulinum toxin antibodies at all post-baseline visits. The second subject tested positive at the end of study visit only, otherwise all other tests were negative. The last subject had a positive test on the day-30 visit, she then tested negative at all other visits.

Reviewer's comment: *Laboratory findings were unremarkable after a careful review of the single-dose and multiple-dose pooled safety groups.*

7.3.4. Safety Results

Deaths

One subject died during the five clinical studies as part of the JEUVEAU development program. Subject (b) (6) was a 43-year-old female who participated in the open-label multiple-dose clinical trial. She was reported as a serious adverse event as a drug overdose that resulted in death. The subject was on two concomitant medications, alprazolam (Xanax) and temazepam (Restoril). She also had a bilateral mastectomy for breast cancer on week prior to study entry.

Reviewer's comment: *After careful review of the case narrative for this subject, this reviewer determined that the death was not related to the investigational drug product.*

Serious Adverse Events

A summary of the severity in the pooled safety population is presented in the table below. Most subjects experienced adverse events that were assessed as mild or moderate in severity across all the analysis treatment groups. All JEUVEAU subjects and Botox® subjects had similar percentages of subjects who experienced mild, moderate and severe adverse events: mild (30.4% JEUVEAU and 32.1% Botox®), moderate (13.8% JEUVEAU and 12.2% Botox®), and severe (1.9% JEUVEAU and

2.0% Botox®). In pooled placebo subjects, 24.2% experienced a mild adverse event, 7.6% moderate, and 0.9% severe.

Table 20: Treatment-Emergent Adverse Events by Severity – Safety Population

	Controls		**JEUVEAU**			**Total** (N=1659) n (%) [E]
	Pooled Placebo (N=211) n (%) [E]	Botox® (N=246) n (%) [E]	US Pooled Single Dose (N=492) n (%) [E]	**Pooled Single Dose** (N=737) n (%) [E]	Pooled Multiple Dose (N=922) n (%) [E]	
Severity of Adverse Event [a]						
All Adverse Events	64 (30.3) [104]	103 (41.9) [165]	162 (32.9) [272]	254 (34.5) [424]	383 (41.5) [740]	637 (38.4) [1164]
Mild	51 (24.2) [78]	79 (32.1) [124]	121 (24.6) [187]	199 (27.0) [302]	306 (33.2) [492]	505 (30.4) [794]
Moderate	16 (7.6) [22]	30 (12.2) [35]	61 (12.4) [81]	83 (11.3) [107]	146 (15.8) [223]	229 (13.8) [330]
Severe	2 (0.9) [4]	5 (2.0) [6]	4 (0.8) [4]	12 (1.6) [15]	20 (2.2) [25]	32 (1.9) [40]

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. "n" = the number of subjects at each level of summarization; (%) = percentage of subjects; [E] = the number of events.

a. Severity as assessed by the investigator

In the JEUVEAU Pooled All group, most severe adverse events were reported in the class of nervous system disorders (0.6%, 10/1659) and neoplasms (0.4%, 6/1659). The two most common adverse events assessed as severe, and the only two that were reported in more than a single subject, were headache (6/1659, 0.4%) and breast cancer (3/1659, 0.2%).

Table 21: Summary of Severe Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Population

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System Organ Class and Preferred Term	Controls		JEUVEAU			Total (N=1659) n (%)
	Pooled Placebo (N=211) n (%)	Botox® (N=246) n (%)	US Pooled Single Dose (N=492) n (%)	Pooled Single Dose (N=737) n (%)	Pooled Multiple Dose (N=922) n (%)	
All Severe AEs	**2 (0.9)**	**5 (2.0)**	**4 (0.8)**	**12 (1.6)**	**20 (2.2)**	**32 (1.9)**
Nervous System Disorders	**0**	**0**	**2 (0.4)**	**5 (0.7)**	**5 (0.5)**	**10 (0.6)**
Carotid artery stenosis	0	0	0	0	1 (0.1)	1 (<0.1)
Headache	0	0	1 (0.2)	3 (0.4)	3 (0.3)	6 (0.4)
Intracranial aneurysm	0	0	1(0.2)	1 (0.1)	0	1 (<0.1)
Migraine	0	0	0	0	1 (0.1)	1 (<0.1)
Pseudoradicular syndrome	0	0	0	1 (0.1)	0	1 (<0.1)
Neoplasms Benign, Malignant and Unspecified	**1 (0.5)**	**1 (0.4)**	**1 (0.2)**	**1 (0.1)**	**5 (0.5)**	**6 (0.4)**
Basal cell carcinoma	0	0	0	0	1 (0.1)	1 (<0.1)
Breast cancer	1 (0.5)	0	1 (0.2)	1 90.1)	2 (0.2)	3 (0.2)
Cardiac valve fibroelastoma	0	1 (0.4)	0	0	0	0
Malignant anorectal neoplasm	0	0	0	0	1 (0.1)	1 (<0.1)
Uterine Leiomyoma	0	0	0	0	1 (0.1)	1 (<0.1)
Gastrointestinal Disorders	**0**	**0**	**0**	**0**	**3 (0.3)**	**3 (0.2)**
Abdominal Pain upper	0	0	0	0	1 (0.1)	1 (<0.1)
Pancreatitis	0	0	0	0	1 (0.1)	1 (0.1)
Small intestinal obstruction	0	0	0	0	1 (0.1)	1 (<0.1)
Infections and Infestations	**0**	**2 (0.8)**	**0**	**1 (0.1)**	**1 (0.1)**	**2 (0.1)**
Acrodermatitis	0	1 (0.4)	0	0	0	0
Gastroenteritis viral	0	0	0	0	1 (0.1)	1 (<0.1)
Influenza	0	0	0	1 (0.1)	0	1 (<0.1)
Nasopharyngitis	0	1 (0.4)	0	0	0	0
Injury, Poisoning and Procedural complications	**0**	**1 (0.4)**	**0**	**0**	**2 (0.2)**	**2 (0.1)**
Contusion	0	1 (0.4)	0	0	0	0
Overdose	0	0	0	0	1 (0.1)	1 (<0.1)
Wrist fracture	0	0	0	0	1 (0.1)	1 (<0.1)

