Results of a Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Botulinum Toxin Type A Topical Gel for the Treatment of Moderate-to-Severe Lateral Canthal Lines

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Background: Injections of botulinum toxin type A are commonly used to treat facial wrinkles; however, undesirable effects are associated with injections (e.g., pain, bruising, ptosis, immunogenicity, and needle aversion) to address these issues, RT001 Botulinum Toxin Type A Topical Gel is being developed for the treatment of lateral canthal lines.

Objectives: To assess the safety and efficacy of RT001 for the treatment of lateral canthal lines in a randomized, double-blind, placebo-controlled study.

Materials & Methods: Adult subjects were enrolled to receive a single treatment of RT001 (n=45) or placebo (n=45) applied topically in the lateral canthal area. The primary endpoint was the composite of the Investigator Global Assessment of Lateral Canthal Line Severity (IGA-LCL) and the Patient Severity Assessment of lateral canthal line severity (PSA) defined as a 2-point or greater improvement on both scales.

Results: At four weeks, 44.4 percent of subjects treated with RT001 achieved a 2-point or greater improvement on a rigorous composite of both the IGA-LCL and PSA scales compared to 0.0% for the placebo subjects (*P <0.0001). At four weeks, 88.9 percent of subjects achieved clinically relevant improvement by investigator assessment. Adverse events were mild in severity and unrelated to study treatment.

Conclusions: RT001 appears to be a safe and well-tolerated treatment for improvement of lateral canthal lines.


INTRODUCTION

A substantial body of literature supports the safe and effective use of botulinum toxin type A (BoNTA) injections for temporary improvement of facial wrinkles. Although an off-label use, BoNTA treatment of lateral canthal lines (LCL), also known as periorbital rhytids or crow’s feet, has become a common clinical practice. Clinical practice has evolved substantially since the initial use of BoNTA for treatment of LCL. Current treatment recommendations focus on preserving a natural voluntary smile while softening the wrinkles in a neutral facial position (“at rest”).1 2 This goal has been accomplished through progressive declines in the amount of BoNTA injected as well as broad use of intradermal injections.3 6 LCL at rest have been shown to be the major factor in perception of facial age and a 20 percent improvement in these LCL has been shown to be both readily detected and clinically significant.3 Elimination of the LCL which are normally present during a smile has come to be recognized as aesthetically unappealing. Lack of LCL at smile is perceived as a posed photo-smile, or a fake smile; these smiles are cortical in origin, voluntary, and do not reflect genuine emotion.4 5 6 8 9 The appearance of a photo smile is perceived to be an insincere smile which does not communicate genuine happiness, and a BoNTA-induced insincere smile has been shown to actually decrease subjects’ ability to experience certain positive emotions.4 6 8 9 Even when
not consciously identified, observers have recently been shown to distrust and have a negative perception of individuals who project the insincere smile pattern after BoNTA treatment. As a result, a correction of LCL that abolishes lines at maximum effort is not only aesthetically unappealing, but also may have a detrimental psychological impact for some subjects.

All of these effects have contributed to the current clinical treatment goal of correcting most LCL which are present in a neutral resting facial state while preserving natural smile wrinkle patterns at maximum contraction. This distinction is important because, unlike the glabellar wrinkle pattern, different muscle groups impact LCL at rest versus those at maximal contraction (e.g., smile) so the target muscle for treatment is determined by the selection of LCL at rest. Specifically, the target of BoNTA treatment for LCL is the lateral orbicularis oculi (OO) muscles, which determine the extent of lines at rest versus the combination of the zygomaticus, levator and OO groups which all contribute to the wrinkle pattern at smile.6 The current procedural technique is thus to inject BoNTA into the lateral canthal area (LCA) to weaken the lateral OO muscles and improve the LCL caused by OO activity.11–21 The OO is a superficial muscle group that requires care when injecting into the LCA to avoid adverse effects related to either the injection method or to BoNTA. Flow of injected BoNTA in the upper facial and periorcular areas can potentially result in undesirable ptosis22–23 and diplopia.24 One currently recommended method of birth control during the course of the study.

