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ORIGINAL ARTICLE



# Efficacy and safety of neuronox® for lateral canthal lines: a phase I/III, multicenter, randomized, double-blind, active-controlled study

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**ABSTRACT**

**Introduction:** Neuronox® has not yet been investigated for its efficacy and safety in the treatment of lateral canthal lines (LCL).

**Methods:** This study was a randomized, double-blind, active drug controlled, multicenter, 16 week, Phase I/III study designed to determine the non-inferiority of Neuronox® compared to onabotulinumtoxin A (ONA) in the treatment of moderate to severe LCL. Thirty subjects in Phase I and 220 subjects in Phase III were randomized in a 1:1 ratio to receive a single treatment (24 U) of either Neuronox® or ONA. The primary endpoint of the Phase III study was the responder rate according to the proportion of subjects achieving Grade 0 (none) or 1 (mild) from 2 (moderate) or 3 (severe) in LCL severity at maximum smile as assessed by the investigators at Week 4. Additional efficacy endpoints and safety endpoints (adverse events) were also evaluated.

**Results:** The primary endpoint was achieved as the proportion of responders was 83% for both Neuronox® and ONA, thus, supporting the non-inferiority of Neuronox® compare to ONA. The two groups also showed no statistical differences in safety analyses.

**Conclusion:** Treatment of moderate to severe LCL with Neuronox® was effective and well-tolerated.

**Abbreviations:** ADRs: Adverse drug reactions; AEs: Adverse events; BoNT-A: Botulinum toxin type A; FA: Full analysis; LCL: Lateral canthal lines; ONA: Onabotulinumtoxin A; PP: Per-protocol

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**KEYWORDS**
Botulinum toxin type A; neuronox; lateral canthal lines; onabotulinumtoxin a; efficacy; safety

## Introduction

The use of botulinum toxin type A (BoNT-A) for esthetic purposes has become so popular that the number of BoNT-A treatments globally surpassed any other esthetic/cosmetic procedures performed in 2017 (1). Lateral canthal lines (LCL), also well-known as crow's feet lines, forms due to repeated contraction of the orbicularis oculi muscles responsible for closure of the eyelids. The characteristics of LCL, low hydration level and thin dermis, are prone to the formation of rhytides due to frequent movements during smiling or other facial expressions. Moderate to severe LCL tend not to disappear even if there are no facial expressions (at rest), causing individuals to look older than their chronological age. BoNT-A can reduce the severity of LCL. As the face is central to human communications, rejuvenation of the LCL using BoNT-A can enhance self-esteem and social interactions (2).

Alternatives to BoNT-A such as facial lifting, dermabrasion with laser, and chemical peeling by necrotizing the skin surface with chemicals have been used to reduce the severity of LCL. However, because these methods do not directly restrict contraction of the periocular muscles, the outcomes are expected to be ineffective (3). In contrast, BoNT-A can relax wrinkles by preventing the contraction of the peripheral muscles around the eyes and inhibiting facial expressions. In most cases, BoNT-A treatment for LCL results in improvements within four weeks (4,5). Furthermore, from a randomized, placebo-controlled trial of onabotulinumtoxin A (ONA; Botox®, Allergan Inc., Irvine, CA) that was approved by the US Food and Drug Administration showed significant efficacy in improving moderate or severe LCL (4,5).

Neuronox® (Meditoxin; Medytox Inc., Ochang, Korea) is a BoNT-A product that shows efficacy in the treatment of essential blepharospasm, pediatric lower-limb spasticity, glabellar lines, and post-stroke upper-limb spasticity (6–9). However, it has not been extensively investigated for its efficacy and safety in the treatment of LCL; accordingly, this present study aimed to compare the efficacy and safety of Neuronox® with ONA for the treatment of LCL.

## Methods

### *Study design and subjects*

This study was a randomized, double blind, active drug controlled, multicenter Phase I/III study (ClinicalTrials.gov Identifiers: NCT03317574) designed to evaluate the non-inferiority of

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Neuronox® compared to ONA. First, a Phase I study was performed in a small number of subjects with a shorter follow up time to evaluate the safety of Neuronox® compared with ONA, followed by the Phase III study. Subjects were males or females aged 20 to 65 years with moderate to severe LCL at maximum smile as assessed by the investigator using LCL severity scale (0: none, 1: mild, 2: moderate, 3: severe). The subjects were required to provide written informed consent to participate in the study. Subjects were excluded from the study for neuromuscular disorders, specified facial surgery or permanent esthetic treatments within the past 6 months to a year that would affect the assessment of LCL, deep LCL difficult to lessen even by physical methods, BoNT-A treatment in the past 3 months or plans to receive BoNT-A treatment during study participation, hypersensitivity to any components of the investigational product, or infection at the injection site.