Musculoskeletal and Connective Tissue Disorders	**1 (0.5)**	**0**	**0**	**1 (0.1)**	**1 (0.1)**	**2 (0.1)**
Intervertebral disc protrusion	1 (0.5)	0	0	0	0	0
Muscle spasms	0	0	0	1 (0.1)	0	1 (<0.1)
Myalgia	0	0	0	1 (0.1)	0	1 (<0.1)
Pain in extremity	0	0	0	0	1 (0.1)	1 (<0.1)
Skin and Subcutaneous Tissue Disorders	**0**	**0**	**0**	**1 (0.1)**	**1 (0.1)**	**2 (0.1)**
Rash pruritic	0	0	0	0	1 (0.1)	1 (<0.1)
Urticaria	0	0	0	1 (0.1)	0	1 (<0.1)
Reproductive System and Breast Disorders	**0**	**0**	**0**	**0**	**2 (0.2)**	**2 (0.1)**
Dysfunctional uterine bleed	0	0	0	0	1 (0.1)	1 (<0.1)
Endometrial hyperplasia	0	0	0	0	1 (0.1)	1 (<0.1)
Eye Disorders	**0**	**0**	**0**	**1 (0.1)**	**0**	**1 (<0.1)**
Conjunctival cyst	0	0	0	1 (0.1)	0	1 (<0.1)
General Disorders and Administration Site Conditions	**0**	**1 (0.4)**	**0**	**0**	**1 (0.1)**	**1 (<0.1)**
Device Failure [a]	0	0	0	0	1 (0.1)	1 (<0.1)
Injection site paresthesia	0	1 (0.4)	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**0**	**1 (0.1)**	**0**	**1 (<0.1)**
Oropharyngeal pain	0	0	0	1 (0.1)	0	1 (<0.1)
Psychiatric Disorders	**0**	**0**	**0**	**0**	**1 (0.1)**	**1 (<0.1)**
Anxiety	0	0	0	0	1 (0.1)	1 (<0.1)
Cardiac Disorders	**0**	**0**	**1 (0.2)**	**1 (0.1)**	**0**	**1 (<0.1)**
Stress cardiomyopathy	0	0	1 (0.2)	1 (0.1)	0	1 (<0.1)
Immune System Disorders	**0**	**0**	**0**	**0**	**1 (0.1)**	**1 (<0.1)**
Drug hypersensitivity	0	0	0	0	1 (0.1)	1 (<0.1)
Surgical and Medical Procedures	**1 (0.5)**	**0**	**0**	**0**	**0**	**0**
Breast reconstruction	1 (0.5)	0	0	0	0	0
Mastectomy	1 (0.5)	0	0	0	0	0

Note: At each level of summarization, a subject was counted once if the subject reported one or more events
"n" = the number of subjects at each level of summarization; (%) = percentage of subjects
AE were coded using MedDRA version 17.0

a. Device failure of a pacemaker/defibrillator

None of the severe adverse events described are thought to be related to the study drug. The device failure represented a failed pacemaker/defibrillator. Severe injection site paresthesia was represented by one complaint in the Botox® group.

In subgroup analyses of severe adverse events, the frequency of severe adverse events in the JEUVEAU Pooled All group after initial treatment was 1.3% (22/1659); this was slightly lower than 2.0% (5/246) observed for the active control Botox® group and slightly higher than 0.9% (2/211) reported for Pooled placebo controls. For subjects in the JEUVEAU Pooled All group, analysis by age group did not reveal any notable differences in severe adverse event frequencies between those <65 years of age (1.9%, 29/1505) versus ≥65 years of age (1.9%, 3/154), nor were there any notable differences by age quartiles. Analysis by sex showed a 2.1% (32/1508) frequency of severe adverse events in females versus none in males (0/151) in All JEUVEAU subjects. Similar frequencies were seen in the Botox® active controls; 2.3% (5/215) in females and none in males (0/31). Pooled Placebo controls reported a severe adverse event in 1.1% of female subjects (2/190) and no male subjects (0/21).

