

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761127Orig1s000

MULTI-DISCIPLINE REVIEW

**Clinical Review and Evaluation
Memorandum
Resubmission of BLA 761127**

Supporting Document Number: 49

Sponsor: Revance Therapeutics, Inc.

Drug: daxibotulinumtoxinA-lanm

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: 3/8/2022

Review Date: 9/6/2022

Team Lead: Tong Li-Masters MD, PhD, DDD

Project Manager: Kimberle Searcy

This memorandum is in regard to the resubmission of the BLA 761127 in response to the Agency's Complete Response (CR) letter dated October 14, 2021, for DAXXIFY (daxibotulinumtoxinA) for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults.

The CR letter listed several deficiencies that were all related to drug substance and drug product manufacturing facilities. The Applicant resubmitted the BLA 761127 on March 8, 2022. As per Applicant, this resubmission provides a Complete Response to observations made by the Agency during the pre-licensure inspection (PLI) and described in the Deficiency Letter of October 25, 2021. This resubmission does not contain any new clinical efficacy or safety data.

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

The Applicant provided substantial evidence of effectiveness from two adequate and well-controlled studies that evaluated DAXXIFY for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity. Two replicate randomized, double-blinded, placebo-controlled Phase 3 studies (SAKURA-1 and SAKURA-2) enrolled a combined total of 609 adult subjects with moderate to severe glabellar lines. Subjects were treated with DAXXIFY at a dose of 0.1 mL (8 Units) by intramuscular injection into each of five sites, for a total dose of 40 Units, or with placebo. The primary endpoint was the proportion of subjects who achieved a score of none or mild and at least a 2-point improvement from baseline on both investigator and patient wrinkle severity scales, at Week 4. The proportion of subjects with treatment success at Week 4 was 74% in the DAXXIFY group of studies SAKURA-1 and SAKURA-2 versus 0% in the placebo groups.

The Applicant adequately characterized the safety profile of DAXXIFY through analyses of data from the safety database of 2994 subjects. The numbers of subjects with DAXXIFY exposures at relevant doses exceeded those recommended by the division and the International Conference on Harmonization (ICH) E1A guideline. The safety profile of DAXXIFY was similar to that of other botulinumtoxin A products licensed for the same indication. DAXXIFY was generally well tolerated. The one reported death was not considered treatment-related. No serious adverse event was considered treatment-related. Most reported adverse reactions were either mild or moderate in severity and resolved spontaneously without treatment. The most frequently reported adverse reactions in DAXXIFY treatment groups were injection site reaction 6%; headache 7%; eyelid ptosis 2% and facial paresis 1%. The safety analysis did not identify any new safety signals for this botulinum toxin A product.

The Applicant conducted an open-label study that evaluated the safety of DAXXIFY with repeated treatments. The safety profile of DAXXIFY did not change with repeated product administration.

Labeling negotiations with the applicant were completed during the first review cycle and Final Physicians Insert and Patient Labeling will be included with the Approval letter.

Following the review of submitted data and re-inspection of manufacturing facilities, the product quality team has recommended approval. There are no product quality deficiencies or inspectional items resulting from the Pre-License Inspection that occurred July 11 to July 15, 2022, that preclude approval of this BLA.

Summary and Recommendation:

Because the risk/benefit profile of DAXXIFY has not changed since the previous review cycle and all CMC deficiencies have been addressed by the Applicant, this reviewer recommends approval of daxibotulinumtoxinA-lanm (DAXXIFY), a botulinum neurotoxin type A formulation developed by Revance Therapeutics for the proposed indication of temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults.

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Medical Officer
Division of Dermatology and Dentistry (DDD)
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Center for Drug Evaluation and Research (CDER)

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09/06/2022 06:40:02 PM

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09/06/2022 07:58:28 PM

NDA/BLA Multi-Disciplinary Review and Evaluation

| | |
|--|--|
| Application Type | BLA |
| Application Number(s) | 761127 |
| Priority or Standard | Standard |
| Submit Date(s) | November 24, 2019 |
| Received Date(s) | November 25, 2019 |
| PDUFA Goal Date | November 25, 2020 |
| Division/Office | Division of Dermatology and Dentistry/Office of Immunology and Inflammation |
| Review Completion Date | September 6, 2022 |
| Established/Proper Name | daxibotulinumtoxinA-lanm |
| (Proposed) Trade Name | DAXXIFY |
| Pharmacologic Class | Acetylcholine release inhibitor and neuromuscular blocking agent |
| Code name | |
| Applicant | Revance Therapeutics, Inc. |
| Doseage form | 50 units/vial and 100 units/vial |
| Applicant proposed Dosing Regimen | Single-use, sterile lyophilized powder |
| Applicant Proposed Indication(s)/Population(s) | For the treatment of temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. |
| Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication | |
| Recommendation on Regulatory Action | Approval |
| Recommended Indication(s)/Population(s) (if applicable) | |
| Recommended SNOMED CT Indication Disease Term for each Indication (if applicable) | |
| Recommended Dosing Regimen | 40 Units per treatment session divided into 5 equal intramuscular injections of 8 Units each (2 injections in each corrugator muscle and 1 injection in the procerus muscle) |

Version date: October 12, 2018

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DDD = Division of Dermatology and Dentistry

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OPQ = Office of Pharmaceutical Quality

OPDP = Office of Prescription Drug Promotion

OSE = Office of Surveillance and Epidemiology

DMEPA = Division of Medication Error Prevention and Analysis

DRISK = Division of Risk Management

OMP = Office of Medical Policy

Signatures

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| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED |
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|-------------------------------------|-------------------|-----------------|--|---|
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| Deputy Division Director (Clinical) | Shari Targum | OND/DDD | Sections: All | Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved |
| Statistical Reviewer | Kathleen Fritsch | OTS/OB/DBIII | Sections: 7.2, 8.1, 8.3 | Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved |
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| Statistical Team Leader | Mohamed Alosh | OTS/OB/DBIII | Sections: 7.2, 8.1, 8.3 | Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved |
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Glossary

| | |
|---------|---|
| ADME | absorption, distribution, metabolism, excretion |
| AE | adverse event |
| AESI | adverse event of special interest |
| AR | adverse reaction |
| BLA | biologics license application |
| BoNTA | botulinum neurotoxin type A |
| COA | clinical outcome assessment |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTEP | Cancer Therapy Evaluation Program |
| DARRTS | Document Archiving, Reporting, and Regulatory Tracking System |
| DAXXIFY | daxibotulinumtoxinA |
| DRM | Division of Risk Management |
| ECG | electrocardiogram |
| FDA | Food and Drug Administration |
| GAIS | Global Aesthetic Improvement Score |
| GD | gestation day |
| GCP | good clinical practice |
| GLP | good laboratory practice |
| ICH | International Conference on Harmonisation |
| IGA-FWS | Investigator Global Assessment-Frown Wrinkle Severity |
| IND | investigational new drug application |
| IRB | Institutional Review Board |
| MACE | major adverse cardiovascular event |
| MPA | mouse protection assay |
| MRHD | maximum recommended human dose |
| NAB | neutralizing antibody |
| N-CAM | neural cell adhesion molecule |
| NDA | new drug application |
| NMJ | neuromuscular junction |
| NOAEL | no-observed-adverse-effect level |
| OLS | open-label study |
| OSI | Office of Scientific Investigation |
| PFWS | Patient Frown Wrinkle Severity scale |
| PK | pharmacokinetics |
| PRO | patient reported outcome |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SSRI | selective serotonin reuptake inhibitor |
| TEAE | treatment-emergent adverse event |

1. Executive Summary

1.1. Product Introduction

DaxibotulinumtoxinA-lanm (DAXXIFY) is a botulinum neurotoxin type A (BoNTA) product developed by Revance Therapeutics. DAXXIFY is composed of purified 150 kDa daxibotulinumtoxinA, derived from (b) (4) *Clostridium botulinum* formulated as a lyophilized dosage form from reconstitution with preservative free normal saline prior to intramuscular administration. Purified DAXXIFY is free of accessory proteins and contains no human serum albumin or bacterial hemagglutinins.

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

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

The proposed dosing regimen is 40 Units per treatment session, divided into five equal intramuscular injections of 8 Units each (two injections in each corrugator muscle and one injection in the procerus muscle).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness from two adequate and well-controlled studies that evaluated DAXXIFY for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity. Two replicate randomized, double-blinded, placebo-controlled Phase 3 studies (Study 1620301 [SAKURA-1] and Study 1620302 [SAKURA-2]) enrolled a combined total of 609 subjects with moderate to severe glabellar lines. Adult subjects were treated with DAXXIFY at a dose of 0.1 mL (8 Units) by intramuscular injection into each of five sites, for a total dose of 40 Units, or placebo. The primary endpoint was the proportion of subjects who achieved a score of none or mild and at least a 2-point improvement from baseline on both investigator and patient wrinkle severity scales, at Week 4.

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

- Study 1620301 [SAKURA-1]: 0% placebo vs. 74% DAXXIFY
- Study 1620302 [SAKURA-2]: 0% placebo vs. 74% DAXXIFY

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Division of Dermatology and Dentistry recommends approval of daxibotulinumtoxinA-lanm (DAXXIFY), a botulinum neurotoxin type A (BoNTA) formulation developed by Revance Therapeutics, pending successful preapproval inspection of the drug substance and drug product manufacturing facilities. The proposed indication for DAXXIFY is for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adults.

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

The Applicant provided substantial evidence of effectiveness from two adequate and well-controlled studies that evaluated DAXXIFY for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity. Two replicate randomized, double-blinded, placebo-controlled Phase 3 studies (SAKURA-1 and SAKURA-2) enrolled a combined total of 609 adult subjects with moderate to severe glabellar lines. Subjects were treated with DAXXIFY at a dose of 0.1 mL (8 Units) by intramuscular injection into each of five sites, for a total dose of 40 Units, or with placebo. The primary endpoint was the proportion of subjects who achieved a score of none or mild and at least a 2-point improvement from baseline on both investigator and patient wrinkle severity scales, at Week 4. The proportion of subjects with treatment success at Week 4 was 74% in the DAXXIFY group of studies SAKURA-1 and SAKURA-2 versus 0% in the placebo groups.

The Applicant adequately characterized the safety profile of DAXXIFY through analyses of data from the safety database of 2994 subjects. The numbers of subjects with DAXXIFY exposures at relevant doses exceeded those recommended by the division and the International Conference on Harmonisation (ICH) E1A guideline. The safety profile of DAXXIFY was similar to that of other

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DaxibotulinumtoxinA for Injection

botulinumtoxin A products licensed for the same indication. DAXXIFY was generally well tolerated. The one reported death was not considered treatment related. No serious adverse event was considered treatment related. Most reported adverse reactions were either mild or moderate in severity and resolved spontaneously without treatment. The most frequently reported adverse reactions in DAXXIFY treatment groups were injection site reaction 6%; headache 7%; eyelid ptosis 2% and facial paresis 1%. The safety analysis did not identify any new safety signals for this botulinum toxin A product.

The Applicant conducted an open-label study that evaluated the safety of DAXXIFY with repeated treatments. The safety profile of DAXXIFY did not change with repeated product administration.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|--|--|
| Analysis of Condition | Glabellar lines are vertical lines that develop between the eyebrows upon frowning, and in some cases may be present at rest. Glabellar lines result from bilateral contraction of the horizontally oriented corrugator muscles and the vertically oriented central procerus muscles. Repeated contractions of these muscles over an extended period of time often result in skin remodeling in the area and the presence of vertical lines during contraction and at rest. | BoNTA treatment has been the standard of care for the treatment of unwanted moderate or severe dynamic glabellar lines in adults since the approval of onabotulinumtoxinA for the treatment of glabellar lines in 2002. |
| Current Treatment Options | Historically, treatment has been aimed at improving the cutaneous defect with soft tissue augmentation, resurfacing, or facial surgery. These treatments, however, do not address the underlying musculature that causes the facial lines and carry risk of complications and prolonged recovery. Surgical release of muscles is possible; however, it is invasive, can cause scarring, and is non-reversible. Botulinum toxin products have become a common aesthetic treatment option for glabellar lines caused by underlying hyperfunctional facial musculature. | Botulinum toxin injections produce chemical denervation of muscles, resulting in temporary localized reduction of muscle activity. This allows the physician to tailor the use of botulinum toxin to the clinical presentation and desired outcomes of the patient. DAXXIFY provides an alternative botulinum toxin product for the treatment of moderate or severe dynamic glabellar lines in adults. |
| Benefit | The key benefit of DAXXIFY is aesthetic (i.e., an improvement in the appearance of glabellar lines), of importance to patients who seek out this type of treatment. | Treatment with the botulinum toxin product results in a temporary aesthetic effect and may be discontinued if adverse reactions occur. Other treatments, such as surgical intervention, are more invasive. |

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| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| <p>Risk and Risk Management</p> | <p>Most of the adverse events in the submitted studies were unrelated to the study drug, and most were either mild or moderate in severity. There were no serious adverse events related to the drug treatment. The rate of drop-outs due to drug related adverse events was very low. The most frequently reported adverse reactions were injection site reaction, headache, eyelid ptosis and facial paresis.</p> <p>Labeling will incorporate all relevant warnings and precautions established from the historical use of botulinum toxin products. Product labeling is sufficient to manage the identified risks, if approved.</p> | <p>DAXXIFY has an acceptable risk-benefit profile for the treatment of glabellar lines.</p> <p>The Agency has established that distant spread of toxin is a risk that requires a Boxed Warning, although no events were observed in this development program. Labeling section 5 WARNINGS AND PRECAUTIONS will contain all relevant safety information.</p> <p>Risk management strategies beyond product labeling are not needed for this product, if approved. A risk evaluation and mitigation strategy (REMS) is not required.</p> |

1.4. Patient Experience Data

Table 1. Patient Experience Data Relevant to this Application (check all that apply)

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

2. Therapeutic Context

2.1. Analysis of Condition

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

2.2. Analysis of Current Treatment Options

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

Table 2. FDA-Approved Treatment for Glabellar Lines

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

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

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

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

3.2. Summary of Presubmission/Submission Regulatory Activity

The development of daxibotulinumtoxinA was conducted under investigational new drug application (IND) 129198. A pre-IND/end-of-phase 2 meeting was held on June 8, 2016. The Agency provided recommendations on the development program for the proposed indication.

- The Applicant submitted an initial Pediatric Study Plan on June 23, 2017, requesting a waiver of assessment of pediatric age groups 0 through 17 years for the treatment of moderate to severe glabellar lines because “Studies are impossible or highly impractical (because, for example, the number of pediatric patients is so small or geographically dispersed).” The proposed indication does not apply to pediatric patients 0 through 17 years of age; therefore, studies are impossible or highly impracticable to conduct. An Agreed Initial Pediatric Study Plan-Agreement letter was issued on July 14, 2017.
- A pre-BLA meeting was held on December 20, 2018, during which the content and format of the biologics license application (BLA) were discussed.

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

4.1. Office of Scientific Investigations (OSI)

Rationale for Site Selection

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

INSPECTION RESULTS

1. Joel Cohen, M.D.

Site #102

AboutSkin Dermatology and DermSurgery, PC

5340 S. Quebec St. Suite 300

Greenwood Village, CO 80111

Inspection Dates: 2/12/2020-2/14/2020, 2/18/2020

At this site for Protocol 1620301 (Sakura 1), 23 subjects were screened and 21 were randomized in the trial. The two subjects who were classified as screen fails were noted to violate exclusion criteria for pre-existing facial asymmetry and use of immunosuppressive medications. Twenty subjects from this site completed the protocol, and one subject was lost to follow up. The subject (b) (6) who was lost to follow up was noted to be assigned to the placebo group.

The FDA field investigator was able to review and verify all subject case histories including, but not limited to, informed consent, inclusion and exclusion criteria, medication usage and adverse event reporting. The subject records were noted to be organized, and data listings were

matched to print-outs for corresponding assessments (ECG, laboratory results, etc.). Study documentation related to compliance, medication storage, and monitoring logs were also reviewed. There were no deficiencies identified.

The primary and secondary endpoint data were also assessed for all enrolled subjects. There were no discrepancies noted when the data line listings provided by the sponsor were compared to paper source documentation for the primary and secondary endpoints (IGS-FWS, PFWS, Global Aesthetic Improvement Scale, Frown Line Impact Scale, and Patient Global Satisfaction).

There were no serious adverse events (SAEs) reported at this site. There was no evidence of under-reporting of safety signals or adverse events.

2. John Joseph, M.D.

Site #109
Clinical Testing of Beverly Hills
9400 Brighton Way, Suites 205 & 203
Beverly Hills, CA 90210

Inspection Dates: 3/9/2020 – 3/13/2020

At this site for Protocol 1620301 (Sakura 1), 37 subjects were screened, and 35 subjects were enrolled. Two subjects who were classified as screen fails were noted to violate inclusion criteria for severity of glabellar lines or ability to follow trial procedures. Thirty-two of the enrolled subjects completed the protocol. Of the three subjects who did not complete the protocol, 2 subjects (b) (6) were in the daxibotulinum group and one subject (b) (6) was assigned to the placebo group. The two subjects who were in the daxibotulinum group both withdrew consent. The subject in the placebo group was lost to follow up.

The FDA field investigator was able to review and verify all subject case histories including, but not limited to, informed consent, study entry criteria, adverse event reporting, and efficacy data. Study documentation related to medication storage and accountability, study monitoring logs, and protocol compliance were reviewed. There were no deficiencies identified.

The field investigator was able to review and verify the primary endpoint data for all enrolled subjects by comparing the paper source documentation to the line listings provided by the sponsor. There were 3 SAEs reported from this site (all were deemed unrelated to the study procedures). Two of these events occurred in subjects randomized to daxibotulinum and were dysuria/sepsis (Subject (b) (6)) and bone marrow suppression (Subject (b) (6)). The other SAE was anxiety in a subject assigned to receive the placebo (Subject # (b) (6)). There was no evidence of under-reporting of adverse events.

3. Nowell Solish, M.D.

Site #213 of Protocol 1620302 (Sakura 2)
Sweat Clinics of Canada
66 Avenue Road, Suite 1 (Concourse Level)
Toronto, ON M5R3N8
Canada

The COVID-19 global pandemic has significantly limited OSI's ability to conduct on-site Good Clinical Practice (GCP) inspections. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for planned inspections in support of BLA 761127 were reevaluated based on the completed inspections listed above. Following discussions between OSI and OND, a decision was made that assessment of the application could proceed without this GCP inspection.

4. Arthur Swift, M.D.

Site #214 of Protocol 1620302 (Sakura 2)
4141 suite 230 rue Sherbrooke St. West
Montreal, QC, H3Z 1B7
Canada

After selection of this site, OSI was notified by BIMO International that the site was closed and was unable to be inspected. Site enrollment numbers and site level data from this site were examined and the review division was contacted regarding the inability to inspect this site. At that time, we discussed alternate selections for inspection from the Sakura 2 study, but ultimately deemed that the review could proceed with the remaining inspections.

OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigators Drs. Joel Cohen and John Joseph were inspected in support of this BLA. Based on the results of these inspections, Study 620301 (Sakura 1) appears to have been conducted adequately, and the data generated by these clinical investigators appear reliable in support of the proposed indication. The two sites selected for Study 1620302 (Sakura 2) could not be inspected (see details above). Therefore, at this time, OSI will be unable to determine if Study 1620302 was conducted adequately and whether the study data are reliable in support of the proposed indication.

4.2. Product Quality

There are no product quality approvability issues at this time, pending review of outstanding information requests. However, because of the current public health emergency, The Office of Pharmaceutical Quality has been unable to arrange for a prelicensing inspection to the drug substance and drug product manufacturing facility (Revance Therapeutics, Inc, Newark, CA) during the current review timeline. This dedicated manufacturing facility has no Food and Drug Administration (FDA) inspection history. An on-site inspection of the unlicensed manufacturing facility is required for approval. The absence of a prelicensing inspection is an approvability item.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

Executive Summary

The Applicant has submitted an original BLA under section 351(a) of the Public Health Service Act for DaxibotulinumtoxinA for Injection for the temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adults. The Applicant has conducted a 6-month repeat dose toxicity study in rats with monthly doses of DAXXIFY administered by intramuscular injection, followed by a 3-month treatment-free recovery phase to assess potential recovery. They have also conducted a fertility and early embryonic development study in rats, and both a rodent and rabbit embryofetal development study. Based on the well-known mechanism of action of DAXXIFY, the Applicant was granted a waiver for conduct of a prenatal and postnatal development study. The fertility and early embryonic development study, and the rodent embryofetal development study are reviewed below. The 6-month repeat dose toxicity study in rats and the rabbit embryofetal development study have been reviewed previously and are summarized below.

The DAXXIFY formulation contains a novel excipient, RTP004, which is a synthetic peptide. The Applicant has conducted several nonclinical studies to support the safety of RTP004 in the DAXXIFY formulation. The nonclinical studies that incorporate an RTP004 arm included a 6-month repeat dose toxicity study in rats, fertility studies in male and female rats, and embryofetal development studies in rats and rabbits. No safety signals for RTP004 were noted in any of the conducted nonclinical studies. In addition, a battery of genotoxicity studies conducted with RTP004 were negative. The results from these nonclinical studies conducted with RTP004 support the use of this novel excipient in the DAXXIFY formulation.

DaxibotulinumtoxinA for Injection is approvable from a pharmacology/toxicology perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this BLA.

5.1. Referenced NDAs, BLAs, DMFs

None.

5.2. Pharmacology

Primary Pharmacology

At the presynaptic neuromuscular junction (NMJ), normal release of acetylcholine is mediated by assembly of a synaptic fusion complex that allows the membrane of the synaptic vesicle to fuse with the neuronal cell membrane. After DAXXIFY binds to the presynaptic cholinergic axon terminal neuronal cell membrane, it is internalized into the nerve terminal by endocytosis, translocated into the cytosol, and selectively cleaves the vesicular docking protein, SNAP-25

(synaptosome-associated protein of 25 kDa), which is attached to the inner surface of the nerve terminal. This enzymatic activity results in inhibition of acetylcholine release, leading to temporary muscle relaxation.

Secondary Pharmacology

The secondary pharmacology of DAXXIFY is dependent on the nature of the specific cholinergic nerve endings inhibited by the toxin. For example, inhibiting acetylcholine release at the NMJ blocks cholinergic transmission and paralyzes the associated muscle until impulse transmission is re-established. Thus, the secondary pharmacology of DAXXIFY is dependent on the subsequent role of acetylcholine at its receptor downstream of the target site.

