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A Phase-III Noninferiority, Randomized Controlled Trial of Letibotulinum Toxin A for the Improvement of Moderate-to-Severe Glabellar Wrinkles in China

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Background: Letibotulinum toxin A has an established efficacy and safety profile for aesthetic treatment of glabellar wrinkles. This study was conducted to demonstrate the noninferiority of letibotulinum toxin A versus onabotulinum toxin A in improving the appearance of moderate-to-severe glabellar wrinkles in Chinese patients.

Methods: This phase-III multicenter, randomized, parallel positive control, double-blinded study compared the efficacy and safety of letibotulinum toxin A and onabotulinum toxin A. Eligible participants were randomized 3:1 to receive 20 U of letibotulinum toxin A or onabotulinum toxin A and were observed for 16 weeks postinjection. The primary endpoint was noninferiority in the proportion of study participants receiving a score of 0 or 1 for glabellar wrinkles on a four-point photographic evaluation scale, as assessed by an institution evaluator at maximum frown at week 4. Secondary endpoints included assessments at rest, photographic assessment of efficacy, and subjective self-assessment of the study participants.

Results: The proportion of participants (N = 500) receiving a score of 0 or 1 at maximum frown by the institution evaluator at week 4 was 88.49% for letibotulinum toxin A and 87.39% for onabotulinum toxin A (difference, 1.10%; 95% confidence interval, −5.02 to 8.82; $P = 0.7469$). No significant differences were observed between the treatments for secondary efficacy or safety endpoints. Participants' self-assessment and satisfaction tended to be higher for letibotulinum toxin A than onabotulinum toxin A.

Conclusion: Letibotulinum toxin A is noninferior to onabotulinum toxin A in improving the appearance of moderate-to-severe glabellar wrinkles in Chinese patients.
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INTRODUCTION

The use of botulinum A toxin to reduce the appearance of facial wrinkles is arguably the most popular cosmetic procedure in China,[1] providing predictable results, few adverse effects, and high patient satisfaction.[2] In aesthetic medicine, botulinum A toxin is used to weaken skeletal muscle via the presynaptic inhibition of the exocytosis of vesicles containing acetylcholine at the neuromuscular junction.[3] This leads to the temporary relaxation of the facial muscles that cause wrinkles when tense, including the glabellar complex, resulting in a smoother appearance of the overlying skin.[2]

Letibotulinum toxin A (BOTULAX; Hugel, Chuncheon, Korea) was derived from the CBFC26 strain of *Clostridium botulinum*[4] that was first approved for the

Disclosure statements are at the end of this article, following the correspondence information.

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treatment of glabellar wrinkles in Korea in 2012 and is now available in 28 countries globally. In a phase-III study, letibotulinum toxin A was found to be noninferior to onabotulinum toxin A (BOTOX; Allergan, Irvine, Calif.) for improvement of moderate-to-severe glabellar wrinkles in Korean patients.[4] Response rates at maximum frown were 89.3% in the letibotulinum toxin A group versus 81.9% in the onabotulinum toxin A group at week 4, and treatment-related adverse events (AEs) occurred in 9.0% of the letibotulinum toxin A group versus 11.7% in the onabotulinum toxin A group.[4]

The 16S RNA and protein sequences of the toxin used in letibotulinum toxin A are identical to those of onabotulinum toxin A–producing strains; letibotulinum toxin A undergoes further purification steps to improve quality, including enzyme-free removal of nucleic acids.[4] This is expected to alleviate some of the AEs observed in patients administered botulinum A toxin for aesthetic purposes, including immunogenicity,[5] which may be caused by the presence of enzymes derived from animals or remnant nucleic acids in the final preparation.[4]

Three botulinum A toxin agents are approved by the Chinese Food and Drug Administration for cosmetic use [Hengli (Lanzhou Biological Products Institute, Lanzhou, China), Dysport (Ipsen, Slough, UK), and Botox]. However, a noninferiority study is warranted to demonstrate the efficacy and safety of letibotulinum toxin A, a potential alternative botulinum A toxin product that may offer a cost-effective[4] and potentially more potent[6] botulinum A toxin product for consumers in China. Additionally, as classifications of glabellar wrinkles for White or Korean patients do not accurately reflect characteristics specific to the Chinese population,[1] the results from previous studies of letibotulinum toxin A for the treatment of glabellar wrinkles may not be generalizable to Chinese facial characteristics.