The study was conducted in accordance with Korea Good Clinical Practice and the Declaration of Helsinki. Furthermore, the study was approved by the Ministry of Food and Drug Safety and the Institutional Review Boards of participating hospitals (Seoul National University Bundang Hospital, B-1705/399-005; Samsung Medical Center, SMC-2017-05-036; Ilsan Paik Hospital, ISPAIK-2017-10-007; Kyung Hee University Hospital, HOC17MDDT0135; and Kyungpook National University Hospital, KHUH 2017-10-010).

### Study medication and procedures

Dynamic Allocation was used to randomize eligible subjects in a 1:1 ratio to receive either Neuronox® or ONA on both sides of LCL. Both investigational products, Neuronox® and ONA, were provided in a 50 U vial containing BoNT-A with 0.25 mg of human serum albumin and 0.45 mg of sodium chloride. The investigational products were reconstituted with 1.25 ml of sterile, preservative-free 0.9% sodium chloride. The pharmacist or designee responsible for the reconstitution was kept unblinded, and performed the dilution and preparation of the syringe in a separate room. All other individuals, including investigators and subjects, were kept blinded throughout the study.

All eligible subjects received reconstituted investigational product intramuscularly into three sites on each side (total of six injections) of the lateral orbicularis oculi muscle (Figure 1). Each subject received 4 Units (0.1 ml) into each of three sites, for a total of 24 Units (0.6 ml) on both sides of LCL. During Phase I, subjects visited investigational sites once on Week 4 for follow-up. Follow-up visits for the Phase III trial were at Week 4, 8, 12, and 16. Investigators were trained on the use of the scale by using a standardized photographic guide to minimize variations among investigators.

### Efficacy outcome measures

The primary endpoint of the Phase III study was the responder rate at a maximum smile as assessed by the investigators at Week 4. The subjects were defined as 'responders' if their LCL improved from Grade 2 or 3 at baseline to 0 or 1 on the LCL severity scale.

The secondary endpoints of the Phase III trial included (1) responder rate at maximum smile at Weeks 8, 12, and 16 as assessed by the investigators independently; (2) responder rate at rest at Weeks 4, 8, 12, and 16 as assessed by the investigators independently; (3) responder rate at rest and at maximum smile at Weeks 4, 8, 12, and 16 as assessed by the subject; (4) proportion of subjects with more than 1-grade point and 2-grade point improvements from baseline on the LCL severity scale at maximum smile and at rest as assessed by the investigators at Weeks 4, 8, 12, and 16; (5) proportion of subjects with Grade +2 (moderate improvement) or more on the subjective global assessment (9-point grading scale; from +4, complete improvement, to −4, very marked worsening) at Weeks 4, 8, 12, and 16; (6) proportion of subjects with Grade 6 (satisfied) or above on the subject satisfaction assessment (7-point grading scale; from 7, very satisfied, to 1, very dissatisfied) at Weeks 4, 8, 12, and 16.

The duration of treatment effect was calculated by measuring the time the responder (0 or 1 on LCL severity scale) took to return to baseline (2 or 3 on LCL severity scale) since they were first defined as a responder at Week 4.

### Safety assessments

Safety assessments were conducted throughout the study to monitor for any incidence of adverse events (AEs). The AEs were classified according to their severity using a 3-point grading scale (mild, moderate, and severe). The relationship to study intervention and other measures were also used to follow-up on the