Table 22: Study Drug Related Treatment-Emergent Adverse Events as Assessed by Relationship – Safety Population

System Organ Class and Preferred Term	**Pooled Placebo (N=211)**			**BOTOX (N=246)**			**JEUVEAU Pooled All (N=1659)**		
	Possible	Probable	Definitely	Possible	Probable	Definitely	Possible	Probable	Definitely
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All Related AEs	16 (7.6)	2 (0.9)	1 (0.5)	25 (10.2)	7 (2.8)	5 (2.0)	147 (8.9)	48 (2.9)	34 (2.0)
Nervous System Disorders	**15 (7.1)**	**0**	**1 (0.5)**	**14 (5.7)**	**5 (2.0)**	**2 (0.8)**	**120 (7.2)**	**35 (2.1)**	**12 (0.7)**
Headache	15 (7.1)	0	1 (0.5)	10 (4.1)	3 (1.2)	2 (0.8)	112 (6.8)	31 (1.9)	9 (0.5)
Eye Disorders	**1 (0.5)**	**0**	**0**	**6 (2.4)**	**3 (1.2)**	**1 (0.4)**	**17 (1.0)**	**6 (0.4)**	**12 (0.7)**
Diplopia	0	0	0	0	0	0	0	0	1 (<0.1)
Eyelid Ptosis	0	0	0	0	0	0	6 (0.4)	4 (0.2)	8 (0.5)
Eyelid sensory disorder	0	0	0	3 (1.2)	1 (0.4)	0	1 (<0.1)	0	0
General Disorders and Administration site conditions	**0**	**0**	**0**	**3 (1.2)**	**0**	**1 (0.4)**	**10 (0.6)**	**5 (0.3)**	**7 (0.4)**
Injection site bruising	0	0	0	0	0	0	1 (<0.1)	0	1 (<0.1)
Injection site pain	0	0	0	1 (0.4)	0	0	2 (0.1)	2 (0.1)	3 (0.2)
Injection site pruritus	0	0	0	0	0	0	1 (<0.1)	0	0
Injection site swelling	0	0	0	0	0	0	0	2 (0.1)	1 (<0.1)

Note: not all preferred terms are represented in this table.

By preferred term, the two most common adverse events assessed as related to study drug for JEUVEAU subjects were headache (possibly related for 6.8% of subjects, probably related for 1.9%, and definitely-related for 0.5%) and eyelid ptosis (possibly related for 0.4% of subjects, probably related for 0.2%, and definitely-related for 0.5%). Headache was also the most common adverse event assessed as related to study drug for the control subjects: Botox® (possibly related for 4.1% of subjects, probably related for 1.2%, and definitely-related for 0.8%) and Pooled placebo (possibly related for 7.1% of subjects, probably related for no subjects, and definitely-related for 0.5%). The second most common drug related adverse event in the Botox® controls was eyelid sensory disorder (possibly related for 1.2% of subjects and probably related for 0.4%).

The most common adverse event that occurred in each of the 5 individual studies was headache; it was reported by more than 5% of subjects in the controls (Placebo and

Botox®) as well as in JEUVEAU subjects. In each of the 3 controlled single dose studies, the frequency of the adverse event of headache was slightly higher in the Placebo group compared with JEUVEAU group; a 2-sided 95% CI was calculated for each of the 2 US pivotal controlled single dose studies and both indicated no statistical difference in the frequency of headache between placebo and JEUVEAU subjects. The only other adverse event that was reported by 5% or more of subjects in any of the individual studies was the occurrence of nasopharyngitis in the Botox® active control (11.4%) and JEUVEAU (8.6%) groups of EVB-003; the frequency of nasopharyngitis in the Placebo group in that study was 4.1%.

Table 23: Important Treatment-Emergent Adverse Events Where Preferred Term is ≥ 1% --Safety Population

System Organ Class and Preferred Term	Controls		JEUVEAU			Total (N=1659) n (%)
	Pooled Placebo (N=211) n (%)	BOTOX® (N=246) n (%)	US Pooled Single Dose (N=492) n (%)	Pooled Single Dose (N=737) n (%)	Pooled Multiple Dose (N=922) n (%)	
All Severe AEs ≥ 1%	**46 (21.8)**	**69 (28.0)**	**103 (20.9)**	**167 (22.7)**	**243 (26.4)**	**410 (24.7)**
Nervous System Disorders	**28 (13.3)**	**25 (10.2)**	**27 (11.6)**	**91 (12.3)**	**129 (14.0)**	**220 (13.3)**
Headache	28 (13.3)	25 (10.2)	27 (11.6)	91 (12.3)	129 (14.0)	220 (13.3)
Eye Disorders	**0**	**4 (1.6)**	**8 (1.6)**	**12 (1.6)**	**13 (1.4)**	**25 (1.5)**
Eyelid ptosis	0	0	8 (1.6)	12 (1.6)	12 (1.3)	24 (1.4)
Eyelid sensory disorder	0	4 (1.6)	0	0	1 (0.1)	1 (<0.1)
Investigations	**0**	**0**	**6 (1.2)**	**6 (0.8)**	**0**	**6 (0.4)**
White blood cell count increase	0	0	6 (1.2)	6 (0.8)	0	6 (0.4)
Infections and Infestations	**16 (7.6)**	**39 (15.9)**	**35 (7.1)**	**65 (8.8)**	**105 (11.4)**	**170 (10.2)**
Bronchitis	1 (0.5)	3 (1.2)	2 (0.4)	3 (0.4)	15 (1.6)	18 (1.1)
Gastroenteritis viral	3 (1.4)	0	3 (0.6)	3 (0.4)	15 (1.6)	18 (1.1)
Influenza	2 (0.9)	5 (2.0)	2 (0.4)	5 (0.7)	14 (1.5)	19 (1.1)
Nasopharyngitis	3 (1.4)	28 (11.4)	5 (1.0)	26 (3.5)	17 (1.8)	43 (2.6)
Oral herpes	0	4 (1.6)	1 (0.2)	4 (0.5)	2 (0.2)	6 (0.4)
Sinusitis	5 (2.4)	1 (0.4)	4 (0.8)	7 (0.9)	26 (2.8)	33 (2.0)
Upper respiratory tract infection	3 (1.4)	1 (0.4)	13 (2.6)	13 (1.8)	20 (2.2)	33 (2.0)
Urinary tract infection	1 (0.5)	1 (0.4)	5 (1.0)	6 (0.8)	19 (2.1)	25 (1.5)