This study aimed to establish the noninferiority of letibotulinum toxin A versus onabotulinum toxin A in improving the appearance of moderate-to-severe glabellar wrinkles in a large study of Chinese patients.

Takeaways

Question: How is the efficacy of letibotulinum toxin A in treating glabellar lines compared with onabotulinum toxin?

Findings: In this article, we reported the noninferior efficacy of letibotulinum toxin A compared with onabotulinum toxin A, including the list of adverse events in both groups, which did not show any significant different between two groups. The efficacy analysis was assessed in participants with moderate-to-severe glabellar wrinkles who showed 0 or 1 in posttreatment evaluation.

Meaning: Letibotulinum toxin A was proven to have a noninferior efficacy compared with onabotulinum toxin in treating moderate-to-severe glabellar wrinkles within a Chinese population without any significance adverse effects.

METHODS

Study Design

A phase-III multicenter, randomized, parallel positive control, double-blinded study was conducted to evaluate the efficacy and safety of letibotulinum toxin A compared with onabotulinum toxin A in improving the appearance of moderate-to-severe glabellar wrinkles in China. This study was performed in compliance with the Good Clinical Practice guidelines and the Declaration of Helsinki, and independent ethics committee approval was obtained at each participating institution to ensure compliance with Chinese laws and regulations. All study participants provided written informed consent before enrollment. This study was prospectively registered at Clinicaltrials.gov (NCT05380154).

Study Population

Participants were eligible for enrollment if they were aged 18–65 years, had a score of 2 or more (moderate or severe) at maximum frown on a four-point photographic evaluation scale upon evaluator assessment at screening, were able to follow the study instructions, could rationally foresee the cost-effectiveness of injection, and could adhere to study procedures until the end of the trial. (**See table, Supplemental Digital Content 1**, which displays a four-point photographic evaluation scale at maximum frown. **http://links.lww.com/PRSGO/D9**). Key exclusion criteria included a history of facial nerve palsy, symptoms of ptosis, neuromuscular joint disease, muscle disease, and/or motor neuron disease; obvious scars, infections, skin disease, or malignant lesions and/or nonhealing wounds on the upper part of the face (defined as the facial area from the edge of the nose to the hairline); participants who received botulinum toxin type A or B injections 6 months or less before screening, or were foreseen to during the study period; participants who received hyaluronic acid injections in the upper part of the face 12 months or less before screening; participants who underwent or planned to undergo brow lift, laser resurfacing, skin rejuvenation, intense pulsed light, radiofrequency, dermabrasion, chemical peeling, or other ablative or nonablative procedures on the upper face 6 months before screening; participants who underwent prior surgery or permanent filler injection to remove wrinkles on the face above the eyes, or were foreseen to do so during the study period; participants who planned to undergo other facial plastic surgery during the study period; participants who used topical medications on the upper part of the face 4 weeks or less before screening, or were foreseen to during the study period; participants with a history of hypersensitivity to botulinum toxin type A or B, or any of their excipients; participants taking antithrombotic drugs or nonsteroidal antiinflammatory drugs 2 weeks or less before screening; and participants taking muscle relaxant drugs or antibiotics 4 weeks or less before screening, or were foreseen to during the study period. (**See table, Supplemental Digital Content 2,** which describes the eligibility criteria. **http://links.lww.com/PRSGO/D10.**)

Study Procedures

Participants were randomly assigned in a 3:1 ratio to receive either letibotulinum toxin A or onabotulinum toxin A on day 0 (Fig. 1). Following drug dilution

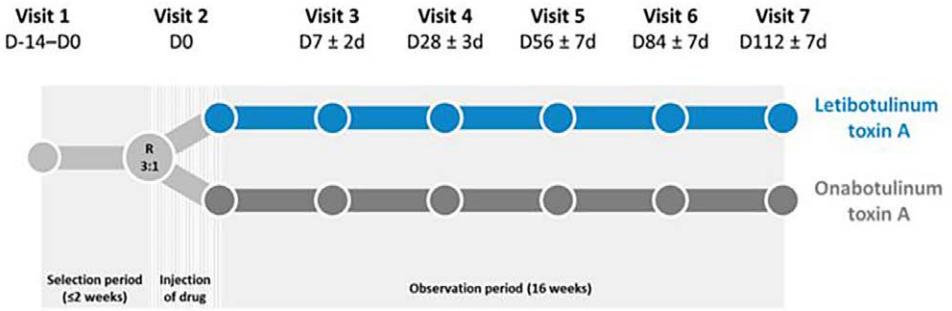

Fig. 1. Study timeline. D, study day; d, days; R, randomization.