Safety Pharmacology

DaxibotulinumtoxinA for Injection is intended as a local treatment and not expected to be present in peripheral blood at levels that can produce systemic pharmacological effects. As per International Conference on Harmonisation (ICH) *S7A, Safety pharmacology studies for human pharmaceuticals* (2001), no safety pharmacology studies have been conducted with DaxibotulinumtoxinA for Injection.

5.3. ADME/PK

DAXXIFY has negligible systemic availability following intramuscular administration of clinically relevant doses. Due to the systemic toxicity of DAXXIFY and the consequent limits on the non-lethal doses that can be administered (<10 ng/kg), the sponsor has not been able to detect DAXXIFY in tissues (including blood and plasma). The synthetic peptide, RTP004, degrades rapidly in plasma, making it difficult to detect in biological samples. There are no available bio-analytical methods sensitive enough to evaluate the pharmacokinetics/ADME/toxicokinetics of DAXXIFY.

5.4. Toxicology

5.4.1. General Toxicology

The Applicant's nonclinical testing program was originally focused on a topical gel known as RTT150 Topical Gel (code name: RT001), but was subsequently changed to RTT150 for Injection (code name: RT002). Both formulations contain DAXXIFY and the synthetic peptide, RTP004. In the following nonclinical section, the Applicant's code names have been used to specifically identify what was tested. A comparison of the two formulations is provided in the chart below. The differences between RT001 and RT002 are negligible, and nonclinical testing done with RT001 stands in support of RT002.

Table 3. Ingredient List for Formulations RT001 and RT002

| | RT001 | RT002 |
|---|-------------------------------|---|
| Active ingredient | daxibotulinumtoxinA (150 kDa) | daxibotulinumtoxinA (150 kDa) |
| Synthetic peptide | RTP004 (b) (4) | RTP004 (12 µg) |
| Reconstitution diluent in intramuscular studies | Saline | Saline |
| Inactive ingredients | (b) (4) | L-histidine L-histidine HCl Polysorbate-20 Trehalose dihydrate |

Source: BLA 761127, section 2.6.1 Introduction

Study title/ number: A 6-month toxicity study of RT001 and RTP004 administered by intramuscular injection to rats with a 3-month recovery period (RT001-NC028).

Once monthly intramuscular administration of RT001 (0, 0.008, 0.04, 0.2 ng/kg/dose DAXXIFY; 10/sex/group for main study and 5/sex/group for recovery) into the gastrocnemius muscle of rats resulted in dose-related decreases in muscle mass, mobility, body weight, and creatinine. Treatment of another group (10/sex/group for main study and 5/sex/group for recovery) with 1.0 mg/kg/dose RTP004 had no effect. The first three monthly injections were administered to the left gastrocnemius muscle, and the last three monthly injections were administered to the right gastrocnemius muscle. Thus, at the end of the 3-month treatment-free recovery period, histological evaluation of the right injection site provided 3-month recovery data, and histological evaluation of the left injection site provided 6-month recovery data. Dose-related decreases in creatinine correlated with dose-related increases in immunohistochemical staining, as measured by neural cell adhesion molecule (N-CAM) expression, and also with reductions in muscle mass in the skeletal muscle at the injection sites, thigh muscle, and cutaneous panniculus muscle of the inguinal skin of the DAXXIFY groups.

Generally, the severity of changes was greater in the right injection site where the last three treatments were administered (Days 105, 140, and 175). RTP004-related changes were limited to the skeletal muscle at the right injection site only (i.e., the more recently injected site), indicative of the transient nature of the changes associated with RTP004. Following the 3-month treatment-free recovery period, more of the DAXXIFY-related histopathological changes persisted at the right injection site than at the left injection site, indicating that progression toward recovery was time-dependent. High-dose animals showed less recovery than low-dose animals, indicating that the degree of denervation and rate of recovery were also dose-dependent.

Reviewer's Comment: In rats, multiple reports indicate widespread expression of N-CAM in regenerating and/or fetal axons and myelinating Schwann cells, with limited or no expression in adult or undamaged myelinating Schwann cells. N-CAM expression in adult rat skeletal muscle fibers is either absent or very limited at baseline, but can be activated following exposure to botulinum toxin type A. Increases in N-CAM expression can be used as a biomarker for denervation, while

a return to baseline (negligible to very low level) of N-CAM expression is a biomarker for re-innervation and functional recovery. This study evaluated the effect of repeated intramuscular administration of DAXXIFY at the neuromuscular level, and demonstrated that the effect is at least partially reversible based on N-CAM expression.

5.4.2. Genetic Toxicology

As per ICH guidance *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012) (section 4.7 Genotoxicity Studies), no genetic toxicology testing is warranted for DAXXIFY.

RTP004 was not mutagenic in *Salmonella typhimurium* (Ames test) and was not clastogenic in both an in vivo mouse micronucleus assay and an in vitro chromosomal aberration assay in human lymphocytes.

5.4.3. Carcinogenicity

As per ICH *S6(R1)* (section 4.8 Carcinogenicity Studies), no carcinogenicity testing is warranted for DAXXIFY.

5.4.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: A fertility and early embryonic developmental to implantation toxicity study of RT002 by intramuscular injection in the rat / RT002-NC1009

Key Study Findings

RTP004 (100 µg/kg) and RT002 (0, 3, 10, and 20 Units/kg DAXXIFY in males; 0, 3, 10, and 30 Units/kg DAXXIFY in females) were administered by weekly intramuscular injection in a male and female rat fertility study. Treated males and treated females were mated with untreated animals. Based on decreased paternal body weight at ≥10 Units/kg and maternal body weight at 30 Units/kg, the no-observed-adverse-effect levels (NOAELs) for paternal or maternal toxicity were 3 or 10 Units/kg DAXXIFY, respectively. Based on secondary effects of DAXXIFY, the NOAELs for male and female fertility are at least 3 and 10 Units/kg, respectively.

Conducting laboratory and location:



GLP compliance:

Yes

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Table 4. Methods for Study RT002-NC1009

| | |
|---|--|
| Dose and frequency of dosing | 0 (vehicle) mg/kg; 100 µg/kg RTP004; 3, 10, 20 Units/kg DAXXIFY (male rats); 3, 10, 30 Units/kg DAXXIFY (female rats) Males: up to 7 doses, 1 week apart Females: 4 doses, 1 week apart |
| Route of administration | Intramuscular in left hindlimb |
| Vehicle | 0.9% sodium chloride with 0.01% (w/w) Tween |
| Species/strain | Rat/Sprague-Dawley |
| Number/sex/group | 22 |
| Study design | Once weekly dosing began in male rats 28 days prior to cohabitation and began in female rats 15 days prior to cohabitation. Dose administration in male rats at 20 Units/kg DAXXIFY was terminated on study day 44 due to declining clinical condition and excessive body weight loss. All surviving treated male rats were euthanized on study days 50-52, and all treated or untreated female rats were euthanized on GD 13. |
| Deviation from study protocol affecting interpretation of results | None |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; GD = gestational day.

Source: A fertility and early embryonic developmental to implantation toxicity study of RT002 by intramuscular injection in the rat / RT002-NC1009

Parameters and Endpoints Evaluated

Mortality (twice daily), clinical signs (at least once weekly), body weights (weekly), body weight gain and feed consumption (at least weekly), mating performance, gross necropsy, sperm motility, sperm concentration, estrous cycle (from 14 days prior to cohabitation until evidence of mating), and ovarian and uterine examination (number, distribution of corpora lutea, implantations, viable/nonviable embryos).

Table 5. Observations and Results for Study RT002-NC1009

| Parameters | Major Findings |
|-------------------|---|
| Mortality | All surviving male rats at 20 Units/kg DAXXIFY were terminated early (study day 44) due to adverse clinical observations, excessive mean body weight loss, reduced feed consumption. Six female rats at 30 Units/kg DAXXIFY were terminated early due to adverse clinical signs similar to those in male rats at 20 Units/kg. |
| Clinical signs | Rats at ≥ 3 Units/kg DAXXIFY had dose-dependent limited use of the left hindlimb, mild dehydration, loss of left hindlimb grip reflex; rats at ≥ 10 Units/kg DAXXIFY displayed thin body condition, swelling in left inguinal area; rats at 20 Units/kg DAXXIFY had hunched posture, chromodacryorrhea, ungroomed coat, urine-stained abdominal fur; rats at 30 Units/kg DAXXIFY exhibited severe dehydration, abnormal gait, pale extremities. |
| Body weights | On study day 50, mean body weights of male rats were 89% and 75% of vehicle control values in the 3 and 10 Units/kg DAXXIFY groups, respectively. On GD 13, mean body weights of female rats in the 3, 10, and 30 Units/kg DAXXIFY dose groups were 91%, 81%, and 65%, respectively, of the mean vehicle control group. |
| Necropsy findings | In male rats at 3 Units/kg DAXXIFY, there were no effects on mating or fertility parameters (i.e., % of male rats that mated, mean days of cohabitation, % of cohabited males producing a pregnancy). At ≥ 10 Units/kg DAXXIFY, effects on male mating and fertility parameters cannot be distinguished from effects due to the poor clinical condition of male rats treated at ≥ 10 Units/kg DAXXIFY. In female rats, there were no effects on mating or fertility parameters at ≤ 10 Units/kg DAXXIFY. At 30 Units/kg DAXXIFY, effects on mating or fertility parameters cannot be distinguished from effects due to poor clinical condition of female rats at 30 Units/kg DAXXIFY. In female rats, there were no treatment-related effects on ovarian or uterine parameters at ≤ 10 Units/kg DAXXIFY. At 30 Units/kg DAXXIFY, mean number of corpora lutea and implantations were reduced. There was an increase in the % preimplantation loss and a reduction in the number of viable embryos at this high dose. An effect on ovarian or uterine parameters of DAXXIFY cannot be distinguished from an effect due to the poor clinical condition of female rats at 30 Units/kg DAXXIFY. |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; GD = gestational day.

Source: A fertility and early embryonic developmental to implantation toxicity study of RT002 by intramuscular injection in the rat / RT002-NC1009

Embryo-Fetal Development

Study title/ number: An embryo-fetal development toxicity study of RT002 by intramuscular injection in the rat / RT002-NC1010

Key Study Findings

DAXXIFY (0, 3, 10, or 30 Units/kg) was administered by intramuscular injection four times during organogenesis (gestation days [GD] 7, 10, 13, 16) to pregnant rats. Based on decreased maternal body weight at ≥ 10 Units/kg DAXXIFY, the NOAEL for maternal toxicity was 3 Units/kg

DAXXIFY. Reductions in fetal body weight and decreased ossification sites (hindlimb phalanges and caudal vertebrae) at 30 Units/kg DAXXIFY are considered to be secondary effects of maternal toxicity. Based on these secondary effects, the NOAEL for embryofetal development was 10 Units/kg DAXXIFY.

Conducting laboratory and location:



GLP compliance:

Yes

Table 6. Methods for Study RT002-NC1010

| | |
|---|--|
| Dose and frequency of dosing | 0 (vehicle) mg/kg; 100 µg/kg RTP004; 3, 10, or 30 Units/kg DAXXIFY GD 7, 10, 13, 16 |
| Route of administration | Intramuscular |
| Vehicle | 0.9% sodium chloride with 0.01% (w/w) Tween |
| Species/strain | Rat/Sprague-Dawley |
| Number/sex/group | 22 time-mated female rats |
| Study design | Time-mated female rats were administered four intramuscular injections on GD 7, 10, 13, and 16 at a dose volume of 0.2 mL/kg. All rats were terminated on GD 21. |
| Deviation from study protocol affecting interpretation of results | No |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; GD = gestational day.

Parameters and Endpoints Evaluated

Maternal:

Mortality (twice daily), clinical signs (once daily), body weights/body weight gain (GD 0, day of arrival at facility, GD 5, daily during dosing and post-dosing periods, day of termination), feed consumption (daily), gross necropsy, ovarian and uterine examination (number, distribution of corpora lutea, implantation sites, placentae, live/dead fetuses, early and late resorptions).

Fetal:

Sex, body weight, external (all fetuses), visceral (half of the fetuses), and skeletal (the other half of the fetuses) examinations.

Table 7. Observations and Results for Study RT002-NC1010

| Parameters | Major Findings |
|--|---|
| Mortality | All rats survived to scheduled termination. |
| Clinical signs | Treatment-related clinical signs included dose-dependent limited use of left hindpaw at ≥ 3 Units/kg DAXXIFY; suspected dehydration (based on skin turgor), hunched posture, thin appearance, eye discharge, ungroomed fur at 30 Units/kg DAXXIFY. |
| Body weights | Mean maternal body weight gain at 3, 10, or 30 Units/kg DAXXIFY was reduced relative to vehicle control values for the GD 7-21 interval (88%, 73%, and 39% of vehicle control, respectively). |
| Necropsy findings Cesarean section data | Pregnancy was confirmed in 22, 21, 21, 22, and 22 females in the vehicle control, 100 $\mu\text{g}/\text{kg}$ RTP004, and 3, 10, and 30 Units/kg DAXXIFY groups, respectively. No RTP004- or DAXXIFY-related effects on ovarian or uterine parameters were noted in this study. The litter means for corpora lutea, implantations, percentage of preimplantation loss, and percentage of live male fetuses were similar among treated groups and did not differ significantly from the vehicle control. |
| Necropsy findings Offspring | Decreased fetal body weights were noted at 30 Units/kg DAXXIFY (89% of vehicle control). The mean number of ossified hindlimb phalanges and caudal vertebrae were lower than in vehicle control at 30 Units/kg DAXXIFY. This finding is considered related to the decreased fetal body weights observed at this dose. All other ossification sites were similar across all groups. No RTP004- or DAXXIFY-related external, visceral, or skeletal malformations were noted in this study. |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; GD = gestational day.

Source: An embryo-fetal development toxicity study of RT002 by intramuscular injection in the rat / RT002-NC1010

Study title/ number: An embryo-fetal development toxicity study of RT001 and RTP004 by intramuscular injection in the rabbit / RT001-NC035

DAXXIFY (0 [vehicle control], 0.02, 0.1, 0.48, and 2.4 Units/kg/day) was administered by intramuscular injection to pregnant rabbits (20/group) daily during organogenesis (GD 7 to 19). The vehicle control consisted of 0.9% sodium chloride with 0.01% Tween 20. An additional dose group of 50 units/kg/day RTP004 was included in this study. Severe maternal toxicity, as evidenced by lethality, resulted in early termination of the 2.4 Units/kg/day dose. Maternal toxicity, as evidenced by decreased body weight gain (61% of vehicle control) and reduced feed intake, was observed at 0.48 Units/kg/day. The litter averages for corpora lutea, implantations, percentages of pre- and postimplantation loss, litter size, live fetuses, early and late resorptions, fetal body weight, percentage of resorbed conceptuses, and percentage of live male fetuses were comparable among the remaining treated groups and did not differ significantly from vehicle control group values. The NOAEL for embryofetal development was 0.48 Units/kg/day DAXXIFY. No treatment-related effects were noted in the 50 units/kg/day RTP004 dose group.

Prenatal and Postnatal Development

Based on the well-understood biological activity of DAXXIFY, the sponsor was granted a waiver for conduct of the prenatal and postnatal development study.

6. Clinical Pharmacology

6.1. Executive Summary

DaxibotulinumtoxinA (DAXXIFY) for injection is a new botulinum neurotoxin type A (BoNTA), derived from (b) (4) *Clostridium botulinum*. DAXXIFY inhibits acetylcholine release, blocks neuromuscular transmission, and reduces muscle activity following intramuscular injection. In this BLA, the Applicant proposed a dose of DAXXIFY at 0.1 mL (8 Units) by intramuscular injection into each of five injection sites, for a total of 40 Units per treatment for the (b) (4) temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

The active pharmaceutical ingredient, DAXXIFY, is composed of purified 150 kDa BoNTA, formulated in a lyophilized powder containing a novel peptide excipient (RTP004). Purified DAXXIFY is free of accessory proteins (i.e., contains no human serum albumin or bacterial hemagglutinins) and human- or animal-derived components.

The same drug product formulation for DAXXIFY for injection was used throughout all clinical studies in the glabellar lines program.

To support this indication, the Applicant has submitted five clinical trials: three Phase 3 trials (1620301 and 1620302 [Phase 3], and 1620303 [Open-label study, OLS]) and two Phase 1/2 trials (RT002-CL001 [Phase 1/2] and RT002-CL002 [Phase 2]).

Due to the low dose of DAXXIFY administered for the treatment of glabellar lines (picogram [pg] quantities), the resultant systemic drug concentrations are very low and undetectable by existing modern bioanalytical technologies. Therefore, no pharmacokinetic (PK) or absorption, distribution, metabolism, or excretion studies were conducted to evaluate bioavailability of DAXXIFY or the novel excipient, RTP004, following intramuscular injection at the intended clinical dose.

6.1.1. Recommendations

From a clinical pharmacology standpoint, DAXXIFY for injection for the treatment of glabellar lines is approvable with the proposed dosing regimen in the target population.

6.1.2. Postmarketing Requirement and Commitments

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Due to the low dose of DAXXIFY administered for the treatment of glabellar lines (picogram [pg] quantities), the resultant systemic drug concentrations are expected to be very low and undetectable by existing modern bioanalytical technologies. Therefore, the Applicant did not perform PK assessments and requested a waiver for bioavailability studies for both DAXXIFY and the novel excipient, RTP004, following intramuscular injection at the intended clinical dose.

The sponsor stated that in the Phase 1/2 efficacy/safety trials of DAXXIFY (RT002-CL001 and RT002-CL002), there were no systemic side effects after single DAXXIFY applications at different dose levels. Based on all of the evidence provided, the PK waiver for bioavailability studies for both DAXXIFY and RTP004 in this application is acceptable.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The efficacy results in Phase 3 trials appear to support the acceptability of the proposed dosing regimen: a dose of DAXXIFY at 0.1 mL (8 Units) by intramuscular injection into each of five injection sites, for a total of 40 Units per treatment. The dose might need to be repeated within 3 to 4 months.

Therapeutic Individualization

Not applicable.

Outstanding Issues

There are no outstanding issues that would preclude the approval of DAXXIFY for the (b) (4) temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacokinetics (PK)

The Applicant did not assess PK in this application due to the low dose of DAXXIFY administered, and that resultant systemic drug concentrations are expected to be very low, and therefore undetectable. Furthermore, there is no validated bioanalytical method available for the assessment of systemic exposure.

Immunogenicity

Overall, the findings from the submitted Phase 1/2, Phase 2, and Phase 3 trials demonstrate a low incidence of treatment-induced or treatment-boosted binding antibodies in subjects receiving up to three treatments of DAXXIFY for injection in the treatment of glabellar lines. In the Phase 1/2 and Phase 2 trials, GL-Mexico and GL-Belmont, no antibodies were detected. In the Phase 3 trials and in the open-label safety study (trials 1620301 and 1620302 [Phase 3], and 1620303 [Open-label study, OLS]), a small number of subjects ($\leq 1.5\%$) developed treatment-related antibodies to DAXXIFY injection. Of those subjects that developed treatment-related binding antibodies to DAXXIFY, no subjects developed neutralizing antibodies, and all subjects demonstrated treatment efficacy. The presence of anti-drug antibodies was not associated with immune-related treatment-emergent adverse events (TEAEs), nor with local injection site reactions. It should be noted that it is not feasible to evaluate the impact of immunogenicity on PK due to the lack of PK data.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Not applicable.

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

Not applicable.

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

Not applicable.

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

Not applicable.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The following studies were submitted in support of the current application and are listed in [Table 8](#) below.

Table 8. Tabular Listing of All Clinical Studies

| Trial Identity | Trial Design | Regimen/Schedule/Route | Study Endpoints | Treatment Duration/Follow Up | No. of Subjects Enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---------------------------------|--|-------------------------------------|
| <i>Controlled Studies to Support Efficacy and Safety</i> | | | | | | | |
| SAKURA1 | Double-blind, placebo-controlled, efficacy and safety | 0.1 mL injections at five sites; or placebo | <ul style="list-style-type: none"> Proportion of subjects with a 2-point or greater improvement from baseline on both the investigator and subject ratings of frown wrinkle severity (IGA-FWS and PFWS) at Week 4 | Up to 38 weeks with a 24 to 36-week post-treatment follow-up period | 303 | Moderate to severe glabellar lines in healthy adults, 18-75 years of age | US – 15 centers |
| SAKURA2 | Double-blind, placebo-controlled, efficacy and safety | 0.1 mL injections at five sites; or placebo | <ul style="list-style-type: none"> Proportion of subjects with a 2-point or greater improvement from baseline on both the investigator and subject ratings of frown wrinkle severity (IGA-FWS and PFWS) at Week 4 | Up to 38 weeks with a 24 to 36-week post-treatment follow-up period | 306 | Moderate to severe glabellar lines in healthy adults, 18-75 years of age | US and Canada – 15 centers |
| <i>Studies to Support Safety</i> | | | | | | | |
| SAKURA-OLS | Non-Randomized, Open-Label Safety Study of Multiple Doses | 0.1 mL injections at five sites; or placebo | <ul style="list-style-type: none"> Long-term safety of DAXXIFY for the treatment of moderate to severe glabellar lines following single and repeat administration | 12 to 84-week follow-up period | 2691 | Moderate to severe glabellar lines in healthy adults, 18-75 years of age | US and Canada – 65 centers |
| GL-Belmont | Dose ranging study (double-blind, placebo-controlled) | 0.1 mL injections at five sites; or placebo | <ul style="list-style-type: none"> Safety and efficacy of a single treatment of RT002 (DAXXIFY) at three dosage levels for the treatment of glabellar lines vs. BOTOX Cosmetic. Duration of effect of a single treatment of RT002 (DAXXIFY) at three dosage levels vs. BOTOX Cosmetic | Up to 38 weeks with a 24 to 36-week post-treatment follow-up period | 268 | Moderate to severe glabellar lines in healthy adults, 30-65 years of age | Canada – 9 centers |

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| Trial Identity | Trial Design | Regimen/Schedule/Route | Study Endpoints | Treatment Duration/Follow Up | No. of Subjects Enrolled | Study Population | No. of Centers and Countries |
|-----------------------|--|-------------------------------|--|--|---------------------------------|---|-------------------------------------|
| GL-Mexico | Dose escalation/tolerability study; open-label | | <ul style="list-style-type: none"> • Safety and efficacy of a single treatment of RT002 (DAXXIFY) for the treatment of glabellar lines. • Duration of effect (response). | Up to 34 weeks with a 6 to 32-week post-treatment follow-up period | 48 | Moderate to severe glabellar lines in healthy adults, 30- 60 years of age | Mexico – 1 center |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; IGA-FWS = Investigator Global Assessment Frown Wrinkle Severity; PFWS = Patient Frown Wrinkle Severity.
Source:

7.2. Review Strategy

Data Sources

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

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

Data and Analysis Quality

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

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

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

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Design for Studies 1620301 and 1620302

Trial Design

Study 1620301 (SAKURA-1 or Study 301) and Study 1620302 (SAKURA-2 or Study 302) were identical randomized, double-blind, placebo-controlled Phase 3 trials that evaluated DAXXIFY 40 Units for the temporary improvement in the appearance of moderate to severe glabellar

lines. The trials enrolled subjects 18 to 75 years of age. Subjects were to have moderate or severe glabellar lines at maximum frown based on the Investigator Global Assessment-Frown Wrinkle Severity (IGA-FWS) scale and the Patient Frown Wrinkle Severity (PFWS) scale. Each trial was designed to enroll approximately 300 subjects randomized 2:1 to DAXXIFY or placebo. Subjects were treated with 40 Units of DAXXIFY or placebo on Day 0 and were followed for 24 to 36 weeks. Subjects were evaluated on Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36. Subjects discontinued visits on or after Week 24 if both their scores on the IGA-FWS and PFWS had returned to baseline values.

