# Efficacy and Safety of RelabotulinumtoxinA Liquid Botulinum Toxin in the Treatment of Lateral Canthal Lines: Results From the Phase 3 READY-2 Study

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**BACKGROUND** RelabotulinumtoxinA (RelaBoNT-A) is a complex-free, ready-to-use, liquid botulinum toxin A.

**OBJECTIVE** Efficacy/safety of RelaBoNT-A treatment for lateral canthal lines (LCL).

**METHODS** Randomized adults received RelaBoNT-A (30 U/side; $n = 230$) or placebo ($n = 73$) during a 6-month, double-blind, Ph3 study (Relabotulinumtoxin Aesthetic Development Study-2 [READY-2]). Primary end points (Month 1, maximum smile) comprised: composite ≥2-grade responder rate using concurrent LCL severity investigator live assessment (LCL-ILA) and subject live assessment (LCL-SLA); LCL-ILA 0 (none)/1 (mild) responder rate. Subject satisfaction and adverse events were also reported.

**RESULTS** Month 1 composite ≥2-grade responder rates were 51.8% (RelaBoNT-A) and 1.4% (placebo; ($p < .001$). Month 1 none/mild LCL-ILA responder rates were 87.2% (RelaBoNT-A) and 11.9% (placebo; $p < .001$). Onset was reported Day 1 by 34%. At Month 6, LCL-ILA responder rates for RelaBoNT-A remained at 23.3% (none/mild) and 35.9% (≥1-grade improvement). Median return to baseline severity was 24.7 weeks; 64% (RelaBoNT-A group) had not returned to baseline at Month 6. RelaBoNT-A satisfaction was high through Month 6 (71%). Mild/moderate treatment-related adverse events occurred in 6.1% (RelaBoNT-A) and 5.5% (placebo).

**CONCLUSION** RelaBoNT-A (60 U) treatment provided statistically significant improvement of moderate-to-severe LCL. One-third of subjects reported onset within 1 day and improvements were maintained through Month 6. Treatment satisfaction was high. RelaBoNT-A was well tolerated.

Botulinum toxin type A (BoNT-A) is the most frequently used treatment for the aesthetic correction of age-associated dynamic facial lines/wrinkles, including lateral canthal lines (LCL), or crow's feet, and glabellar lines (GL).[1–8] Lateral canthal lines are among the earliest aesthetic signs of aging, usually noticeable by the age of 35 years.[7,9,10] Lines in the canthus area, caused by repeated contraction of muscles involved in smiling and squinting, are the sign of most concern for people seeking cosmetic enhancement for aging.[7,9] In practice, LCL are often treated in combination with GL to achieve greater overall subject satisfaction,[8,11–13] with treatments ideally

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having a short time to onset and sustained effect. However, while GL improvements can be sustained for up to 6 months after BoNT-A treatment, LCL improvements have generally been reported to last for around 3 to 4 months, with treatments in the canthus area complicated by heterogeneity of line patterns.[8,10,14–23]

Outcomes are herein reported from the Relabotulinumtoxin Aesthetic Development Study-2 (READY-2) examining LCL correction with a new BoNT-A formulation, relabotulinumtoxinA (RelaBoNT-A).[24,25] While most approved BoNT-A formulations contain accessory proteins and protein-based excipients (e.g. sucrose, serum albumin), RelaBoNT-A is a potent, complex-free, ready-to-use liquid.[1,24–26] This innovative formulation aims to eliminate potential variability, errors, and risks associated with reconstitution of freeze-dried/vacuum-dried products.[1,24–26] RelaBoNT-A is purified from a proprietary strain of *Clostridium botulinum* type A1 using Precipitation-free Extraction and Activity-preserving, Refined Liquid (PEARL) technology.[24,25] Multiple diafiltration and chromatography steps are performed, including ion-exchange and size-exclusion chromatography.[24,25] Each stage retains the core neurotoxin protein in liquid suspension in its original conformation, and denaturation/unfolding is minimized during state changes to preserve activity.[24,25] READY-2 was among the 4 Phase 3 randomized studies examining indications for RelaBoNT-A. Relabotulinumtoxin Aesthetic Development Study-2 assessed the efficacy and safety of a single RelaBoNT-A (60 U) treatment in the improvement of moderate-to-severe LCL.