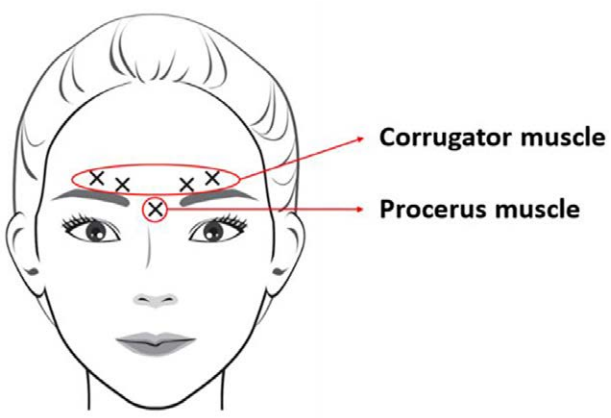

Fig. 2. Recommended sites of injection. While injection sites were subject to change according to the severity of the participant's glabellar wrinkles, the following sites were recommended (indicated by ×): a total of five sites, including two sites on both sides of the corrugator muscle at frown and one site in the procerus muscle.

according to the manufacturer's instructions by the institution formulation officer, the skin at the site of injection was cleaned and a total of 20 U of study drug was injected by the investigator into the glabellar muscle complex at the specified injection sites using a 30 G needle, comprising five 0.1-mL injections containing 4 U of study drug per injection (Fig. 2). The study participants, investigators, evaluators, and photographers were blinded to the study drugs to avoid bias and subjective judgement during the evaluations.

After injection of the study drug, the participants were required to stay at the study institution for 30 minutes to monitor their safety. The participants were then observed for 16 weeks, including five postinjection visits at weeks 1, 4, 8, 12, and 16 (Fig. 1).

Study Assessments

At each visit, the institution evaluator assessed wrinkle severity using a four-point photographic evaluation scale at both maximum frown and at rest. The institution photographer took photographs of the study participants at maximum frown and at rest at each visit to submit to the independent evaluation committee (IEC) for assessment. Study participants also self-assessed the treatment effects at each visit using a nine-point improvement rating table and a seven-point satisfaction evaluation table. (**See table, Supplemental Digital Content 3,** which displays a nine-point improvement rating table. **http://links.lww.com/PRSGO/D11**.) (**See table, Supplemental Digital Content 4,** which displays a seven-point satisfaction evaluation table. **http://links.lww.com/PRSGO/D12**.)

Study Endpoints

The primary study endpoint was the proportion of study participants who received a score of 0 or 1 on the four-point photographic evaluation scale by the institution evaluator who assessed glabellar wrinkles at maximum frown at week 4.

Secondary endpoints included the proportion of study participants receiving a score of 0 or 1 on the four-point photographic evaluation scale by the institution evaluator who assessed glabellar wrinkles at maximum frown in weeks 1, 8, 12, and 16 posttreatment; the proportion of study participants receiving a score of 0 or 1 on the four-point photographic evaluation scale by the institution evaluator who assessed glabellar wrinkles at rest in weeks 1, 4, 8, 12, and 16 posttreatment; the proportion of study participants receiving a score of 0 or 1 on the four-point photographic evaluation scale by the IEC based on photographs of glabellar wrinkles at maximum frown in weeks 1, 4, 8, 12, and 16 posttreatment; the proportion of study participants receiving a score of 0 or 1 on the four-point photographic evaluation scale by the IEC based on photographs of glabellar wrinkles at rest in weeks 1, 4, 8, 12, and 16 posttreatment; the proportion of study participants who self-assessed that the treatment was effective (by giving a score of +2 or more in the nine-point satisfaction rating scale) in weeks 1, 4, 8, 12, and 16 posttreatment; and the proportion of study participants who were satisfied with the treatment effect (study participant satisfaction rating of 6 or 7 in the seven-point satisfaction evaluation scale) in weeks 1, 4, 8, 12, and 16 posttreatment.

Safety was evaluated in all participants who received the study drug. The incidence of AEs, serious adverse events (SAEs), and adverse drug reactions (ADRs) was monitored throughout the study and recorded by the primary system organ class (SOC) and preferred term (PT)

using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.

Statistical Analysis

The full analysis set (FAS), defined as the intention-to-treat population that received treatment after randomization, was used to determine the baseline characteristics and demographics of the overall study population. The per-protocol set (PPS), defined as the treated population who completed all posttreatment visits and excluded participants who violated the study protocol seriously enough to affect the analysis, was used to evaluate the efficacy endpoints. The safety set (SS), which included all participants in the FAS who completed at least one postinjection visit for safety observations, was used to evaluate the safety endpoints.

