Safety, tolerability, and efficacy of repeat-dose injections of incobotulinumtoxinA in the treatment of upper facial lines

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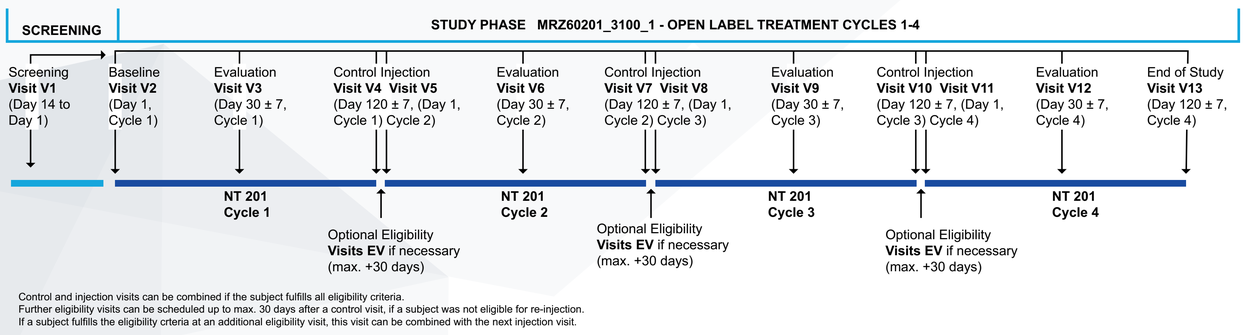
BACKGROUND

- IncobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals, GmbH) is indicated worldwide for the correction of glabellar frown lines (GFL) and in Europe for lateral periorbital lines (LPL; crow's feet) and upper facial lines (UFL; i.e., simultaneous treatment of GFL, LPL, and horizontal forehead lines [HFL]).[1]
  - The efficacy of incobotulinumtoxinA in the treatment of multiple or singular facial areas has been extensively demonstrated.[2-10]
- Although retrospective data on the repeat use of incobotulinumtoxinA are available, prospective safety and efficacy data for the combined treatment of UFL in more than two consecutive dosing cycles are needed.
- The purpose of this study was to investigate the safety, tolerability, and efficacy for up to four repeat-dose injections of incobotulinumtoxinA in the combined treatment of moderate to severe UFL.
  - Safety and tolerability also included monitoring for immunogenicity and formation of neutralizing antibodies.

METHODS

- This prospective, open-label, phase III study was comprised of a maximum of four 120-day treatment cycles with an additional ≤ 30 days for eligibility re-assessment between each cycle.
- The subjects received injections with a flexible total dose of 54 to 64 U incobotulinumtoxinA, administered at Day 1 of each respective treatment cycle, to three upper facial areas.
- The total volume of 1.35 to 1.6 mL was distributed to three different areas: the forehead (0.25 to 0.5 mL where the dose was within a range of 10 to 20 U), the glabellar area (0.5 mL; 20 U), and each lateral eye area (0.3 mL; 12 U per facial side).
- An overview of the assessment schedule is provided in **Figure 1**.

Figure 1. Study design



Control and injection visits can be combined if the subject fulfills all eligibility criteria.
Further eligibility visits can be scheduled up to max. 30 days after a control visit, if a subject was not eligible for re-injection.
If a subject fulfills the eligibility crteria at an additional eligibility visit, this visit can be combined with the next injection visit.

Efficacy Assessment

- As the focus of the study was safety and tolerability of incobotulinumtoxinA, no primary efficacy endpoint was defined. Secondary efficacy variables included:
  - (1) An investigator-assessed score of "none" or "mild" on the MAS for the three treated areas, evaluated individually at maximum contraction on Day 30 of each treatment cycle
  - (2) A subject-assessed score of "much improved" or "very much improved" for overall appearance of upper face on the Global Impression of Change Scale (GICS) at Day 30 of each treatment cycle.
  - (3) An investigator-assessed score of "much approved" or "very much improved" for overall appearance of the upper face on the GICS at Day 30 of each treatment cycle
  - (4) A subject-assessed score on a two-item balanced 5-point scale for treatment satisfaction with overall facial appearance and disappearance of facial lines at Day 30 of each treatment cycle.

Safety Assessment

- The primary endpoint of the study was the demonstration of the safety and tolerability of incobotulinumtoxinA, which was evaluated using the incidence of treatment-emergent adverse events (TEAEs) during the overall period of the study.
- Secondary safety endpoints included: (1) incidence of TEAEs per treatment cycle and (2) incidence of TEAEs of special interest (TEAESI) during the overall study period and per treatment cycle.

TEAEs were defined as AEs with onset or worsening at or after the first injection, up to and including the end of study visit, while TEAESIs were defined as TEAEs that were thought to possibly indicate toxin spread.

RESULTS

Baseline Demographics

- In total, 145 subjects were screened and 140 were enrolled.
- • In all three treated areas, more subjects had a severity of severe than had a moderate severity at study baseline.
- A lower percentage of severe baseline ratings and a higher percentage of moderate baseline ratings were reported for cycles 2-4 compared to cycle 1 for all treated areas.