Preferred terms with frequency ≥ 1% in any DWP-450 or control group are presented. "n" = the number of subjects at each level of summarization; (%) = percentage of subjects. AEs were coded using MedDRA version 17.0.

Reviewer's comment: *The treatment-emergent adverse events ≥ 1% will represent the*

Clinical Trials Experience in the physicians insert label should the application be approved. This reviewer recommends that the US pooled single-dose experience is represented in the label to be consistent with the efficacy presentation. The pooling of EV-003, the European trial, is to review all the safety data associated with JEUVEAU.

Dropouts and/or Discontinuations Due to Adverse Effects

Altogether in the US single-dose clinical trials, 3 serious adverse events resulted in study discontinuation. One Botox® subject (1/246, 0.4%) discontinued the study due to cardiac valve fibroelastoma and two JEUVEAU subjects (2/1659, 0.1%) discontinued the study due to an adverse event: one due to a transient ischemic attack and one due to an unrelated drug overdose that resulted in the subject's death.

In the pooled JEUVEAU clinical development program (5 clinical trials), 4 events that led to study discontinuation in the 4 JEUVEAU subjects included 1 transient ischemic attack, 1 post-procedural worsening of a wrinkle above the eyebrow at rest, 1 headache, and one unrelated drug overdose that resulted in death.

Reviewer's comment: *The summaries for each of the subjects that discontinued were reviewed. Only one of the subjects were assessed as investigational drug related. Subject* (b) (6) *was a 59-year-old female who experienced post-procedural worsening of a wrinkle above eyebrow at rest (coded by the preferred term muscle tone disorder) assessed as mild in severity. The onset was 9 days after the receiving the initial treatment; the event resolved after 126 days and was assessed as probably related to study drug. She withdrew from the study 8 days prior to resolution of the event, approximately one month after the Day-90 visit.*

Significant Adverse Events

Other significant adverse events reported for studies in the JEUVEAU development program included adverse events that led to study discontinuation, adverse events of special interest, and adverse events identified as possible hypersensitivity reactions. A total of 56 adverse events of special interest were reported by 2.8% (47/1659) of subjects in the JEUVEAU Pooled All group. In comparison, 1.6% (4/246) of Botox® subjects and 0.5% (1/211) of pooled Placebo subjects reported an adverse event of special interest.

Table 24: Treatment-Emergent Adverse Events of Special Interest by SOC and PT – Safety Population

System Organ Class and Preferred Term	Controls		JEUVEAU			Total (N=1659) n (%)
	Pooled Placebo (N=211) n (%)	BOTOX® (N=246) n (%)	US Pooled Single Dose (N=492) n (%)	Pooled Single Dose (N=737) n (%)	Pooled Multiple Dose (N=922) n (%)	
All AEs of Special Interest	**1 (0.5)**	**4 (1.6)**	**13 (2.6)**	**20 (2.7)**	**27 (2.9)**	**47 (2.8)**
Nervous System Disorders	**0**	**0**	**01 (0.2)**	**1 (0.1)**	**2 (0.2)**	**3)0.2)**
Speech disorder	0	0	0	0	2 (0.2)	2 (0.1)
Transient ischemic attack	0	0	1 (0.2)	1 (0.1)	0	1 (<0.1)
Eye Disorders	**0**	**4 (1.6)**	**11 (2.2)**	**15 (2.0)**	**17 (1.8)**	**32 (1.9)**
Blepharospasm	0	2 (0.8)	1 (0.2)	1 (0.1)	3 (0.3)	4 (0.2)
Brow ptosis	0	1 (0.4)	2 (0.4)	2 (0.3)	3 (0.3)	5 (0.3)
Diplopia	0	0	1 (0.2)	1 (0.1)	0	1 (<0.1)
Eyelid ptosis	0	0	8 (1.6)	12 (1.6)	12 (1.3)	24 (1.4)
Presbyopia	0	0	0	0	1 (0.1)	1 (<0.1)
Strabismus	0	1 (0.4)	0	0	0	0
Vision blurred	0	0	2 (0.4)	2 (0.3)	2 (0.2)	4 (0.2)
Gastrointestinal Disorders	**0**	**0**	**0**	**1 (0.1)**	**2 (0.2)**	**3 (0.2)**
Dysphagia	0	0	0	1 (0.1)	2 (0.2)	3 (0.2)
Cardiac Disorders	**0**	**0**	**0**	**0**	**4 (0.4)**	**4 (0.2)**
Brady cardia	0	0	0	0	2 (0.2)	2 (0.1)
Respiratory, Thoracic and Mediastinal Disorders	**1 (0.5)**	**0**	**1 (0.2)**	**2 (0.3)**	**2 (0.2)**	**4 (0.2)**
Dysphonia	0	0	0	1 (0.1)	0	1 (<0.1)
Dyspnea	1 (0.5)	0	1 (0.2)	1 (0.1)	2 (0.2)	3 (0.2)
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**0**	**1 (0.1)**	**0**	**1 (<0.1)**
Muscle twitching	0	0	0	1 (0.1)	0	1 (<0.1)