The primary efficacy endpoint was analyzed using the noninferiority test hypothesis, with the noninferiority margin set at 10% [$\alpha = 0.025$ (single side)], based on results from a previous Korean study. The Miettinen–Nurminen method was used to determine the 95% confidence intervals (CIs) and *P* values. Secondary efficacy endpoints were compared between the two study groups using a chi-square test or direct probability test, depending on the distribution characteristics. AEs, ADRs, serious ADRs (sADRs), and SAEs were presented using descriptive statistics.

RESULTS

Study Participants

A total of 564 potential participants were screened across 13 institutions in China, and 500 were enrolled in the study (Fig. 3). Enrolled participants were randomly assigned to receive either letibotulinum toxin A (n = 377) or onabotulinum toxin A (n = 123).

Of the 498 participants who received treatment, 457 received injections at the five recommended sites

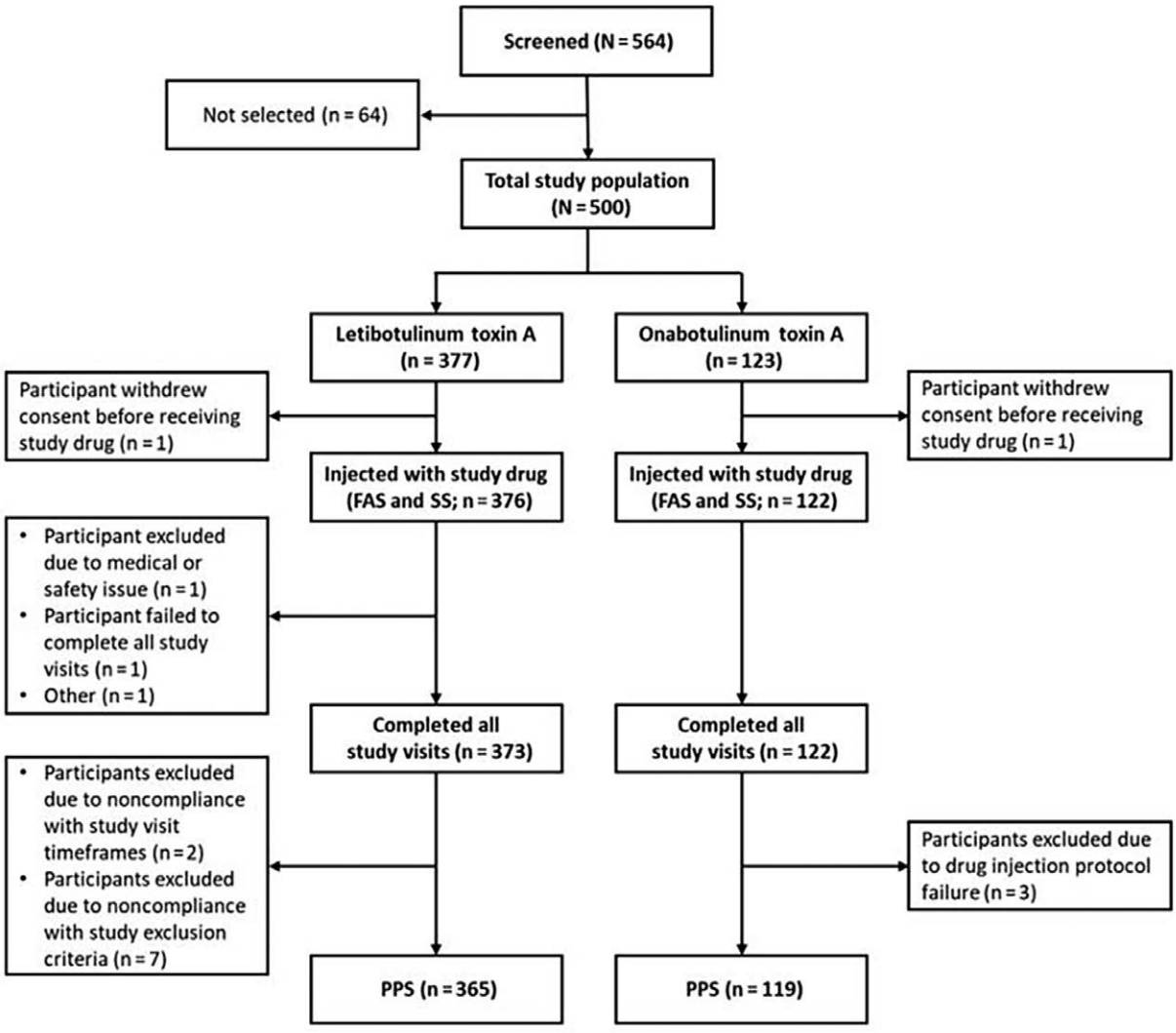

Fig. 3. CONSORT flow diagram.