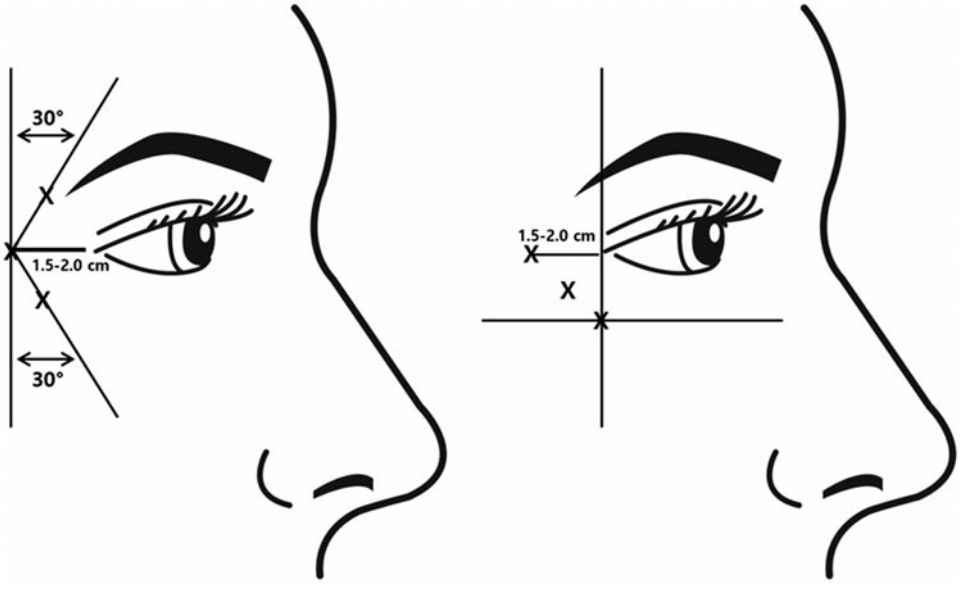


Figure 1. Injection pattern and allowed modification for the treatment of Lateral Canthal lines.

reported AEs. Vital signs and physical examination were conducted on every visit, but laboratory tests and pregnancy tests were only conducted during the screening visit and end of the trial.

### Statistical analyses

The primary analysis will be based on the Full Analysis (FA) set, which includes all randomized subjects who received treatment and with at least one efficacy evaluations in Phase III. The per-protocol (PP) set was also used as a supportive analysis. The PP set includes all subjects in the FA set who completed the study without any major protocol deviations that have an impact on the LCL severity assessment. The FA set and PP set were used to evaluate the efficacy outcomes of both Phase I and III studies. Safety sets included all subjects who received the investigational products and had their safety data evaluated by the investigators.

Fisher's exact test and 95% confidence intervals were used to evaluate the efficacy endpoints. The fisher's exact test was used to compare the responder rate between treatment and control groups. The 95% confidence interval was used to evaluate the primary efficacy endpoint of Phase III. Non-inferiority to ONA was met if the Neuronox® responder rate at maximum smile as assessed by the investigator at Week 4 did not exceed the lower limit of 95% Wald confidence interval (−0.278). Unless otherwise stated, statistical significance was defined as a *p*-value less than .05. The Kaplan-Meier analysis was used to estimate the duration of the treatment response.

## Results

### Disposition of subjects

In the Phase I study, a total of 30 subjects were screened at two different sites, and all were randomized (without any screen failures) for treatment.

In the Phase III study, a total of 229 subjects were screened at six different sites, with nine excluded due to screen failure. Of the remaining 220 subjects, 110 were randomized to Neuronox®, and the remaining subjects were randomized to ONA. All 220 subjects were included in the FA and Safety set as they all received investigational products and were evaluated for primary efficacy endpoints (Week 4). However, the PP set included 213 subjects due to major protocol deviation by seven subjects (two from Neuronox® and five from ONA (Figure 2).

At baseline, the mean subject age was 47.14 ± 7.87 years for Neuronox® and 49.03 ± 8.28 years for ONA. Both groups were predominantly female, with 88 females (80.00%) in the Neuronox® group and 91 females (83.64%) in the ONA group (Table 1). The number of subjects who were rated with moderate LCL (LCL severity scale of 2) at maximum smile was 29 (26.00%) in the Neuronox® group and 35 (32.00%) in the ONA group, and the remaining subjects were categorized with LCL severity scale of 3 (severe). The majority of subjects were toxin-naïve, and other demographics or baseline characteristics were not statistically different (Table 1).

### Efficacy assessments

For the Phase III primary efficacy endpoint at Week 4, the responder rate from the FA set was 83% (91/110) for both study and control groups. In the PP set, the responder rate was 83% (90/108) for the study group and 82% (86/105) for the control group. The lower limit of the 95% confidence interval for the difference in primary efficacy endpoint between the study group and control group was −0.0999, which was higher than the non-inferiority margin of −0.278, supporting the non-inferiority of Neuronox® compared to ONA.

