Safety of IncobotulinumtoxinA for Treating Facial Lines: A Pooled Analysis of Randomized, Prospective, Controlled Clinical Studies

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BACKGROUND

- IncobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH) is a highly purified formulation of botulinum toxin type A without complexing proteins.
  - Because of its advanced manufacturing process, incobotulinumtoxinA contains only the pure neurotoxin, and the vials can be stored at room temperature for up to 3 years prior to reconstitution.
- The safety and efficacy of incobotulinumtoxinA for aesthetic indications has been established in multiple studies[1-6]
  - An increasing body of clinical literature demonstrates that incobotulinumtoxinA also has the same performance and duration of treatment effect as onabotulinumtoxinA though 4 months[4,5]
- Although individual studies have been reported, a combined assessment of incobotulinumtoxinA safety across studies is not available
- The objective of this pooled analysis was to assess the frequency of adverse events (AEs) across randomized, prospective, controlled incobotulinumtoxinA studies in aesthetic indications: glabellar frown lines (GFL), crow's feet (CF), and upper facial lines (UFL)

METHODS

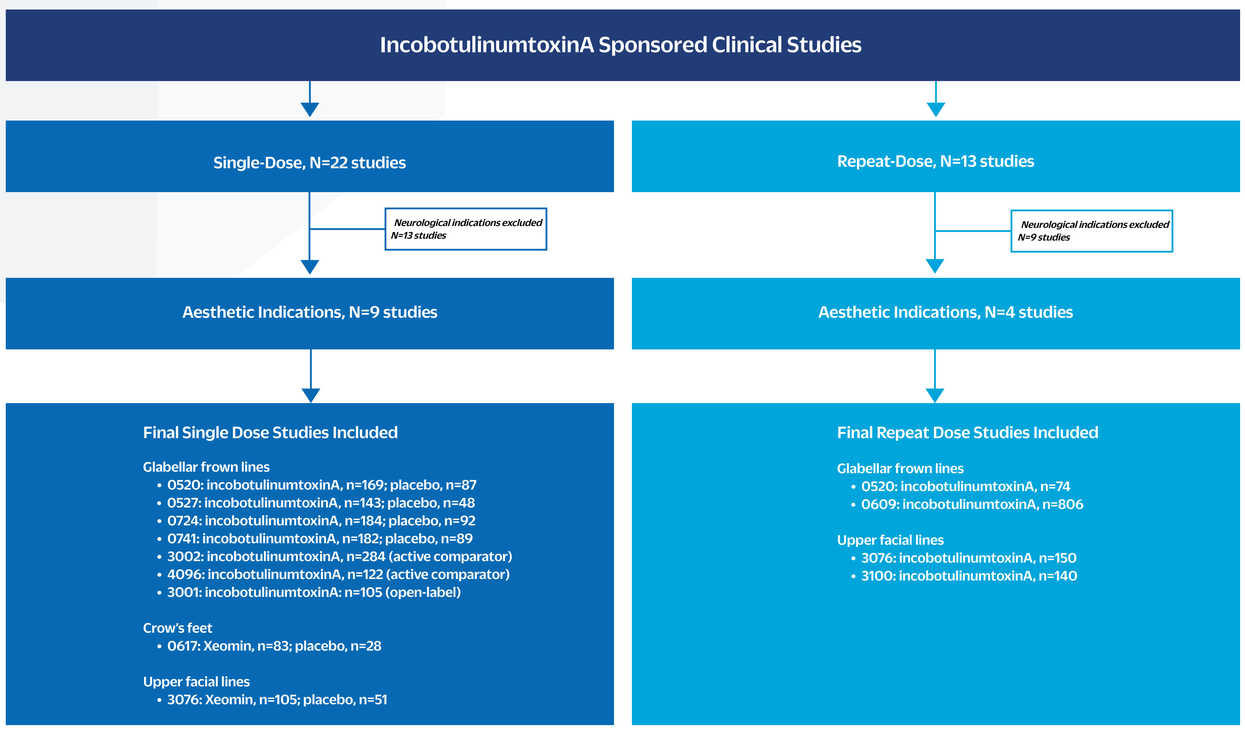
Study Selection

- Data source: Integrated database of Merz-sponsored studies
  - Neurological indications were excluded
- Analyses were separated by single- and repeat-dose studies (**Figure 1**)
  - Single-dose: those with only a single treatment of incobotulinumtoxinA was provided in a placebo- or active-controlled setting or without any control
  - Repeat-dose: those in which subjects received multiple treatments with incobotulinumtoxinA over ≥2 cycles; however, subjects who for any reason received only 1 incobotulinumtoxinA treatment in a repeat-dose study were also included in the safety analyses

Assessments

- Single-dose studies
  - Overall incidence of adverse events (AEs), treatment-related AEs, and serious treatment-related AEs
  - Most frequent AEs (≥2% frequency in any group)
  - Most common treatment-related AEs (≥2 subjects in any group)
  - Occurrence of adverse events of special interest (AESIs), defined as those possibly indicating toxin spread
- Repeat-dose studies
  - Overall incidence of AEs, treatment-related AEs, and serious treatment-related AEs by treatment cycle