Study Endpoints

Efficacy was assessed using the IGA-FWS and PFWS scales. Both scales used the same levels and descriptors. These scales are presented in [Table 9](#).

Table 9. Investigator Global Assessment-Frown Wrinkle Severity (IGA-FWS) and Patient Frown Wrinkle Severity (PFWS) Scales

| Rating Score | Frown Wrinkle Severity | Description |
|--------------|------------------------|----------------------------|
| 0 | None | No wrinkles |
| 1 | Mild | Very shallow wrinkles |
| 2 | Moderate | Moderate wrinkles |
| 3 | Severe | Deep and furrowed wrinkles |

Investigators and subjects also assessed improvement from baseline using the Global Aesthetic Improvement Score (GAIS), which is a 7-point scale ranging from -3 = Very Much Worse to +3 = Very Much Improved.

The primary efficacy endpoint is the proportion of subjects achieving a score of 0 or 1 (none or mild) and an improvement of at least two points from baseline to Week 4 concurrently, on both the IGA-FWS and PFWS scales. The Applicant refers to this endpoint as “2-point composite response.”

The protocol specified 10 secondary efficacy endpoints, many of which were evaluated at multiple time points. These secondary endpoints evaluated different definitions of success based on the IGA-FWS and/or PFWS, time to worsening, and response based on the GAIS. Based on FDA feedback, the sponsor reduced the number of secondary endpoints. The final list of secondary endpoints was defined in the appendix to the Statistical Analysis Plan and included two endpoints evaluated at seven timepoints as follows:

- The proportion of subjects who achieve a score of 0 or 1 (none or mild) on the IGA-FWS at maximum frown at Weeks 2, 4, 8, 12, 16, 20, and 24.
- The proportion of subjects who achieve a score of 0 or 1 (none or mild) on both the IGA-FWS and PFWS at maximum frown at Weeks 2, 4, 8, 12, 16, 20, and 24.

Statistical Analysis Plan

The primary analysis population was the intent-to-treat population defined as all subjects who were randomized and received treatment. The primary and secondary endpoints were analyzed with a Cochran-Mantel-Haenszel test stratified by trial center. The protocol specified that 95% confidence intervals would be calculated with the stratified Newcombe confidence limits for the common risk difference. To check for consistency, the summary score estimates of the common risk difference were also to be calculated.

Reviewer Comment:

The Newcombe method cannot compute confidence limits for the common risk difference if there are zero-frequency rows, columns, or cells¹. This can happen, for example, if the observed response rate in the placebo arm is 0%, which occurred in Study 301. Thus, the Newcombe confidence limits could not be calculated for the primary endpoint in Study 301. Because the study report for Study 301 presented confidence intervals described as Newcombe confidence intervals, the Applicant was queried in the Filing Communication sent on February 4, 2020 regarding the actual method used. The Applicant responded in a February 18, 2020 Information Amendment that the data was analyzed using Newcombe confidence intervals per the protocol and statistical analysis plan. However, review of the statistical programs provided by the Applicant in the original submission indicated that the programs were designed to output the Mantel-Haenszel confidence intervals, even if an alternate method such as the Newcombe method was specified as an input to the program. This reviewer verified that the confidence intervals for the primary endpoint presented in the study reports for both Study 301 and Study 302 are based on the Mantel-Haenszel method. Because the Mantel-Haenszel intervals are commonly used, and this method can be used with zero-frequency rows, columns, or cells, this reviewer also presents the confidence interval results using the Mantel-Haenszel method. For consistency across studies, this reviewer presents the Mantel-Haenszel intervals for both Studies 301 and 302, even in situations where the Newcombe confidence intervals can be calculated.

Missing data was handled with “worst/best outcome” imputation. For this imputation:

- Subjects with no post-baseline efficacy data are classified as non-responders.
- For subjects who dropout, the worst outcome (for subjects on the DAXXIFY arm) or best outcome (for subjects on the placebo arm) from all available post-baseline values of the timepoint will be used.

¹ Yan, X and X Gang Su, 2010, Stratified Wilson and Newcombe Confidence Intervals for Multiple Binomial Proportions, *Statistics in Biopharmaceutical Research*, 2:3, 329-335.

- For subjects with interim missing values, the worst outcome (for subjects on the DAXXIFY arm) or best outcome (for subjects on the placebo arm) of available values at the timepoint immediately prior and immediately after will be used.

As a sensitivity analysis, a multiple imputation approach to handling missing data was used. The Markov chain Monte Carlo method was used with 10 imputations. For this analysis, the data were analyzed with logistic regression stratified on trial center.

To control the multiplicity across the secondary endpoints, the secondary endpoints were analyzed in sequential order. For each timepoint (Week 2, 4, 8, 12, 16, 20, and 24 in the listed order), the endpoint based on the IGA-FWS was tested first, followed by the endpoint based on both the IGA-FWS and the PFWS.

Protocol Amendments

Protocols 301 and 302 were amended once prior to the initiation of the study to add additional information on safety assessments and to make administrative changes. In addition, the Statistical Analysis Plan was updated prior to database lock to reduce the number of secondary endpoints and modify the plan for controlling multiplicity across the secondary endpoints.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that the trials were conducted in compliance with the protocols: the ICH guidance for industry *E6 Good Clinical Practice (GCP): Consolidated Guidance* (April 1996) and the applicable regulatory requirements, and the Declaration of Helsinki. Trial protocols, subject information and informed consent forms, and subject recruitment procedures were reviewed by the responsible independent Ethics Committees and/or Institutional Review Board (IRB). The Applicant obtained an approval from the IRB prior to trial initiation.

Financial Disclosure

Please see Appendix [19.2](#).

Patient Disposition

Study 301 enrolled 303 subjects, of which 201 were randomized to DAXXIFY and 102 were randomized to placebo. Study 302 enrolled 306 subjects, of which 204 were randomized to DAXXIFY and 102 were randomized to placebo. However, one subject randomized to placebo in Study 302 was treated with DAXXIFY. Initially, an appropriate placebo treatment kit (Kit # (b) (6)) was pulled for Subject (b) (6). However, due to syringe malfunction, a large air bubble could not be purged. Thus, the next sequential kit (Kit # (b) (6)) was used to treat this subject. However, Kit # (b) (6) was a DAXXIFY kit. In the Applicant's analyses, Subject (b) (6) is included "as-randomized" (placebo) in efficacy analyses, and "as treated" (DAXXIFY) for safety analyses.

Approximately 98% of subjects completed the Week 4 visit and 92% of subjects completed study follow-up. The most common reasons for study discontinuation were withdrawal of consent and lost to follow-up. See [Table 10](#).

Table 10. Disposition of Subjects (Studies 301 and 302)

| | Study 301 | | Study 302 | |
|-----------------------------|------------------|------------------|------------------|------------------|
| | DAXXIFY N=201 | Placebo N=102 | DAXXIFY N=204 | Placebo N=102 |
| Subjects randomized | 201 | 102 | 204 | 102 |
| Completed Week 4 Visit | 196 (98%) | 97 (95%) | 203 (99%) | 99 (97%) |
| Completed study | 182 (91%) | 93 (91%) | 191 (94%) | 93 (91%) |
| Reasons for discontinuation | | | | |
| Subject withdrew consent | 8 (4%) | 4 (4%) | 9 (4%) | 5 (5%) |
| Lost to follow-up | 6 (3%) | 4 (4%) | 1 (<1%) | 3 (3%) |
| Protocol deviation | - | 1 (1%) | 1 (<1%) | 1 (1%) |
| Investigator discretion | 1 (<1%) | - | 1 (<1%) | - |
| Other | 4 (2%) | - | 1 (<1%) | - |

Abbreviations: DAXXIFY = daxibotulinumtoxinA.

Source: pg 58 of Study Report 301 and pg 57 of Study Report 302 and reviewer analysis.

Protocol Violations/Deviations

Approximately 9 to 12% of DAXXIFY subjects and 12 to 23% of placebo subjects were excluded from the per protocol population due to protocol violations. [Table 11](#) presents the reasons for exclusions. The most common reasons were the Week 4 visit off-schedule by more than ± 3 days, violating inclusion/exclusion criteria, and missing the Week 4 visit.

Table 11. Per Protocol (PP) Analysis Set (Studies 301 and 302)

| | Study 301 | | Study 302 | |
|---|------------------|------------------|------------------|------------------|
| | DAXXIFY N=201 | Placebo N=102 | DAXXIFY N=204 | Placebo N=102 |
| Subjects excluded from the PP analysis set | 25 (12%) | 23 (23%) | 18 (9%) | 12 (12%) |
| Primary reason for exclusion | | | | |
| Week 4 visit off-schedule (± 3 days) | 15 (8%) | 12 (12%) | 9 (4%) | 6 (6%) |
| Violated inclusion/exclusion criteria | 6 (3%) | 6 (6%) | 7 (3%) | 2 (2%) |
| Missed Week 4 visit | 5 (3%) | 5 (5%) | 1 (<1%) | 3 (3%) |
| Missed IGA-FWS or PFWS evaluation at Week 4 | 5 (3%) | 5 (5%) | 1 (<1%) | 3 (3%) |
| Used prohibited medication prior to Week 4 | 1 (<1%) | 1 (1%) | 1 (<1%) | - |
| Subject received incorrect treatment kit | 1 (<1%) | - | - | 1 (1%) |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; IGA-FWS = Investigator Global Assessment Frown Wrinkle Severity; PFWS = Patient Frown Wrinkle Severity.

Subjects may have been excluded for more than one reason.

Source: pg 60 of Study Report 301 and pg 59 of Study Report 302 and reviewer analysis.

Table of Demographic Characteristics

The baseline demographics were generally balanced across the treatment groups in both studies (see [Table 12](#)). The majority of subjects were female, white, and not Hispanic or Latino. The mean age was 50 years.

Table 12. Demographics (Studies 301 and 302)

| | Study 301 | | Study 302 | |
|------------------------|------------------|------------------|------------------|------------------|
| | DAXXIFY N=201 | Placebo N=102 | DAXXIFY N=204 | Placebo N=102 |
| Age (years) | | | | |
| Mean | 50.9 | 49.0 | 49.6 | 50.5 |
| Range | 23-74 | 22-74 | 21-73 | 27-75 |
| 18-45 years | 58 (28.9%) | 32 (31.4%) | 30 (29.4%) | 62 (30.4%) |
| 46-55 years | 68 (33.8%) | 41 (40.2%) | 42 (41.2%) | 91 (44.6%) |
| 56-75 years | 75 (37.3%) | 29 (28.4%) | 30 (29.4%) | 51 (25.0%) |
| Gender | | | | |
| Female | 174 (86.6%) | 88 (86.3%) | 183 (89.7%) | 87 (85.3%) |
| Male | 27 (13.4%) | 14 (13.7%) | 21 (10.3%) | 15 (14.7%) |
| Race | | | | |
| White | 173 (86.1%) | 81 (79.4%) | 180 (88.2%) | 92 (90.2%) |
| Black or Afric.-Amer. | 10 (5.0%) | 8 (7.8%) | 9 (4.4%) | 3 (2.9%) |
| Other | 10 (5.0%) | 7 (6.9%) | 3 (1.5%) | 1 (1.0%) |
| Asian | 7 (3.5%) | 2 (2.0%) | 11 (5.4%) | 5 (4.9%) |
| Multiple | 1 (0.5%) | 2 (2.0%) | 1 (0.5%) | 1 (1.0%) |
| Am. Ind./ AK Native | 0 | 1 (1.0%) | 0 | 0 |
| Native HI/ Pac. Isl. | 0 | 1 (1.0%) | 0 | 0 |
| Ethnicity | | | | |
| Not Hispanic or Latino | 154 (76.6%) | 77 (75.5%) | 185 (90.7%) | 92 (90.2%) |
| Hispanic or Latino | 47 (23.4%) | 25 (24.5%) | 19 (9.3%) | 10 (9.8%) |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; Am. Ind. = American Indian; AK = Alaska; HI = Hawaiian; Pac. Isl. = Pacific Islander.

Percentages may not sum to 100% due to rounding

Source: pg 61 of Study Report 301 and pg 61 of Study Report 302 and reviewer analysis.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease characteristics were balanced across treatment arms. Approximately 45% of subjects in Study 301 and 59% of subjects in Study 302 had prior botulinum toxin Type A use. Similar proportions of subjects in Study 301 were classified as moderate on both the IGA-FWS and PFWS. A higher proportion of subjects were rated as moderate on the IGA-FWS than on the PFWS in Study 302 (see [Table 13](#)).

Table 13. Baseline Disease Characteristics (Studies 301 and 302)

| | Study 301 | | Study 302 | |
|----------------------------|------------------|------------------|------------------|------------------|
| | DAXXIFY N=201 | Placebo N=102 | DAXXIFY N=204 | Placebo N=102 |
| Prior botulinum toxin use | | | | |
| Yes | 92 (45.8%) | 45 (44.1%) | 121 (59.3%) | 60 (58.8%) |
| No | 109 (54.2%) | 57 (55.9%) | 83 (40.7%) | 42 (41.2%) |
| IGA-FWS (at maximum frown) | | | | |
| Moderate | 123 (61.2%) | 66 (64.7%) | 129 (63.2%) | 67 (65.7%) |
| Severe | 78 (38.8%) | 36 (35.3%) | 75 (36.8%) | 35 (34.3%) |
| PFWS (at maximum frown) | | | | |
| Moderate | 120 (59.7%) | 64 (62.7%) | 106 (52.0%) | 49 (48.0%) |
| Severe | 81 (40.3%) | 38 (37.3%) | 98 (48.0%) | 53 (52.0%) |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; IGA-FWS = Investigator Global Assessment Frown Wrinkle Severity; PFWS = Patient Frown Wrinkle Severity.

Percentages may not sum to 100% due to rounding

Source: pg 61-62 of Study Report 301 and pg 61-62 of Study Report 302 and reviewer analysis.

Efficacy Results – Primary Endpoint

DAXXIFY was superior to placebo in Study 301 and Study 302 for the primary endpoint of proportion of subjects achieving a score of 0 or 1 (none or mild) and an improvement of at least two points from baseline to Week 4 concurrently, on both the IGA-FWS and PFWS scales. The IGA-FWS had response rates that were 10 to 15% higher than the PFWS (see [Table 14](#)).

Table 14. Primary Efficacy Endpoint at Week 4 (Studies 301 and 302; ITT – as randomized)

| | Study 301 | | | Study 302 | | |
|-------------------|------------------|------------------|------------------------------------|------------------|------------------|------------------------------------|
| | DAXXIFY N=201 | Placebo N=102 | Estimate 95% CI p-value | DAXXIFY N=204 | Placebo N=102 | Estimate 95% CI p-value |
| Treatment success | 148 (73.6%) | 0 (0%) | 74.2% (68.2%, 80.2%) <0.0001 | 151 (74.0%) | 1 (1.0%) | 72.9% (66.6%, 79.1%) <0.0001 |
| IGA-FWS | 176 (87.6%) | 1 (1.0%) | | 187 (91.7%) | 3 (2.9%) | |
| PFWS | 155 (77.1%) | 0 (0%) | | 156 (76.5%) | 1 (1.0%) | |

P-values are from the Cochran-Mantel-Haenszel test stratified on analysis center. Confidence intervals are from the Mantel-Haenszel estimate for the common risk difference. Missing IGA-FWS and PFWS imputed using same rules as the primary endpoint. Abbreviations: ITT = intent-to-treat; IGA-FWS = Investigator Global Assessment-From Wrinkle Severity scale; PFWS = Patient Frown Wrinkle Severity Scale; DAXXIFY = dax botulinumtoxinA.

Source: pg 65 of Study Report 301 and pg 65 of Study Report 302 and reviewer analysis.

As discussed in Section [8.1.1](#) regarding the Statistical Analysis Plan, the protocol specified that the confidence intervals for the common risk difference would be calculated using Newcombe's method. However, the Newcombe confidence intervals cannot be calculated if there are zero-frequency rows, columns, or cells, which is the case in Study 301 where the placebo treatment success rate is 0%. However, for the analysis presented in [Table 14](#), the Newcombe confidence interval for Study 302 can be calculated. For reference, the point estimate remains the same (72.9%), and the Newcombe confidence interval is (61.6%, 78.6%).

One subject in Study 302 was randomized to placebo, but treated with DAXXIFY. This subject met the primary efficacy endpoint criteria at Week 4 and is the only subject analyzed in the placebo arm classified as a responder. None of the subjects treated with placebo in Study 301 and 302 were classified as responders. The as-treated results for Study 302 are presented in [Table 15](#). Shifting one subject from the placebo arm to the DAXXIFY arm had minimal impact on the results.

Table 15. Primary Efficacy Endpoint at Week 4 (Study 302; as treated)

| | Study 302 | | Estimate 95% CI p-value |
|-------------------|------------------|------------------|------------------------------------|
| | DAXXIFY N=205 | Placebo N=101 | |
| Treatment success | 152 (74.2%) | 0 (0%) | 72.8% (67.7%, 79.8%) <0.0001 |
| IGA-FWS | 188 (91.7%) | 2 (2.0%) | |
| PFWS | 157 (76.6%) | 0 (0%) | |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; IGA-FWS = Investigator Global Assessment Frown Wrinkle Severity; PFWS = Patient Frown Wrinkle Severity.

P-values are from the Cochran-Mantel-Haenszel test stratified on analysis center. Confidence intervals are from the Mantel-Haenszel estimate for the common risk difference. Missing IGA-FWS and PFWS were imputed using same rules as the primary endpoint.

Source: reviewer analysis.

Data Quality and Integrity

In addition to the issue described above, where one subject randomized to placebo was treated with DAXXIFY due to a problem with the intended syringe, the Applicant identified two additional data quality issues.

One issue was caused by incorrect data entry by study personnel. Two subjects at Site 103 in Study 301, were randomized on the same day and treated correctly (one subject treated with DAXXIFY and one with placebo). However, when site personnel entered the kit numbers for these two subjects into the electronic database, the treatment kit numbers were reversed, causing these two subjects to have incorrect treatment assignments in the database. Subject (b) (6) (treated with DAXXIFY, but listed in the database as placebo) dropped out of the study after Day 8 and did not participate in any post-baseline efficacy assessments. Thus, this subject was classified as a failure on all efficacy assessments. Subject (b) (6) (treated with placebo, but listed in the database as DAXXIFY) completed the study and was classified as “severe” on both the IGA-FWS and PFWS at each study visit. Thus, this subject was classified as a failure on all efficacy assessments. The Applicant identified the data entry error after database lock, while reviewing the data, as it was unusual for a subject supposedly treated with DAXXIFY to not show any improvement following treatment. Because both subjects were classified as failures on all assessments, the Applicant decided not to modify the database and analyzed the two subjects as entered into the database. This decision had no impact on the results.

The second issue with data quality was identified through routine site monitoring. During a site audit, the investigator at Site 106 in Study 301 was observed to have failures related to informed consent, source documentation deficiencies, and insufficient maintenance of essential documents. The Applicant notes that these issues were addressed and resolved by the site. However, this investigator also participated in Study 1620303 (a long-term, open-label study that included subjects rolled over from Study 301 and new subjects), and additional issues were identified at the site in Study 1620303. The investigator was determined to be non-compliant with the investigational plan by being absent from the study site for a significant amount of time, missing subject visits, and failing to document review of subjects' safety assessments prior to enrollment. Because of these issues with the investigator, the Applicant conducted subgroup analyses excluding Site 106 from the analyses of Study 301. Site 106 enrolled eight subjects (five DAXXIFY and three placebo). Site 106 enrolled the fewest subjects of any site in Study 301. No subjects on either arm met the primary endpoint response criteria. Thus, the removal of this site from analyses had minimal impact on the overall results.

Table 16. Primary Efficacy Endpoint at Week 4 Excluding Site 106 (Study 301; ITT - as randomized)

| | Study 301 (Excluding Site 106) | | | Site 106 | | |
|-------------------|--------------------------------|-----------------|-----------------------------------|----------------|----------------|-------------------------------|
| | DAXXIFY N=196 | Placebo N=99 | Estimate 95% CI p-value | DAXXIFY N=5 | Placebo N=3 | Estimate 95% CI p-value |
| Treatment success | 148 (75.5%) | 0 (0%) | 76.0% (70.1%, 81.9%) <0.001 | 0 (0%) | 0 (0%) | NA |
| IGA-FWS | 175 (89.3%) | 1 (1.0%) | | 1 (20%) | 0 (0%) | |
| PFWS | 155 (79.1%) | 0 (0%) | | 0 (0%) | 0 (0%) | |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; IGA-FWS = Investigator Global Assessment Frown Wrinkle Severity; NA = not applicable; PFWS = Patient Frown Wrinkle Severity.