For secondary efficacy endpoints, all outcomes are described using data from the FA sets. In all secondary endpoints, the study group was comparable with the control group. The responder rates at maximum smile at Weeks 8, 12, and 16 as assessed by

**Table 1.** Demographic and baseline characteristics (phase III).

| Item | Neuronox® (*N* = 110) | Onabotulinumtoxin A (*N* = 110) | *p*-value |
|---|---|---|---|
| Age, years (%) | 47.14 (±7.87) | 49.03 (±8.28) | .0676 |
| Gender, *n* (%) | | | |
| Female | 88 (80.00) | 92 (83.64) | .6004 |
| Male | 22 (20.00) | 18 (16.36) | |
| LCL severity scale (at maximum smile), *n* (%) | | | |
| Moderate | 29 (26.0) | 35 (32.0) | .3731 |
| Severe | 81 (74.0) | 75 (68.0) | |
| Previous botulinum toxin treatment, *n* (%) | | | |
| Yes | 14 (12.73) | 17 (15.45) | .6989 |

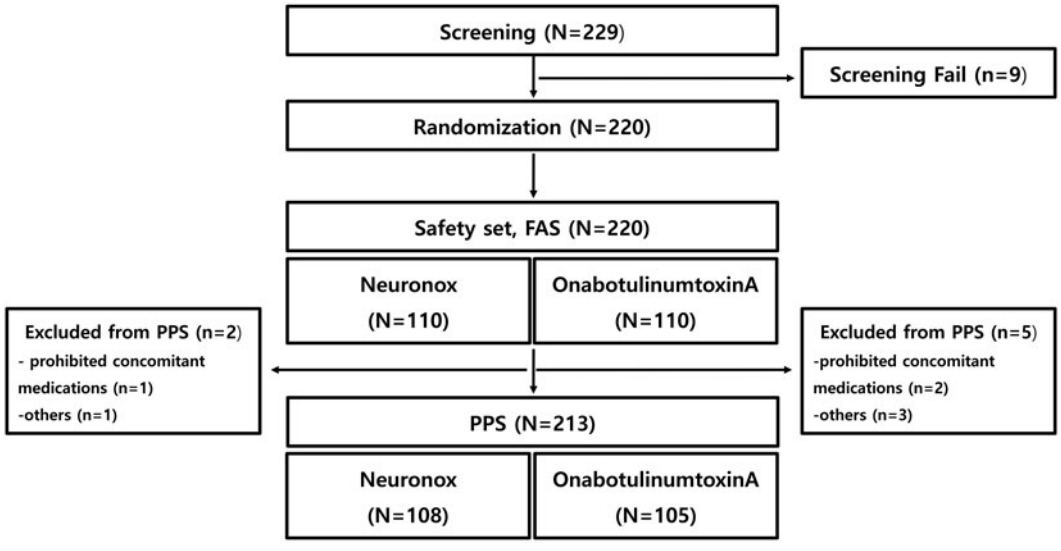


**Figure 2.** Disposition of subjects (phase III). FAS: full analysis set; N: number of subjects; PPS: per-protocol set.

the investigators using the LCL severity scale were 81%, 65%, and 45% for the Neuronox® group and 83%, 60%, and 39% for the ONA group, respectively (Figures 3 and 4). Meanwhile, the responder rate at rest in Weeks 4, 8, 12, and 16 as assessed by the investigators using the LCL severity scale were 92%, 92%, 83%, and 71% for the Neuronox® group and 89%, 92%, 74%, and 64% for the ONA group, respectively.

The responder rate from subject-evaluated LCL severity was lower than investigator-evaluated LCL severity. The LCL improvement rates at maximum frown assessed by the subjects using the LCL severity scale at Weeks 4, 8, 12, and 16 were 69%, 72%, 57%, 42% for the Neuronox® group and 69%, 70%, 55%, 43% for the ONA group, respectively (Figure 5). At rest, the proportion of responders were 87%, 92%, 78%, 68% for the Neuronox® group and 89%, 83%, 68%, 66% for the ONA group, respectively.