Figure 1. Study Selection Scheme. Final set of studies included 3 indications



CONCLUSIONS

- **Overall, these results support and extend the generally favorable safety and tolerability profile of incobotulinumtoxinA for the treatment of GFL, CF, and UFL**
- **There were no new or unexpected safety findings, and no treatment-related serious AEs were observed**
- **Incidence of treatment-related AEs in all studies was low, and the severity was mostly mild to moderate.**
- **Subjects in the UFL study received 20 separate injections across 3 areas of the upper face with a total dose of incobotulinumtoxinA 2–3 fold higher than for CF or GFL individually.**
  - **This combined treatment of UFL remained well tolerated, with a similar AE profile as the individual treatment areas and no marked increase in AE incidence and/or severity.**
- **No subjects treated with incobotulinumtoxinA demonstrated new formation of neutralizing antibodies and no secondary treatment failure occurred**

References: 1.Carruthers A, Carruthers J, Coleman WP, 3rd, Donofrio L, et al. Multicenter, randomized, phase III study of a single dose of incobotulinumtoxinA, free from complexing proteins, in the treatment of glabellar frown lines. *Dermatol Surg.* 2013;39(4):551-558; 2. Hanke CW, Narins RS, Brandt F, Cohen JL, et al. A randomized, placebo-controlled, double-blind phase III trial investigating the efficacy and safety of incobotulinumtoxinA in the treatment of glabellar frown lines using a stringent composite endpoint. *Dermatol Surg.* 2013;39(6):891-899; 3. Kerscher M, Rzany B, Prager W, Turnbull C, et al. Efficacy and Safety of IncobotulinumtoxinA in the Treatment of Upper Facial Lines: Results From a Randomized, Double-Blind, Placebo-Controlled, Phase III Study. *Dermatol Surg.* 2015;41(10):1149-1157; 4. Sattler G, Callander MJ, Grablowitz D, Walker T, et al. Noninferiority of incobotulinumtoxinA, free from complexing proteins, compared with another botulinum toxin type A in the treatment of glabellar frown lines. *Dermatol Surg.* 2010;36 Suppl 4:2146-2154; 5. Kane MA, Gold MH, Coleman WP, 3rd, Jones DH, et al. A Randomized, Double-Blind Trial to Investigate the Equivalence of IncobotulinumtoxinA and OnabotulinumtoxinA for Glabellar Frown Lines. *Dermatol Surg.* 2015;41(11):1310-1319; 6. Rzany B, Flynn TC, Schlobe A, Heinz M, et al. Long-term results for incobotulinumtoxinA in the treatment of glabellar frown lines. *Dermatol Surg.* 2013;39(1 Pt 1):95-103.