Safety

- During the four-cycle study period, 71.4% of total subjects experienced a TEAE and 17.1% of total subjects experienced a treatment-related TEAE (**Table 1**).

Table 1. Overall summary of treatment emergent adverse events (TEAE)

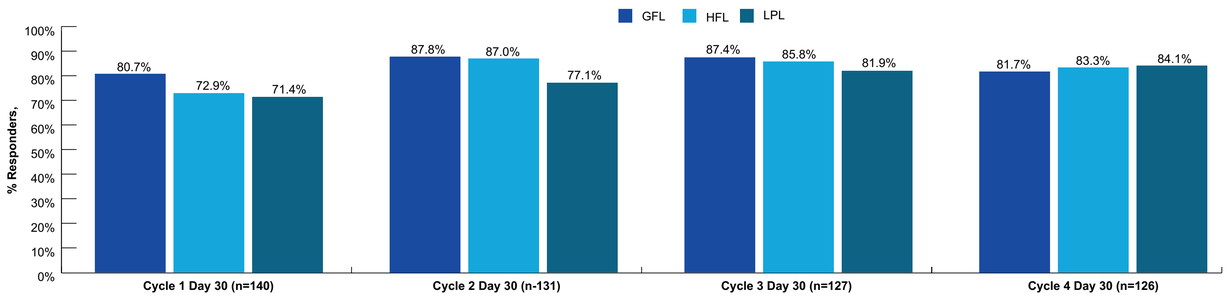
	Overall (N=140)		Cycle 1 (N=140)		Cycle 2 (N=132)		Cycle 3 (N=127)		Cycle 4 (N=126)	
Number (%) of subjects with	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any TEAE	100	(71.4)	55	(39.3)	53	(40.2)	33	(26.0)	23	(18.3)
Any related TEAE	24	(17.1)	18	(12.9)	7	(5.3)	4	(3.1)	2	(1.6)
Any TEAE of special interest	9	(6.4)	5	(3.6)	3	(2.3)	2	(1.6)	0	
Any TEAE of related special interest	6	(4.3)	4	(2.9)	2	(1.5)	1	(0.8)	0	
Any serious TEAE	10	(7.1)	4	(2.9)	2	(1.5)	3	(2.4)	1	(0.8)
Any related serious TEAE	0		0		0		0		0	
Any TEAE leading to discontinuation	4	(2.9)	4	(2.9)	0		0		0	
Any related TEAE leading to discontinuation	0		0		0		0		0	
Any fatal TEAE	0		0		0		0		0	
Any related fatal TEAE	0		0		0		0		0	

- TEAEs occurred most frequently in the system organ class "infections and infestations"; the most common AEs (≥ 3% of subjects in a single treatment cycle) were nasopharyngitis (total: 29.3%; cycles 1 to 4 (%): 7.1, 16.7, 9.4, 3.2, respectively) and headache (total: 10.7%; cycle 1: 7.9%; cycles 2 to 4: <3%).
- TEAESIs were documented in nine subjects (6.4%).
- Over the complete study, 11 serious TEAEs occurred in 10 subjects (7.1%). No serious TEAEs were related to treatment.

Efficacy Measurements

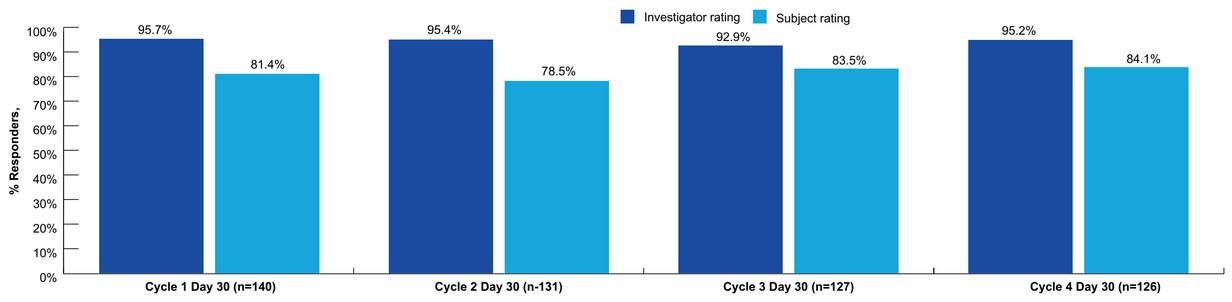
- Investigator-assessed scores of "none" (0) or "mild" (1) on the MAS for GFL, HFL, and LPL at maximum contraction on Day 30 of each treatment cycle demonstrated high treatment response rates, (**Figure 2**). A response rate of greater than 80% was reported for all areas except HFL in cycle 1 (72.9%) and LPL in cycle 1 (71.4) and cycle 2 (77.1%).