The proportion of subjects with more than 1-grade point improvement from baseline on the LCL severity scale at maximum smile as assessed by the investigator at Weeks 4, 8, 12, and 16 was 97%, 95%, 88%, and 82% for Neuronox® and 97%, 98%, 89%, and 82% for ONA, respectively (Figure 6). At rest, the proportion was were 90%, 89%, 83%, and 75% for the Neuronox® group and 95%, 95%, 78%, and 73% for the ONA group, respectively. Similarly, the proportion of subjects with more than 2-grade points improvement at maximum smile at Weeks 4, 8, 12, and 16 was 68%, 69%, 50%, and 31% for the Neuronox® group and 64%, 64%, 45%, and 25% for the ONA group, respectively. At rest, the proportions were 46%, 45%, 35%, and 30% for the Neuronox® group and 38%, 42%, 37%, and 26% for the ONA group, respectively.

The subjects were also evaluated with the global assessment (9-point grading scale) and satisfaction assessment (7-point grading scale). The proportion of subjects with Grade +2 or higher on the global assessment at Weeks 4, 8, 12 and 16 was 82%, 83%, 82%, and 63% for the Neuronox® group and 81%, 89%, 80%, and 75% for the ONA group, respectively. The proportion of subjects with Grade 6 or above on the satisfaction assessment at Weeks 4, 8, 12, 16 was 74%, 73%, 71%, and 64% for the Neuronox® group and 66%, 73%, 64%, and 64% for the ONA group, respectively (Figure 7).

**Table 2.** Incidence of adverse drug reactions (phase III).

| ADR Term | Neuronox® $N = 110$ $n$ (%), (case) | Onabotulinumtoxin A $N = 110$ $n$ (%), (case) |
|---|---|---|
| Cervicogenic headache | 1 (0.91%), (1) | 0 (0.00%), (0) |
| Migraine | 1 (0.91%), (1) | 0 (0.00%), (0) |
| Occipital neuralgia | 1 (0.91%), (1) | 0 (0.00%), (0) |
| Headache | 0 (0.00%), (0) | 1 (0.91%), (1) |
| Eyelid ptosis | 1 (0.91%), (1) | 0 (0.00%), (0) |
| Fibromyalgia | 1 (0.91%), (1) | 0 (0.00%), (0) |
| Musculoskeletal pain | 1 (0.91%), (1) | 0 (0.00%), (0) |
| Myalgia | 1 (0.91%), (1) | 0 (0.00%), (0) |
| Injection site bruising | 0 (0.00%), (0) | 1 (0.91%), (1) |
| Herpes simplex | 0 (0.00%), (0) | 1 (0.91%), (1) |

