EFFICACY AND SAFETY OF INCobotulinumToxina
IN THE COMBINED TREATMENT OF UPPER FACIAL LINES: RESULTS OF THE FIRST PROSPECTIVE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTRE, PHASE III STUDY

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Background

• IncobotulinumtoxinA (XEOMIN Cosmetic™/Xeomin®/Xeomeen®/Bocouture®; botulinum toxin type A, free from complexing proteins) is indicated worldwide for the correction of glabellar frown lines (GFL) and, in Europe, also for the correction of lateral periorbital lines (LPL)
  – Additionally, it has proven efficacy in other aesthetic indications, such as the correction of horizontal forehead lines (HFL)\(^1\)\(^–\)\(^7\)

• Aesthetic practice commonly involves treating combined indications, such as upper facial lines (UFL), i.e. GFL, HFL and LPL

• This study aimed to provide the first placebo-controlled evidence of the efficacy and safety of incobotulinumtoxinA for moderate-to-severe UFL
Methods

• Subjects were identified using the criteria presented in Table 1 and were randomised (2:1) to incobotulinumtoxinA or placebo
• In total, 54–64 U incobotulinumtoxinA were administered (GFL: 20 U; HFL: 10–20 U; LPL: 24 U, i.e. 12 U per eye area) as shown in Figure 1
• Placebo subjects received an equal volume of placebo solution in the same manner
• The study design is presented in Figure 2
Table 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria (main study period*)</th>
<th>Exclusion criteria (main study period*)</th>
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</thead>
<tbody>
<tr>
<td>• Male or female subjects, aged 18 years or older</td>
<td>• Treatment with any BoNT/A in any treatment area in the 6 months before study</td>
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<tr>
<td>• Calculated cut-off score below 0 in evaluation based on the FLQA-k</td>
<td>• Any facial cosmetic procedure in any planned treatment area in the 8 months before study</td>
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<tr>
<td>• Investigator-assessed moderate-to-severe HFL, GFL, and symmetrical LPL at maximum contraction according to MAS (Table 2)</td>
<td>• Any previous insertion of permanent material in any planned treatment area</td>
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<td>• Stable medical condition</td>
<td>• Any facial cosmetic procedure planned for within the study period</td>
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<td></td>
<td>• Very severe HFL, GFL or LPL at maximum contraction, as assessed by the investigator according to the MAS</td>
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<td></td>
<td>• Inability to substantially lessen HFL, GFL, LPL by physically spreading them apart</td>
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<td></td>
<td>• Marked facial asymmetry, eyelid/brow ptosis or a history of facial nerve palsy</td>
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<td>• Any surgery, scars, infection and/or inflammation at the planned injection points</td>
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</tbody>
</table>

*An open-label extension period followed the main period. The poster presents the results of the main period only. BoNT/A, botulinum toxin type A; FLQA-k, Freiburg Life Quality Assessment - ‘Lebensqualität, Haut und Kosmetik’ Questionnaire; GFL, glabellar frown lines; HFL, horizontal forehead lines; LPL, lateral periorbital lines; MAS, Merz Aesthetics Scales.
Table 2. Merz Aesthetics Scales (MAS)

<table>
<thead>
<tr>
<th>Wrinkle severity</th>
<th>Score</th>
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<tbody>
<tr>
<td>No lines</td>
<td>0</td>
</tr>
<tr>
<td>Mild lines</td>
<td>1</td>
</tr>
<tr>
<td>Moderate lines</td>
<td>2</td>
</tr>
<tr>
<td>Severe lines</td>
<td>3</td>
</tr>
<tr>
<td>Very severe lines</td>
<td>4</td>
</tr>
</tbody>
</table>

Figure 1. Division of the total administered dose of incobotulinumtoxinA (54–64 U) across the three aesthetic treatment areas

GFL, glabellar frown lines; HFL, horizontal forehead lines; LPL, lateral periorbital lines; MAS, Merz Aesthetics Scales.
Figure 2. Study design

<table>
<thead>
<tr>
<th>Screening</th>
<th>Double-blind period</th>
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<tbody>
<tr>
<td>Visit 1</td>
<td>Main period</td>
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<tr>
<td>Day -14–3</td>
<td></td>
</tr>
<tr>
<td>Visit 2</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Control visits</td>
<td></td>
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<tr>
<td>Visits 3–6</td>
<td></td>
</tr>
<tr>
<td>Days 8±3, 30±7, 60±7, 90±7</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Randomisation = 2:1</td>
<td></td>
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<tr>
<td>IncobotulinumtoxinA:Placebo</td>
<td></td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td></td>
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<tr>
<td>Injection</td>
<td></td>
</tr>
</tbody>
</table>
Efficacy and safety assessments

• The Merz Aesthetics Scales (MAS) scores were re-assessed on Days 8, 30, 60, 90 and 120.

• The primary efficacy measure was a response of ‘none’ (score = 0) or ‘mild’ (score = 1) according to the investigator’s MAS assessment at maximum contraction on Day 30 for GFL, HFL and LPL individually and also combined as UFL (sum score ≤3).

• The secondary efficacy measures included: (1) either investigator- or subject-assessed MAS scores at rest or maximum contraction for each area at all timepoints, where a response was a ‘none’ or ‘mild’ score; (2) investigator- and subject-assessed responses on Day 30 for the overall appearance of the upper face according to the clinician’s and subject’s Global Impression of Change Scale (GICS).