## Methods

Relabotulinumtoxin Aesthetic Development Study-2 was a 6-month, Phase 3, multicenter, randomized, double-blind, placebo-controlled study, conducted at 10 clinics across the United States and Canada between February 2020 and February 2021 (NCT04249687). The study was implemented according to the principles of the Declaration of Helsinki and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice. Subjects provided written informed consent, and institutional review board ethical approval was obtained.

Subjects attended study visits at screening, baseline, Day 7, Day 14, Month 1, and monthly through Month 6. Due to the ongoing COVID-19 pandemic, remote study visits could be conducted via video and/or telephone.

### Study Population

Males/females aged ≥18 years with moderate-to-severe bilaterally symmetrical LCL were included and assessed at maximum smile using both the investigator live assessment (LCL-ILA) and the subject live assessment (LCL-SLA) photographic scales. The LCL-ILA and LCL-SLA scales used a 4-point grading system: 0 (none), 1 (mild), 2 (moderate), and 3 (severe).

Subjects were excluded if they had allergy/hypersensitivity to RelaBoNT-A components (or any botulinum toxin serotype) or had received/anticipated need for facial botulinum toxin treatment (any serotype; within 9 months). Other exclusion criteria included excessive skin laxity in the treatment/periorbital area, history of (or predisposition to) eyelid/eyebrow ptosis or amblyopia (lazy eye), previous/planned hyaluronic acid soft tissue augmentation (within 6 months), or other aesthetic procedures/surgery or eye surgery (within 12 months).

### Study Treatment

RelaBoNT-A (100 U/mL in a buffer containing sodium chloride, sodium phosphate, potassium chloride, L-tryptophan, polysorbate, and water for injection) and placebo (buffer only) were provided as sterile solutions for injection. The RelaBoNT-A and placebo solutions were identical in appearance to ensure blinding. At baseline (Day 0), subjects were randomized 3:1 (stratified by study center) to receive RelaBoNT-A (total dose: 60 U; 30 U each side) or placebo, respectively, given as 0.1-mL intramuscular injection at 6 prespecified sites (3 each side) in the lateral canthus areas (20°–30° angle to the skin). Two injection patterns were used (Figure 1), with treatment administered according to appearance of lines and physician discretion. The protocol stipulated that the same pattern of injection should be used on each side.

### Efficacy and Safety End Points

Separate Statistical Analysis Plans (SAPs) were written for the United States (US) Food and Drug Administration (FDA) and the European Union (EU) to meet respective regulatory requirements. The study protocol defined the primary end point as composite ≥2-grade responder rate at Month 1 (US FDA requirement). Composite responders achieved LCL severity scores of 0 (none)/1 (mild) and ≥2-grade improvement from baseline at maximum smile on concurrent LCL-ILA and LCL-SLA scales. The EU SAP

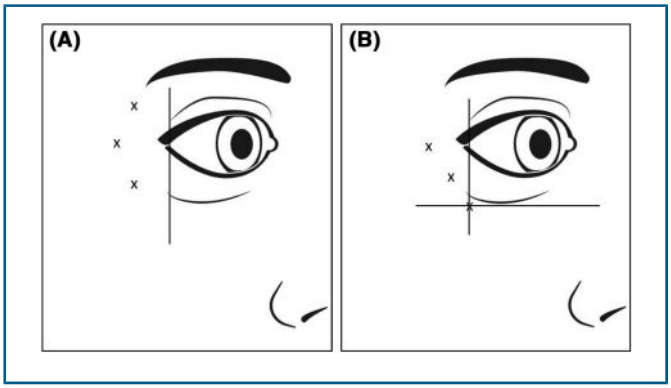


**Figure 1.** The 2 injection site options used during the READY-2 trial. Injection site pattern (3 sites per side) were chosen according to appearance of lines and physician discretion. (A) Option 1 addressed lines above and below the lateral canthus. (B) Option 2 addressed lines mainly below the lateral canthus. Injections were very superficial and performed at 20 to 30° angles to the skin (bevel of needle tip pointed up and away from the eye). All injection points were at the external part of the orbicularis oculi muscle (≥1–2 cm from orbital rim), separated by 1 to 1.5 cm. READY-2, Relabotulinumtoxin Aesthetic Development Study-2.

primary end point was Month 1 responder rate for subjects achieving LCL severity scores of 0 (none)/1 (mild) at maximum smile on the LCL-ILA scale.