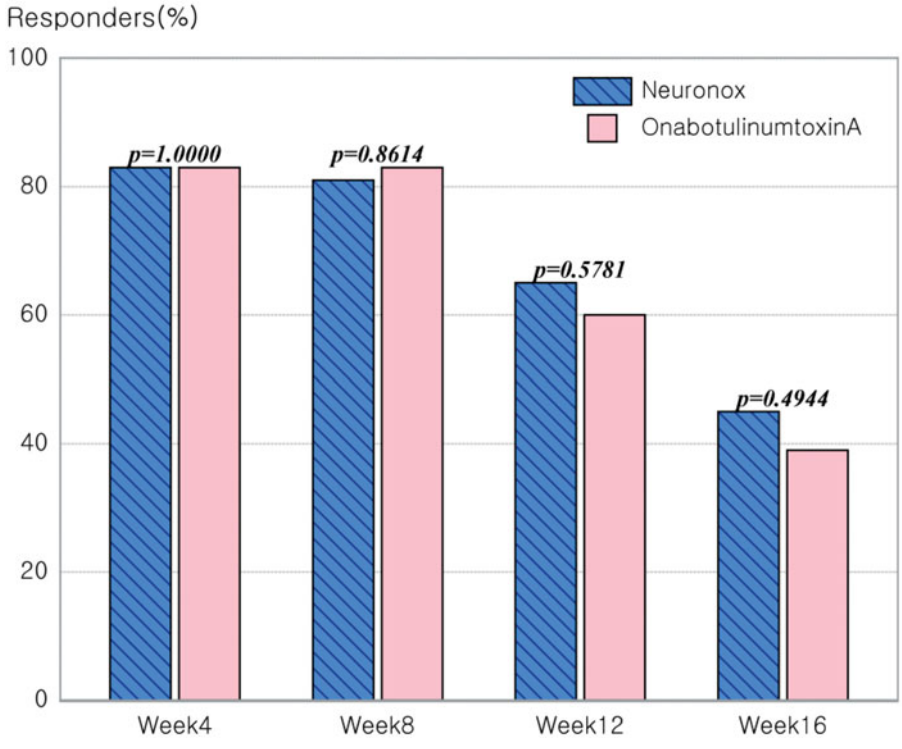


**Figure 3.** Responder rates (grade 0 or 1 LCL severity) at maximum smile as confirmed by investigator live assessment.

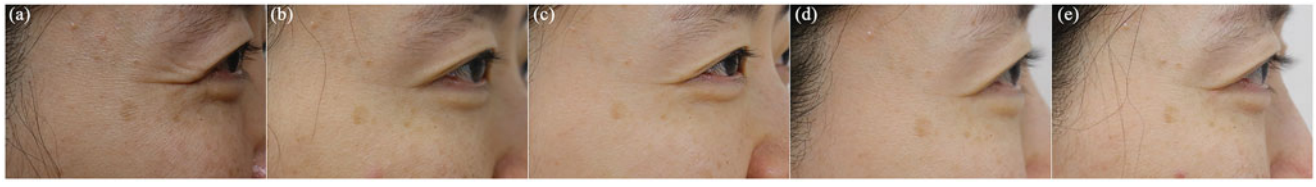


**Figure 4.** Representative photographs of LCL at maximum smile in a subject with Neuronox® injection at (A) baseline, (B) Week 4, (C) Week 8, (D) Week 12 and (E) Week 16.