Table 1. Demographics and Baseline Characteristics of the FAS Study Population

Baseline Characteristics	Letibotulinum Toxin A (n = 376)	Onabotulinum Toxin A (n = 122)	Total (N = 498)	*P*
Age, years, mean (SD)	44.9 (10.4)	44.9 (10.7)	44.9 (10.5)	>0.999
Sex, n (%)				
Female	306 (81.4)	106 (86.9)	412 (82.7)	0.162
Male	70 (18.6)	16 (13.1)	86 (17.3)	
Ethnicity, n (%)				
Han Chinese	361 (96.0)	118 (96.7)	479 (96.2)	>0.999
Other	15 (4.0)	4 (3.3)	19 (3.8)	
Body weight, kg, mean (SD)	60.5 (10.2)	59.8 (9.9)	60.3 (10.1)	0.507
Glabellar wrinkle assessment at maximum frown, n (%)				
Moderate (two points)	213 (56.7)	69 (56.6)	282 (56.6)	0.986
Severe (three points)	163 (43.4)	53 (43.4)	216 (43.4)	

(91.8%). The demographics and baseline characteristics of the study population were well balanced across the two study groups, with no statistically significant differences observed (Table 1). Most participants were women (82.7%) and Han Chinese (96.2%), with a mean (SD) age of 44.9 (10.5) years. At baseline, 56.65% and 43.55% of participants in the letibotulinum toxin A group received a score of 2 or 3, respectively, on the four-point photographic evaluation scale. Similarly, 56.56% and 44.43% of the participants in the onabotulinum toxin A group received a score of 2 or 3, respectively, at baseline (Table 1).

Efficacy

Assessment by Institution Evaluator Using the Four-point Photographic Evaluation Scale

The proportion of participants receiving a score of 0 or 1 for glabellar wrinkles at maximum frown by the institution evaluator at week 4 was 88.49% in the letibotulinum toxin A group and 87.39% in the onabotulinum toxin A group (percentage difference, 1.10; 95% CI, –5.02 to 8.82; $P = 0.7469$). This trend was maintained at 1, 8, 12, and 16 weeks after treatment, with no statistically significant differences between the groups (Fig. 4A).

The proportion of participants who received a score of 0 or 1 for glabellar wrinkles at rest by the institution evaluator at week 4 was 84.66% in the letibotulinum toxin A group and 84.87% in the onabotulinum toxin A group ($P = 0.9546$). This trend was also maintained at all time points, with no statistically significant differences between the groups at weeks 1, 8, 12, and 16 (Fig. 4B).

Assessment by IEC Using the Four-point Photographic Evaluation Scale

The proportion of participants receiving a score of 0 or 1 for glabellar wrinkles at maximum frown by the IEC based on photographs at week 4 was 95.07% for the letibotulinum toxin A group and 94.12% in the onabotulinum toxin A group ($P = 0.6840$). This trend was maintained at 1, 8, 12, and 16 weeks posttreatment, with no statistically significant differences between the groups (Fig. 5A).

The proportion of participants who received a score of 0 or 1 for glabellar wrinkles at rest by the IEC based on photographs at week 4 was 92.88% for the letibotulinum toxin A group and 93.28% for the onabotulinum toxin A group ($P = 0.8820$). This trend was maintained at all time points, with no statistically significant differences between the groups (Fig. 5B).