Other end points assessed at maximum smile during all post-treatment visits included responder rate for scores of 0 (none)/1 (mild) using separate LCL-ILA and LCL-SLA scales, LCL-ILA responder rates (≥1 grade improvement from baseline), and time to onset of treatment response (subject diary card data). Duration of treatment effect used concurrent LCL-ILA and LCL-SLA assessments for the time to loss of 0 (none)/1 (mild) score and the time to return to baseline score/worse. Subject satisfaction assessments used the Facial Lines Treatment Satisfaction Questionnaire.[27] Safety end points examined the incidence and severity of treatment-emergent adverse events (TEAEs), physical examination findings, vital signs, electrocardiograms (ECGs), and laboratory parameters (hematology and blood chemistry).

### Statistical Analysis

All analyses used the SAS system (Version 9.4). A sample size of 300 subjects (RelaBoNT-A: $n = 225$; placebo: $n = 75$) was required for detection of between-group differences (>99% power) using a Cochran–Mantel–Haenszel (CMH) 2-sided test on 5% significance level (assuming 5% dropout rate). Multiple imputation and baseline observation carried forward analysis was used for missing values. The CMH test compared RelaBoNT-A and placebo outcomes. $p$-values <0.05 denoted statistical significance. Kaplan–Meier analysis estimated duration of treatment effect.

The intention-to-treat (ITT) and safety populations comprised all randomized subjects receiving RelaBoNT-A or placebo. The modified ITT (mITT) population (US and EU primary end points) included all ITT subjects who did not have their Month 1 study visit remotely.

## Results

The ITT population included 303 subjects randomized to RelaBoNT-A ($n = 230$) and placebo ($n = 73$). Most were female (86.8%) and White (94.1%), and mean age was 50.1 (range 24–75) years (see **Supplemental Digital Content 1**, Table S1, http://links.lww.com/DSS/B545). Thirteen subjects (4.3%) discontinued prematurely (7 RelaBoNT-A; 6 placebo), and 290 subjects completed the study. No subjects withdrew due to adverse events. Investigators rated LCL severity as moderate for 57.0% (RelaBoNT-A) and 60.3% (placebo) of participants and severe for remaining subjects. Subjects received a consistent pattern of injection on each side of the face (per protocol), with the exception of 1 subject in the RelaBoNT-A group who received Option 1 on the left side and Option 2 on the right. Option 1 was used most for RelaBoNT-A (75.7% left; 76.1% right) and placebo (83.6% both sides) administration.

## Efficacy Outcomes

The composite ≥2-grade responder rate at Month 1 (maximum smile; concurrent LCL-ILA/LCL-SLA assessments) was significantly higher for RelaBoNT-A recipients (51.8%) versus placebo (1.4%; $p < .001$; mITT population; Figure 2A). Month 1 LCL-ILA responder rate for subjects achieving scores of 0 (none)/1 (mild) at maximum smile was 87.2% with RelaBoNT-A and 11.9% with placebo ($p < .001$; mITT population; Figure 2B).

Efficacy was visible within 1 day after treatment for 34% of RelaBoNT-A recipients (diary card data; see **Supplemental Digital Content 1**, Figure S1, http://links.lww.com/DSS/B545). Median time to onset of treatment effect was 2 days. Figure 3 shows photographic outcomes for 2 subjects achieving scores of 0 (none)/1 (mild) at maximum smile on the LCL-ILA.