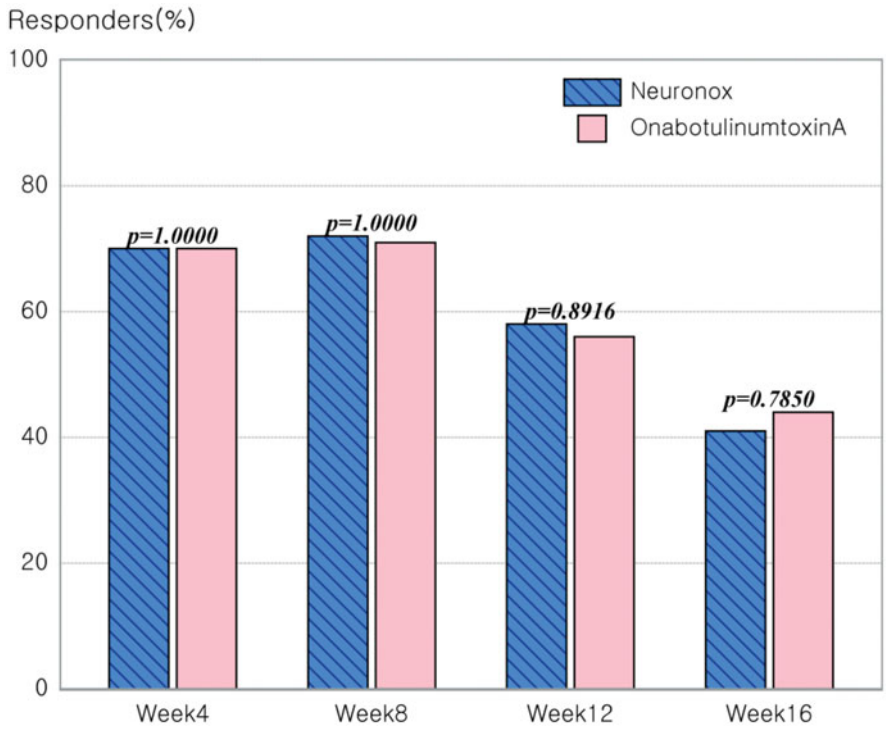


**Figure 5.** Response rates (grade 0 or 1 LCL severity) at maximum smile as confirmed by subject live assessment.

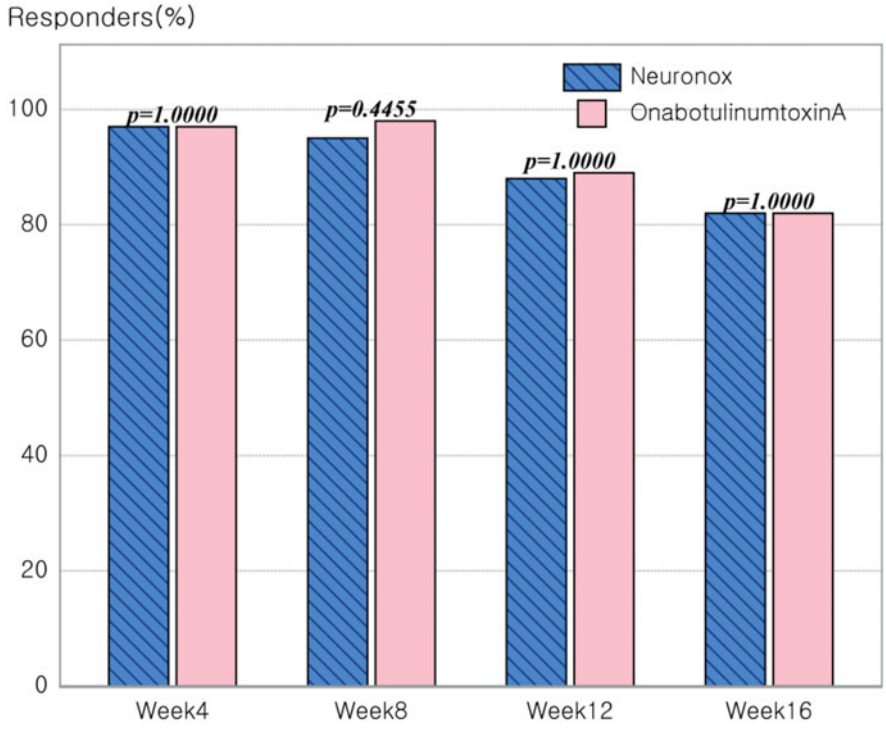


**Figure 6.** Proportion of subjects achieving an improvement from baseline of at least 1 grade in LCL severity.

In the FA set, the difference in all primary and secondary efficacy outcomes between the study and control groups was not statistically significant ($p > .05$). The outcome of the PP set was similar to the outcome of the FA set, and the efficacy outcomes of the Phase I and III studies were also similar.

The median duration of effect for responders to maintain LCL severity scale of none or mild (maximum smile) in both groups after week 4 was 112 days based on investigator assessments.

### *Safety assessments*

A total of 30 subjects from the Phase I study and 220 subjects from the Phase III study who received investigational product were included in the safety analyses.

In the Phase I cohort, the incidence rates of AEs was 33.33% (5/15) for Neuronox® and 33.33% (5/15) for ONA, and the severity of all reported AEs was 'mild.' Adverse drug reactions (ADRs) that occurred in Neuronox®-treated subjects included 'Injection site