Subjects
The study enrolled generally healthy male and female subjects between 18 and 65 years of age. Subjects were required to have bilateral (both eyes) LCL graded as either moderate (3) or severe (4) in a neutral facial state based on the 5-point Investigator Global Assessment of Lateral Canthal Line (IGA-LCL) Severity Scale (Absent, Minimal, Mild, Moderate, Severe). In addition, subjects also had to assess themselves as having either moderate (3) or severe (4) wrinkles based on the 5-point Patient Severity Assessment (PSA; Absent, Minimal, Mild, Moderate, Severe). Each subject agreed to refrain from the use of facial fillers, laser treatments, and any product affecting skin remodeling or which might cause an active dermal response during the course of the study. Women of child-bearing potential were required to have a negative urine pregnancy test and agree to use an accepted method of birth control during the course of the study.

In order to evaluate the safety and efficacy of a single administration of RT001 Botulinum Toxin Type A Topical Gel (RT001) for the treatment of moderate-to-severe LCL, 90 subjects were enrolled in a randomized, double-blind, placebo-controlled study with results presented below. RT001 is an investigational topically applied BoNTA product being studied for the treatment of moderate-to-severe LCL observed in a neutral facial state. RT001 consists of a purified 150kD BoNTA molecule combined with a proprietary peptide which serves as an absorption enhancer and enables transcutaneous delivery without the use of patches, needles or any other devices. The peptide employs protein transduction domains to accomplish transcutaneous delivery without covalent modification of the BoNTA.25 A topical approach is particularly promising because local pain and bruising have been reported to occur in 6–25 percent of BoNTA-injected subjects14,18 and approximately 10 percent of the general population suffers from belonephobia, or an unreasonable fear of needles.29

METHODS
Ethics
This study adhered to the ethical principles of the Declaration of Helsinki, 21 CFR Part 50, and the International Conference on Harmonisation Good Clinical Practice guidelines. The protocol was approved by an Institutional Review Board/Independent Ethics Committee for each participating study center. Written informed consent was obtained from all subjects prior to performing any study-related procedures.

Reasons for excluding subjects from the study included: a neurological condition that might place them at increased risk from BoNTA exposure, such as amyotrophic lateral sclerosis or myasthenia gravis; inability to substantially lessen their LCL by physically reducing them apart; recent use of topical prescription-strength retinoids (within three months), chemical peels of medium or greater depth (within nine months), periorbital surgery, brow lift or related procedures, laser skin resurfacing, soft tissue augmentation or any procedures affecting the lateral canthal region (within 12 months); eyelid ptosis; muscle weakness or paralysis, active skin disease or irritation, excessive dermatochalasis, or deep dermal scarring at the treatment areas; prior facial treatment with BoNTA or recent treatment with >200 U BoNTA anywhere else in the body (within six months); prior immunization with any botulinum toxin serotype or a history of allergy or sensitivity to any components of the study medication; concurrent use of other therapeutic agents that might interfere with neuromuscular transmission, such as aminoglycoside antibiotics; any medical condition or illness which, in the Investigator’s opinion, put the subject at significant risk or might confound the study results. Subjects with a history of hypokalemia, torsade de pointe, unstable angina, myocardial infarction, congestive heart failure or family history of prolonged QT interval (long QT syndrome) were also excluded.

Investigational Drug
RT001 contains a lyophilized cake consisting of a purified 150kD BoNTA molecule combined with the proprietary peptide absorption enhancer that is reconstituted with a poloxamer-based diluent which gels when in contact with skin. RT001 is a purified form of BoNTA without albumin or animal-derived materials,
thus eliminating risk of prion-based and blood-based diseases from the product. RT001 is dosed based on mass concentration (25 ng/mL). RT001 was administered within six hours of reconstitution. The placebo treatment consisted of the poloxamer-based diluent and all ingredients of RT001 except the toxin and peptide. Approximately 1 mL of RT001 was applied to each subject.