Responder rates for subjects scoring 0 (none)/1 (mild) at maximum smile was significantly greater with RelaBoNT-A versus placebo at all post-treatment visits according to LCL-ILA ($p \leq .002$) and LCL-SLA ($p < .001$; ITT population) assessments (Figure 4). Month 1 and Month 6 LCL-ILA responder rates were 87.5% and 23.3%, respectively, with RelaBoNT-A and <15% with placebo. LCL-SLA responder rates were 79.6% (Month 1) and 23.8% (Month 6) with RelaBoNT-A and ≤9.2% with placebo. LCL-ILA improvements (≥1-grade) were seen in 92.9% (Month 1) and 35.9% (Month 6) with RelaBoNT-A and 19.4% (Month 1) and 14.5% (Month 6) with placebo ($p < .001$; ITT population; Figure 5).

Median time to loss of 0 (none)/1 (mild) score (concurrent LCL-ILA/LCL-SLA assessments) was 162 days (almost 6 months) after RelaBoNT-A treatment (ITT population). Median time to return to baseline severity/worse for subjects achieving scores of 0 (none)/1 (mild) was 173 days (24.7 weeks; ITT population; see **Supplemental Digital Content 1**, Figure S2, http://links.lww.com/DSS/B545). Approximately 64% did not return to baseline severity within 6 months of RelaBoNT-A treatment.

Facial Lines Treatment Satisfaction Questionnaire data indicated that subjects were satisfied with how natural their face looked after RelaBoNT-A treatment at Month 1 (92%) and Month 6 (85%). Satisfaction with RelaBoNT-A was high from Month 1 (87%) through Month 6 (71%).

### Safety End Points

Treatment-emergent adverse events were reported in 26.1% ($n = 60$) with RelaBoNT-A treatment and 24.7% ($n = 18$) with placebo. Overall, 6.1% ($n = 14$) of RelaBoNT-A and 5.5% ($n = 4$) of placebo recipients reported treatment-related/procedure-related TEAEs, which were mild in intensity and generally resolved within 2 weeks (see **Supplemental Digital Content 1**, Table S2, http://links.lww.com/DSS/B545). Injection-site bruising was the most common treatment-related TEAE in the RelaBoNT-A (4.8%; $n = 11$) and placebo (4.1%; $n = 3$) groups. No serious treatment-related TEAEs or remote toxin spread effect occurred. One subject experienced mild muscle weakness (subjective alteration in smile), believed to be due to local toxin spread, which resolved within 31 days. No clinically meaningful mean changes from baseline were observed regarding clinical laboratory, vital sign, or ECG parameters.