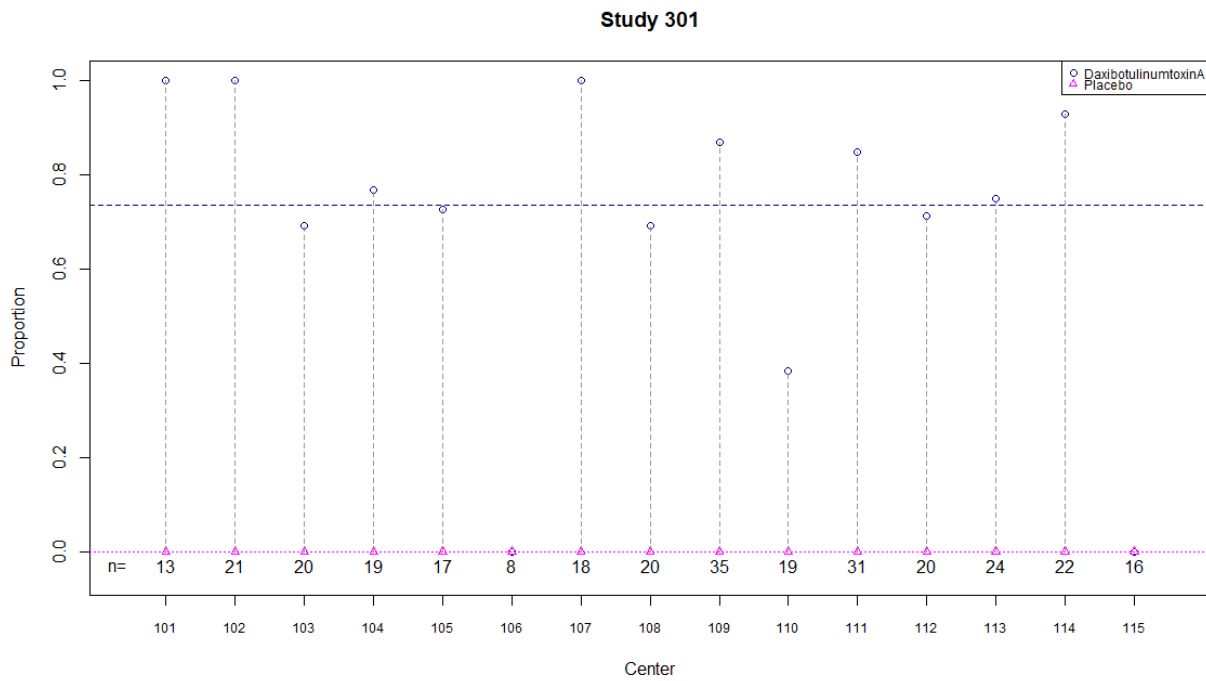
P-values are from the Cochran-Mantel-Haenszel test stratified on analysis center. Confidence intervals are from the Mantel-Haenszel estimate for the common risk difference. Missing IGA-FWS and PFWS were imputed using same rules as the primary endpoint.

Source: pg 210 of Study Report 301 and reviewer analysis.

Efficacy by Center

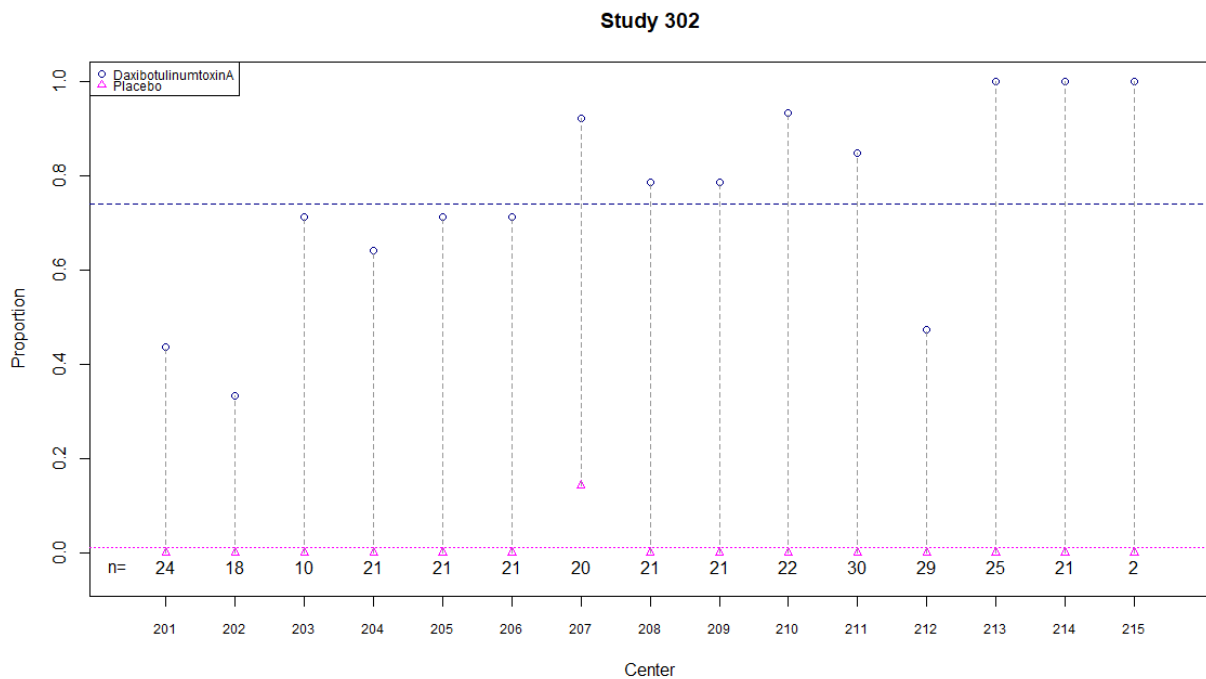
Study 301 enrolled subjects at 15 sites. Two sites, Site 101 with 13 subjects and Site 106 with 8 subjects, were combined into an analysis center for the analysis. Study 302 enrolled subjects at 15 sites. Two sites, Site 203 with 10 subjects and Site 215 with 2 subjects, were combined into an analysis center for the analysis. Results were generally consistent across centers for the primary efficacy endpoint (see [Figure 1](#) and [Figure 2](#)).

Figure 1. Primary Efficacy Endpoint by Center (Study 301; ITT – as randomized)



The total sample size (n) is presented for each center.
 Source: reviewer analysis.

Figure 2. Primary Efficacy Endpoint by Center (Study 302; ITT – as randomized)



The total sample size (n) is presented for each center.
 Source: reviewer analysis.

Missing Data Handling

Missing data was handled with “worst/best outcome” imputation. For this imputation:

- Subjects with no post-baseline efficacy data are classified as non-responders.
- For subjects who dropout, the worst outcome (for subjects on the DAXXIFY arm) or best outcome (for subjects on the placebo arm) from all available post-baseline values of the timepoint will be used.
- For subjects with interim missing values, the worst outcome (for subjects on the DAXXIFY arm) or best outcome (for subjects on the placebo arm) of available values at the timepoint immediately prior and immediately after will be used.

In Study 301, 10 subjects (5 DAXXIFY and 5 placebo) were missing Week 4 assessments. In Study 302, 4 subjects (1 DAXXIFY and 3 placebo) were missing Week 4 assessments. All 8 placebo subjects across both studies were imputed as failures on the primary efficacy endpoint, as none of these subjects were classified as responders on neighboring visits. Of the 6 DAXXIFY subjects across both studies, 4 were classified as responders and 2 were classified as non-responders. Three of these subjects had observed data at a later week (after the primary timepoint of Week 4) at which the subject was classified as a responder. The fourth subject was observed as a responder on Week 1, but had no additional study visits. The Applicant’s justification for imputing these subjects as responders is that subjects treated with DAXXIFY who meet the responder definition, generally meet the criteria within the first few weeks, and then slowly worsen over time until the response criteria are no longer met (see also Figure 3 and Figure 4 below). The missing data patterns for these subjects is presented in [Table 17](#). Missing data had limited impact on the primary efficacy analysis because of the large effect size and small proportion of subjects with missing data.

Table 17. Observed Primary Endpoint Data and Week 4 “Worst/Best” Imputation for Subjects Treated with DaxibotulinumtoxinA and Missing Week 4 Data (Studies 301 and 302)

| Subject | Week | | | | | Week 4 Imputation |
|---------|------|---|---|---|----|-------------------|
| | 1 | 2 | 4 | 8 | 12 | |
| (b) (6) | . | . | . | Y | Y | Y |
| | . | . | . | . | . | N |
| | Y | Y | . | Y | Y | Y |
| | N | N | . | . | . | N |
| | Y | . | . | . | . | Y |
| | . | . | . | . | Y | Y |

Abbreviations: Y = met the primary endpoint criteria; N = did not meet the primary endpoint criteria; (.) = missing data.
Source: reviewer analysis.

As a sensitivity analysis, a multiple imputation approach (the Markov chain Monte Carlo method) to handling missing data was used. The results of the multiple imputation analysis were very similar to the primary analysis based on “worst/best outcome” imputation. See [Table 18](#).

Table 18. Primary Efficacy Endpoint at Week 4 Using Multiple Imputation (Studies 301 and 302; ITT – as randomized)

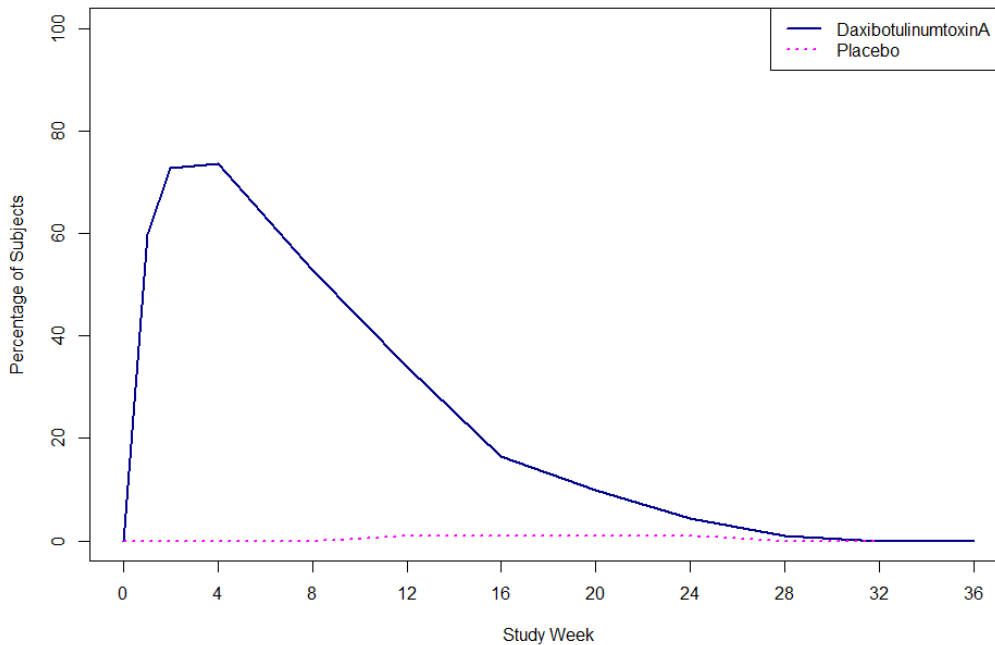
| | Study 301 | | | Study 302 | | |
|-------------------|------------------|------------------|------------------------------------|------------------|------------------|------------------------------------|
| | DAXXIFY N=201 | Placebo N=102 | Estimate 95% CI p-value | DAXXIFY N=204 | Placebo N=102 | Estimate 95% CI p-value |
| Treatment success | 73.4% | 0% | 73.4% (67.3%, 79.6%) <0.0001 | 73.9% | 1.0% | 72.8% (66.5%, 79.1%) <0.0001 |

Abbreviations: ITT = intent-to-treat; DAXXIFY = daxibotulinumtoxinA.
P-values are from the Cochran-Mantel-Haenszel test stratified on analysis center. Confidence intervals are from the Mantel-Haenszel estimate for the common risk difference. Missing IGA-FWS and PFWS imputed using same rules as the primary endpoint.
Source: pg 211 of Study Report 301 and pg 210 of Study Report 302 and reviewer analysis.

Efficacy Over Time

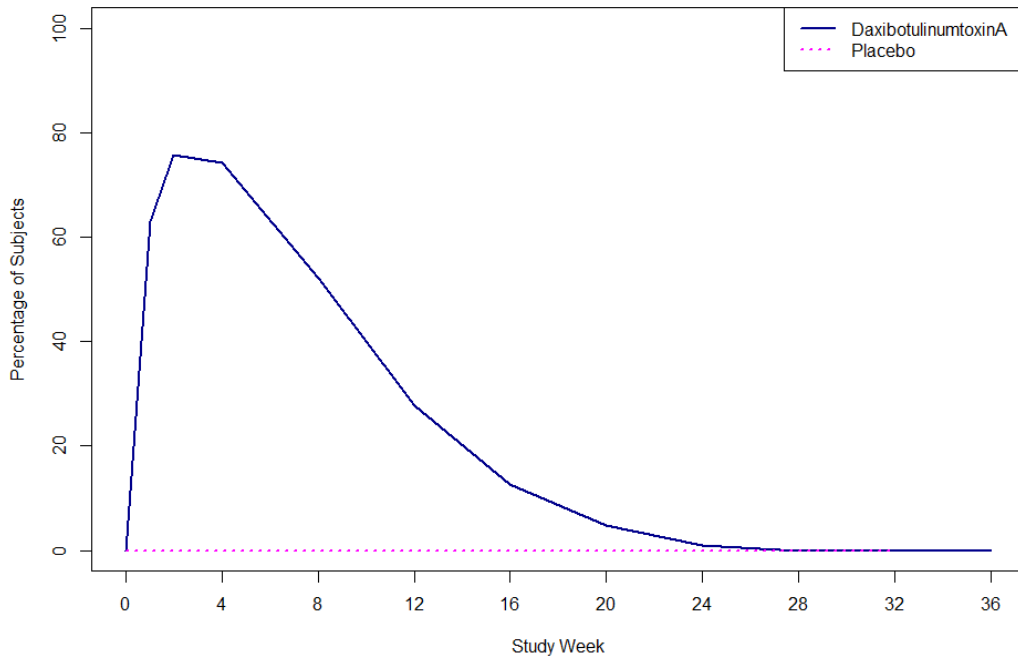
The primary efficacy outcome achieved its highest proportion at Weeks 2 and 4 for subjects treated with DAXXIFY, and decreased over time (see [Figure 3](#) and [Figure 4](#)).

Figure 3. Primary Efficacy Endpoint Over Time (Study 301; ITT – as randomized)



Abbreviations: ITT = intent-to-treat.
Source: Reviewer analysis.

Figure 4. Primary Efficacy Endpoint Over Time (Study 302; ITT – as randomized)



Abbreviations: ITT = intent-to-treat.
Source: Reviewer analysis.

Efficacy Results – Secondary and Other Relevant Endpoints

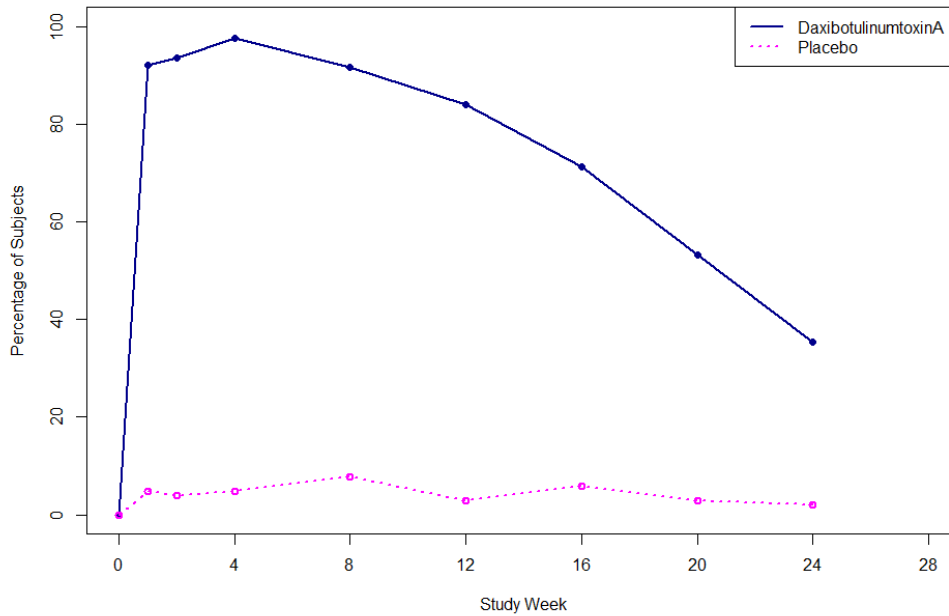
The final list of secondary endpoints included two endpoints evaluated at seven timepoints as follows:

- The proportion of subjects who achieve a score of 0 or 1 (none or mild) on the IGA-FWS at maximum frown at Weeks 2, 4, 8, 12, 16, 20, and 24.
- The proportion of subjects who achieve a score of 0 or 1 (none or mild) on both the IGA-FWS and PFWS at maximum frown at Weeks 2, 4, 8, 12, 16, 20, and 24.

To control the multiplicity across the secondary endpoints, the secondary endpoints were analyzed in sequential order. For each timepoint (Week 2, 4, 8, 12, 16, 20, and 24 in the listed order), the endpoint based on the IGA-FWS was tested first, followed by the endpoint based on both the IGA-FWS and the PFWS.

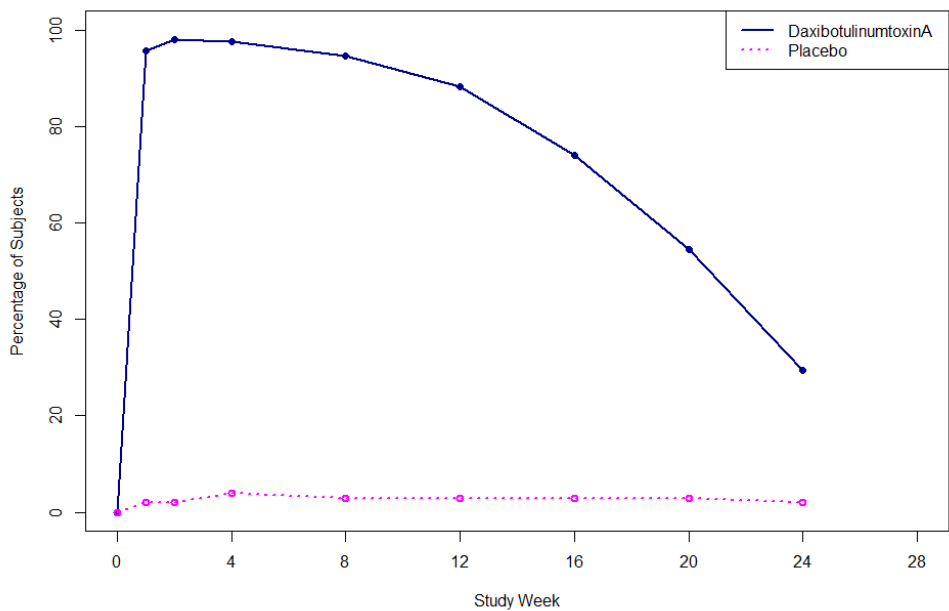
The proportion of subjects who achieved a score of 0 or 1 (none or mild) on the IGA-FWS at maximum frown are presented in [Figure 5](#) and [Figure 6](#). The proportion of subjects who achieved a score of 0 or 1 (none or mild) on both the IGA-FWS and PFWS at maximum frown are presented in [Figure 7](#) and [Figure 8](#). The proportions for these secondary endpoints are higher than for the primary endpoint because the criteria are less strict. Although the exact results for each secondary endpoint are not tabulated in this review, the specified secondary endpoints were all statistically significant when analyzed in the prespecified order.

Figure 5. Percentage of Subjects Who Achieved None or Mild on the IGA-FWS at Maximum Frown (Study 301; ITT – as randomized)



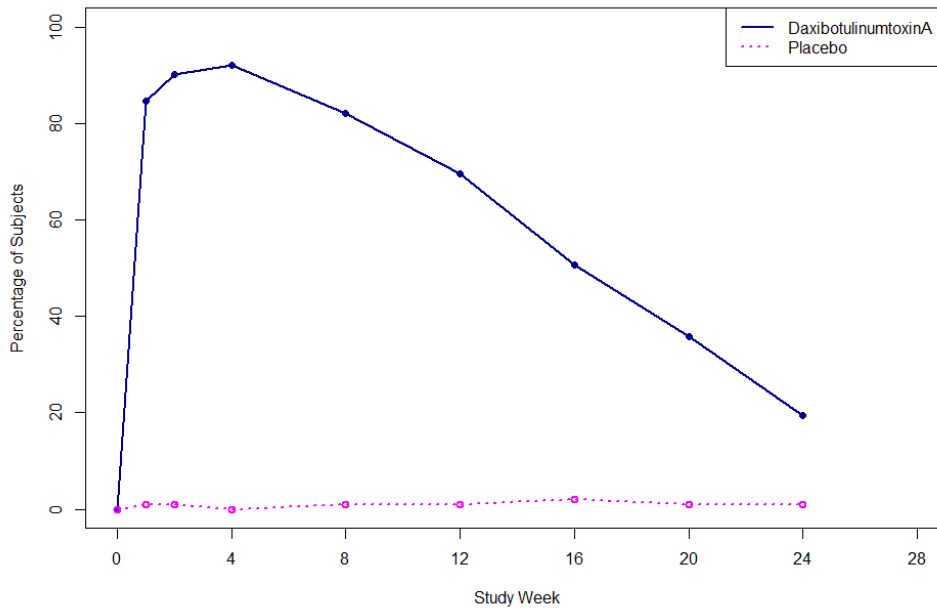
Abbreviations: ITT = intent-to-treat; IGA-FWS = Investigator Global Assessment Frown Wrinkle Severity.
Source: reviewer analysis.

