Safety and Tolerability of Topical Botulinum Toxin Type A in Healthy Adults

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Background

Injectable botulinum neurotoxin type A (BoNT-A) is widely used for the treatment of aesthetic indications on most areas of the face and neck, including lateral canthal lines ("crow's feet").[1,2] Limitations of injectable BoNT-A include anxiety resulting from needle-phobia, pain, and bruising.[3,4] Bruising is of particular concern in the lateral canthus region, where the blood vessels are superficial and the skin is thin.

Topical application of BoNT-A obviates the undesirable side effects of BoNT-A injection, such as pain and bruising and is therefore well suited to offer a practical, painless, and safe mode of administration.

A topical drug product, RT001 Botulinum Toxin Type A Topical Gel, is being studied for the treatment of moderate to severe lateral canthal lines (LCLs). RT001 contains a proprietary, purified 150 kilodalton (kDa) BoNT-A combined with a novel peptidyl macromolecule transport system, which facilitates percutaneous delivery without altering the function of BoNT-A. RT001 may be well suited to offer a practical, painless, and safe mode of administration of BoNT-A for a variety of indications.

Objectives

The objectives of the study were to:

- Evaluate the potential for irritation and sensitization with RT001.
- Evaluate the topical and systemic safety of RT001.
- Evaluate the systemic immunogenicity of RT001.

Clinical Hypotheses

RT001 administered topically:

- Is well-tolerated and has a low potential to irritate or cause sensitization.
- Has an acceptable safety profile in healthy adult volunteers.
- Does not cause systemic immunogenicity.

Study Design

Phase 1, randomized, double-blind, controlled study in 41 healthy adult volunteers.

Study conducted in 3 phases:

- ***Induction Phase*:** treatments applied to defined area on each forearm on Days 0, 14, and 28.
- ***Rest Phase*:** Days 29 to 41, no treatments.
- ***Challenge Phase*:** treatments applied to new area on each forearm on Day 42.

30-minute treatments with RT001 (300U) or placebo applied to the forearms under Tegaderm™ occlusion.

Subjects randomized as to which arm received which treatment.

Follow-up evaluations on Days 2, 16, 30, 44, 45 (if required), and 56.

Evaluations

- Skin irritation and sensitization evaluations (erythema, edema, scaling, fissures, crusts, vesicles, burning or stinging sensation, itching).
- Adverse events (AEs).
- Clinical laboratory tests.
- Serum BoNT-A antibodies.
- Muscle strength grip.

Subject Demographics

Table 1: Subject Demographics

Age (years): Mean (SD)	33.0 (11.0)
Min, max	18.6, 63.0
Sex: N (%): Male	11 (26.8%)
Female	30 (73.2%)
Ethnicity: N (%)	
Hispanic/Latino	5 (12.2%)
Not Hispanic/ Latino	36 (87.8%)
Race: N (%)	
White	39 (95.1%)
American Indian/Alaska Native	1 (2.4%)
Asian	1 (2.4%)
Dominant Hand: N (%)	
Right	34 (82.9%)
Left	7 (17.1%)

Results

Skin Irritation and Sensitization

Induction Phase:

One subject had minimal erythema on the RT001 treated site on Day 2.

No other subject had any erythema at any time during the induction phase.

There was no significant difference between the RT001 and placebo-treated sites for cumulative skin irritancy during the induction phase.

Table 2: Skin Irritation during the Induction Phase

Cumulative Irritancy Index	RT001	Placebo	Difference
Mean (SD)	0.03 (0.16)	0.00 (0.00)	0.03 (0.16)
Range	0.00, 1.00	0.00, 0.00	0.00, 1.00
P-value			*0.324*

Scores based on a scale of 0 (no reaction) to 5 (severe reaction)

Challenge Phase:

All subjects had erythema scores <2 on Days 44 and 56.

No subject had definite erythema (≥2) at any time during the Challenge Phase.

No subject showed any sensitization at the end of the study.

Clinical Signs and Symptoms:

No clinical signs or symptoms (edema, scaling, fissures, crusts, vesicles, burning or stinging sensation, or itching) reported for any subject at any time.

Adverse Events

Three subjects had a total of five treatment emergent AEs:

- One subject with moderate bilateral application site pruritus and papules on Day 28, definitely related to study treatment, resolved within 24 hours.
- One subject with 2 events of mild arthralgia of the wrist on Days 14 and 28, possibly related to study treatment, resolved within 24 hours.
- One subject with moderate contact dermatitis, unrelated to study treatment.

No serious AEs and no subject discontinued the study due to an AE.

Clinical Laboratory Results

- Few subjects had laboratory values that changed from within normal range at Screening to above or below normal range at Day 28 or Day 56.
- The most frequently observed changes were increases in glucose, uric acid, and platelet count.
- No subject had any clinically significant laboratory values.
- There were no notable changes from Screening to Day 28 or Day 56 in mean values for any laboratory variables.
- All subjects were negative for BoNT-A antibodies at Screening and End of Study.

Muscle Grip Strength

There were no notable changes in muscle grip strength during the study with either RT001 or placebo treatment.

Conclusions

RT001 administered topically to the forearms:

- Is well tolerated.
- Has a low potential to irritate or cause sensitization.
- Has an acceptable safety profile.
- Does not cause systemic immunogenicity.

References

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Presented at the 69th Annual Meeting of the Society for Investigative Dermatology, Montreal, Canada, May 2009