• Adverse events (AEs) were to be reported from the time of providing each subject with the informed consent form until 120±7 days after the administration of incobotulinumtoxinA or placebo.
Results

• As shown in Figure 3, 156 subjects were treated (incobotulinumtoxinA, n=105; placebo, n=51) and 139 completed the study (incobotulinumtoxinA, n=94; placebo, n=45)

Primary efficacy measure
• Investigator-assessed MAS scores of ‘none’ or ‘mild’ at maximum contraction showed a significant (p<0.0001; hierarchical testing procedure, logistic regression) response of incobotulinumtoxinA vs placebo on Day 30 for GFL, HFL and LPL, individually and for the UFL combination (Figure 4 shows observed cases, full analysis set; FAS)

GFL, glabellar frown lines; HFL, horizontal forehead lines, LPL, lateral periorbital lines; MAS, Merz Aesthetics Scales; UFL, upper facial lines.
Figure 3. Patient flow diagram

Screened 240

Not randomised* 84

IncobotulinumtoxinA

Randomised/treated

105

Discontinued

11

Withdrawal by subject 3

Lost to follow-up 3

Other 5

Placebo

Randomised/treated

51

Discontinued

6

Withdrawal by subject 2

Lost to follow-up 4

*The high rate of screening failures was mainly caused by FLQA-k inclusion criterion failure.

FLQA-k, Freiburg Life Quality Assessment - ‘Lebensqualität, Haut und Kosmetik’ Questionnaire.
Figure 4. Response rates for investigator-assessed scores of ‘none’ (0) or ‘mild’ (1) on the 5-point MAS for GFL, HFL, LPL and a sum score of 3 or lower in the UFL combination at maximum contraction on Day 30 – observed cases, FAS.

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*Score of ‘none’ (0) or ‘mild’ (1); †Sum score of 3 or lower.

P-values derived from a logistic regression model with site and treatment as factors, hierarchical test procedure.

FAS, full analysis set; GFL, glabellar frown lines; HFL, horizontal forehead lines, LPL, lateral periorbital lines; MAS, Merz Aesthetics Scales; UFL, upper facial lines.

**p ≤ 0.0001
Secondary efficacy measures

- At each timepoint, the proportion of subjects with a response (score of ‘none’ or ‘mild’) in all three areas at maximum contraction, based on the investigator’s rating, was significantly higher in the incobotulinumtoxinA group than in the placebo group (Figure 5).
- A greater response was seen at rest, including a notable response to placebo, indicating the difficulty of rating at rest – despite this, a significant effect of incobotulinumtoxinA was seen vs placebo (Figure 6).
- Investigator-assessed and subject-assessed ratings for ‘much improved’ (an increase of 2 points) or ‘very much improved’ (an increase of 3 points) on the GICS were significantly more common in the incobotulinumtoxinA group compared with the placebo group (p<0.0001; Figure 7).

GICS, Global Impression of Change Scale.
Figure 5. Investigator- and subject-assessed MAS scores at maximum contraction (FAS, observed cases).

GFL

Proportion of subjects with investigator-assessed MAS score of 'none' or 'mild' (%)

HFL

Proportion of subjects with self-assessed MAS score of 'none' or 'mild' (%)

LPL

Proportion of subjects with self-assessed MAS score of 'none' or 'mild' (%)

***p<0.0001

**p<0.001

*p<0.05

MAS, Merz Aesthetics Scale.
Figure 6. Investigator- and subject-assessed MAS scores at rest

GFL

Proportion of subjects with investigator-assessed MAS score of 'none' or 'mild' (%)

HFL

Proportion of subjects with investigator-assessed MAS score of 'none' or 'mild' (%)

LPL

Proportion of subjects with investigator-assessed MAS score of 'none' or 'mild' (%)

IncobotulinumtoxinA
Placebo

***p<0.0001
**p<0.001
*p<0.05

MAS, Merz Aesthetics Scale.
Figure 7. Proportion of subjects with investigator- and subject-assessed GICS ratings of ‘much improved’ (an increase of 2 points) or ‘very much improved’ (an increase of 3 points) at Day 30

**86.4%**

**77.7%**

***p<0.0001 compared with placebo

GICS, Global Impression of Change Scale.
Safety

- Treatment-emergent AEs (TEAEs) occurred in 61.9% of subjects in the incobotulinumtoxinA group and 54.9% of subjects in the placebo group.
- Serious TEAEs were reported in four subjects in the incobotulinumtoxinA group: none of them were related to the treatment.
- TEAEs of special interest were documented for three subjects in the incobotulinumtoxinA group: two mild cases of eyelid ptosis, with one case being unilateral and the other being bilateral (n=2; 1.9%) and two cases of dry eyes (n=2; 1.9%).
Conclusions

• IncobotulinumtoxinA is effective for the treatment of UFL (HFL, GFL and LPL) over at least 120 days
• The high response rates reported by the subjects themselves support the investigator-assessed results indicating a high level of treatment success
• IncobotulinumtoxinA was well tolerated for the combined treatment of UFL (HFL, GFL and LPL)

GFL, glabellar frown lines; HFL, horizontal forehead lines, LPL, lateral periorbital lines; UFL, upper facial lines.
References

Acknowledgements

The authors would like to thank the co-investigators: Martina Kerscher, Welf Prager, Patrick Trevidic, Christopher Inglefield and also the following experts: Barbara Ellers-Lenz, (Biostatistician), Moritz Heinz (Biostatistician), Alev Heilbronn (Study Manager) and the Merz study team. Editorial assistance was provided by Scientific Communications & Information, Oxford, UK, and funded by Merz Pharmaceuticals GmbH, Frankfurt, Germany.

Disclosures

Berthold Rzany has acted as a speaker and/or advisor for IPSEN, Kythera, Merz, Q-Med/Galderma, Teoxane and Sinclair. Derek Jones has been consultant and investigator for Merz Pharmaceuticals GmbH and Allergan Inc. Petra Weissenberger is an employee of Merz Pharmaceuticals GmbH.