**Efficacy Measures**

Evaluation of LCL while the face was in a neutral facial state was made by the Investigator using the IGA-LCL Severity Scale at baseline (pre-application) and four weeks post-treatment. LCL length and depth were assessed bilaterally. The average length of LCL in each LCA was measured using a specially designed caliper and recorded. The IGA-LCL Severity Scale is a validated scale which includes length and depth as key parameters of LCL severity. All subjects were assessed in person by the blinded investigator during study visits.

Each subject independently completed the PSA at both baseline and week 4. While viewing themselves in a handheld mirror, subjects rated the severity of the LCL in the RT001 treatment area using the PSA. This was a static assessment as subjects were not asked to compare severity of their wrinkles at week 4 to baseline. Subjects also completed a 7-point Likert scale, the Patient Global Impression of Change assessment (PGIC) at week 4. All subject assessments were completed before the Investigator completed the IGA-LCL assessment.

The primary efficacy endpoint was the composite of the IGA-LCL score and the PSA scores. Subjects were classified as responders at week 4 if there was a 2-point or greater improvement on both sides of the face between baseline (day 0) and the week 4 follow-up visit for both the IGA-LCL Severity (bilateral improvement) and the PSA. In order to avoid issues with multiplicity in the primary endpoint, secondary endpoints included the discrete investigator and subject assessments as measured by 1-point or greater and 2-point or greater improvements on the IGA-LCL and by 1-point or greater and 2-point or greater improvements on the PSA and PGIC scales.

**Safety Measures**

Safety measures obtained at the screening visit (1-14 days prior to treatment) and at week 4 included a 12-lead electrocardiogram (ECG), and non-fasting samples for hematology, clinical chemistry, and urinalysis. Subjects were required to have a score of baseline Skin Erythema Assessment and Clinical Signs/Symptom Descriptors scores 1 or less (mild) for both LCAs. Skin erythema was re-evaluated following application to determine if there was an immediate reaction to RT001 and again at week 4 using an erythema rating scale plus the addition of clinical descriptors.28,30

Assessments made by the Investigators at baseline pre- and post-application and week 4 included ocular irritation rated by the presence of erythema, stinging, burning, itching, dryness, or foreign body sensation using a 4-point scale from None (0) to Severe (3) and adverse event (AE) severity using the Cancer Therapy Evaluation Program-Common Terminology Criteria for Adverse Events (CTEP-CTCAE) version 4.0. In order to quantitatively and directly assess any potential local or regional spread of BoNTA, assessment of cranial nerve II–VII function was done at baseline and each follow-up visit.31 The Regional House-Brackmann Facial Nerve Grading System was used to assess cranial nerve VII as part of this evaluation. This approach allowed for direct and specific evaluation of muscle strength for each muscle adjacent to OO and thus allowed for discrete evaluation of any potential spread to each adjacent structure.

**Statistical Methods**

All statistical programming was performed using SAS Version 9.1 or higher. The primary analysis was a comparison of efficacy results for RT001 and placebo. Inferential statistics based on Fisher’s exact test or Pearson’s chi-square test were used to analyze the composite primary endpoint and each of the secondary endpoints. Subjects were classified as responders on primary efficacy at week 4 if they simultaneously demonstrated a 2-point or greater improvement in both LCAs from baseline on the IGA-LCL and a 2-point or greater improvement on the PSA. Secondary efficacy evaluations included clinically relevant (>1-point) or marked (>2-point) bilateral improvement by IGA-LCL, clinically relevant (>1-point) or marked (>2-point) improvement by PSA, and the proportion of subjects with marked improvement (a rating of “improved” or “much improved”) based on the PGIC assessment.

The safety population included all randomized subjects who were treated. The outcomes of all safety evaluations were tabulated. Treatment-emergent AEs were classified using Medical Dictionary for Regulatory Activities (MedDRA, version 11.1) and summarized by treatment group, system organ class, preferred term, severity, relationship, and seriousness.