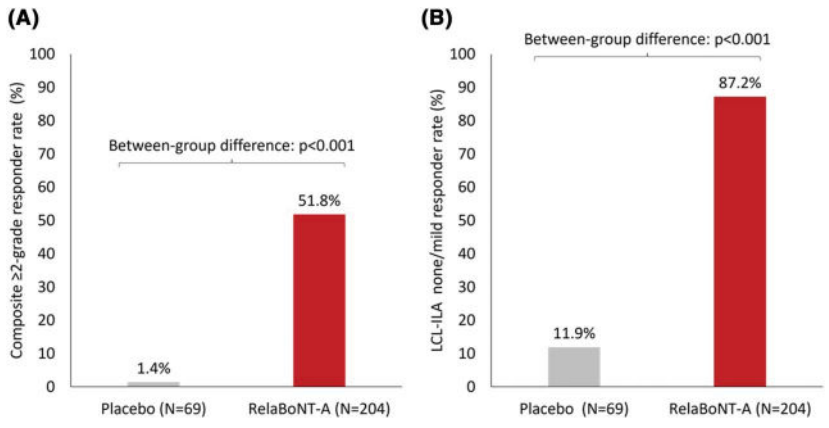


**Figure 2.** Primary efficacy outcomes (mITT population). (A) Month 1 composite ≥2-grade responder rate (US primary end point). (B) Month 1 LCL-ILA none/mild responder rate (EU primary end point). a) Composite ≥2-grade responder rate at month 1 among subjects achieving a severity score of 0 (none)/1 (mild) using concomitant LCL-ILA and LCL-SLA live assessments (maximum smile; US primary end point). Month 1 between-group difference: $p < .001$. b) Responder rate for subjects achieving a severity score of 0 (none)/1 (mild) using LCL-ILA assessments (maximum smile; EU primary end point). Month 1 between-group difference: $p < .001$. Comparisons used the Cochran–Mantel–Haenszel test stratified by site (5% significance; 2-sided). Abbreviations: LCL-ILA, LCL investigator live assessment; LCL-SLA, LCL subject live assessment; mITT, modified intention to treat, RelaBoNT-A, RelabotulinumtoxinA. EU, European Union; ILA, investigator live assessment; LCL, lateral canthal lines; mITT, modified intention-to-treat; SLA, subject live assessment; US, United States.

## Discussion

The READY-2 study demonstrated that a single 60 U RelaBoNT-A treatment was well tolerated and effective in the aesthetic correction of moderate-to-severe LCL, with fast onset and long duration of effect and high subject satisfaction throughout the 6-month study period. The results reflect outcomes from the Phase 3 READY-1 study (examining RelaBoNT-A in moderate-to-severe GL correction) and provide additional support for RelaBoNT-A use in the treatment of upper facial lines.[23]

Primary efficacy end points were met and RelaBoNT-A treatment demonstrated significant improvements in LCL severity, versus placebo, from Day 7 through Month 6. Month 1 composite ≥2-grade response was significantly higher with RelaBoNT-A (51.8%) compared with placebo (1.4%; $p < .001$), and responder rate among subjects achieving LCL-ILA scores of 0 (none)/1 (mild) at Month 1 was also significantly greater with RelaBoNT-A (87.2%) versus placebo (11.9%; $p < .001$). These results compare favorably with similar studies examining other BoNT-A treatments, such as onabotulinumtoxinA, which reported composite ≥2-grade response rates of 20% and 26% and none/mild responder rates of 55% to 67% at Month 1 in adults with moderate-to-severe LCLs.[11,19,20,28,29]

One-third (34%) experienced RelaBoNT-A treatment effect by Day 1 and median time to onset was 2 days. These outcomes are similar to those of the READY-1 study, in which 39% saw GL improvements from Day 1.[23] READY-2 participants maintained statistically significant investigator-assessed improvements (≥1 grade) with RelaBoNT-A (36%) versus placebo (15%) through Month 6 ($p < .001$). Median time to return to baseline severity/worse was 24.7 weeks (concomitant LCL-ILA/LCL-SLA assessments). These data indicate enhanced durability of RelaBoNT-A effect compared with other botulinum toxins (e.g. onabotulinumtoxinA), which report median duration of investigator-assessed response to be between 17 and 19 weeks for LCL correction.[19–22] The full range of RelaBoNT-A durability could not be evaluated as approximately 64% had not returned to baseline severity during the 6-month study period. Again, these results align with READY-1 observations showing that GL severity remained improved from baseline at 24 weeks for 75% of RelaBoNT-A recipients.[23] LCL treatment effect is usually slightly shorter compared with GL correction, based on previous BoNT-A studies.[16–23]

Choice of RelaBoNT-A LCL dose (60 U; 30 U per side) was extrapolated from Phase 2 dose-finding study data for GL correction and relative dosing used in prior LCL and GL studies for other BoNT-As.[19,20,30,31] Direct comparisons regarding dosing units cannot be made for different products as potency assessments are proprietary, product-specific, and not equivalent.[31–33]

The PEARL technology used to produce RelaBoNT[24] may help explain the rapid onset of action and long duration observed in this LCL study and in the prior READY-1 study in GLs.[23] In addition, in a study testing usability of another liquid formulation of BoNT-A versus a powder BoNT-A,[34] investigators reported time savings with the ready-to-use formulation with more time to focus on their patients, and a decrease in materials used (less environmental impact),