Figure 6. Percentage of Subjects Who Achieved None or Mild on the IGA-FWS at Maximum Frown (Study 302; ITT – as randomized)



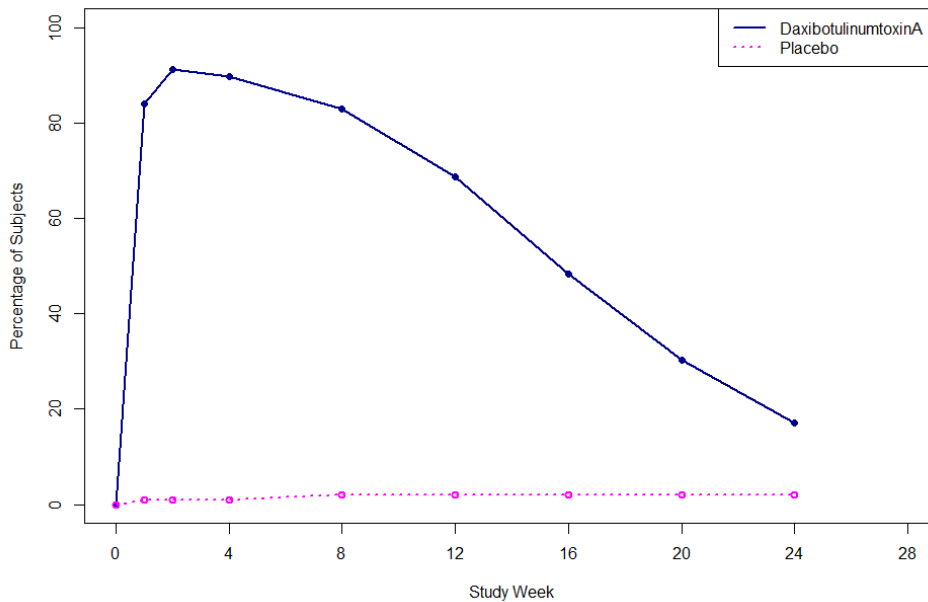
Abbreviations: ITT = intent-to-treat; IGA-FWS = Investigator Global Assessment Frown Wrinkle Severity.
Source: reviewer analysis.

Figure 7. Percentage of Subjects Who Achieved None or Mild on the IGA-FWS and PFWS at Maximum Frown (Study 301; ITT – as randomized)



Abbreviations: ITT = intent-to-treat; IGA-FWS = Investigator Global Assessment Frown Wrinkle Severity; PFWS = Patient Frown Wrinkle Severity
Source: reviewer analysis.

Figure 8. Percentage of Subjects Who Achieved None or Mild on the IGA-FWS and PFWS at Maximum Frown (Study 302; ITT – as randomized)



Abbreviations: ITT = intent-to-treat; IGA-FWS = Investigator Global Assessment Frown Wrinkle Severity; PFWS = Patient Frown Wrinkle Severity.
Source: reviewer analysis.

Findings in Special/Subgroup Populations

Treatment effects were generally consistent across age, gender, race, and ethnicity subgroups. The studies enrolled few subjects in the American Indian/Alaskan Native and Native Hawaiian/Pacific Islander groups (see [Table 19](#)).

Table 19. Primary Efficacy Endpoint by Subgroup (Studies 301 and 302)

| | Study 301 | | Study 302 | |
|------------------------|------------------|------------------|------------------|------------------|
| | DAXXIFY N=201 | Placebo N=102 | DAXXIFY N=204 | Placebo N=102 |
| Age (years) | | | | |
| 18-45 years | 50/58 (86%) | 0/32 (0%) | 49/62 (79%) | 1/30 (3%) |
| 46-55 years | 45/68 (66%) | 0/41 (0%) | 70/91 (77%) | 0/42 (0%) |
| 56-75 years | 53/75 (71%) | 0/29 (0%) | 32/51 (63%) | 0/30 (0%) |
| Gender | | | | |
| Female | 134/174 (77%) | 0/88 (0%) | 136/183 (74%) | 1/87 (1%) |
| Male | 14/27 (52%) | 0/14 (0%) | 15/21 (71%) | 0/15 (0%) |
| Race | | | | |
| White | 126/173 (73%) | 0/81 (0%) | 133/180 (74%) | 1/92 (1%) |
| Black or Afric.-Amer. | 8/10 (80%) | 0/8 (0%) | 8/9 (89%) | 0/3 (0%) |
| Other | 7/10 (70%) | 0/7 (0%) | 2/3 (67%) | 0/1 (0%) |
| Asian | 6/7 (86%) | 0/2 (0%) | 7/11 (64%) | 0/5 (0%) |
| Multiple | 1/1 (100%) | 0/2 (0%) | 1/1 (100%) | 0/1 (0%) |
| Am. Ind./ AK Native | - | 0/1 (0%) | - | - |
| Native HI/ Pac. Isl. | - | 0/1 (0%) | - | - |
| Ethnicity | | | | |
| Not Hispanic or Latino | 109/154 (71%) | 0/77 (0%) | 136/185 (74%) | 0/92 (0%) |
| Hispanic or Latino | 39/47 (83%) | 0/25 (0%) | 15/19 (79%) | 1/10 (10%) |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; Am. Ind. = American Indian; AK = Alaska; HI = Hawaiian; Pac. Isl. = Pacific Islander.

Source: reviewer analysis.

8.1.3. Assessment of Efficacy Across Trials

Primary Endpoints

The results for the primary efficacy endpoints were consistent across Studies 301 and 302. Both studies demonstrated statistical significance versus placebo for the primary efficacy endpoint of the proportion of subjects achieving a score of 0 or 1 (none or mild) and an improvement of at least two points from baseline to Week 4 concurrently, on both the IGA-FWS and PFWS scales. The efficacy results are summarized in [Table 20](#). The results for the secondary endpoints and subgroup analyses were supportive of the primary efficacy endpoints.

To minimize confusion in labeling, it may be appropriate to present the results as-treated rather than as-randomized, due to the subject in Study 302 who was randomized to placebo, yet treated with DAXXIFY. Because the observed response rate for the primary endpoint was so low in subjects treated with placebo (0%) in both studies, presenting the results as-treated may

provide more interpretable results, even if they are not presented as-randomized. With this approach, safety and efficacy tables would both present as-treated study results. The as-treated results are also presented in [Table 20](#).

Table 20. Primary Efficacy Endpoint at Week 4 (Studies 301 and 302)

| | Study 301 | | | Study 302 | | |
|---------------|--------------------|---------------|------------------------------------|--------------------|-----------------|------------------------------------|
| | DAXXIFY | Placebo | Estimate 95% CI p-value | DAXXIFY | Placebo | Estimate 95% CI p-value |
| As-randomized | 148/201 (73.6%) | 0/102 (0%) | 74.2% (68.2%, 80.2%) <0.0001 | 151/204 (74.0%) | 1/102 (1.0%) | 72.9% (66.6%, 79.1%) <0.0001 |
| As-treated | 148/201 (73.6%) | 0/102 (0%) | 74.2% (68.2%, 80.2%) <0.0001 | 152/205 (74.2%) | 0/101 (0%) | 72.8% (67.7%, 79.8%) <0.0001 |

Abbreviations: DAXXIFY = daxibotulinumtoxinA.

P-values are from the Cochran-Mantel-Haenszel test stratified on analysis center. Confidence intervals are from the Mantel-Haenszel estimate for the common risk difference. Missing IGA-FWS and PFWs were imputed using same rules as the primary endpoint.

Source: pg 65 of Study Report 301 and pg 65 of Study Report 302 and reviewer analysis.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary focus of the safety review is the data obtained from two Phase 3 studies, SAKURA-1 and SAKURA-2. The data from these two studies will be pooled to compare incidences of adverse events (AEs). These studies were chosen as the focus of the safety review because they were of placebo-controlled design, enrolled similar study populations, and studied the doses that reflect anticipated use. Data obtained from these studies will allow the direct comparison of AE rates in DAXXIFY-treated subjects to those in placebo-treated subjects.

Data from the repeat-dose, open-label study (SAKURA-OLS) will be used to assess potential safety signals that may occur following repeated administration of DAXXIFY. However, data from this study may be difficult to interpret due to lack of a comparison arm.

The Phase 2 study (RT002-CL002) will be analyzed separately because, in addition to the to-be-marketed dose for DAXXIFY, other doses of DAXXIFY (20 Units and 60 Units) and an active comparator (BOTOX) were used during the conduct of the study.

8.2.2. Review of the Safety Database

The development program for DAXXIFY included a total of 3139 subjects. Of these, 2994 subjects were exposed to DAXXIFY at any dose, and 2839 subjects were exposed to the to-be-marketed dose of 40 Units. Of these subjects, 568 subjects received a total of three treatments, 314 received two treatments, and 1957 received a single 40-Unit treatment.

Table 21. Safety Population

| Number of Subjects | GL-Mexico | GL-Belmont | SAKURA-1 | SAKURA-2 | SAKURA-OLS | All Studies Combined |
|------------------------------|-----------|------------|----------|----------|------------|----------------------|
| SAKURA-1 and SAKURA-2 | | | | | | |
| Placebo | | | 102 | 101 | | 203 |
| DAXXIFY 40 U | | | 201 | 205 | | 406 |
| All Studies | | | | | | |
| Placebo | | 54 | 102 | 101 | | 257 |
| DAXXIFY 20 U | | 54 | | | | 54 |
| DAXXIFY 40 U | | 53 | 201 | 205 | 2691 | 2839 |
| DAXXIFY 60 U | | 53 | | | | 53 |
| BOTOX 20 U | | 54 | | | | 54 |
| DAXXIFY 25 U | 12 | | | | | 12 |
| DAXXIFY 50 U | 12 | | | | | 12 |
| DAXXIFY 75 U | 12 | | | | | 12 |
| DAXXIFY 100 U | 12 | | | | | 12 |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; U = units.

Source: Adapted from ISS Table 14.1.1 Subjects included in Analysis Populations (All Studies Integrated Population)

Adequacy of the Safety Database

The safety database submitted by the Applicant is sufficient to characterize the safety profile of DAXXIFY.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of DAXXIFY.

Categorization of Adverse Events

AEs were categorized as follows:

- Deaths
- Other Serious Adverse Events (SAEs)
- AEs that led to study discontinuation
- Other significant AEs, including:
 - Adverse Events of Special Interest (AESIs), including AEs of local and potential distant spread of toxin

- Hypersensitivity reactions
- Treatment Emergent Adverse Events and Adverse Reactions
 - Severe TEAEs
 - Common TEAEs
 - Adverse Reactions (ARs): study drug treatment-related TEAEs

According to the Applicant, across all clinical trials, AEs were graded based on the Cancer Therapy Evaluation Program (CTEP)-Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for severity, where applicable. AEs for which the CTEP-CTCAE grading scale was not applicable were graded as mild, moderate, severe, or life-threatening.

Adverse Event

In all studies, an AE was defined as any untoward medical occurrence that emerged or worsened following administration of investigational product and until the end of study participation that may not necessarily have a causal relationship to the administration of the investigational product.

Treatment-Emergent Adverse Event

A TEAE is an AE that occurs after any period of exposure to treatment.

Severity of Adverse Event

Mild: Event may have been noticeable to the subject; did not influence daily activities; usually did not require intervention.

Moderate: Event may have been of sufficient severity to make the subject uncomfortable; performance of daily activities may have been influenced; intervention may have been needed.

Severe: Event may have caused severe discomfort; usually interfered with daily activities; subject may not have been able to continue in the study; treatment or other intervention was usually needed.

Adverse Reaction

An AR is defined as an AE that is definitely, possibly, or probably caused by the study treatment.

The Relationship of an AE to the Study Drug

Definite: There was a clinically plausible time sequence between the onset of the AE and the administration of the investigational product; when the event responded to withdrawal of investigational product and/or recurred with re-administration of investigational product.

Probable: There was a clinically plausible time sequence between the onset of the AE and the administration of investigational product; the AE was unlikely to be caused by the concurrent/underlying illness, other drugs, or procedures.

Possible: There may or may not have been a clinically plausible time sequence between the onset of the AE and the administration of investigational product, and a cause could not be ruled out.

Unrelated: There was no temporal or causal relationship to investigational product administration.

Serious Adverse Events

An SAE was defined as any untoward medical occurrence that results in any of the following outcomes:

- Death
- Life-threatening
- Persistent or significant disability/incapacity or substantial disruption of the subject's ability to carry out normal life functions
- Requires in-patient hospitalization or prolongs hospitalization
- Congenital anomaly/birth defect
- Does not meet any of the above serious criteria, but based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Adverse Events of Special Interest

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

An AE list of potential distant spread of toxin terms was developed from the FDA draft guidance for industry: *Upper Facial Lines: Developing Botulinum Toxin Drug Products* (August 2014). An additional four terms were added after discussion with the Agency to broaden the list of AEs, to capture a wider range of symptoms suggestive of botulism (Module 1.6.3, Study May Proceed Letter; dated October 28, 2016).

Routine Clinical Tests

During the placebo-controlled and open-label studies, the investigators performed safety assessments. The safety results from SAKURA-1 and SAKURA-2 were pooled for analysis.

In the SAKURA-1 and SAKURA-2 studies, non-fasting samples for hematology, chemistry, prothrombin time (PT), and urinalysis were collected at Screening, Week 4, and at the Final Evaluation Visit. At Screening and Week 2, 4, and 12 visits, blood samples for antibodies were collected.

In SAKURA-OLS, for each treatment cycle, non-fasting samples for hematology, chemistry, PT (Screening only), and urinalysis were collected at Screening, Week 4 visits, prior to Retreatment (as applicable), and at the Final Evaluation Visit. At Screening and Week 2, 4, and 12 visits, a blood sample for antibodies was collected.

The following safety assessments were performed:

- Hematology, chemistry, urinalysis, PT
- Urine pregnancy test for women of childbearing potential
- Serum antibody tests for DAXXIFY (RTT150) and RTP004
- Injection site evaluation
- Cranial nerves II-VII assessment
- Evaluation of facial muscle strength
- 12-lead electrocardiogram (ECG) (not in SAKURA-OLS)
- Vital signs
- Physical examination

The safety assessments allowed adequate characterization of the safety of DAXXIFY.

8.2.4. Safety Results

Deaths

During the development of DAXXIFY, a single death was reported. Subject (b) (6) was a victim of a homicide, and therefore death was unrelated to study treatment.

Serious Adverse Events

In both Phase 3 studies (SAKURA-1 and SAKURA-2), a total of 4 subjects treated with DAXXIFY reported 4 SAEs (see [Table 22](#)). In open-label study SAKURA-OLS, a total of 29 subjects treated with DAXXIFY reported 31 SAEs.

No SAEs occurred in the Phase 1 (GL-Mexico) or Phase 2 studies (GL-Belmont).

Placebo-Controlled Studies (SAKURA-1 and SAKURA-2)

In the Phase 3 (SAKURA-1 and SAKURA-2) studies, three SAEs were reported in each study. None of the SAEs were considered by the investigator to be treatment-related.

Table 22. Serious Adverse Events (SAKURA-1 and SAKURA-2)

| Subject | Dosing Group | Adverse Event | Outcome |
|---------|--------------|--------------------------|-------------------|
| (b) (6) | DAXXIFY 40 U | Bone marrow failure | Lost to follow-up |
| | DAXXIFY 40 U | Sepsis | Resolved |
| | Placebo | Anxiety | Resolved |
| | DAXXIFY 40 U | Uterine perforation | Resolved |
| | DAXXIFY 40 U | Uterine leiomyoma | Resolved |
| | Placebo | Leiomyosarcoma recurrent | Not resolved |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; U = units.

Source: Adapted from Table 37: Listing of Serious Adverse Events (SAKURA-1 and -2 Pooled Population) in Clinical Summary of Safety.

Open-Label Study (SAKURA-OLS)

In the study SAKURA-OLS, a total of 29 (1.1%) subjects reported 31 SAEs. None of the SAEs were considered by the investigator to be treatment-related. SAEs reported in this study are presented in [Table 23](#) below.

Table 23. Serious Adverse Events (SAKURA-OLS)

| Subject | Dosing Group/ Cumulative Dose | Adverse Event | Outcome |
|---------|----------------------------------|----------------------------------|--|
| (b) (6) | B/40 U | Humerus fracture | Resolved - study discontinuation |
| | B/120 U | Papillary thyroid cancer | Resolved |
| | B/40 U | Rib fracture | Resolved |
| | A/120 U | Foot fracture | Resolved |
| | A/120 U | Optic neuritis | Resolved with sequelae - study discontinuation |
| | B/40 U | Diverticulitis | Resolved |
| | B/40 U | Metastatic neoplasm | Resolved |
| | A/80 U | Invasive ductal breast carcinoma | Not resolved |
| | | Sepsis | Resolved |

| Subject | Dosing Group/ Cumulative Dose | Adverse Event | Outcome |
|---------|----------------------------------|---|------------------------|
| (b) (6) | A/120 U | Adenomyosis | Resolved |
| | B/80 U | Cholelithiasis | Resolved |
| | A/120 U | Breast cancer | Unknown if resolved |
| | B/120 U | Nephrolithiasis | Resolved |
| | B/120 U | Influenza | Resolved |
| | B/40 U | Cellulitis | Resolved |
| | B/120 U | Paraesthesia | Resolved |
| | B/120 U | Abdominal pain | Resolved |
| | B/40 U | Bile duct cancer | Study discontinuation |
| | B/40 U | Upper limb fracture | Resolved |
| | B/40 U | Wrist fracture | Resolved |
| | B/40 U | Gastroesophageal reflux disease | Resolved |
| | B/40 U | Gastroenteritis | Lost to follow-up |
| | B/40 U | Pelvic inflammatory disease | Resolved |
| | B/40 U | Breast cancer | Resolved |
| | B/40 U | Hodgkin's disease | Not Resolved |
| | B/40 U | Intestinal obstruction | Resolved |
| | B/120 U | Intraductal proliferative breast lesion | Resolved |
| | B/120 U | Cholecystitis infective | Resolved with sequelae |
| | | Pulmonary embolism | Resolved with sequelae |
| | B/40 U | Pancreatitis acute | Resolved |
| | B/40 U | Impaired gastric emptying | Resolved |

Abbreviations: U = units.

Source: Adapted from Table 38: Listing of Serious Adverse Events (SAKURA-OLS) in Clinical Summary of Safety

Reviewer's Comment: All narratives for SAEs were reviewed. This reviewer agrees with the investigator's assessment that none of the SAEs reported in DAXXIFY and placebo groups were related to study treatment.

Dropouts and/or Discontinuations Due to Adverse Effects

No subject discontinued due to TEAEs in studies SAKURA-1, SAKURA-2, GL-Mexico, or GL-Belmont. Five subjects in SAKURA-OLS experienced five TEAEs resulting in discontinuation. All subjects in SAKURA-OLS were treated with DAXXIFY. Out of the five TEAEs resulting in discontinuation, only one (brow spocking) was considered treatment-related.

1. Subject (b) (6) (a 60 year-old white female) was withdrawn after she tripped and fell at home, which resulted in a fracture of the left humerus.
2. Subject (b) (6) (a 37 year-old white female) was withdrawn due to SAE of optic neuritis of unknown cause.
3. Subject (b) (6) (a 65 year-old white female) was withdrawn due to SAE of bile duct cancer.
4. Subject (b) (6) (a 58 year-old white female) was withdrawn due to SAE of basal cell carcinoma near the left eye.

5. Subject (b) (6) (a 45 year-old white female) was withdrawn due to a procedure complication (brow spocking) after receiving her first and only treatment with DAXXIFY. She had no prior history of treatment with botulinum toxin products. Subject discontinued from the study on Day 22 due to brow spocking that did not resolve.

Reviewer's Comment: The narratives for each of the subjects that discontinued were reviewed. This reviewer agrees with the assessment that only the AE of brow spocking in Subject (b) (6) was treatment-related.

Significant Adverse Events

Adverse Events of Local and Potential Distant Spread of Toxin

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

In the SAKURA-1 and SAKURA-2 studies, 18 subjects experienced AEs considered related to the local spread of toxin, as presented in [Table 24](#) below. There were no reports of distant spread of toxin.

Reviewer's Comment: This reviewer pooled facial asymmetry and facial paresis because detailed information indicated that Subject (b) (6) experienced left forehead asymmetry with motion post-DAXXIFY treatment which is consistent with facial paresis.

Table 24. Subjects With AEs of Local Spread of Toxin (SAKURA-1 and SAKURA-2)

| Adverse Event | Placebo | DAXXIFY 40 U |
|----------------|----------------|----------------|
| | n (%) N=203 | n (%) N=406 |
| Eyelid ptosis | 0 | 9 (2.2) |
| Facial paresis | 0 | 5 (1.2) |
| Brow ptosis | 0 | 3 (0.7) |
| Vision blurred | 0 | 1 (0.2) |

Facial paresis: Includes facial asymmetry and facial paresis.

At each level of summarization, a subject was counted once if the subject reported one or more events.

Abbreviations: DAXXIFY = daxibotulinumtoxinA; n = number of subjects with adverse events; U = units.

Percentages are based on the number in the analysis group, N.

Source: Adapted from Table 30 in Summary of Clinical Safety

In the open-label study (SAKURA-OLS), there were no reports of distant spread of toxin. The AEs of local spread of toxin in SAKURA-OLS are presented in [Table 25](#) below.

Table 25. Subjects With AEs of Local Spread of Toxin (SAKURA-OLS)

| Adverse Event | Subject n (%) |
|----------------------|--------------------------|
| | N=2691 |
| Eyelid ptosis | 34 (1.30) |
| Brow ptosis | 11 (0.41) |
| Facial paresis | 10 (0.37) |
| Dry eye | 5 (0.19) |
| Vision blurred | 4 (0.15) |
| Diplopia | 1 (0.04) |
| Dysphagia | 1 (0.04) |
| Hypoaesthesia oral | 1 (0.04) |

Dry eye: Includes dry eye and xerophthalmia

Facial paresis: Includes facial asymmetry, muscular weakness (left forehead) and facial paresis.

At each level of summarization, a subject was counted once if the subject reported one or more of the same events.

Abbreviations: DAXXIFY = daxibotulinumtoxinA; n = number of subjects with adverse events.

Percentages are based on the number in the analysis group, N.

Source: This table was made from data and narratives submitted by the Applicant.

Reviewer's Comment: After reviewing all of the narratives, this reviewer assessed that DAXXIFY could not be ruled out as a cause for the following AEs in addition to the AESIs listed above:

1. Subject (b) (6), a 28 year-old female with a history of asthma, experienced pulmonary aspiration on Day 11 of treatment cycle 3 which resolved on Day 15 after treatment with salbutamol HFA.
2. Subject (b) (6), a 60 year-old female with a history of left upper lid chalazion incision and drainage on (b) (6), experienced left upper lid ptosis on (b) (6) (Day 57 of her only DAXXIFY treatment) which resolved on Day 85 after treatment with Refresh artificial tears.
3. Subject (b) (6), a 44 year-old female, experienced bilateral blurred vision on Day 68 of her only DAXXIFY treatment which resolved on Day 130 without treatment.
4. Subject (b) (6), a 54 year-old female, experienced headache on Day 1 of her only DAXXIFY treatment which resolved on Day 11 without treatment.