Note: At each level of summarization, a subject was counted once if the subject reported one or more events. "n" = the number of subjects at each level of summarization; (%) = percentage of subjects. AEs were coded using MedDRA version 17.0.

The only system organ class with more than 1% of subjects in any treatment group experiencing an adverse event of special interest was eye disorders, reported by 1.9% (32/1659) of All JEUVEAU subjects, 1.6% (4/246) of Botox® subjects, and no pooled Placebo subjects. By preferred term, the only adverse event of special interest reported by more than 1% of subjects in any treatment group was eyelid ptosis, reported by 1.4% (24/1659) of All JEUVEAU subjects and no Control subjects.

There were 56 adverse events of special interest reported by subjects in the JEUVEAU Pooled All group, 51 were of mild severity (51/56, 91.1%), 5 were of moderate severity (5/56, 8.9%), and none were severe. Of the 4 adverse events of special interest reported by Botox® subjects, 3 were of mild severity (3/4, 75.0%), 1 was of moderate severity (1/4, 25.0%) and none were severe. The one adverse event of special interest reported by a Pooled Placebo subject was mild in severity.

Reviewer's comment: *The 5 JEUVEAU subjects with adverse events of special interest and assessed as moderate in severity was reviewed. Four subjects had eyelid ptosis or blurred vision or diplopia after treatment with JEUVEAU. All subjects completed the study and all adverse events resolved.*

Vital Signs

Vital sign data were available for 1659 subjects treated with JEUVEAU in the 5 studies of the US/EU clinical development program following the initial treatment. On review, no significant variations in the patterns of mean changes in any of the vital signs over time.

Electrocardiograms (ECGs)

ECGs were not collected in the EVB-003 study; therefore, the Pooled Placebo and Pooled JEUVEAU groups for the single dose studies are pooled from the US pivotal EV-001 and EV-002 studies only.

Reviewer's comment: *No significant ECG changes were seen.*

QT

Pooled placebo and pooled JEUVEAU subjects who participated in the 3 single-dose studies were highly similar in their mean QTcB and QTcF values at each of the baseline, Day 30 and EOS (Day 150)/ET visits. No differences were evident between groups at any time point assessed, and no changes from baseline were apparent. The maximum changes from baseline in QTcB values were 5.9 ± 13.76 msec and 6.6 ± 16.90 msec for pooled placebo and pooled DWP-450 subjects, respectively; similarly, the maximum changes for QTcF values were 3.8 ± 11.23 msec and 3.8 ± 13.60 msec, respectively.

Pooled JEUVEAU subjects who participated in the 2 multiple dose studies were highly similar in their mean QTcB and QTcF values at each of the baseline, Day 30 and EOS (Day 150)/ET visits to the pooled placebo subjects and pooled JEUVEAU subjects who participated in the single dose studies. No changes from baseline were apparent. The maximum change from baseline in QTcB values was 6.3 ± 16.57 for pooled JEUVEAU subjects; the maximum change in QTcF values was 3.4 ± 13.56. Again, these values did not differ from those reported for the pooled Placebo subjects and pooled JEUVEAU subjects who participated in the single dose studies.

Immunogenicity

A total of 34 adverse events identified as possible hypersensitivity reactions were reported by 1.8% (30/1659) of subjects in the JEUVEAU Pooled All group. In comparison, 2.0% (5/246) of Botox® subjects reported 6 events and 1.4% (3/211) of Placebo subjects reported 3 events. None of the adverse events identified as possible hypersensitivity reactions were serious and none led to study discontinuation.

The median time to onset for all adverse events identified as possible hypersensitivity reactions in the JEUVEAU Pooled All group was 16.0 days after treatment, with a mean of 38.4 ± 48.82 days; the median duration was 8.5 days, with a mean of 21.2 ± 46.60 days. The median time to onset of study drug related adverse events identified as possible hypersensitivity reactions was 4.0 days, with a mean of 8.0 ± 8.60 days; the median duration was 4.0 days, with a mean of 6.0 ± 27.19 days. Botox® subjects had a similar median time to onset and duration of all adverse events identified as possible hypersensitivity reactions as All JEUVEAU subjects; the median time to onset was 17.5 days (with a mean of 51.0 ± 65.04) and the median duration was 5.0 days (with a mean of 4.8 ± 3.43 days).

When evaluating hypersensitivity reactions as reported to be severe. Three subjects in the JEUVEAU group was identified as possible severe hypersensitivity reactions from the EVB-003 and EV-006 studies. A summary is provided.