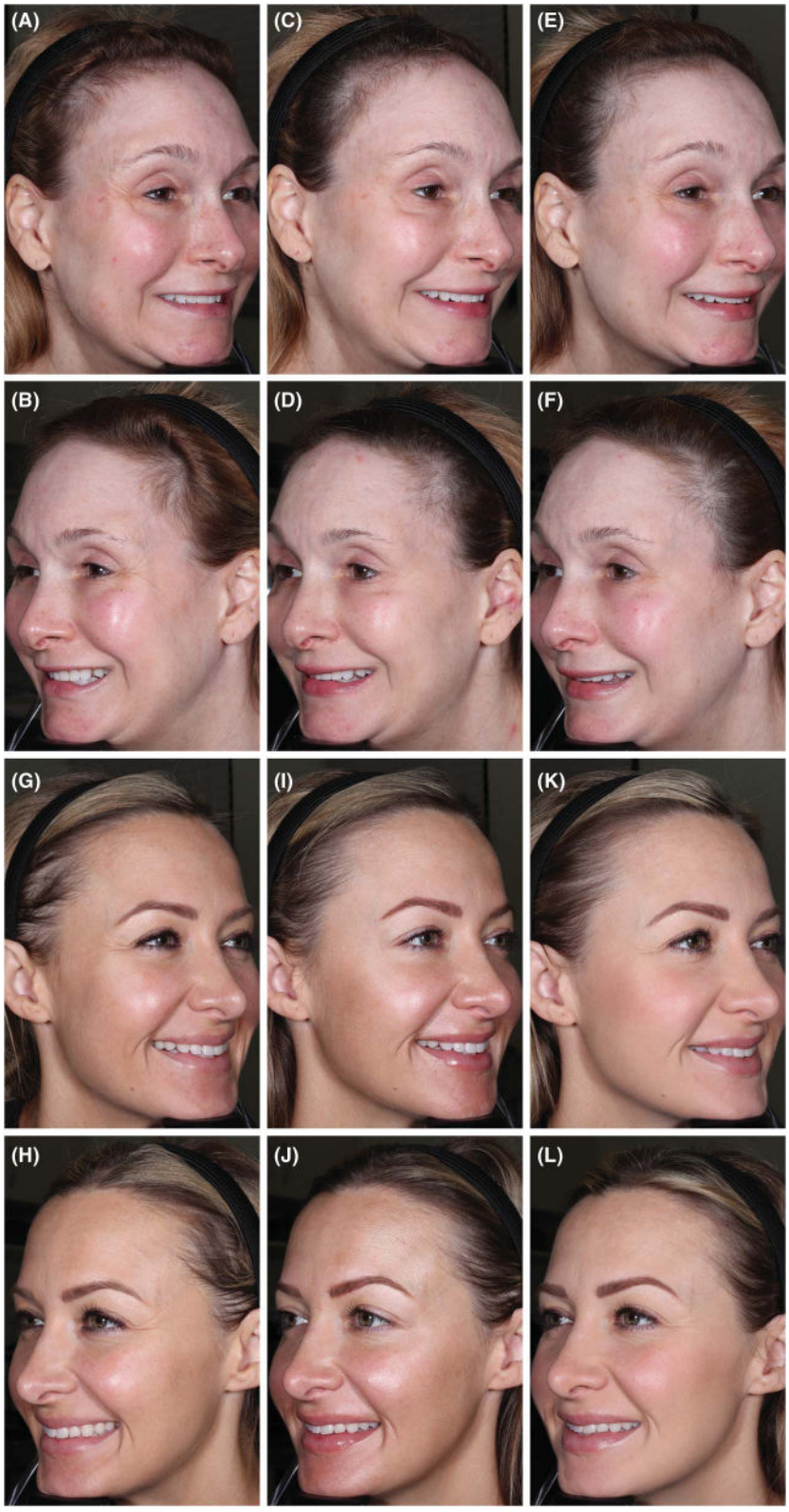


**Figure 3.** Photographic outcomes for 2, female subjects, aged 50 years (images A–F) and 38 years (images G–L) who received RelaBoNT-A. (A, B, G, H) At baseline, (C, D, I, J) Month 1, and (E, F, K, L) Month 6. LCL-ILA scores at maximum smile on both sides of the face (A, B, G, H) 2; (C, D, I, J) 0; (E and F) 0; (K and L) 1. ILA, investigator live assessment; LCL, lateral canthal lines.

suggesting that a ready-to-use formulation can provide benefits for both the treating clinicians and patients. A future investigation would be interesting to verify this also for the RelaBoNT-A ready-to-use formulation.