A summary of the AEs of local spread of toxin in SAKURA-OLS by treatment cycle is listed in [Table 26](#).

Table 26. Subjects With Local Spread of Toxin by Treatment Cycle (SAKURA-OLS)

| Adverse Event | Treatment Cycle 1 | Treatment Cycle 2 | Treatment Cycle 3 |
|--------------------|-------------------|-------------------|-------------------|
| | n (%) N=2380 | n (%) N=882 | n (%) N=568 |
| Eyelid ptosis | 23 (1.00) | 7 (0.79) | 4 (0.70) |
| Brow ptosis | 9 (0.38) | 0 | 2 (0.35) |
| Facial paresis | 8 (0.34) | 2 (0.23) | 0 |
| Dry eye | 5 (0.21) | 0 | 0 |
| Vision blurred | 2 (0.08) | 2 (0.23) | 0 |
| Diplopia | 1 (0.04) | 0 | 0 |
| Dysphagia | 1 (0.04) | 0 | 0 |
| Hypoaesthesia oral | 1 (0.04) | 0 | 0 |

Dry eye: Includes dry eye and xerophthalmia

Facial paresis: Includes facial asymmetry, muscular weakness (left forehead) and facial paresis.

At each level of summarization, a subject was counted once if the subject reported one or more of the same events.

Abbreviations: n = number of subjects with adverse events.

Percentages are based on the number in the analysis group, N.

Source: This table was made from data and narratives submitted by the Applicant.

Reviewer's Comment: This reviewer agrees with the Applicant that:

- 1. No AE was associated with potential distant spread of toxin in the Phase 3 placebo-controlled studies (SAKURA-1 and SAKURA-2) or in the open-label study (SAKURA-OLS).*
- 2. The AEs of local spread of toxin only occurred in the DAXXIFY group in the placebo-controlled studies.*
- 3. The incidence of AEs of local spread of toxin in the open-label study (SAKURA-OLS) declined with additional treatment cycles.*

In addition, this reviewer recommends:

- 1. DAXXIFY labeling carry a Boxed Warning, describing the potential for distant spread of toxin effect, that adequately informs healthcare providers of this potential complication of therapy. No modification or additions to the Boxed Warning are recommended based on the trial experience for DAXXIFY for the proposed indication.*
- 2. The potential of DAXXIFY to cause eyelid ptosis should be addressed in the labeling.*

Hypersensitivity

After reviewing the submitted information, this reviewer found no AE that indicated hypersensitivity to the study drug in the SAKURA-1 and SAKURA-2 Pooled Population.

In the SAKURA-OLS study, one subject experienced an AE that was possibly due to hypersensitivity to DAXXIFY.

Subject (b) (6), a 53 year-old black female, experienced edema of the left upper and lower eyelid on Day 12 after DAXXIFY injection which resolved on Day 20 after treatment with topical

hydrocortisone and oral loratadine. The investigator assessed the event as mild and possibly related to DAXXIFY treatment.

Reviewer's Comment: This reviewer agrees with the Applicant that overall, the occurrence of AEs possibly secondary to hypersensitivity to DAXXIFY was low. Additionally, there was no increase in hypersensitivity AEs over successive treatment cycles.

The Applicant stated in the labeling, section 4 CONTRAINDICATIONS, subsection 4.1 Hypersensitivity:

"TRADENAME is contraindicated in patients with known hypersensitivity to any of the components in the formulation." This reviewer recommends more detailed information in the labeling on Hypersensitivity Reactions, such as "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 TRADENAME should be discontinued, and appropriate medical therapy immediately instituted. The use of TRADENAME in patients with known hypersensitivity to any of the components in the formulation could lead to a life-threatening allergic reaction".

Treatment-Emergent Adverse Events and Adverse Reactions

A summary of the severity of TEAEs in the pooled placebo-controlled studies (SAKURA-1 and SAKURA-2) is presented in [Table 27](#) below.

Table 27. Subjects With Treatment-Emergent Adverse Events by Severity (SAKURA-1 and SAKURA-2)

| Adverse Event Severity | DAXXIFY n (%) N=406 | Placebo n (%) N=203 |
|-------------------------------|------------------------------------|------------------------------------|
| MILD | 208 (51.2) | 51 (25.1) |
| MODERATE | 56 (13.8) | 16 (7.9) |
| SEVERE | 5 (1.2) | 0 |

At each level of summarization, a subject was counted once if the subject reported one or more of the same events. Abbreviations: DAXXIFY = daxibotulinumtoxinA; n = number of subjects with adverse events. Percentages are based on the number in the analysis group, N. Source: This table was made from data submitted by the Applicant.

Severe Treatment-Emergent Adverse Events

Pooled Placebo-Controlled Single-Dose Studies (SAKURA-1 and SAKURA-2)

In SAKURA-1, two subjects reported four severe TEAEs (influenza, carpal tunnel syndrome, respiratory tract congestion, and nephrolithiasis). In SAKURA-2, one subject reported a severe TEAE of conjunctivitis. None of these AEs were considered treatment-related.

Repeat-Dose Study (SAKURA-OLS)

In SAKURA-OLS, 23 subjects experienced 30 severe TEAEs, of which injection site pain (4 events in 3 subjects, related to DAXXIFY treatment) and nephrolithiasis (2 events in 2 subjects, unrelated to DAXXIFY treatment) were the most common. Other severe TEAEs in SAKURA-OLS that were considered related to DAXXIFY treatment included headache and facial paresis. The rest of the severe TEAEs were considered unrelated to DAXXIFY treatment. A summary of severe TEAEs in SAKURA-OLS is presented in [Table 28](#) below.

Table 28. Subjects With Severe Treatment-Emergent Adverse Events (SAKURA-OLS)

| Adverse Event | Subject n (%) N=2691 |
|---------------------------------|----------------------------|
| Injection site pain | 3 (0.11) |
| Nephrolithiasis | 2 (0.07) |
| Headache | 1 (0.04) |
| Facial paresis | 1 (0.04) |
| Basal cell carcinoma | 1 (0.04) |
| Abdominal pain | 1 (0.04) |
| Shoulder pain | 1 (0.04) |
| Severe knee pain | 1 (0.04) |
| Left hip bursitis | 1 (0.04) |
| Acute appendicitis | 1 (0.04) |
| Respiratory tract infection | 1 (0.04) |
| Fall | 1 (0.04) |
| Pulled tendon | 1 (0.04) |
| Urinary tract infection | 1 (0.04) |
| Tubo-ovarian abscess | 1 (0.04) |
| Toothache | 1 (0.04) |
| Endometriosis | 1 (0.04) |
| Left breast DCIS | 1 (0.04) |
| Facial paralysis (Bell's Palsy) | 1 (0.04) |
| Pancreatitis | 1 (0.04) |
| Fractured T12 vertebrae | 1 (0.04) |
| Torn left retina | 1 (0.04) |
| Pelvic prolapse | 1 (0.04) |
| Post-knee replacement pain | 1 (0.04) |
| Nasopharyngitis | 1 (0.04) |
| Migraine | 1 (0.04) |

Abbreviation: DCIS = ductal carcinoma in situ.

Source: Clinical Summary of Safety, Section 2.2.6.2

Analysis of Adverse Events by Severity

Common Treatment-Emergent Adverse Events

The most common TEAEs in the pooled single-dose, placebo-controlled studies (SAKURA-1 and SAKURA-2) are listed in [Table 29](#). [Table 29](#) lists TEAEs that occurred in ≥1% of subjects.

Table 29. Common Treatment-Emergent Adverse Events That Occurred in ≥1% of Subjects (SAKURA-1 and SAKURA-2)

| Adverse Event | DAXXIFY n (%) N=406 | Placebo n (%) N=203 |
|-----------------------------------|------------------------------------|------------------------------------|
| Headache | 38 (9.4) | 5 (2.5) |
| Upper respiratory tract infection | 28 (6.9) | 10 (4.9) |
| Injection site reaction | 25 (6.2) | 13 (6.4) |
| Eyelid ptosis | 9 (2.2) | 0 |
| Influenza | 6 (1.5) | 2 (1.0) |
| Urinary tract infection | 5 (1.2) | 0 |
| Facial paresis | 5 (1.2) | 0 |
| Prothrombin time prolonged | 2 (0.5) | 3 (1.5) |

At each level of summarization, a subject was counted once if the subject reported one or more of the same events.

Abbreviations: DAXXIFY = daxibotulinumtoxinA; n = number of subjects with adverse events.

Percentages are based on the number in the analysis group, N.

Headache: Includes headache and tension headache.

Injection site reaction: Includes injection site reaction, injection site pain, injection site erythema, injection site oedema, injection site bruising, injection site haematoma, injection site papule, and injection site pruritus.

Upper respiratory tract infection: Includes upper respiratory tract infection, viral upper respiratory tract infection, and nasopharyngitis.

Facial paresis: Includes facial asymmetry and facial paresis.

Source: This table was made from data submitted by the Applicant.

Table 30. Injection Site Reactions (SAKURA-1 and SAKURA-2)

| Preferred Term | DAXI n (%) N=406 | Placebo n (%) N=203 |
|--------------------------|---------------------------------|------------------------------------|
| Injection site pain | 15 (3.7) | 8 (4.0) |
| Injection site erythema | 5 (1.2) | 4 (2.0) |
| Injection site oedema | 5 (1.2) | 3 (1.5) |
| Injection site bruising | 1 (0.2) | 0 |
| Injection site haematoma | 0 | 1 (0.5) |
| Injection site papule | 1 (0.2) | 0 |
| Injection site pruritus | 1 (0.2) | 0 |

At each level of summarization, a subject was counted once if the subject reported one or more events.

Abbreviations: DAXXIFY = daxibotulinumtoxinA; n = number of subjects with adverse events.

Percentages are based on the number in the analysis group, N.

Source: This table was made from data submitted by the Applicant.

The most common TEAEs in the repeat-dose, open-label study (SAKURA-OLS) were injection site reaction, upper respiratory infection, and headache, as listed in [Table 31](#).

Table 31. Common Treatment-Emergent Adverse Events That Occurred in ≥1% of Subjects (SAKURA-OLS)

| Adverse Event | Subject n (%) N=2691 |
|-----------------------------------|-------------------------------------|
| Injection site reaction | 263 (9.8) |
| Upper respiratory tract infection | 193 (7.2) |
| Headache | 163 (6.1) |
| Erythema | 56 (2.1) |
| Sinusitis | 49 (1.8) |
| Oedema | 47 (1.7) |
| Urinary tract infection | 42 (1.6) |
| Influenza | 37 (1.4) |
| Eyelid ptosis | 35 (1.3) |

At each level of summarization, a subject was counted once if the subject reported one or more of the same events.

Abbreviations: n = number of subjects with adverse events.

Percentages are based on the number in the analysis group, N.

Headache: Includes headache and tension headache.

Injection site reaction: Includes injection site reaction, injection site pain, injection site erythema, injection site oedema, injection site bruising, injection site papule, and injection site pruritus.

Upper respiratory tract infection: Includes upper respiratory tract infection, viral upper respiratory tract infection, and nasopharyngitis.

Source: This table was made from data submitted by the Applicant.

A summary of the common TEAEs in SAKURA-OLS by treatment cycle is listed in [Table 32](#).

Table 32. Common Treatment-Emergent Adverse Events That Occurred in ≥1% of Subjects by Treatment Cycle (SAKURA-OLS)

| Adverse Event | Treatment Cycle 1 | Treatment Cycle 2 | Treatment Cycle 3 |
|-----------------------------------|--------------------------|--------------------------|--------------------------|
| | n (%) N=2380 | n (%) N=882 | n (%) N=568 |
| Injection site reaction | 216 (9.1) | 60 (6.8) | 21 (3.7) |
| Headache | 136 (5.7) | 18 (2.0) | 14 (2.5) |
| Upper respiratory tract infection | 131 (5.5) | 56 (6.4) | 12 (2.1) |
| Erythema | 55 (2.3) | 3 (0.3) | 1 (0.2) |
| Oedema | 46 (1.9) | 4 (0.5) | 0 |
| Sinusitis | 37 (1.6) | 9 (1.0) | 3 (0.5) |
| Urinary tract infection | 30 (1.3) | 11 (1.2) | 3 (0.5) |
| Influenza | 25 (1.1) | 10 (1.1) | 2 (0.4) |
| Eyelid ptosis | 24 (1.0) | 7 (0.8) | 4 (0.7) |

At each level of summarization, a subject was counted once if the subject reported one or more of the same events.

Abbreviations: n = number of subjects with adverse events.

Percentages are based on the number in the analysis group, N.

Headache: Includes headache and tension headache.

Injection site reaction: Includes injection site reaction, injection site pain, injection site erythema, injection site oedema, injection site bruising, injection site papule, and injection site pruritus.

Upper respiratory tract infection: Includes upper respiratory tract infection, viral upper respiratory tract infection, and nasopharyngitis.

Source: This table was made from data submitted by the Applicant.

Reviewer's Comment: This reviewer agrees with the Applicant that:

- 1. The severity of TEAEs in SAKURA-1 and SAKURA-2 were similar and comparable to those in the Pooled Population.*

2. TEAEs occurred more often in the DAXXIFY group, with higher incidences across all severities compared to the placebo group.
3. The AE profile in the repeat-dose study (SAKURA-OLS) was similar to that reported in single-dose studies (SAKURA-1 and SAKURA-2). However, this reviewer noted higher incidence of injection site reactions in the repeat-dose study compared to the single-dose studies, which was likely due to repeated injections.
4. The incidence of common TEAEs did not increase with multiple re-treatments.

Adverse Reactions

The ARs in single-dose, placebo-controlled studies (SAKURA-1 and SAKURA-2) are summarized in [Table 33](#) below.

Table 33. Adverse Reactions That Occurred in $\geq 1\%$ of Subjects (SAKURA-1 and SAKURA-2)

| Adverse Reaction | DAXXIFY | Placebo |
|-------------------------|----------------|----------------|
| | n (%) N=406 | n (%) N=203 |
| Injection site reaction | 25 (6.2) | 13 (6.4) |
| Headache | 26 (6.4) | 4 (2.0) |
| Eyelid ptosis | 9 (2.2) | 0 |
| Facial paresis | 5 (1.2) | 0 |

At each level of summarization, a subject was counted once if the subject reported one or more of the same events.

Abbreviations: DAXXIFY = daxibotulinumtoxinA; n = number of subjects with adverse events.

Percentages are based on the number in the analysis group, N.

Headache: Includes headache and tension headache.

Injection site reaction: Includes injection site reaction, injection site pain, injection site erythema, injection site oedema, injection site bruising, injection site haematoma, injection site papule, injection site pruritus.

Facial paresis: Includes facial asymmetry and facial paresis.

Source: This table was made from data submitted by the Applicant.

The ARs in the repeat-dose, open-label study (SAKURA-OLS) are summarized in [Table 34](#) and [Table 35](#) below. No specific information was provided by the Applicant to determine if the ARs of erythema and oedema were located at the injection site.

Table 34. Adverse Reactions That Occurred in ≥1% of Subjects (SAKURA-OLS)

| Adverse Reaction | Subject n (%) N=2691 |
|-------------------------|-------------------------------------|
| Injection site reaction | 243 (9.0) |
| Headache | 125 (4.7) |
| Erythema | 48 (1.8) |
| Oedema | 44 (1.6) |
| Eyelid ptosis | 34 (1.3) |

At each level of summarization, a subject was counted once if the subject reported one or more of the same events.

Abbreviations: n = number of subjects with adverse events.

Percentages are based on the number in the analysis group, N.

Headache: Includes headache and tension headache.

Injection site reaction: Includes injection site reaction, injection site pain, injection site erythema, injection site oedema, injection site bruising, injection site papule, injection site pruritus.

Source: This table was made from data submitted by the Applicant.

Table 35. Adverse Reactions That Occurred in ≥1% of Subjects by Treatment Cycle (SAKURA-OLS)

| Adverse Reaction | Treatment Cycle 1 n (%) N=2380 | Treatment Cycle 2 n (%) N=882 | Treatment Cycle 3 n (%) N=568 |
|-------------------------|---|--|--|
| Injection site reaction | 200 (8.4) | 55 (6.3) | 19 (3.3) |
| Headache | 103 (4.3) | 13 (1.5) | 12 (2.1) |
| Erythema | 47 (2.0) | 3 (0.3) | 1 (0.2) |
| Oedema | 43 (1.8) | 4 (0.5) | 0 |
| Eyelid ptosis | 23 (1.0) | 7 (0.8) | 4 (0.7) |

At each level of summarization, a subject was counted once if the subject reported one or more of the same events.

Abbreviations: n = number of subjects with adverse events.

Percentages are based on the number in the analysis group, N.

Headache: Includes headache and tension headache.

Injection site reaction: Includes injection site reaction, injection site pain, injection site erythema, injection site oedema, injection site bruising, injection site papule, injection site pruritus.

Source: This table was made from data submitted by the Applicant.

Reviewer’s Comment: This reviewer assessed that after pooling by preferred term, injection site reaction and headache are the two most common ARs in both DAXXIFY and placebo groups. Eyelid ptosis and facial paresis occurred in the DAXXIFY group, but not in the placebo group, which was consistent with the mechanism of action of botulinum toxin.

In the repeat-dose open-label study (SAKURA-OLS), injection site reaction and headache are the two most common ARs, similar to findings in the placebo-controlled single-dose studies (SAKURA-1 and SAKURA-2).

This reviewer agrees with the statement “The incidence of these adverse reactions did not increase with multiple re-treatments” in labeling section 6 ADVERSE REACTIONS, subsection 6.1 Clinical Trial Experience, Glabellar Lines. However, this reviewer recommends using data in table A and B for this section.

As DAXXIFY is a botulinum toxin product, this reviewer recommends addition of the following in labeling section 5 WARNINGS and PRECAUTIONS. These risks are discussed in the labels of other botulinum toxin products:

1. *Serious Adverse Reactions with Unapproved Use*

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received botulinum toxin injections for unapproved uses. In these cases, the adverse reactions may have resulted from the administration of botulinum toxin products to the site of injection and/or adjacent structures. In some cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of botulinum toxin products.

2. *Ophthalmic Adverse Reactions in Patients Treated with Botulinum Toxin Products*

Dry eye has been reported with the use of botulinum toxin products in the treatment of glabellar lines. Reduced tear production, reduced blinking, and corneal disorders may occur with use of botulinum toxins, including TRADENAME. If symptoms of dry eye (e.g., eye irritation, photophobia, or visual changes) persist, consider referring patient to an ophthalmologist.

3. *Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders*

Patients with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored for increased neuromuscular compromise following botulinum toxin treatment.

4. *Pre-Existing Conditions at the Injection Site*

Caution should be exercised when administering TRADENAME to patients with surgical alterations to the facial anatomy, marked facial asymmetry, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, inflammation at the injection site(s) and pre-existing eyelid or eyebrow ptosis.

Laboratory Findings

After reviewing the submitted laboratory information, this reviewer agrees with the assessment that the laboratory test results were generally similar between the two treatment groups in both single-dose placebo-controlled studies (SAKURA-1 and SAKURA-2).

The majority of hematology/coagulation and clinical chemistry laboratory test values were within normal range.

In SAKURA-OLS, most of the hematology/coagulation and clinical chemistry laboratory test values were within normal range. Clinically significant leukopenia occurred in one subject in SAKURA-OLS (Subject (b) (6)). This subject was subsequently diagnosed with Hodgkin's disease.

Reviewer's Comment: This reviewer agrees with the Applicant that across all studies, as well as within each individual study, hematology/coagulation and clinical chemistry laboratory data were generally unremarkable. No clinically meaningful trend in laboratory parameters due to DAXXIFY treatment was observed.

Vital Signs

After reviewing the submitted vital sign information, this reviewer agrees with the assessment that no clinically meaningful changes or trends from baseline were noted in systolic/diastolic blood pressure or heart rate between treatment groups throughout the studies (SAKURA-1 and SAKURA-2, or SAKURA-OLS).

Electrocardiograms (ECGs)

Placebo-Controlled Studies

Twelve-lead ECGs were obtained in the Phase 3 trials (SAKURA-1 and SAKURA-2) and were evaluated by a central reader designated for each study. The Applicant reported that in SAKURA-1, clinically relevant abnormal ECG findings occurred in six subjects, three in each treatment group.

DAXXIFY Group

- Subject (b) (6) experienced a mild AE of flat T waves on Day 28 which resolved on Day 58 without treatment.
- Subject (b) (6) experienced a mild AE of abnormal ECG (first degree atrioventricular block) on Day 29 which resolved on the same day without treatment. The abnormal ECG was considered an artifact, and not clinically significant.
- Subjects (b) (6) had a mild AE of abnormal ECG on Day 29 (PR prolongation to 205) which resolved on the same day without treatment.

Placebo Group

- Subject (b) (6) experienced a mild AE of abnormal ECG on Day 33 (no specific information was provided) which resolved on the same day with no treatment.
- Subject (b) (6) experienced a mild AE of flat T waves on Day 27 which resolved on Day 91 without treatment.
- Subject (b) (6) had a mild AE of incomplete right bundle branch block on Day 29 which resolved on Day 37 without treatment.

None of the above subjects presented clinical symptoms with ECG abnormalities, and all abnormalities resolved without treatment.

No subjects in SAKURA-2 exhibited ECG abnormalities.

SAKURA-OLS

- Subject (b) (6) had a moderate AE of first-degree atrioventricular block and chest pain on study Day 188 (20 days from the most recent DAXXIFY treatment) that resolved on the same day without treatment. This was assessed by the investigator as unrelated to study treatment.
- Subject (b) (6) had an AE of mild exacerbation of pre-existing sinus arrhythmia at 213 days post-DAXXIFY treatment that lasted 3 days and was considered unrelated to treatment by the investigator.
- Subject (b) (6) had moderate AEs of bradycardia, right bundle branch block, and hypertension beginning on Day 368 of the study (119 days from the most recent DAXXIFY treatment) that were not resolved at the end of the study, but were considered unrelated to treatment by the investigator.

Reviewer's Comment: After reviewing the submitted information, this reviewer concluded that the prevalence of ECG abnormalities was similar between the DAXXIFY and placebo treatment groups. None of the subjects presented clinical symptoms with their ECG abnormalities, and all abnormalities resolved without treatment. None of the abnormalities were considered related to the study treatment.

QT Prolongation

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

Immunogenicity

See the Clinical Pharmacology review.