- Subject (b) (6) was a 31-year-old female who experienced severe urticaria with onset 22 days after her single dose treatment and a duration of 2 days. The event was assessed as not study drug related.
- Subject (b) (6) was a 58-year-old female who experienced an adverse event reported as allergic reaction to Nucynta (trouble breathing and itching), coded by the preferred term drug hypersensitivity and with onset 18 days after receiving RT2. Nucynta (tapentadol) is an opioid pain medication that was used to treat the subject's knee pain. The event was resolved within 6 hours and was assessed as severe and not related to study drug. The subject received 3 treatments before she completed the study. No other hypersensitivity reactions were reported.
- Subject (b) (6) was a 46-year-old female who experienced an adverse event reported as pruritic rash located on the body throughout (coded by the preferred term rash pruritic) with onset 99 days after treatment 1. She was treated with prednisone and the event, which resolved within 25 days, was assessed as severe and not related to study drug. The subject subsequently received treatment 2 before she completed the study. No recurrent pruritic rash or other hypersensitivity reactions were reported.

Reviewer's comment: *After careful review of the hypersensitivity data collected in the safety population, this reviewer finds no evidence that this product causes more hypersensitivity in this population than any of the other botulinum toxin products for the treatment of glabellar lines. The recommended labeling in section 5.4 will be sufficient to convey this safety issue.*

5.4 Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported for botulinum toxin products. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of **PRODUCT NAME** should be discontinued and appropriate medical therapy immediately instituted. The use of **PRODUCT NAME** in patients with a known hypersensitivity to any botulinum neurotoxin or to any of the components in the formulation could lead to a life threatening allergic reaction [*See Known Hypersensitivity to Botulinum Toxin (4.1)].*

7.3.5. Analysis of Submission-Specific Safety Issues

A positive anti-botulinum toxin antibody test result was considered to a significant event. This safety issue was discussed in the laboratory section of this review.

7.3.6. Safety Analyses by Demographic Subgroups

Evaluation of the subgroups in the multiple-dose trials revealed some meaningful differences. For example, male subjects had a higher median exposure than did females: 80 U versus 60 U JEUVEAU. Most subjects (664/784, 84.7%) who completed the multiple dose studies received a total of 3 or 4 JEUVEAU treatments. Of the 784 study completers:

- 1.4% (n=11) received only the initial treatment
- 13.9% (n=109) received 2 treatments – i.e., the IT + RT1
- 38.4% (n=301) received a total of 3 treatments – i.e., the IT + RT1 + RT2
- 46.3% (n=363) received the maximum of 4 treatments – i.e., the IT + RT1 + RT2 + RT3.

The examination of differences between subpopulations in the extent of exposure was limited, in some cases, by the small number of subjects represented in some categories. As might be expected, exposure for those subjects who received 4 treatments paralleled that observed for the total dose:

- 16.6% more subjects 65 years of age and older received 4 treatments than did those less than 65 (61.3% versus 44.7%)
- 25.2% more subjects in the oldest age quartile received 4 treatments than did those in the youngest (60.7% versus 35.5%)
- 33.8% more subjects who had a GLS score of severe by Investigator assessment at baseline received 4 treatments than did those with a score of moderate (55.6% versus 21.8%)
- 27.9% more males received 4 treatments than did females (71.9% versus 44.0%).

No differences in the extent of exposure based on the number of treatments received were evident among subpopulations differentiated by race or Fitzpatrick skin type.

Table 25: Extent of Exposure (Units and Number of Treatments), Multiple Dose Studies Only, Overall and by Subgroups – Safety Population

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			Total Treatment, U – All Subjects			Total Numbers of treatment, n (%) – Completers Only		
Subgroup Analysis	**n**	**Mean ± SD**	**Median**	**N**	**1**	**2**	**3**	**4**
All Subjects	922	61.3±18.98	60	784	11 (1.4)	109 (13.9)	301 (38.4)	363 (46.3)
By Age Group								
≤ 65 years	838	60.6±19.11	60	709	10 (1.4)	105 (14.8)	277 (39.1)	317 (44.7)
≥ 65 years	84	67.7±16.38	80	75	1 (1.3)	4 (5.3)	24 (32.0)	46 (61.3)
By Age Quartile [a]								
≤25%	213	55.7±19.72	60	197	1 (0.5)	42 (21.3)	84 (42.6)	70 (3.5)
>25% - ≤50%	249	62.0±17.53	60	195	3 (1.5)	34 (17.4)	78 (40.0)	80 (41.0)
>50% - ≤75%	219	61.3±19.59	60	196	4 (2.0)	19 (9.7)	79 (40.3)	94 (48.0)
>75%	241	65.5±18.07	80	196	3 (1.5)	14 (7.1)	60 (30.6)	119 (60.7)
By Sex								
Female	841	61.1±18.66	60	720	9 (1.3)	104 (14.4)	290 (40.3)	317 (44.0)
Male	81	63.2±22.01	80	64	2 (3.1)	5 97.8)	11 (17.2)	46 (71.9)
By Race [b]								
White	756	61.5±19.06	60	645	8 (1.2)	91 (14.1)	243 (37.7)	303 (47.0)
Black or African American	47	61.3±19.74	60	41	2 (4.9)	6 (14.6)	13 (31.7)	20 (48.8)
Asian	9	66.7±20.00	80	8	0 (0.0)	0 (0.0)	3 (37.5)	5 (62.5)
Other	103	58.8±17.89	60	84	1 (1.2)	11 (13.1)	42 (50.0)	30 (35.7)
Multiple	7	68.6±19.52	80	6	0 (0.0)	0 (0.0)	0 (0.0)	5 (83.3)
By Fizparick Skin Type								