Limitations of this study include that follow-up time ended at 6 months, and limited diversity of the study population regarding ethnicity, age and sex, and future studies could investigate upper facial line correction or

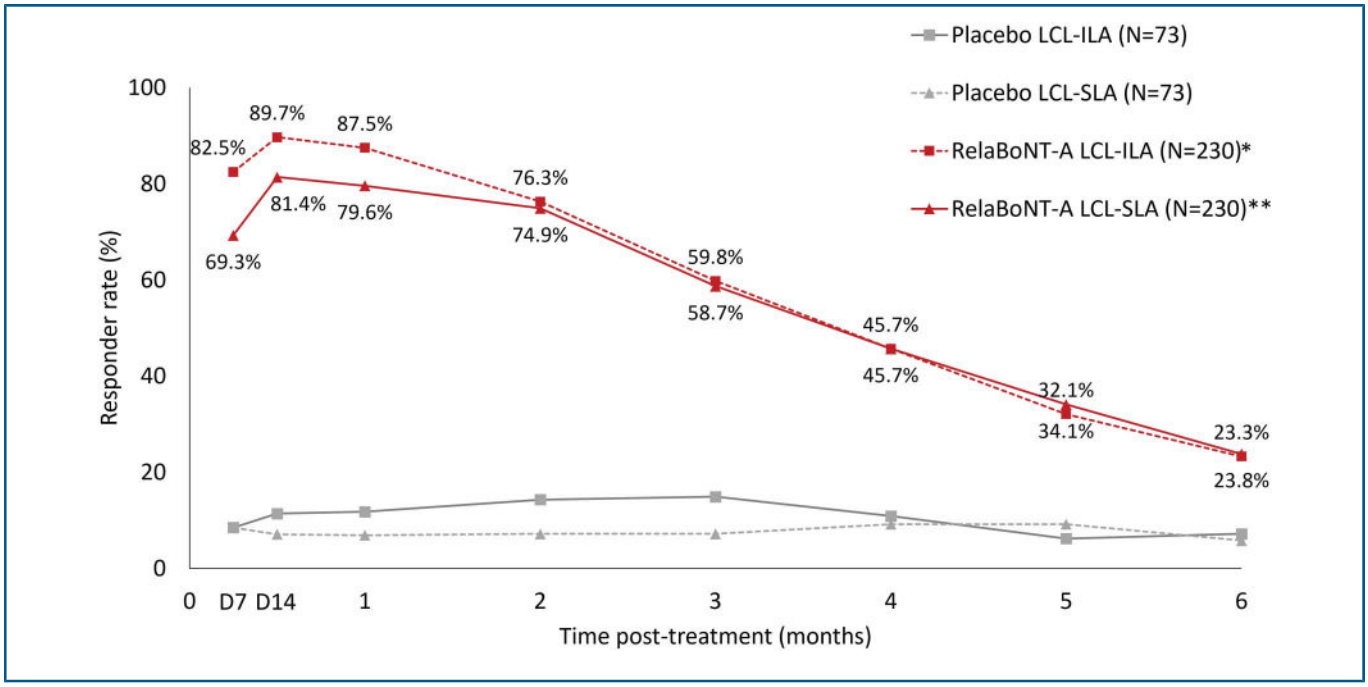


**Figure 4.** Lateral canthal lines-ILA and LCL-SLA none-or-mild responder rate (ITT population). Responder rates for subjects achieving scores of 0 (none)/1 (mild) at maximum smile. *Responder rate between-group difference: D7 through Month 5 $p < .001$; month 6 $p = .002$. **Responder rate between-group difference (all visits): $p < .001$. Comparisons used the Cochran–Mantel–Haenszel test stratified by site (5% significance; 2-sided). D, day; ITT, intention to treat; LCL-ILA, lateral canthal lines investigator live assessment; LCL-SLA, lateral canthal lines subject live assessment; RelaBoNT-A, RelabotulinumtoxinA.

prevention in key groups (e.g. younger people).[9,10] However, the study population was representative of those receiving aesthetic treatments in the United States.