**RESULTS**

The study enrolled 90 subjects who were randomized to receive treatment with RT001 (n=45) or placebo (n=45). Demographics were similar between RT001 and placebo as detailed in Table 1 as...
were baseline characteristics in IGA-LCL (Table 2) and PSA (Table 3). Overall, 88 subjects had follow up at week 4 and are included in the primary efficacy analysis. Two subjects were lost to follow up at week 4, but all 90 subjects are included in the safety results.

Efficacy
RT001 group achieved the primary efficacy endpoint at 4 weeks: 44.4 percent of subjects treated with RT001 attained a composite 2-point or greater improvement in both IGA-LCL (bilateral response) and PSA scales while 0.0 percent of control subjects were responders \( (P<0.0001) \) (Figure 1). RT001 also achieved each of the five secondary efficacy endpoints. RT001 achieved significant efficacy over placebo based on both individual responder rates for the IGA-LCL severity alone (1- and 2-point improvement, Figure 2) and both responder rates for the PSA alone (1-point and 2-point improvement, Figure 3). Specifically, RT001 showed significant efficacy compared to placebo (57.8 percent vs. 14.0 percent; \( P<0.0001 \)) based on responder rates where a subject was considered a responder if both LCL showed at least a 2-point improvement from baseline in IGA-LCL severity scores. RT001 achieved a significant treatment benefit compared to placebo (44.4 percent vs. 2.3 percent; \( P<0.0001 \)) based on responder rates where a subject was considered a responder if subject showed at least a 2-point change in the PSA. RT001 also attained significant efficacy over placebo (88.9 percent vs. 279 percent; \( P<0.0001 \)) based on responder rates where a subject was considered a responder if both LCL showed at least a 1-point improvement from baseline in IGA-LCL severity scores. Additionally, RT001 achieved a significant treatment benefit compared to placebo (64.4 percent vs. 14.0 percent; \( P<0.0001 \)) based on responder rates where a subject was considered a responder if subject showed at least a 1-point or greater improvement in PSA. Most importantly for an aesthetic indication, RT001 achieved significant efficacy over placebo (57.8 percent vs. 4.7 percent; \( P<0.0001 \)) based on an individual responder rate on a PGIC categorization of marked improvement (much improved or improved, Figure 4).

Safety
There were no clinically meaningful or significant differences in safety assessments observed between RT001 and placebo. Safety findings included:

Across all subjects, including the 45 subjects treated with 25 ng RT001, there were no definitely, probably or possibly related AEs. Overall AEs (all unrelated) occurred at a very low rate in RT001 treated subjects. Three (3) subjects (6.7%) treated with RT001 reported a total of eight AEs post-treatment, one of which was an unrelated serious adverse event (SAE) of mild severity (transient ischemic attack). Five (5) of the AEs were mild in intensity and three were moderate. Six (6) subjects (13.3%) treated with placebo reported a total of six AEs post-treatment. All six AEs were mild in severity. No subject discontinued due to an AE. There were no severe AEs. There were no related SAEs.

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TABLE 1. Demographic Characteristics (ITT Subjects)

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<tr>
<th></th>
<th>RT001 (n=45)</th>
<th>Placebo (n=45)</th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean (STD)</td>
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<td>51.6 (8.0)</td>
<td>53.1 (7.8)</td>
</tr>
<tr>
<td>Median (Min. to Max.)</td>
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<td>52.0 (32 to 65)</td>
<td>53.0 (32 to 65)</td>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Male</td>
<td>6 (13.3%)</td>
<td>6 (13.3%)</td>
<td>12 (13.3%)</td>
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<tr>
<td>Female</td>
<td>39 (86.7%)</td>
<td>39 (86.7%)</td>
<td>78 (86.7%)</td>
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<tr>
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<td>20 (44.4%)</td>
<td>36 (40.0%)</td>
</tr>
<tr>
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<td>29 (64.4%)</td>
<td>25 (55.6%)</td>
<td>54 (60.0%)</td>
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<tr>
<td><strong>Race</strong></td>
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<tr>
<td>White</td>
<td>45 (100.0%)</td>
<td>43 (95.6%)</td>
<td>88 (97.8%)</td>
</tr>
<tr>
<td>Black/African American</td>
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<td>1 (2.2%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Other*</td>
<td>0 (0.0%)</td>
<td>1 (2.2%)</td>
<td>1 (1.1%)</td>
</tr>
</tbody>
</table>