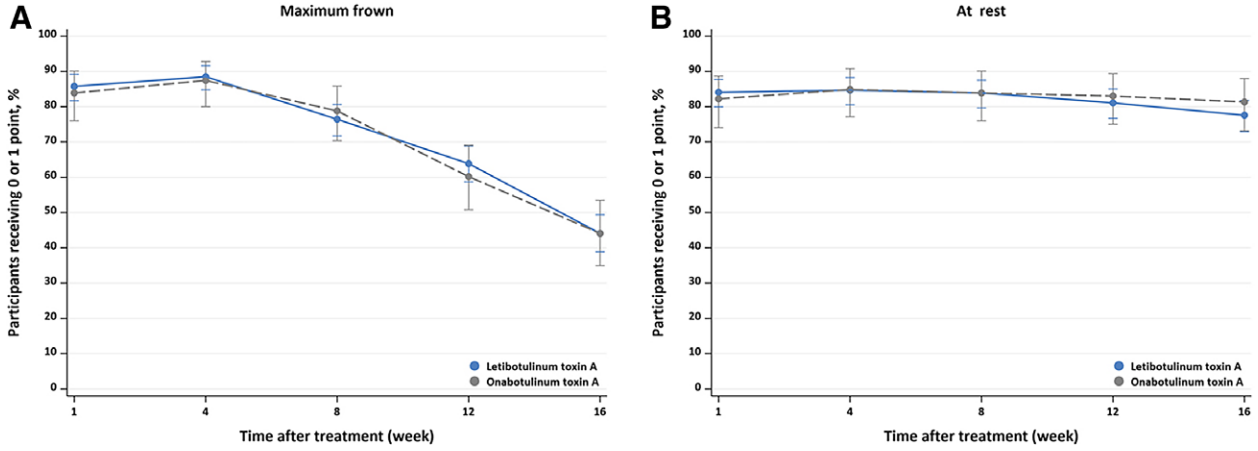

Fig. 4. The proportion of study participants in the PPS receiving a score of 0 or 1 on the four-point photographic evaluation scale for glabellar wrinkles at maximum frown (A) and at rest (B) as determined by the institution evaluator from week 1 to 16.

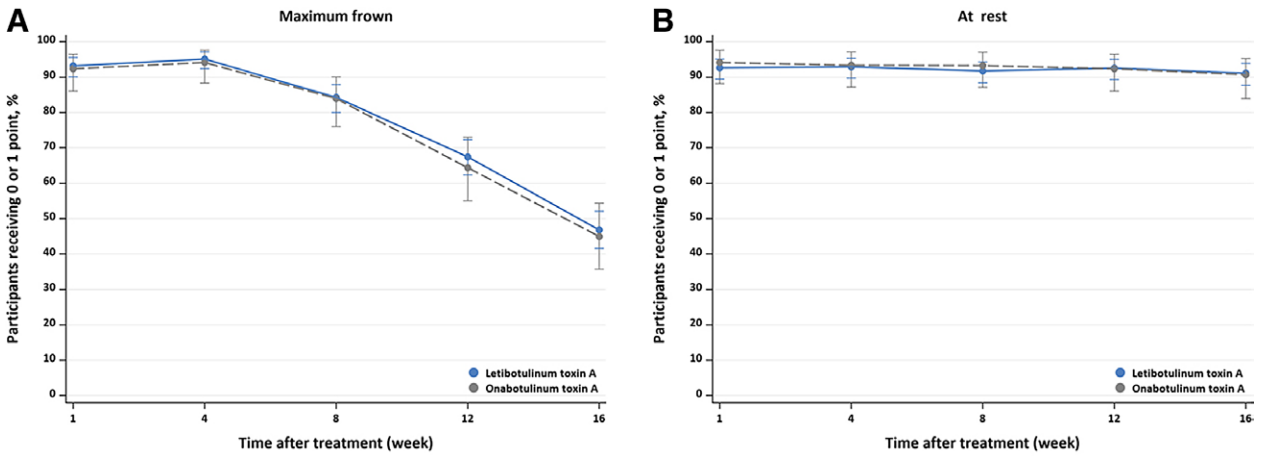

Fig. 5. The proportion of study participants in the PPS receiving a score of 0 or 1 on the four-point photographic evaluation scale based on photographs of glabellar wrinkles at maximum frown (A) and at rest (B) as determined by the IEC from week 1 to 16.