Figure 2. Responder rates (score of none [0] or mild [1] at maximum contraction), investigator's rating according to MAS at Day 30, by cycle and treatment area - FAS (full analysis set)



- For the overall appearance of the upper face, subject-assessed and investigator-assessed ratings of "much improved" or "very much improved" on the GICS also demonstrated high response rates. Subject-assessed GICS demonstrated a response rate of greater than 80% of subjects in cycles 1, 3, and 4 and 78.5% of subjects in cycle 2, as detailed in (**Figure 3**) while investigator-assessed GICS demonstrated a response rate of > 90% of subjects in each cycle.

Figure 3. Global Impression of Change Scale (GICS), investigator's and subject's rating — Responder analysis, FAS



Subject Satisfaction

- The percentage of subjects rating satisfaction with overall facial appearance and disappearance of facial lines increased over the four cycles and are detailed in **Table 2** and **Table 3**.

Table 2. Subject's treatment satisfaction with disappearance of facial lines at Day 30, FAS

	Score						
	2 n (%)	1 n (%)	0 n (%)	-1 n (%)	-2 n (%)	Missing n (%)	Total n (%)
Cycle 1	79 (56.4)	51 (36.4)	6 (4.3)	3 (2.1)	1 (0.7)	0	140 (100.0)
Cycle 2	81 (61.4)	42 (31.8)	1 (0.8)	5 (3.8)	1 (0.8)	2 (1.5)	132 (100.0)
Cycle 3	81 (63.8)	44 (34.6)	1 (0.8)	1 (0.8)	0	0	127 (100.0)
Cycle 4	81 (64.3)	41 (32.5)	3 (2.4)	0	1 (0.8)	0	126 (100.0)

n = number of subjects; Total = number of subjects exposed in the respective cycle
+2=very satisfied, +1=somewhat satisfied, 0=neither satisfied nor dissatisfied, -1=somewhat dissatisfied, -2=very dissatisfied

Table 3. Subject's treatment satisfaction with overall facial appearance at Day 30, FAS

	Score						
	2 n (%)	1 n (%)	0 n (%)	-1 n (%)	-2 n (%)	Missing n (%)	Total n (%)
Cycle 1	81 (57.9)	47 (33.6)	7 (5.0)	3 (2.1)	2 (1.4)	0	140 (100.0)
Cycle 2	79 (59.8)	43 (32.6)	4 (3.0)	2 (1.5)	2 (1.5)	2 (1.5)	132 (100.0)
Cycle 3	81 (63.8)	42 (33.1)	2 (1.6)	2 (1.6)	0	0	127 (100.0)
Cycle 4	84 (66.7)	38 (30.2)	3 (2.4)	1 (0.8)	0	0	126 (100.0)

n = number of subjects; Total = number of subjects exposed in the respective cycle
+2=very satisfied, +1=somewhat satisfied, 0=neither satisfied nor dissatisfied, -1=somewhat dissatisfied,-2=very dissatisfied

CONCLUSIONS

- **This study provides strong evidence for the safety and tolerability of repeat-dose treatments with incobotulinumtoxinA in UFL.**
- **No formation of neutralizing antibodies was noted, supporting the assumption that incobotulinumtoxinA can be considered non-immunogenic in aesthetic indications.**
- **Efficacy results showed a high effect in the treatment of GFL, HFL, and LPL alone, as well as for all areas combined, with consistently high responder rates at Day 30. Importantly, aesthetic effects were maintained for up to 120 days.**

References: 1. Bocouture. Summary of Product Characteristics. Frankfurt, Germany: Merz Pharmaceuticals GmbH; 2016; 2. Carruthers A, Carruthers J, Coleman WP III, 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; 39:551-8; 3. 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; 39:891-9; 4. Imhof M, Kühne U. A phase III study of incobotulinumtoxinA in the treatment of glabellar frown lines. *J Clin Aesthet Dermatol* 2011; 4:28-34; 5. Lee JH, Park JH, Lee SK, Han KH, et al. The efficacy and safety of incobotulinumtoxinA in periocular rhytides and masseteric hypertrophy: side by side comparison with onabotulinum toxin A. *J Dermatolog Treat* 2014; 25:326-30; 6. Oliveira de Morais O, Matos Reis-Filho E, Vilela Pereira L, Martins Gomes C, et al. Comparison of four botulinum neurotoxin type A preparations in the treatment of hyperdynamic forehead lines in men: a pilot study. *J Drugs Dermatol* 2012; 11:216-9; 7. Prager W, Wissmüller E, Kollhorst B, Williams S, et al. Comparison of two botulinum toxin type A preparations for treating crow's feet: a split-face, double-blind, proof-of-concept study. *Dermatol Surg* 2010; 36(Suppl 4):2155-60; 8. Sattler G, Callander M, 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):2146-54; 9. Kerscher M, Rzany B, Prager W, Turnbull C, Trevidic P, Inglefield C. 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):1149-57; 10. Trevidic P, Connolly S, Biwer B, Ellers-Lenz B, Harrington L, Kestemont P, Noah E, Sattler G, Weissenberger P, Kerscher M. IncobotulinumtoxinA is an Effective and Well-Tolerated Treatment for Upper Facial Lines: Results from an Open-Label Extension Period of a Phase III Study. *Dermatol Surg*. 2017; 43(10):285-292).

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