*Bangladeshi.

Application site findings: no RT001 subject experienced application site erythema. Only one subject (placebo) had erythema at any time during the study (minimal erythema on the right and left LCAs at baseline occurring both pre- and post-application and no erythema thereafter). No subjects encountered application site edema, scaling, fissures, crusts, vesicles, burning, stinging, or itching at any evaluation.

Ocular findings: There were no reports of stinging, burning, dryness, or foreign body sensation in either eye at any time during the study. A few mild erythema events occurred; these were typically present in subjects with seasonal allergies and all were present prior to treatment. No subject randomized to RT001 had itching in either eye at any time during the study while one (1) subject randomized to placebo had mild itching in the right eye at week 4. There were no individually clinically significant abnormal lab test results reported during the study. Laboratory test results did not demonstrate any safety signals, individually or collectively. ECG findings were all unrelated, were all considered to be not clinically relevant, and occurred at similar rates in each group which parallel findings in the normal population. Cranial nerve assessments, which specifically and quantitatively evaluate any spread of toxin, revealed no abnormalities and no evidence of muscle weakening beyond the OO. Thus, no spread of toxin to any structures beyond the target lateral OO was detectably present in spite of marked impact on OO-dependent LCL. There was no evidence of systemic exposure in any subject and there were no clinically significant changes in laboratory values or ECGs related to treatment.

DISCUSSION

In this study, RT001 Topical Gel achieved sufficient transcutaneous penetration of BoNTA to reduce OO muscle spasm and produce a marked treatment effect on LCL without evidence of adverse ocular, neurological or other systemic effects. No weakening of adjacent muscles was observed despite the magnitude of the OO effects.

A single topical administration of RT001 in the LCA resulted in significant reduction of LCL at 4 weeks versus placebo on investi-
gator and subject assessments both as composite and as discrete measurements. It is noteworthy that RT001 achieved significant improvement in LCL versus placebo even on a rigorous pre-specified stringent primary endpoint which required that investigators score a subject as markedly improved bilaterally (in both eyes) and required that the same subject self-rate a marked improvement in severity as well. Considering the stringency of the endpoint as reflected in a 0.0 percent placebo rate, the 44.4 percent response rate on this endpoint is quite promising in magnitude. Based on the Investigators’ evaluations, 88.9 percent of subjects achieved a clinically relevant (≥1-point) improvement at week 4 with RT001 while the majority (57.8%) exhibited a marked level of clinical response (≥2-point improvement) in severity. Finally, by a validated subject rating of improvement (PGIC), 578 percent of subjects realized marked improvement compared to their baseline. Typically, subjects intuitively evaluate the effect of a treatment based on their own comparative assessment of improvement relative to their pre-treatment state. Since patients seek a particular degree of improvement, scores on improvement scales such as the PGIC often prove to be the most relevant indicator of a product’s future acceptance. While there has been no direct comparative study with RT001 versus injectable BoNTA and it is difficult to compare data across studies, response rates with RT001 appear to be quite similar to previous literature reports of LCL improvement after BoNTA injections, and quite effective overall.