RelaBoNT-A was well tolerated throughout the study period. Treatment-related TEAEs were all mild-to-moderate and nonserious, occurring in just 6.1% of RelaBoNT-A–treated subjects (vs 5.5% with placebo). The most common treatment-related TEAE (injection-site bruising) was observed at comparable rates across groups and reflected previous studies with no new safety signals.[11,16,19–22,28]

## Conclusion

A single RelaBoNT-A (60 U) treatment provided statistically significant improvements in moderate-to-severe LCL

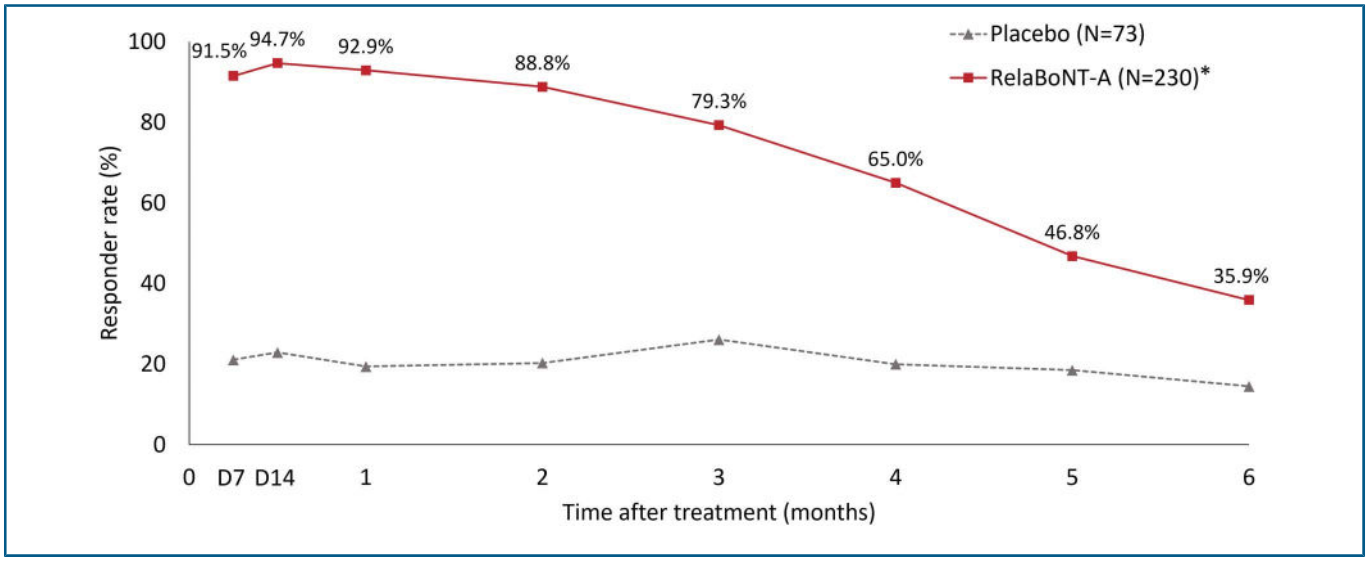


**Figure 5.** Lateral canthal lines-ILA responder rate for ≥1-grade improvement from baseline (ITT population). *Responder rate between-group difference at all visits: $p < .001$ comparisons used the Cochran–Mantel–Haenszel test stratified by site (5% significance; 2-sided). D, day; ITT, intention to treat; LCL-ILA, lateral canthal lines investigator live assessment; RelaBoNT-A, relabotulinumtoxinA.

(crow's feet) correction through Month 6. Treatment effect was reported within 1 day by 34% of RelaBoNT-A recipients, and aesthetic improvements were maintained from Day 1 through Month 6 in about one-third of subjects. Treatment satisfaction was rated highly, with recipients reporting natural aesthetic results, and RelaBoNT-A was well tolerated.


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