8.2.5. Analysis of Submission-Specific Safety Issues

Cranial Nerve Assessment

The Applicant reported that a total of four subjects (1.0%) in the DAXXIFY-treated population were found to have abnormal cranial nerve assessments. One subject in SAKURA-2 had a non-clinically significant, unilateral, optic nerve abnormality (abnormal pupillary reaction to light and accommodation) that was observed prior to treatment and persisted unchanged through the final evaluation. Three subjects (two in SAKURA-1 and one in SAKURA-2) were recorded as having non-clinically significant abnormalities in oculomotor function, each at a single post-treatment timepoint, which had resolved at the subsequent study visit (no details provided). No subject demonstrated an abnormality of trigeminal nerve function pre-or post-treatment with DAXXIFY.

In SAKURA-OLS, the Applicant reported that most cranial nerve II-VII assessments were normal at post-treatment visits for all three Treatment Evaluable Populations, except in Treatment Cycle 1 (three abnormalities were deemed clinically significant within the first 16 weeks of treatment which all returned to normal by the next visit). These abnormalities are listed below:

- Subject (b) (6) had an optic nerve abnormality at Week 4 (abnormal pupillary reaction to light and accommodation on the left side) which returned to normal by Week 8. This subject also experienced left eyelid ptosis of moderate severity that began on Day 9 and lasted until Day 43.
- Subject (b) (6) had an abnormal gross sensation in the trigeminal nerve distribution on the left side at Week 4 which returned to normal by Week 8.
- Subject (b) (6) had an abnormal left oculomotor nerve movement at Week 2 which returned to normal at Week 4. The same subject then had a left optic nerve abnormality (abnormal pupillary reaction to light and accommodation) at Week 16 which resolved by Week 20. This subject also reported a mild left eyelid ptosis that began on Day 10 and lasted until Day 29 post-treatment.

The majority of abnormal cranial nerve II-VII findings that were deemed not clinically significant returned to normal before the next follow up visit. The incidence of abnormal cranial nerve assessments that were not clinically significant decreased with successive treatment cycles.

Reviewer's Comment: There were no clinically significant abnormalities due to DAXXIFY treatment in cranial nerve assessment in the Phase 3 studies. The clinically significant cranial nerve abnormalities in SAKURA-OLS were most likely due to local spread of toxin.

Regional House-Brackmann Facial Nerve Grading System

The Applicant reported that by Regional House-Brackmann Facial Nerve Grading System, assessments of the mid-face, mouth, and synkinesis after treatment with either placebo or

DAXXIFY were generally found to be normal following treatment with DAXXIFY in SAKURA-1 and SAKURA-2 with the following exceptions:

SAKURA-1

DAXXIFY Group

- Subject (b) (6) had mild weakness in left eyelid closure at Week 2 only.
- Subject (b) (6) had mild weakness in left eyelid closure at an unscheduled visit between Week 1 and Week 2 which had resolved by the Week 2 visit but was present again at the Week 4 visit, after which all assessments were normal.
- Subject (b) (6) had obvious eyelid weakness but was able to close eyes on the right side at Week 2 only.
- Subject (b) (6) had mild weakness in left eyelid closure at Week 8 only.

Placebo Group

- Subject (b) (6) reported mild (obvious but not disfiguring) synkinesis on the left side at Week 2 but at no other visit.

SAKURA-2

DAXXIFY Group

- Subject (b) (6) had mild weakness in left eyelid closure at Week 20 which resolved by the next visit.
- Subject (b) (6) had mild synkinesis on Day 0 post-treatment that was resolved by Week 1.

For the forehead assessments in the pooled SAKURA-1 and SAKURA-2 population, all subjects demonstrated normal frontalis strength, bilaterally, immediately following treatment on Day 0. Up to 30% of DAXXIFY group subjects displayed less than normal movement between Week 2 to Week 4, after which normal movement was restored in the majority (99.5%) of subjects by Week 16.

In SAKURA-OLS, the Applicant reported that by Regional House-Brackmann Facial Nerve Grading System, assessments of eyelid closure, mid-face, mouth, and synkinesis after treatment were mostly (>99.3%) unchanged at post-treatment assessment visits. The forehead assessment showed that up to 30% of subjects displayed less than normal movement beginning at Week 1 post-treatment, which reached a peak at Week 2 to Week 4, after which normal movement was restored in the majority (>80%) of subjects by Week 12 post-treatment.

Reviewer's Comment: After assessing the submitted information, this reviewer concludes that:

- 1. Weakness in eye closure and change in frontalis strength in the DAXXIFY group were most likely due to local spread of toxin.*
- 2. Synkinesis was most likely not related to DAXXIFY treatment.*

Facial Muscle Strength Assessment

The Applicant reported that in all clinical trials, facial muscle strength was evaluated using the Medical Research Council Scale for the Assessment of Muscle Power in the orbicularis oculi (eyelid), lateral brow elevators, and zygomaticus muscles.

In SAKURA-1 and SAKURA-2, most subjects demonstrated normal power in all muscle assessments at all visits post-treatment in both the DAXXIFY and placebo treatment groups. In the DAXXIFY group, 75 (18%) subjects displayed less than normal muscle strength in one or more assessed muscles at any timepoint, with 8 (4%) subjects in the placebo group presenting a similar finding. In 43 of the DAXXIFY-treated subjects, abnormal scores were confined to slight decreases in muscle strength in one or two muscles (generally lateral brow elevators, unilaterally or bilaterally) within the expected time window of maximal effect of botulinum toxin. In two subjects, from a single trial center, no movement was noted in all three assessed muscle groups at a single timepoint (Week 24), and this was improved to normal power by the next treatment visit. In the other 30 DAXXIFY-treated subjects from six trial centers with abnormal scores, all were rated as having zero muscle function or flicker contraction only in all assessed muscles at one or more timepoints from screening to Week 32. Two of these study trial centers (accounting for 24 of the subjects with zero muscle function or flicker contraction) later acknowledged that they had inadvertently reverse-scored those subjects. For the remaining six subjects (at four study trial centers), this observation of zero muscle function or flicker contraction was only present at a single study visit and was not associated with any AEs.

In SAKURA-OLS, <6% of muscle evaluations were found to be abnormal at any timepoint following treatment. In general, the frequency of abnormal findings reached a peak following treatment at Week 2, and declined over subsequent treatment visits.

Reviewer's Comment: This reviewer agrees that abnormal facial muscle strength generally occurred within the expected timeframe of maximal effect of botulinum toxin, indicating the effects of local spread of toxin.

Major Adverse Cardiovascular Events (MACEs)

The Applicant assessed for possible major adverse cardiovascular events (MACEs) in the two Phase 3 studies (SAKURA-1 and SAKURA-2) and the open-label study (SAKURA-OLS). Analyses

were performed using a predefined search for MACEs, as defined in the FDA guidance for industry on *Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (December 2008) as events of cardiovascular mortality, myocardial infarction, stroke, hospitalization for acute coronary syndrome, and urgent revascularization procedures.

No cardiac AEs were reported during the development of DAXXIFY.

Three neurologic events were reported during the development of DAXXIFY:

- In SAKURA-2, Subject (b) (6) presented with mild hemiparesis that began on Day 16 and ended on Day 30 following injection. This AE was considered treatment-related. A subsequent interview with the treating investigator after database lock revealed that the AE coded as hemiparesis was, in fact, “right side forehead paresis.”
- In SAKURA-OLS, Subject (b) (6) presented with moderate hemiparesis that began on Day 17 after treatment, ended on Day 31, and was assessed by the investigator as possibly treatment-related. A subsequent interview with the treating investigator after database lock revealed that the subject’s reports of “eyelid paralysis” and “muscle weakness” were referencing “droopy eyelid” and “it took a lot of effort to blink.” The muscle weakness did not affect any other part of her body.
- In SAKURA-OLS, Subject (b) (6) reported symptoms described as mild aphasia beginning on Day 15 after injection that resolved on Day 35 without treatment. The aphasia was assessed by the investigator as being unrelated to study treatment.

Reviewer’s Comment: This reviewer agrees with the Applicant that both events that occurred in Subjects (b) (6) suggest local spread of toxin to muscles adjacent to the glabellar region, instead of MACEs. Although there were no reports of cardiovascular ARs, this reviewer recommends inclusion of a warning for cardiovascular ARs in a manner similar to that of ARs reported and labeled for other botulinum toxin products (see labeling section 5 WARNINGS and PRECAUTIONS):

“Cardiovascular System

There have been reports following administration of botulinum toxins of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease.”

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

There was no COA analysis informing safety/tolerability.

8.2.7. Safety Analyses by Demographic Subgroups

After reviewing the submitted information, this reviewer agrees with the Applicant that there was no evidence of a drug-demographic influence on the incidence of TEAEs in the pooled single-dose placebo-controlled studies (SAKURA-1 and SAKURA-2). No consistent pattern of increased incidence rates of TEAEs, SAEs, or severe events with DAXXIFY treatment was identified for any demographic group (i.e., gender, age, ethnicity, race).

This reviewer agrees with the Applicant that in the pooled single-dose placebo-controlled studies (SAKURA-1 and SAKURA-2), there were no notable differences in incidence rates of TEAEs, SAEs, or severe events between subjects with baseline IGA-FWS score of moderate and severe, or between subjects who received prior treatment with BoNTA and those who were BoNTA naïve.

8.2.8. Specific Safety Studies/Clinical Trials

There was no specific safety study.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No genotoxicity, carcinogenicity, or pre- and postnatal development studies are warranted for DAXXIFY (see Section [5.5](#)).

The Applicant provided their rationale for not conducting carcinogenicity studies: “Carcinogenicity studies were not conducted with DAXXIFY for injection or RTP004 based upon ICH guidelines *S1A The Need for Long-Term Rodent Carcinogenicity Study of Pharmaceuticals* (March 1996) and *S6R1 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012) (Module 2.4, Nonclinical Overview, section 2.4.4.4):

- Neither DAXXIFY nor RTP004 is characterized by a class of compound that potentially promotes cell growth/differentiation/proliferation or immunomodulation.
- There has been no cause for concern from nonclinical study results to date that would suggest carcinogenic potential, for example:
 - No microscopic findings at the injection sites following DAXXIFY or RTP004 administration to warrant a concern (e.g., lack of finding for hyperplasia, cellular hypertrophy, and atypical cellular foci)
 - Negative genotoxicity results for RTP004; Study RT001-NC006; Module 2.6.6, section 4.1.2.1

- Postmarketing surveillance of BoNTA products has provided no evidence of carcinogenicity². No precedence of carcinogenicity in marketed toxin products has been observed.”

In addition, the infrequent dosing regimen (dosing at proposed 3-month intervals or longer) and low injected dose into the target muscle provides for low systemic exposure to DAXXIFY.

The Applicant stated “Genotoxicity studies were not conducted for DAXXIFY for injection per ICH guideline *S6R1 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012), but were performed using RTP004 to support its use as a novel excipient in the to-be-marketed formulation of DAXXIFY for injection. RTP004 was negative in all genotoxicity assays including the *Salmonella-Escherichia coli*/mammalian-microsome reverse mutation assay, the in vitro chromosomal aberration assay in cultured human peripheral blood lymphocytes, and the in vivo chromosomal aberration assay of mouse bone marrow cells (Module 2.4, Nonclinical Overview, section 2.4.4.3).”

Neoplasm (skin and solid tumors) were reported during the development program of DAXXIFY. A summary of AEs in the System Organ Class of Neoplasm in the placebo-controlled studies is presented in [Table 36](#).

Table 36. TEAEs in the System Organ Class of Neoplasm Benign, Malignant, and Unspecified (SAKURA-1 and SAKURA-2)

| Preferred Term | DAXXIFY | Placebo |
|----------------------------|----------------|----------------|
| | n (%) N=406 | n (%) N=203 |
| Basal cell carcinoma | 2 (0.5) | 0 (0) |
| Benign pancreatic neoplasm | 1 (0.2) | 0 (0) |
| Leiomyosarcoma recurrent | 0 (0) | 1 (0.2) |
| Uterine leiomyoma | 1 (0.2) | 0 (0) |

Abbreviations: DAXXIFY = daxibotulinumtoxinA; n = number of subjects with adverse events. Percentages are based on the number in the analysis group, N.

Reviewer’s Comment: Given the timepoints at which neoplasms were reported (not reflective of the generally long latency periods for development of neoplasms), it is in this reviewer’s opinion that the study drug is unlikely a causative agent. No pattern to the type of neoplasms was observed. However, short duration of studies and follow-up, use of relatively small doses per treatment, and intermittent administration does not allow for adequate carcinogenicity evaluation.

² BOTOX® (Botulinum Toxin Type A) Material Safety Data Sheet, 2010. Available at: <https://www.mycardinalmsds.com/MSDS/B9232-01.pdf>

Human Reproduction and Pregnancy

The Applicant stated that there are no well-controlled studies in pregnant or lactating women for DAXXIFY, or for other botulinum toxins currently approved for cosmetic or therapeutic use in the United States. As a class, botulinum toxins have been historically labeled as category C. The DAXXIFY clinical studies in this application were not designed to evaluate pregnancies. However, a total of nine pregnancies were reported by the Applicant in SAKURA-OLS, of which two pregnancies were lost to follow-up, and seven were followed to term. No pregnancies occurred in other studies. There were five uneventful pregnancies with normal live births, and one subject had elective abortion.

One subject had miscarriage/late spontaneous abortion that was considered by the investigator as unrelated to the DAXXIFY treatment. According to the Applicant, the subject who had a spontaneous abortion reported the event at the Week 16 visit, and also reported taking sertraline, a selective serotonin reuptake inhibitor (SSRI), which has been shown to increase risk of spontaneous abortion.

Reviewer's Comment: Considering the timing of the reported spontaneous abortion, the exposure of SSRI, and the 15 to 20% rate of spontaneous abortions in the general population, this reviewer concludes that this case of spontaneous abortion was most likely unrelated to DAXXIFY treatment.

Pediatrics and Assessment of Effects on Growth

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

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

The Applicant stated that doses of DAXXIFY in the clinical studies were prepared and administered under the direct supervision of a qualified healthcare provider. Under these conditions, overdose is considered unlikely.

Reviewer's Comment: This reviewer agrees that the labeling for DAXXIFY, in section 10 OVERDOSAGE, adequately informs prescribers of monitoring and treatment procedures that should be taken in case of DAXXIFY overdose. No labeling changes are warranted based on the product development experience submitted for the indication of treatment of glabellar lines.

Drug Abuse Potential

The Applicant stated that DAXXIFY is not expected to be present in the peripheral blood at detectable levels following intramuscular injection at the intended clinical doses. In addition,

DAXXIFY does not cross the blood-brain barrier, and is therefore unlikely to have a potential for abuse or dependency³

Reviewer's Comment: This reviewer agrees that there is a lack of overlap between botulinum toxin's mechanism of action and known abuse mechanisms. Therefore, no dependence or abuse potential for DAXXIFY is foreseen.

Withdrawal and Rebound

The Applicant stated that there was no evidence of withdrawal or rebound effects in the clinical trials of DAXXIFY. The mechanism of action of botulinum toxin is inconsistent with drugs that cause a withdrawal syndrome.

Reviewer's Comment: This reviewer agrees that although the effect of DAXXIFY decreased over time, it is not expected that the severity of glabellar lines would increase in a rebound fashion. This reviewer found no evidence of rebound effect during review of this submission.

Drug-Drug Interactions

The Applicant stated that no formal drug interaction studies have been performed with DAXXIFY. The Applicant also stated that co-administration of DAXXIFY and aminoglycoside antibiotics, or with other agents that interfere with neuromuscular transmission (e.g., tubocurarine-type muscle relaxants), should only be performed with caution as these agents may potentiate the effect of the BoNTA. Use of anticholinergic drugs after administration of DAXXIFY may potentiate systemic anticholinergic effects. Muscle weakness may also be exaggerated by administration of a muscle relaxant during the period of botulinum toxin activity.

According to the Applicant, the effect of administering different botulinum toxin products at the same time, or within several months of each other, is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin product prior to the resolution of the effect of the previously administered botulinum toxin. For this reason, physicians should be aware of whether patients are receiving treatment with other botulinum toxin products for other indications.

Reviewer's Comment: This reviewer agrees that the potential drug-drug interactions were addressed in the labeling for DAXXIFY in section 7 DRUG INTERACTIONS. No labeling changes are recommended.

³ Dressler, D and F Adib Saberi, 2005, Botulinum Toxin: Mechanisms of Action, European Neurology, 53(1):3-9.

Effect on Ability to Drive or Operate Machinery

This reviewer agreed with the Applicant that the treatment-related adverse events reported with DAXXIFY treatment that could potentially affect an individual's ability to drive or operate machinery included eyelid ptosis, brow ptosis, and blurred vision.

Reviewer's Comment: This reviewer agrees that the potential effects on ability to drive or operate machinery were addressed in the labeling for DAXXIFY section 17 PATIENT COUNSELING INFORMATION, Ability to Operate Machinery or Vehicles, "advises patients if they develop any unusual symptoms such as loss of strength, muscle weakness, blurred vision, or drooping eyelids, they should avoid driving a car or engaging in other potentially hazardous activities". No labeling changes are recommended.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

DAXXIFY is not currently marketed for any indication.

Expectations on Safety in the Postmarket Setting

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

8.2.11. Integrated Assessment of Safety

The intended use of DAXXIFY for the indication of treatment of glabellar lines in adults is an aesthetic indication. The clinical studies showed that DAXXIFY was effective and has an expected safety profile. The performance of DAXXIFY is similar to that of the currently marketed botulinum toxin products for the same indication. Most of the AEs in the submitted studies were unrelated to the study drug, and were either mild or moderate in severity. There were no SAEs related to the drug treatment. The rate of drop-outs due to drug-related AEs was low. There were four drug-related AEs with a frequency of $\geq 1\%$ (injection site reaction, headache, eyelid ptosis, and facial paresis). Most of these events were either mild or moderate in severity and resolved spontaneously without treatment. In summary, DAXXIFY has an acceptable risk-benefit profile for the treatment of glabellar lines in adults.

8.3. Statistical Issues

No significant statistical issues were identified. The statistical method used to calculate confidence intervals had to be modified from what was specified in the statistical analysis plan because the originally specified method was not appropriate for data with 0% response rates. The protocol specified that the confidence intervals for the common risk difference would be calculated using Newcombe's method. However, the Newcombe confidence intervals cannot be calculated if there are zero-frequency rows, columns, or cells, which is the case in Study 301 where the placebo treatment success rate is 0%. Instead, Mantel-Haenszel confidence intervals were used as they are commonly used, and can be applied to zero-frequency rows, columns, or cells.

8.4. Conclusions and Recommendations

To establish the efficacy and safety of DAXXIFY, the Applicant submitted data from two identical, randomized, double-blinded, placebo-controlled Phase 3 studies (Study 1620301 [SAKURA-1] and Study 1620302 [SAKURA-2]). These studies enrolled subjects 18 years of age and older with moderate to severe glabellar lines at maximum frown as assessed independently by both investigator and subject using the Frown Wrinkle Severity scale. The primary efficacy endpoint consisted of the proportion of subjects who achieved at least a 2-point composite improvement from baseline on both investigator and patient rating scales of frown wrinkle severity (i.e., a 2-point composite response) at Week 4 with a single dose of 40 Units of DAXXIFY against placebo. In both studies, DAXXIFY was statistically superior to placebo for the primary endpoint at Week 4.

The safety profile of DAXXIFY was similar to the safety of other BoNTA products licensed for the same indication. DAXXIFY was generally well tolerated. One reported death was not treatment-related. No SAE was considered treatment-related. Most of reported ARs were either mild or moderate in severity and resolved spontaneously without treatment. The most frequently reported ARs in DAXXIFY treatment groups were injection site reaction 6%, headache 7%, eyelid ptosis 2%, and facial paresis 1%. The safety analysis did not identify any new safety signals for this BoNTA.

This reviewer recommends to Division and Office leadership that DAXXIFY be approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients at a dose of 0.1 mL (8 Units) by intramuscular injection into each of five sites, for a total dose of 40 Units.

9. Advisory Committee Meeting and Other External Consultations

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

10. Pediatrics

The Applicant submitted an initial pediatric study plan (iPSP) on January 31, 2017, requesting a waiver from conducting studies in patients 17 years of age and younger based on the rationale that trials are “impossible or highly impractical”. This full waiver request was made in accordance with FDA draft guidance for industry *Upper Facial Lines: Developing Botulinum Toxin Drug Products* (August 2014), “Because upper facial lines are uncommon in the pediatric population, the sponsor may request a waiver for the requirement to submit a pediatric assessment in the pediatric study plan.”

On March 22, 2017, the Division presented the initial Pediatric Study Plan (iPSP) to the Pediatric Review Committee (PeRC). The Division agreed with the requested Full Waiver of Pediatric Studies for pediatric patients from age 0 to 16 years and 11 months because studies are impossible or highly impractical due to the extremely low prevalence of glabellar lines in the pediatric population. The full waiver was granted on July 14, 2017 for subjects less than 18 years of age.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The medical officer has reviewed all labeling. Labeling negotiations were pending at the time of closure of this review. Refer to discussions in the sessions of the corresponding safety review.

12. Risk Evaluation and Mitigation Strategies (REMS)

The risks associated with daxibotulinumtoxinA are risks labeled for the entire class of botulinum toxins. DaxibotulinumtoxinA does not appear to have risks that exceed those of other approved botulinum toxin products, nor are there any serious safety risks that are unique to daxibotulinumtoxinA. As with the other products in this class, a REMS is not necessary to ensure the benefits outweigh the risks. The risk of distant spread of toxin will be communicated in a boxed warning and a Medication Guide, to inform prescribers and patients of the risk.

Please see the separate consult from the Division of Risk Management (DRM) in DARRTS for complete details.

13. Postmarketing Requirements and Commitment

No postmarketing requirements or commitments are recommended.

14. Division Director (DPT-II) Comments

Not applicable.

15. Division Director (OCP) Comments

Not applicable.

16. Division Director (OB) Comments

Not applicable.

17. Division Director (Clinical) Comments

I concur with the review team's recommendation for licensure of BLA 761127, pending final labeling and a required preapproval facility inspection per the Office of Pharmaceutical Quality.

DaxibotulinumtoxinA is a botulinum neurotoxin type A product that acts as an acetylcholine release inhibitor and neuromuscular blocking agent. The proposed cosmetic indication is for the treatment of temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. As shown in Section [2.2](#), there are currently four U.S.-licensed botulinum toxin products for the treatment of glabellar lines.