The marked efficacy results presented in this study are accompanied by a promising overall safety profile. Compared to placebo-treated subjects, there was no increase in the frequency, severity or duration of AEs or other safety parameters. There were no treatment-related AEs. AEs were generally mild, local and transient. The few reported adverse events were determined to be unrelated to treatment. There was no evidence of regional weakness in muscles other than OO with RT001, and, based on discrete quantitative evaluation of all adjacent structures, there was no evidence of regional or local spread after application. Additionally, there was no evidence of systemic exposure and there were no clinically significant changes in laboratory values or ECGs related to RT001 treatment. Based upon increasing concern regarding unintended spread of BoNTA outside of the target muscle after injection, assessment for LCL at rest may represent not only the most desirable and direct measure of paralysis for the target muscle, but also the most conservative from a safety perspective. Escalating the dose until there had been a significant impact on wrinkles at maximum smile would require that muscles outside the target OO be affected by diffusion of BoNTA to those sites (e.g., zygomaticus). Specifically, although the target of treatment is stated to be OO, dosage escalation on a smile endpoint would have to continue until decrements in zygomaticus were present since this muscle group is dominant for smile.

RT001 consists of a purified 150kD BoNTA molecule combined with a proprietary peptide which serves as an absorption enhancer and enables transcutaneous delivery without the use of patches, needles or any other devices.

### TABLE 2.

Baseline IGA-LCL Characteristics (ITT Subjects)

<table>
<thead>
<tr>
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<th>RT001 (n=45)</th>
<th>Placebo (n=45)</th>
<th>Total (n=90)</th>
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<tr>
<td><strong>IGA-LCL (Right Side of Face)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean (STD)</td>
<td>3.4 (0.50)</td>
<td>3.6 (0.50)</td>
<td>3.5 (0.50)</td>
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<tr>
<td>Median (Min. to Max.)</td>
<td>3.0 (3 to 4)</td>
<td>4.0 (3 to 4)</td>
<td>3.5 (3 to 4)</td>
</tr>
<tr>
<td><strong>Severity Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>24 (53.3%)</td>
<td>20 (44.4%)</td>
<td>44 (48.8%)</td>
</tr>
<tr>
<td>4</td>
<td>21 (46.7%)</td>
<td>25 (55.6%)</td>
<td>48 (51.1%)</td>
</tr>
<tr>
<td><strong>IGA-LCL (Left Side of Face)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean (STD)</td>
<td>3.4 (0.50)</td>
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<td>3.5 (0.50)</td>
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<tr>
<td>Median (Min. to Max.)</td>
<td>3.0 (3 to 4)</td>
<td>3.0 (3 to 4)</td>
<td>3.0 (3 to 4)</td>
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<tr>
<td><strong>Severity Score</strong></td>
<td></td>
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<tr>
<td>3</td>
<td>24 (53.3%)</td>
<td>24 (53.3%)</td>
<td>48 (53.3%)</td>
</tr>
<tr>
<td>4</td>
<td>21 (46.7%)</td>
<td>21 (46.7%)</td>
<td>42 (46.7%)</td>
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</table>
CONCLUSIONS

The application of a novel topical product containing BoNTA achieved marked efficacy versus placebo on multiple endpoints including primary efficacy. RT001 significantly reduced the severity of LCL (crow's feet wrinkles) four weeks after a single treatment. Compared to placebo-treated subjects, there was no increase in the frequency, severity or duration of AEs or other safety parameters among subjects treated with RT001 and no evidence of spread of BoNTA. Since the majority of patients seek treatment of LCL at rest, RT001 and other products which afford a benefit primarily at rest may be applicable to a broad number of patients. Based on these promising results, larger clinical studies to confirm the safety and efficacy of RT001 for the treatment of LCL are warranted.

ACKNOWLEDGEMENTS

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DISCLOSURES

R. Glogau has served as a consultant and clinical investigator for Allergan, Medicis, and Revance. He has served as a consultant for Gerson Lehman and MedaCorp, and as investigator for Contura and Liposonix. A. Blitzer has received research funding from Allergan and Merz, has served as a consultant for Allergan and MyoScience. J. Waugh is an employee and stockholder of Revance Therapeutics.

REFERENCES