RESULTS

- No new or unexpected safety findings
- No treatment related serious AEs were observed in any study
- Incidence of treatment-related AEs in all studies was low, and the severity was mostly mild to moderate
- Incidence of AEs in the UFL study is somewhat higher than for GFL or CF, however the incidence of AEs in the placebo group was also higher compared with the placebo groups in the other included studies; accordingly, the AE ratio for incobotulinumtoxinA to placebeo was comparable across indications.
- Only 4 treatment-related AESIs were observed; all were mild and resolved
- No subjects treated with incobotulinumtoxinA demonstrated new formation of neutralizing antibodies, and no secondary treatment failure occurred

Table 1. GFL Single-dose Studies: Most Common Treatment-related AEs (≥2 subjects in any group)

Treatment-Related Adverse Event, n (%)	Xeomin, GFL studies (all single-dose) N=1189	Xeomin, GFL studies (placebo-controlled) N=678	Placebo N=316
Headache	57 (4.8)	44 (6.5)	10 (3.2)
Muscle disorder	7 (0.6)	7 (1.0)	0 (0.0)
Brow ptosis	7 (0.6)	6 (0.9)	0 (0.0)
Injection site bruising	5 (0.4)	5 (0.7)	1 (0.3)
Eyelid edema	4 (0.3)	2 (0.3)	0 (0.0)
Facial asymmetry	3 (0.3)	1 (0.1)	0 (0.0)
Discomfort	3 (0.3)	3 (0.4)	1 (0.3)
Pruritis	3 (0.3)	2 (0.3)	0 (0.0)
Hematoma	3 (0.3)	1 (0.1)	0 (0.0)
Contusion	2 (0.2)	1 (0.1)	0 (0.0)

Adverse Events of Special Interest (AESIs)

- GFL single-dose studies
  - AESIs were observed in 7 subjects: eyelid ptosis (n=3), blurred vision (n=1), facial paralysis (n=1), pelvic floor muscle weakness (n=1), and dyspnea (n=1)
  - Only 2 subjects reported AESIs that were considered related to treatment (eyelid ptosis and blurred vision, n=1 each); both were mild and resolved
- No AESIs were observed in the CF single-dose study
- UFL single-dose study
  - AESIs were observed in 2 subjects (eyelid ptosis in both); these events were considered related to treatment, mild in intensity, and resolved

Table 2: CF Single-dose Study: Most Common Treatment-related AEs
(≥2 subjects in any group)

Treatment-Related Adverse Event, n (%)	Xeomin, CF study (placebo-controlled) N=83	Placebo N=28
Eyelid edema	3 (3.6)	0 (0.0)
Injection site hematoma	2 (2.4)	0 (0.0)

Table 3: UFL Single-dose Study: Most Common Treatment-related AEs
(≥2 subjects in any group)

Treatment-Related Adverse Event, n (%)	Xeomin, UFL study (placebo-controlled) N=105	Placebo N=51
Headache	12 (11.4)	0 (0.0)
Injection site hematoma	4 (3.8)	3 (5.9)
Facial asymmetry	3 (2.9)	0 (0.0)
Eyelid Ptosis	2 (1.9)	0 (0.0)