All	922	61.3±18.98	60	784	11 (1.4)	109 (13.9)	301 (38.4)	363 (46.3)
I	57	64.9±17.44	60	48	0 (0.0)	6 (12.5)	16 (33.3)	26 (54.2)
II	273	61.6±19.23	60	229	4 (1.7)	27 (11.8)	89 (38.9)	109 (47.6)
III	320	61.4±19.41	60	280	5 (1.8)	45 (16.1)	96 (34.3)	134 (47.9)
IV	211	60.2±18.41	60	173	0 (0.0)	22 (12.7)	79 (45.7)	72 (41.6)
V	39	61.0±18.89	60	32	0 (0.0)	4 (12.5)	13 (40.6)	15 (46.9)
VI	22	58.2±19.43	60	22	2 (9.1)	5 (22.7)	8 (36.4)	7 (31.8)
By Baseline GLS Score [c]								
Moderate	253	53.9±18.07	60	216	7 (3.2)	57 (26.4)	105 (48.6)	47 (21.8)
Severe	669	64.1±18.58	60	568	4 (0.7)	52 (9.2)	196 (34.5)	316 (55.6)

a. For all subjects, the age ranges for each quartile were: 18.661-43.907 years for the 1st quartile; 43.929 – 51.409 years for the 2nd quartile; 51.420 – 58.480 years for the 3rd quartile; and, 58.494-83.240 years for the 4th quartile. For study completers, the age ranges for each quartile were: 23.650 – 45.188 years for the 1st quartile; 45.207 – 51.389 years for the 2nd quartile; 51.409 – 58.864 years for the 3rd quartile; and, 58.811 – 82.086 years for the 4th quartile.
b. No subject in the open-label, multiple-dose EV-004 or EV-006 studies was an American Indian, Alaska Native, Native Hawaiian or Other Pacific Islander
c. At maximum frown by Investigator assessments.

Intrinsic factors of age and sex were included in the exploratory subgroup analyses performed for the safety endpoints of extent of exposure and adverse events. Although the number of subjects who were ≥65 years of age and the number of subjects who were male were relatively small in the individual studies, pooling the subjects from all five studies provided a sample of 154 subjects ≥65 years of age (154/1659, 9.3%) and a sample of 151 male subjects (151/1659, 9.1%) in the JEUVEAU Pooled All group. Neither elder age (≥65 years) nor sex appeared to impact safety outcomes or indicate the need to individualize therapy or patient management based on these factors.

7.3.7. Specific Safety Studies/Clinical Trials

None

7.3.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

None

Pediatrics and Assessment of Effects on Growth

A full pediatric waiver was submitted for subjects <18 years of age. The waiver was discussed with PeRC and will be granted on the rationale that studies are impossible due to low numbers of subjects in the pediatric age groups.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

None

7.3.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No post-marketing is available for this product.

Expectations on Safety in the Postmarket Setting

The safety concerns are consistent for all botulinum toxin product in the market place. The current labeling is acceptable to mitigate the risk involved with this product use.

7.3.10. Integrated Assessment of Safety

The intended use of JEUVEAU (botulinum toxin type A) for the indication of glabellar lines in adults is an aesthetic indication. As expected, the clinical trials show that the candidate product with high effectiveness and an expected adverse events profile. The performance of JEUVEAU is like that of the currently marketed Botox® product for glabellar lines. Most of the adverse events in the study were not drug related and most were either minor or moderate in severity. There were no serious adverse events related to the drug and drop outs due to drug related adverse events were very low. There were only two drug related adverse events with a frequency of 1% or greater, headache and eyelid ptosis. Most of these events were either minor or moderate in severity and importantly, were all self-limited and resolved spontaneously, without need for treatment. In this regard, JEUVEAU (botulinum toxin type A) has an acceptable risk-benefit profile for the treatment of glabellar lines in adults. It is in this Clinical Reviewer's opinion that the safety profile in combination with the risk-benefit profile of this drug product are acceptable for approval if the product quality issues are adequately addressed (see Section 4.2).

7.4. SUMMARY AND CONCLUSIONS

7.4.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects were large and consistent across trials and endpoints.

The applicant carried out efficacy analysis using the observed data (i.e., randomized subjects who had Day 0 and Day 30 primary efficacy data) although the Agency had commented that the primary efficacy analysis should use the ITT population (i.e., all randomized subjects) and address the issue of missing data. The statistical reviewer carried out efficacy analysis using the ITT population and the method of Multiple Imputation (MI) for handling the missing data, which assumes missingness is at random. The results of the statistical reviewer's analysis and those of the applicant's analysis showed that DWP-450 is statistically superior to placebo in the two pivotal trials (EV-001 and EV-002) (see Table 11).