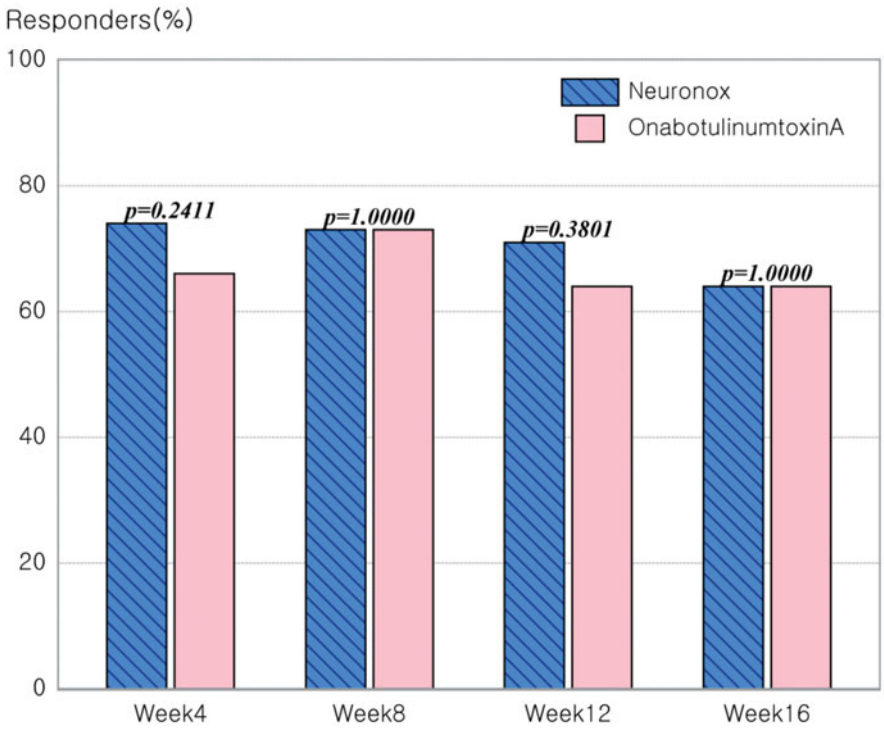


**Figure 7.** Proportion of subjects rating themselves as 'satisfied' or 'very satisfied' on the satisfaction scale.

bruising' in 13.33% (2/15 subjects, 2 cases), 'Injection site edema' in 6.67% (1/15 subject, 1 case), and 'Injection site pain' in 6.67% (1/15 subject, 1 case). None of the subjects dropped-out due to AEs.

In the Phase III trial, incidence rates of AEs were 30.00% (33/110) for the Neuronox® group and 34.55% (27/110) for the ONA group, and the severity of all AEs were 'mild' or 'moderate.' The incidence rate of ADRs was 2.73% (3/110) for Neuronox® and 2.73% (3/110) for ONA (Table 2). The difference in the incidence rate of AEs and ADRs was not statistically significant between the two groups, and there were no reports of serious AEs. Furthermore, no significant findings were found in vital signs, laboratory tests, and physical examinations.

## Discussion

This study was conducted to evaluate the non-inferiority of Neuronox® compared to ONA for the treatment of moderate to severe LCL.

The use of BoNT-A for the treatment of LCL in South Korea is common, but the efficacy and safety of BoNT-A for LCL treatment has not been well established. The only available randomized controlled trial in Koreans had a split-face design, where the subjects received study or control drug on alternate sides of the orbicularis oculi muscles (10), but this design does not determine the safety of a study drug. Therefore, this randomized, multi-centered, active-controlled, double-blind Phase I/III study was designed to evaluate the efficacy and safety of Neuronox® for the treatment of LCL when administered on LCL on both sides. To check the safety of Neuronox® compared with ONA, a Phase I study was initially conducted. All 30 subjects treated with Neuronox® or ONA completed the study without any serious AEs.

The non-inferiority of Neuronox® compared to ONA was determined during the Phase III study, which was conducted after successful assessment of the safety of the investigational product for the treatment of LCL through the Phase I study. In Phase III, the primary and secondary efficacy endpoints of both groups were satisfied and confirmed the clinical equipotency of both products when used at a 1:1 dose ratio.

Response rates for primary efficacy endpoints at Week 4 for both groups were 83%, supporting the non-inferiority of Neuronox® compare to ONA. This finding parallels the work of Carruthers et al. conducted primarily in Caucasians with a 66.7% responder rate in the ONA group (24 U) compared with 6.7% for the placebo group (4).

The subject-evaluated responder rate at maximum smile assessed by LCL severity scale was at its peak at Week 4 (69%; 76/110) in both groups, similar to the result found by Carruthers et al. (4). The differences between Neuronox® and ONA for both global assessment and satisfaction assessment were not statistically significant. However, the subject-evaluated responder rate was lower than the investigator-evaluated responder rate, although such a trend has previously been observed (4). The following factors may have influenced the evaluation of LCL severity by the subjects: (1) subjects were not as experienced as the investigators, making it less likely they would identify subtle improvements; and (2) the self-assessment was done using a mirror, which may obstruct a clear view compared to direct-view assessment (4).

The result of the safety analyses showed no statistically significant differences in the incidence of AEs and ADRs between the Neuronox® group and the ONA group. Furthermore, no serious AEs were found, and most of the AEs were either mild or moderate.

In conclusion, differences in the efficacy analyses of Neuronox® and ONA, as assessed by the investigator- and subject-evaluation tools, were statistically insignificant supporting the non-inferiority of Neuronox® compared to ONA in reducing LCL severity. The two groups also showed no statistical differences in safety analyses. In fact, subjects who allocated to receive Neuronox®

treatment had more severe LCL grade (LCL grade 2: Neuronox® vs ONA 29 vs 35 subject; grade 3: 38 vs 75, respectively). However, responder rate in the primary endpoint was the same in both groups. Therefore, it can be concluded that Neuronox® is an alternate treatment option to ONA for LCL.

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## Disclosure statement

W.S. Lee is an employee of Medytox Inc. The other authors have no conflict of interest.

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