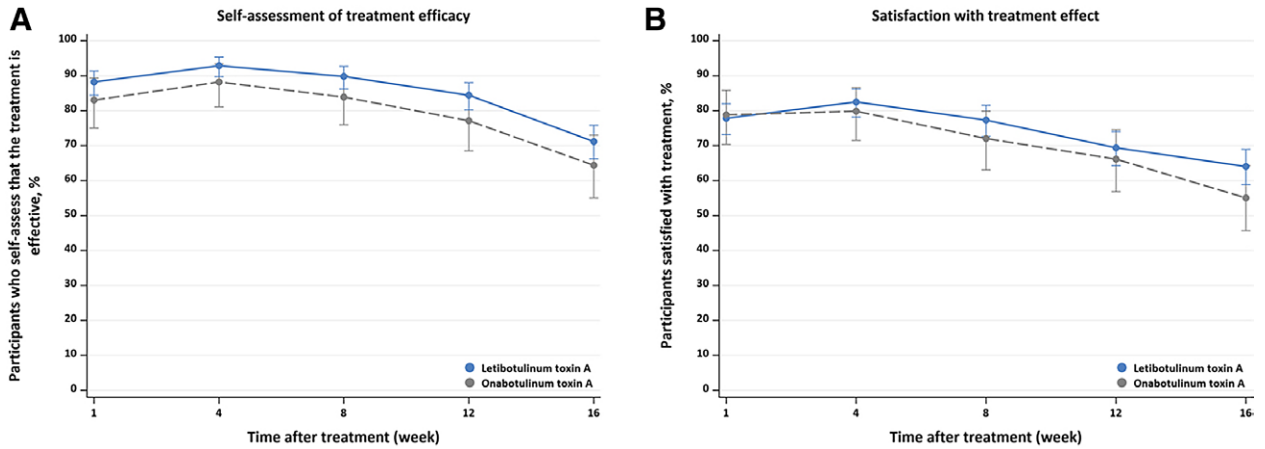

Fig. 6. The proportion of study participants in the PPS who self-assessed that the treatment is effective using the nine-point satisfaction rating scale (A) and the proportion of study participants in the PPS satisfied with the treatment effect using the seven-point satisfaction evaluation scale (B).

Participants' Self-evaluation Using the Nine-point Satisfaction Rating Scale and the Seven-point Satisfaction Evaluation Scale

The proportion of participants who self-reported that treatment was effective (by giving a score of ≥+2) at week 4 was 92.88% for the letibotulinum toxin A group and 88.24% for the onabotulinum toxin A group ($P = 0.1103$). This trend was consistent at weeks 1, 8, 12, and 16 post-treatment, with no statistically significant differences between the groups (Fig. 6A).

The proportion of participants who were satisfied with the treatment effect (by giving a satisfaction rating of 6 or 7) at week 4 was 82.47% for the letibotulinum toxin A group and 79.83% for the onabotulinum toxin A group ($P = 0.5177$). This trend was maintained for all study time-points, with no statistically significant differences between groups at weeks 1, 8, 12, and 16 posttreatment (Fig. 6B).

Safety

AEs of any grade considered by the investigators to be related to the study drug occurred in 33.5% of the 376 participants in the letibotulinum toxin A group and 40.2% of the 122 participants in the onabotulinum toxin A group (Table 2). SAEs occurred in 1.6% of the participants in the letibotulinum toxin A group and 2.5% of the participants in the onabotulinum toxin A group. Only one SAE was determined to be an sADR, which occurred in one participant in the letibotulinum toxin A group (eyelid ptosis). None of the participants in either treatment group discontinued the study because of AEs, and no deaths were reported during the study.

The most common primary SOC affected by ADRs were eye disorders (1.9% in the letibotulinum toxin A group and 1.6% in the onabotulinum toxin A group; Table 3). The only PT with an incidence of 1% or more in either treatment group was headache in the letibotulinum toxin A group (1.1%; Table 3).

DISCUSSION

In this phase-III multicenter, randomized, parallel positive control, double-blind study of the use

Table 2. Incidence of AEs and SAEs in the SS Study Population

	Letibotulinum Toxin A (n = 376)		Onabotulinum Toxin A (n = 122)		
	Participants, n (Prevalence, %)	Events, n	Participants, n (Prevalence, %)	Events, n	*P*
All AEs	142 (37.8)	221	53 (43.4)	80	0.264
Severity of AEs					
Light	117 (31.1)	194	43 (35.2)	66	0.537
Intermediate	25 (6.6)	27	9 (7.4)	13	
Serious	0	0	1 (0.8)	1	
Relevance to study drug					
Unrelated*	126 (33.5)	203	49 (40.2)	76	0.748
Related†	16 (4.3)	18	4 (3.3)	4	
AEs leading to study discontinuation	0	0	0	0	NA
SAEs	6 (1.6)	6	3 (2.5)	4	0.463
sADRs‡	1 (0.3)	1	0	0	>0.999

*AEs unrelated to study drug include AEs classified as "not related" and "may not be related."
†AEs related to study drug include AEs classified as "maybe related," "highly probably related," and "definitely related."
‡The sADR in the letibotulinum toxin A group was classified as MedDRA primary SOC (PT): eye disorders (eyelid ptosis).