Figure 2. Single-Dose Studies: Overall Incidence of AEs

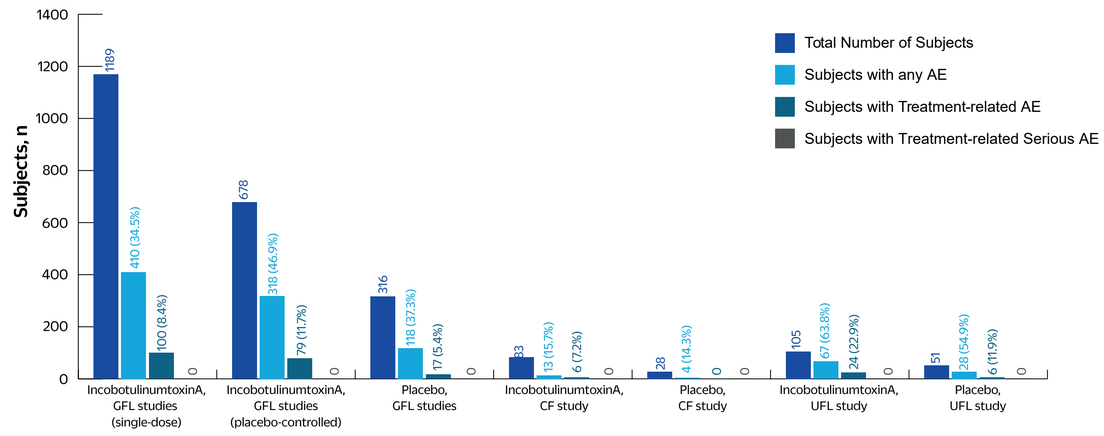


Figure 3. GFL Repeat-Dose Studies: Overall Incidence of AEs by Treatment Cycle

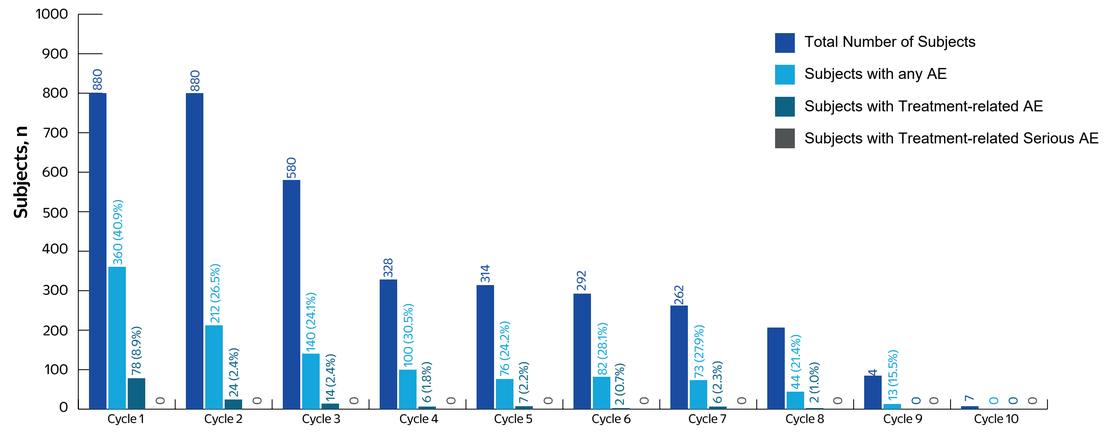
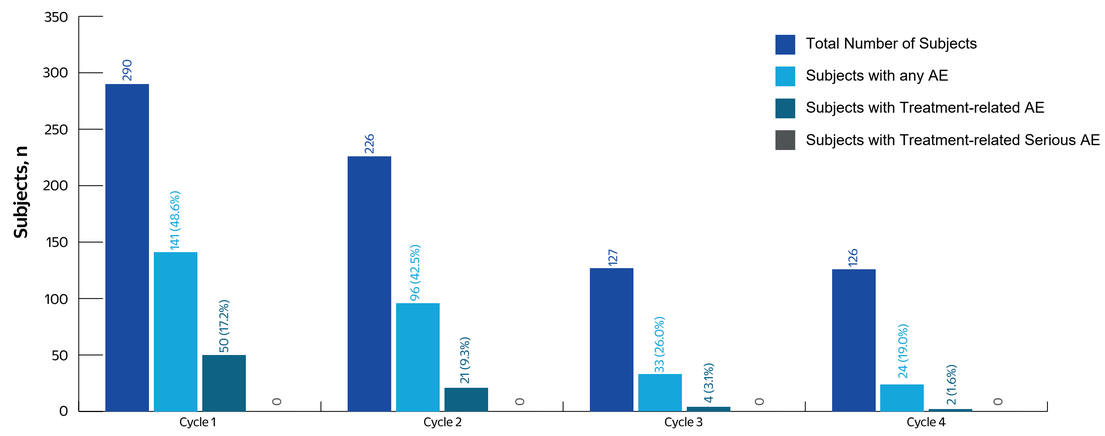


Figure 4. UFL Repeat-Dose Studies: Overall Incidence of AEs by Treatment Cycle



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