The magnitude of missing data was relatively small (< 4%) at Day 30 (i.e., the primary efficacy timepoint). For handling the missing data, the applicant conducted sensitivity analyses using the following methods: (i) worst case scenario (WCS), (ii) best case scenario (BCS), and (iii) counting as success any subject who is missing Day 30 value and was classified as a success on Day 14 and Day 90. The statistical reviewer conducted an additional sensitivity analysis for the handling of missing data using the non-responder imputation (NRI) method. DWP-450 remained statistically superior to placebo based on the primary efficacy endpoint in both pivotal trials (EV-001 and EV-002) for all sensitivity analyses considered by the applicant and/or the statistical reviewer (p-values < 0.001).

In both trials, subgroup analyses by age, sex and race are not meaningful due to the small number of subjects in the subgroups of ≥65 years of age, male, and Non-White. For baseline disease severity at maximum frown, subjects with 'severe' glabellar lines, as assessed by each of the investigator and the subject, had a higher treatment effect compared to those with 'moderate' glabellar lines. However, more than twice as many subjects had 'severe' glabellar lines at baseline compared to 'moderate' glabellar lines.

7.4.2. Conclusions and Recommendations

To establish the efficacy of JEUVEAU (Botulinum toxin type A), the applicant submitted data from two randomized, multicenter, placebo-controlled, parallel-group, pivotal Phase 3 trials (EV-001 and EV-002). The trials enrolled subjects 18 years of age and older with moderate-to-severe glabellar lines at maximum frown as assessed independently by the investigator and the subject using the Glabellar Line Scale (GLS). The primary efficacy endpoint was the proportion of subjects at Day 30 achieving at least a 2-point improvement at maximum frown from baseline, as assessed by both the investigator and the subject using the GLS. In both trials, JEUVEAU (botulinum toxin type A) was statistically superior to placebo for the primary endpoint at Day 30 (p-values < 0.001; see Table 11 in Section 7.2.1.4).

8 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting is required. The review team determined early in the application review cycle that this new product for glabellar lines presented no novel or complex regulatory issues that required the input of an advisory committee.

9 Pediatrics

A full waiver for patients under 18 years of age was requested.

- Since the proposed indication (treatment of moderate to severe glabellar lines) does not occur in any of the pediatric subsets and due to the risks indicated, the benefit/risk ratio does not justify the use of this product in any pediatric subset and a waiver is requested.

- Pediatric studies are unfeasible due to the onset of the condition occurring in adults and the unlikeliness of this product being used in a substantial number of pediatric patients, making enrolment into pediatric studies difficult and impractical.

Reviewer's comment:
A full pediatric waiver should be granted. The Pediatric Review Committee concurred with this proposal.

10 Labeling Recommendations

10.1. Prescribing Information

The draft prescribing information is presented in this section. The final agreed-upon label will be included in the action package.

(b) (4)

[redacted]

17 Pages have been Withheld in Full as Draft Labeling Immediately Following this Page

(b) (4)

[redacted]

10.2. Patient Labeling

Patient labeling will be provided on approval of the drug product.

11 Risk Evaluation and Mitigation Strategies (REMS)

REMS will not be required for this application.

12 Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are suggested.

13 Appendices

13.1. References

None

13.2. Financial Disclosure

Financial certification was obtained for all investigators with US clinical sites.

Covered Clinical Study (Name and/or Number): EV-001, EV-002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 41		
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: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
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) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Clinical/Biostatistics

Scale Used to Evaluate Efficacy

Figure 8: Glabellar Line Scale (GLS)

(b) (4)

[redacted]

Source: Applicant's study reports

13.4. Nonclinical Pharmacology/Toxicology

Clean version of the recommended nonclinical portions of labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

JEUVEAU is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

8.1 Pregnancy

Risk Summary

There are no available data on JEUVEAU use in pregnant women to inform a drug associated risk of adverse developmental outcomes. An embryofetal developmental study conducted with JEUVEAU in pregnant rats revealed no treatment-related effects to the developing fetus when JEUVEAU was administered intramuscularly during organogenesis at doses up to 12 times the maximum recommended human dose (MRHD) [*see Data*].

Data

Animal Data

In an embryofetal developmental study, intramuscular doses up to 4 unit/kg JEUVEAU were administered to pregnant rats once daily during organogenesis (gestation days 6 to 16). No maternal or embryofetal toxicities were observed at doses up to 4 unit/kg (12 times the MRHD of 20 units, based on unit/kg comparison).

12.1 Mechanism of Action

JEUVEAU blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, JEUVEAU produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by JEUVEAU.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic, mutagenic or impairment of fertility potential of JEUVEAU.

13.5. OCP Appendices (Technical documents supporting OCP recommendations)

None

14 Office Director (ODE III)

I concur with the Division of Dermatology and Dental Products that the submitted clinical studies of JEUVEAU (botulinum toxin type A) support the conclusion that the clinical benefits of temporary improvement in the appearance of glabellar lines in adults outweigh the identified risks. However, the review of this BLA has identified numerous product quality and microbiology deficiencies that preclude marketing approval at this time. A Complete Response letter will be issued to the applicant that will describe these deficiencies in detail and provide recommendations for addressing them.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
05/15/2018

KENDALL A MARCUS
05/15/2018

JULIE G BEITZ
05/15/2018