Two replicate, randomized, double-blind, placebo-controlled trials (SAKURA-1 and SAKURA-2) provided the basis for clinical effectiveness. The primary endpoint, the proportion of subjects achieving a score of 0 or 1 (none or mild) and an improvement of at least two points from baseline to Week 4 on both the IGA-FWS and PFWS scales, showed a large treatment effect that was statistically significant and consistent across trials and across scales. The safety profile is consistent with other botulinum products for the same indication; eyelid ptosis and facial paresis events appear consistent with local toxin spread. Labeling will include appropriate monitoring and guidance, including a boxed warning for distant spread (as with other botulinum toxin products for this indication).

18. Office Director Comments

I concur with the recommendation from the Division of Dermatology and Dentistry to approve daxibotulinumtoxinA-lanm for the treatment of temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. Consistent with other approved botulinum toxin products, daxibotulinumtoxinA-lanm: 1) acts as an acetylcholine release inhibitor and neuromuscular blocking agent, 2) has demonstrated efficacy compared to placebo treatment in randomized controlled trials, and 3) poses a risk for local and distant toxin spread. Approval of daxibotulinumtoxinA-lanm will provide an alternative botulinum toxin product for this cosmetic use.

Final regulatory action on this application is pending successful preapproval inspection of the drug substance and drug product manufacturing facilities and completion of labeling negotiations.

19. Appendices

19.1. References

See footnotes.

19.2. Financial Disclosure

Table 37. Covered Clinical Study (Name and/or Number): 1620301 (SAKURA-1)

| | | |
|---|---|--|
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant) |
| Total number of investigators identified: <u>32</u> | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u> | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u> | | |
| 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: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor: <u>0</u> Sponsor of covered study: <u>0</u> | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u> | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

Table 38. Covered Clinical Study (Name and/or Number): 1620302 (SAKURA-2)

| | | |
|--|---|---|
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant) |
| Total number of investigators identified: <u>40</u> | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u> | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u> | | |

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DaxibotulinumtoxinA for Injection

| | | |
|---|---|--|
| 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: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor: <u>0</u> Sponsor of covered study: <u>0</u> | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u> | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

Table 39. Covered Clinical Study (Name and/or Number): 1620303 (SAKURA-OLS Rollover)

| | | |
|---|---|--|
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant) |
| Total number of investigators identified: <u>66</u> | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u> | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u> | | |
| 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: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor: <u>0</u> Sponsor of covered study: <u>0</u> | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u> | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

Table 40. Covered Clinical Study (Name and/or Number): 1620303 (SAKURA-OLS Nonrollover)

| | | |
|---|---|--|
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant) |
| Total number of investigators identified: <u>110</u> | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u> | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u> | | |
| 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: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor: <u>1</u> Sponsor of covered study: <u>0</u> | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u> | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

19.3. Nonclinical Pharmacology/Toxicology

Revisions to the sponsor's proposed wording for the nonclinical and related sections of the label are provided below. Reviewer proposed deletions are annotated as ~~double-strikeout~~ text and reviewer proposed additions are annotated as double underlined text.

HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

TRADENAME is an acetylcholine release inhibitor and neuromuscular blocking agent indicated for the (b) (6) temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Individual Study Summary

In the current BLA, the Applicant submitted five clinical trials: three Phase 3 trials (1620301 and 1620302 [Phase 3], and 1620303 [Open-label study, OLS]) and two Phase 1/2 trials (RT002-CL001 [Phase 1/2] and RT002-CL002 [Phase 2]).

19.4.2. Study 1620301 (SAKURA-1)

Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Trial to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection to Treat Moderate to Severe Glabellar Lines (SAKURA-1).

Methods

This was a Phase 3, randomized, double-blind, placebo-controlled, multi-center trial that enrolled subjects with moderate to severe glabellar lines. Subjects were randomly assigned in a 2:1 ratio to DAXXIFY for injection (40 Units) or placebo.

After a Screening Visit conducted up to 2 weeks prior to randomization, subjects were treated at Day 0 (henceforth referred to as Day 1), and were followed for a minimum of 24 weeks and up to a maximum of 36 weeks post-treatment for efficacy and safety assessments, with study visits at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36.

The Final Evaluation Visit occurred at Week 24 if both Patient Frown Wrinkle Severity (PFWS) and Investigator Global Assessment-Frown Wrinkle Severity (IGA-FWS), scored at maximum frown, returned to baseline. If both IGA-FWS and PFWS returned to baseline at a visit between Week 24 and Week 36, then the visit at which the score was recorded was deemed the Final Evaluation Visit for the subject. Efficacy assessments included subject and investigator assessments of improvement in glabellar line severity and satisfaction with treatment, as assessed using questionnaires. Safety assessments included clinical laboratory tests (i.e., hematology, chemistry, urinalysis, prothrombin time), serum antibody tests, injection site evaluations, cranial nerves II-VII assessment, facial muscle strength, 12-lead electrocardiogram (ECG), concomitant medications, adverse event (AE) collection, AEs of special interest (events due to the distant spread of toxin), vital signs, and physical examinations. After the Final Evaluation Visit, all qualified subjects had the option to enroll in an open-label trial to evaluate the long-term safety of repeat-use of DAXXIFY for injection for the treatment of moderate to severe glabellar lines.

The investigator, trial center staff, subjects, and Sponsor remained blinded to study treatment throughout the trial. Only the statistician responsible for the randomization codes was unblinded to the treatment assignments during the trial.

Immunogenicity Assessment

Blood samples for antibody testing were collected at Screening and Weeks 2, 4, and 12. Antibody samples were batched for analysis and test results were reviewed by the Applicant. All samples that tested positive for anti-DAXXIFY binding antibodies were subjected to a mouse protection assay (MPA) test for detecting the presence of DAXXIFY neutralizing antibodies (NABs). The placebo contained RTP004 and was tested for anti-RTP004 binding antibodies.

Immunogenicity Results

The SAKURA-1 study enrolled a total of 303 subjects who received treatment with placebo (n=102) or 40 Units DAXXIFY for injection (n=201; SAKURA-1 CSR, section 12.3.2.1.2). Of the subjects that received DAXXIFY for injection, 2 subjects (1.0%) developed treatment-induced binding antibodies and no subjects (0.0%) developed treatment-boosted antibodies to DAXXIFY. Neither subject had been previously exposed to botulinum toxin treatment, nor did they test positive for anti-DAXXIFY NABs. In addition, 3 different subjects (1.5%) that received DAXXIFY for injection, and 2 subjects (2.0%) that received placebo, developed treatment-induced binding antibodies to RTP004. No subjects demonstrated a treatment-boosted antibody response to RTP004. Overall, reported titers were less than or equal to 1:50 for DAXXIFY injection except for 1 subject (b) (6) with a single DAXXIFY titer result of 1:400, 8 times the minimum dilution. This subject received DAXXIFY for injection and achieved the 2-point composite response at the primary time point of Week 4 and maintained a none or mild response by investigator assessment through Week 16. All subjects that received DAXXIFY for injection who had treatment-induced binding antibodies to DAXXIFY or RTP004 were assessed as having clinical efficacy to DAXXIFY for injection by investigator assessment. In subjects that received either DAXXIFY for injection or placebo, none experienced immune-related adverse events. Overall, local injection site reactions for the entire study were infrequent. These reactions were most frequently pain, edema, and burning/stinging, and generally occurred and were resolved on the day of treatment.

19.4.3. Study 1620302 (SAKURA-2)

Title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Trial to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection to Treat Moderate to Severe Glabellar Lines (SAKURA-2).

Methods

This was a Phase 3, randomized, double-blind, placebo-controlled, multi-center trial that enrolled subjects with moderate to severe glabellar lines. Subjects were randomly assigned in a 2:1 ratio to DAXXIFY for injection (40 Units) or placebo.

After a Screening Visit conducted up to 2 weeks prior to randomization, subjects were treated at Day 0 (henceforth referred to as Day 1), and were followed for a minimum of 24 weeks and up to a maximum of 36 weeks post-treatment for efficacy and safety assessments, with study visits at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36. The Final Evaluation Visit occurred at Week 24 if both Patient Frown Wrinkle Severity (PFWS) and Investigator Global Assessment-Frown Wrinkle Severity (IGA-FWS), scored at maximum frown, returned to baseline. If both IGA-FWS and PFWS returned to baseline at a visit between Week 24 and Week 36, then the visit at which the score was recorded was deemed the Final Evaluation Visit for the subject. Efficacy assessments included subject and investigator assessments of improvement in glabellar line severity and satisfaction with treatment, as assessed using questionnaires. Safety assessments included clinical laboratory tests (i.e., hematology, chemistry, urinalysis, prothrombin time), serum antibody tests, injection site evaluations, cranial nerves II-VII assessment, facial muscle strength, 12-lead electrocardiogram (ECG), concomitant medications, adverse event (AE) collection, AEs of special interest (events due to the distant spread of toxin), vital signs, and physical examinations. After the Final Evaluation Visit, all qualified subjects had the option to enroll in an open-label trial to evaluate the long-term safety of repeat-use of DAXXIFY for injection for the treatment of moderate to severe glabellar lines.

The investigator, trial center staff, subjects, and Sponsor remained blinded to study treatment throughout the trial. Only the statistician responsible for the randomization codes was unblinded to the treatment assignments during the trial.

Immunogenicity Assessment

Blood samples for antibody testing were collected at Screening and Weeks 2, 4, and 12. Antibody samples were batched for analysis and test results were reviewed by the Applicant. All samples that tested positive for anti-DAXXIFY binding antibodies were subjected to a mouse protection assay (MPA) test for the presence of DAXXIFY neutralizing antibodies (NABs). The placebo contained RTP004 and was tested for anti-RTP004 binding antibodies.

Immunogenicity Results

The SAKURA-2 study enrolled a total of 306 subjects who received treatment with placebo (n=101) or 40 Units of DAXXIFY for injection (n=205; SAKURA-2 CSR, section 12.3.2.1.2). Of the subjects that received DAXXIFY for injection, no subject (0.0%) developed treatment-related binding antibodies to DAXXIFY, and 2 subjects (1.0%) developed treatment-induced binding antibodies to RTP004. No treatment-related anti-RTP004 antibodies were detected in subjects that received treatment with placebo. The maximum titer values in the 2 subjects with treatment-induced RTP004 binding antibodies were 1:100 and 1:200. These values were 2- and 4-times greater than the minimal detectable titer of 1:50, and both subjects were assessed as having clinical efficacy to DAXXIFY by investigator assessment. In subjects that received either DAXXIFY for injection or placebo, none experienced immune-related adverse events. Subject (b) (6) presented with edema (Days 1 to 8), hordoleum (Days 75 to 142), and sinusitis (Days 75 to 81) during the study, which were considered unrelated to treatment by the investigator. Overall, local injection site reactions for the entire study were infrequent. These reactions were

most frequently pain, edema, and burning/stinging, and were generally limited to the day of treatment.

19.4.4. Study 1620303 (SAKURA-OLS)

Title

An Open-Label, Multi-Center Trial to Assess the Safety of Single and Repeat Treatments of DaxibotulinumtoxinA for Injection for Treatment of Moderate to Severe Glabellar Lines (SAKURA OPEN-LABEL SAFETY)

Methods

This was a Phase 3, open-label, multi-center trial to assess the long-term safety of single and repeat administration of DAXXIFY for injection in subjects with moderate to severe glabellar lines. By amendment, the SAKURA open-label safety (OLS) study targeted enrollment of 2100 subjects to receive at least one treatment, and 400 to 600 subjects to receive repeat treatments. Therefore, once enrollment numbers for subjects to receive three treatments were met, any subject enrolled thereafter was eligible only to receive a single treatment. Subjects were eligible to participate in the SAKURA-OLS study either as newly enrolled subjects in the SAKURA program, or as rollover subjects from the SAKURA-1 (Protocol No. 1620301; NCT03014622) and SAKURA-2 (Protocol No. 1620302; NCT03014635) Phase 3 pivotal trials. Eligible subjects that completed the SAKURA-1 and SAKURA-2 trials were offered the opportunity to receive additional treatments in this open-label trial. A total of 2691 adult subjects were enrolled in the study, including 477 rollover subjects who received their initial treatment in the SAKURA-1 and SAKURA-2 Phase 3 trials, and 2214 subjects who were newly enrolled into the OLS trial. After obtaining informed consent from all participating subjects (rollover or newly enrolled), a Screening Visit was conducted up to 2 weeks prior to treatment. Subjects were treated with a single administration of DAXXIFY for injection (40 Units) at Day 0 (henceforth referred to as Day 1). Subjects were followed for a minimum of 12 weeks, and up to 36 weeks, in treatment cycle 1 and, if designated for repeat treatments, in treatment cycle 2, and for a maximum of 12 weeks in treatment cycle 3. Study visits were conducted at Weeks 1, 2, 4, 8, and 12 in all subjects, and additionally at Weeks 16, 20, 24, 28, 32, and 36 depending upon subject eligibility. The first visit at Week 12 or later, at which both the Investigator Global Assessment-Frown Wrinkle Severity (IGA-FWS) and the Patient Frown Wrinkle Severity (PFWS), assessed at maximum frown, had returned to baseline, was considered the Final Evaluation Visit or the Retreatment Visit. This was the final evaluation for subjects not identified to receive retreatment. For subjects who were eligible for multiple treatments, this was their Retreatment Visit. Subjects eligible to receive multiple treatments had a Final Evaluation Visit at Week 12 following their final eligible treatment. Blinding of the pivotal trial treatment assignment was maintained for all subjects who rolled over from the SAKURA-1 and SAKURA-2 studies; therefore, rollover subjects received up to two treatments in the SAKURA-OLS study. Subjects who received a single treatment were followed for a maximum of 36 weeks and retreatment subjects were followed for a maximum of 84 weeks.

Safety assessments conducted at the study visits included: clinical laboratory tests (i.e., hematology, chemistry, urinalysis, prothrombin time), urine pregnancy test for women of childbearing potential, serum antibody tests (active ingredient and novel excipient), injection site evaluations, cranial nerves II-VII assessment, facial muscle strength evaluation, concomitant medications, adverse event (AE) collection, treatment-emergent AEs (TEAEs) of special interest (events deemed by the investigator to be potentially related to the distant spread of toxin) collection, vital signs, and physical examinations. Efficacy assessments included subject and investigator assessments of improvement in frown lines, as assessed using validated scales with a photonumeric guide. Mandatory photographs were taken at baseline to assess for the presence of eyelid ptosis at baseline in the event that a subject reported eyelid ptosis at a post-treatment visit.

Immunogenicity Assessment

Blood samples for antibody testing were collected at Screening and Weeks 2, 4, and 12 following each treatment. Antibody samples were batched for analysis and test results were reviewed by the Applicant. All samples that tested positive for anti-DAXXIFY binding antibodies were subjected to an MPA test for the presence of DAXXIFY NABs.

Immunogenicity Results

The SAKURA-OLS study enrolled a total of 2691 subjects who received up to three treatments of DAXXIFY for injection. A total 2380 subjects received one treatment, 882 subjects received two treatments, and 568 subjects received three treatments. A number of the SAKURA-OLS subjects (n=477) were enrolled from SAKURA-1 and SAKURA-2. Of these, 166 received placebo and 311 received DAXXIFY for injection during SAKURA-1 and SAKURA-2 (SAKURA-OLS CSR, section 10). [Table 41](#) summarizes the treatment-related binding antibody results for anti-DAXXIFY and anti-RTP004 antibodies following each treatment, and study totals. Percentages reported are based on the number of subjects receiving the specified treatment with a baseline result and at least one post-baseline result.

A total of 19 (0.7%) subjects developed treatment-induced (n=18, 0.7%) or treatment-boostered (n=1, <0.05%) anti-DAXXIFY binding antibodies during the study. Three (3) of the 19 responders were subjects who received their first DAXXIFY for injection treatment during SAKURA-1. The incidence of treatment-related anti-DAXXIFY antibody responses in subjects who received one, two, or three DAXXIFY for injection treatments was 10 (0.4%), 4 (0.5%), and 5 (0.9%), respectively. No subjects who developed treatment-related anti-DAXXIFY binding antibodies tested positive for NABs.

A total of 28 (1.1%) subjects developed treatment-induced anti-RTP004 binding antibodies, and none developed treatment-boostered anti-RTP004 antibodies. Five (5) of these were subjects who rolled over from SAKURA-1 or SAKURA-2 when they were first exposed to RTP004 while receiving either placebo or DAXXIFY for injection. The incidence of treatment-related anti-RTP004 antibody responses in subjects who received one, two, or three DAXXIFY for injection treatments was 20 (0.9%), 4 (0.5%), and 7 (1.2%), respectively.

In general, treatment-related anti-DAXXIFY and anti-RTP004 titer results occurred at one to two visits for each subject. Titer values for these subjects were less than or equal to 1:200 (4 times the minimal detectable titer of 1:50).

All subjects with treatment-related binding antibodies to DAXXIFY or RTP004 were assessed as having clinical efficacy to DAXXIFY for injection by investigator assessment. All subjects with treatment-related DAXXIFY antibodies showed a clinical response by at least a 1-point improvement in the investigator assessments after one or more treatments with DAXXIFY for injection, and 18 of the 19 subjects showed a 2-point improvement on the investigator assessments. All subjects with treatment-related RTP004 antibodies demonstrated a positive clinical response by having at least a 2-point improvement in the investigator assessments after one or more treatments with DAXXIFY for injection. In subjects that received up to three treatments of DAXXIFY for injection and had treatment-related binding antibodies to DAXXIFY and RTP004 at any time during the study, all demonstrated at least a 2-point improvement in the investigator assessments after the third treatment.

No subjects with treatment-related DAXXIFY or RTP004 antibodies reported serious adverse events during the SAKURA-OLS study. Of the 19 subjects with treatment-related DAXXIFY antibodies, 9 subjects (47.4%) reported at least one TEAE during the SAKURA-OLS. This number was similar to the proportion of subjects who reported TEAEs without having treatment-induced (38.9%) or treatment-boosted DAXXIFY antibodies (54.5%). Of the 28 subjects with treatment-related RTP004 antibodies, 14 subjects (50.0%) reported at least one TEAE during the SAKURA-OLS study, and this was similar to the proportion of subjects with TEAE reported for subjects without treatment-induced (38.8%) or treatment-boosted RTP004 antibodies (43.4%).

For subjects with treatment-related antibodies, hypersensitivity reactions were reported in 2 subjects. Subject (b) (6) reported an unspecified allergic reaction at Day 49, following the first injection, that lasted 3 days and was deemed unrelated to treatment by the investigator. Subject (b) (6) reported an injection site rash on Days 171 to 207. Local injection site reactions occurred in 2 of 19 subjects with treatment-related anti-DAXXIFY antibodies, and in 8 of 28 subjects with anti-RTP004 treatment-related antibodies. These reactions were usually erythema or edema and, in general, only occurred on the day of treatment. The occurrence of hypersensitivity reactions or injection site findings did not coincide with the occurrence of anti-DAXXIFY or anti-RTP004 antibodies, and are considered unrelated to antibody formation in these subjects.

For subjects that were missing a baseline result and were subsequently deemed not evaluable for immunogenicity, only one subject (b) (6) had post-DAXXIFY for injection treatment antibodies. This subject was positive for anti-RTP004 antibodies at Week 2 and Week 12, and reported a single adverse event of acne during the study, starting on Day 25 and lasting 7 days,

that was deemed unrelated to treatment by the investigator. Subject (b) (6) was assessed as having clinical efficacy to DAXXIFY for injection by investigator assessment.

No subjects with treatment-related antibodies to DAXXIFY were found to have NABs to DAXXIFY. When serum from all subject samples that confirmed positive for binding anti-DAXXIFY antibodies were tested in the MPA, only one SAKURA-OLS de novo subject (b) (6) was found to have NABs to DAXXIFY. This subject was positive for the presence of binding and NABs at their study screening visit and maintained a consistent antibody titer (1:200) across all samples tested. As a result, this subject was not classified as having treatment-induced or treatment-boosted antibody response. The subject reported no adverse events nor any local injection site reactions in the study at any study visit. Furthermore, this subject had no clinical response to DAXXIFY as evaluated by either the blinded evaluator or the subject themselves. This subject had exposure to botulinum toxin prior to entering the study, and their last exposure was approximately 31 months prior to study enrollment.

Based on these findings, it was concluded that the incidence of binding antibodies to DAXXIFY or RTP004 in subjects receiving up to three treatments of 40 Units DAXXIFY for injection in the treatment of glabellar lines is low, and no subjects developed NABs upon repeat-administration of DAXXIFY for injection. The presence of binding antibodies was not associated with clinically significant immune-related adverse events, nor with local injection site reactions.

Table 41. Treatment-Induced and Treatment-Boosted Response from SAKURA Open-Label Safety Study Following Each DAXXIFY for Injection Treatment

| | Antibody Response Type | Anti-DAXI Antibody Results | Anti-RTP004 Antibody Results |
|-------------------------------------|------------------------------|----------------------------|------------------------------|
| Treatment 1 N = 2380 | Treatment-Induced Antibodies | 10 (0.4%) | 20 (0.9%) |
| | Treatment-Boosted Antibodies | 1 (<0.05%) | 0 (0.0%) |
| Treatment 2 N = 882 | Treatment-Induced Antibodies | 4 (0.5%) | 4 (0.5%) |
| | Treatment-Boosted Antibodies | 0 (0.0%) | 0 (0.0%) |
| Treatment 3 N = 568 | Treatment-Induced Antibodies | 5 (0.9%) | 7 (1.2%) |
| | Treatment-Boosted Antibodies | 0 (0.0%) | 0 (0.0%) |
| Overall (Any Treatment) N = 2691 | Treatment-Induced Antibodies | 18 (0.7%) | 28 (1.1%) |
| | Treatment-Boosted Antibodies | 1 (<0.05%) | 0 (0.0%) |

DAXI = daxibotulinumtoxinA, RTP004 = peptide RTP004, the novel excipient of daxibotulinumtoxinA for injection.

N = number of treated subjects, source: SAKURA-OLS CSR, Table 14.1.1.1.

Percentages are based on the number of subjects receiving the specified treatment with a baseline result and at least 1 post-baseline result, N-trt, source: SAKURA-OLS CSR, Table 14.2.5.17.

19.5. Additional Clinical Outcome Assessment Analyses

Not Applicable.

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/

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