Table 3. ADRs by MedDRA PT in the SS Study Population

SOC	Letibotulinum Toxin A (n = 376)		Onabotulinum Toxin A (n = 122)		
PT	Participants, n (Prevalence, %)	Events, n	Participants, n (Prevalence, %)	Events, n	*P*
All ADRs	16 (4.3)	18	4 (3.3)	4	0.794
Eye disorders	7 (1.9)	8	2 (1.6)	2	>0.999
Eyelid ptosis	3 (0.8)	4	1 (0.8)	1	>0.999
Periorbital swelling	2 (0.5)	2	1 (0.8)	1	0.570
Eyelid function disorder	1 (0.3)	1	0	0	>0.999
Asthenopia	1 (0.3)	1	0	0	>0.999
Nervous system disorders	6 (1.6)	6	0	0	0.344
Headache	4 (1.1)	4	0	0	0.577
Dizziness	2 (0.5)	2	0	0	>0.999
General disorders and systemic administration site conditions	2 (0.5)	2	1 (0.8)	1	0.570
Injection site pain	1 (0.3)	1	1 (0.8)	1	0.430
Injection site erythema	1 (0.3)	1	0	0	>0.999
Investigations	1 (0.3)	1	0	0	>0.999
ALT increased	1 (0.3)	1	0	0	>0.999
Skin and subcutaneous tissue disorders	1 (0.3)	1	1 (0.8)	1	0.430
Pruritus	1 (0.3)	1	0	0	>0.999
Dermatitis	0	0	1 (0.8)	1	0.245

ALT, alanine aminotransferase.

of botulinum A toxin to improve the appearance of moderate-to-severe glabellar wrinkles, the efficacy of letibotulinum toxin A was noninferior to that of OTA, with a comparable safety profile. This finding is consistent with the results of a previous phase-III noninferiority study comparing letibotulinum toxin A and onabotulinum toxin A in a Korean population (noninferiority margin, 14.57%), despite the more stringent noninferiority margin used in this study (−10%).[4] In this study, the lower limit of the 95% CI for the treatment difference between the letibotulinum toxin A and onabotulinum toxin A groups (−5.02%) was larger than the predetermined noninferiority standard (−10%), and letibotulinum toxin A was shown to be noninferior to onabotulinum toxin A in Chinese patients.

No statistically significant differences were observed between the groups for any of the secondary endpoints assessed in this study. However, improvement in the appearance of glabellar wrinkles as self-assessed by the study participants showed a slightly higher trend for the letibotulinum toxin A group than for the onabotulinum toxin A group overall, with more than 90% of study participants in the letibotulinum toxin A group, indicating that the treatment was effective at week 4.

Although improvement in the appearance of glabellar wrinkles was evident from the earliest time point, the peak efficacy for all endpoint assessments was observed at week 4. This is consistent with previous studies that have shown that the improvement in the appearance of glabellar wrinkles is most apparent 2–4 weeks after treatment with letibotulinum toxin A.[4,7]

The scores given by the IEC using the four-point photographic evaluation scale tended to be higher than the on-site institution evaluator scores. Variations in scoring may be attributed to the cooperation of the study participants or differences in photography techniques.

As consumers often receive repeated treatments with botulinum A for many years to maintain glabellar smoothness, the safety and tolerability profile of botulinum toxin A should be evaluated in clinical trials, which reflect its actual use in clinical settings.[8] In this study, no new safety signals were identified,[9] and no significant differences were observed between the safety profiles of letibotulinum toxin A and onabotulinum toxin A. The incidences of AE, SAEs, ADRs, and sADRs were comparable between the treatment groups. For the participant in the letibotulinum toxin A group who experienced the eyelid ptosis sADR, the severity level was intermediate, and the participant self-recovered without treatment in 20 days with no sequelae.

A key limitation of this study is the relatively short follow-up duration and single administration of the study drug, which makes it difficult to draw conclusions about the long-term efficacy of letibotulinum toxin A versus onabotulinum toxin A. In addition, as most study participants were women and ethnic Han Chinese, the results of this study may not be generalizable to other patient populations.

CONCLUSION

In summary, letibotulinum toxin A improves the appearance of moderate-to-severe glabellar wrinkles safely and effectively and is noninferior to onabotulinum toxin A in Chinese patients.

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DISCLOSURES

The authors have no financial interest to declare in relation to the content of this article. This study was supported by Hugel, Inc., Chuncheon, Korea.

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