Safety and efficacy of incobotulinumtoxinA doses up to 800 U in limb spasticity

The TOWER study

ABSTRACT

Objective: To evaluate safety (primary objective) and efficacy of increasing doses (400 U up to 800 U) of incobotulinumtoxinA (Xeomin, Merz Pharmaceuticals GmbH) for patients with limb spasticity.

Methods: In this prospective, single-arm, dose-titration study (NCT01603459), patients (18–80 years) with spasticity due to cerebral causes, who were clinically deemed to require total doses of 800 U incobotulinumtoxinA, received 3 consecutive injection cycles (ICs) with 400 U, 600 U, and 800 U incobotulinumtoxinA, respectively, each followed by 12–16 weeks’ observation. Outcomes included adverse events (AEs), antibody testing, Resistance to Passive Movement Scale (REPAS; based on the Ashworth Scale), and Goal Attainment Scale.

Results: In total, 155 patients were enrolled. IncobotulinumtoxinA dose escalation did not lead to an increased incidence of treatment-related AEs (IC1: 4.5%; IC2: 5.3%; IC3: 2.9%). No treatment-related serious AEs occurred. The most frequent AEs overall were falls (7.7%), nasopharyngitis, arthralgia, and diarrhea (6.5% each). Five patients (3.2%) discontinued due to AEs. No patient developed secondary nonresponse due to neutralizing antibodies. Mean (SD) REPAS score improvements from each injection to 4 weeks postinjection increased throughout the study (IC1: –4.6 [3.9]; IC2: –5.9 [4.2]; IC3: –7.1 [4.8]; p < 0.0001 for all). The proportion of patients achieving ≥3 (of 4) treatment goals also increased (IC1: 25.2%; IC2: 50.7%; IC3: 68.6%).

Conclusion: Escalating incobotulinumtoxinA doses (400 U up to 800 U) did not compromise safety or tolerability, enabled treatment in a greater number of muscles/spasticity patterns, and was associated with increased treatment efficacy, improved muscle tone, and goal attainment.

ClinicalTrials.gov identifier: NCT01603459.

Classification of evidence: This study provides Class IV evidence that, for patients with limb spasticity, escalating incobotulinumtoxinA doses (400 U up to 800 U) increases treatment efficacy without compromising safety or tolerability. Neurology® 2017;88:1321-1328

GLOSSARY

AE = adverse event; AESI = adverse event of special interest; AS = Ashworth Scale; BoNT-A = botulinum toxin type A; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; GAS = Goal Attainment Scale; HDA = hemidiaphragm assay; MIP = maximal inspiratory pressure; REPAS = resistance to passive movement scale; SES = safety evaluation set; TOWER = Titration Study in Lower and Upper Limb Spasticity.

Guidelines recommend botulinum toxin type A (BoNT-A) injections as a treatment option for chronic focal upper and lower limb spasticity.1–4 The efficacy and safety of different BoNT-A formulations for spasticity have been demonstrated for labeled doses.5–11 However, in
multifocal disabling upper or lower limb spasticity, total doses required to fulfill goal achievement and patients’ needs may exceed those currently approved.\textsuperscript{12–17} Therefore, physicians have to prioritize treating patterns whose response will have the greatest effect on overall goal achievement, but a more comprehensive treatment approach may improve outcomes and better support implemented neurorehabilitation programs. A recent survey of physicians treating spasticity with any BoNT-A formulation showed that >75\% of physicians believed that using higher total doses may improve treatment outcomes and patient satisfaction.\textsuperscript{18}

The safe use of higher than labeled BoNT-A doses has been reported,\textsuperscript{19–24} but not studied in large prospective clinical trials with a sufficient sample size. Furthermore, the perceived risk of increased immunogenicity and resistance associated with higher than labeled BoNT-A doses in the long term has not been addressed. In phase III trials, doses ≤400 U incobotulinumtoxinA (Xeomin, Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany) were efficacious and well-tolerated by patients with upper limb spasticity.\textsuperscript{6,8–10} Due to the proven tolerability, lack of secondary nonresponse in these clinical trials, and high purity,\textsuperscript{25} incobotulinumtoxinA is a suitable BoNT-A formulation for a study investigating higher than generally used doses (400 U up to 800 U) in patients with severe upper and lower limb spasticity.

The Titration Study in Lower and Upper Limb Spasticity (TOWER) investigated the safety and efficacy of incobotulinumtoxinA for patients with spasticity due to cerebral lesions deemed to require total body doses of 800 U per injection cycle.

**METHODS** **Study design.** The TOWER study was a prospective, nonrandomized, single-arm, multicenter, open-label, dose-titration study. The primary objective was to investigate safety through assessments of adverse events (AEs) and investigators’ global assessment of tolerability. Key efficacy data (muscle tone and resistance to passive movement scale [REPAS]; Goal Attainment Scale [GAS]; investigators’ and patients’ global assessment of efficacy) are also presented here. This study provides Class IV evidence that, for patients with limb spasticity, escalating incobotulinumtoxinA doses (400 U up to 800 U) increases treatment efficacy without compromising safety or tolerability because patients served as their own controls. The safety and efficacy findings from injection cycle 1, when all patients received treatment at the highest approved dose (400 U), were compared with those of cycles 2 and 3, when higher than labeled doses were administered. In addition, in the absence of a placebo control, all AEs had to be attributed to the drug, a bias against incobotulinumtoxinA. Due to word count limitations, additional efficacy data (including Disability Assessment Scale, Functional Ambulation Classification, and quality of life) will be reported separately.

The study comprised 3 injection cycles with escalating fixed total body doses of incobotulinumtoxinA (50 U/mL in normal saline) injected in the same body side (figure 1): 1. 400 U into the upper limb only, the lower limb only, or both 2. 600 U into the upper limb only, the lower limb only, or both 3. 800 U into both the upper and the lower limbs (maximum dose 600 U per limb)

If a dose of 800 U incobotulinumtoxinA was clinically not indicated or in the case of safety concerns, a lower dose (≤600 U) could be administered as an exception in cycle 3. Individual doses for each clinical pattern were flexible within the range

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**Figure 1** Study design

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection</td>
<td>Baseline</td>
<td>Injection</td>
</tr>
<tr>
<td>Day 0</td>
<td></td>
<td>Week 12-16</td>
</tr>
<tr>
<td>TC2</td>
<td>TC1</td>
<td>TC2</td>
</tr>
<tr>
<td>Week 2</td>
<td>Week 1</td>
<td>Week 2</td>
</tr>
<tr>
<td>Control visit 2</td>
<td>Control visit 2</td>
<td>Control visit 2</td>
</tr>
<tr>
<td>Week 8</td>
<td>Week 20-24</td>
<td>Week 28-36</td>
</tr>
<tr>
<td>TC1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 13-17</td>
<td>Weeks 16-20</td>
<td>Weeks 25-33</td>
</tr>
<tr>
<td>Maximum of 400 U per limb</td>
<td>Maximum of 600 U per limb</td>
<td>Maximum of 600 U per limb</td>
</tr>
<tr>
<td>Total body dose 400 U</td>
<td>Total body dose 600 U</td>
<td>Total body dose 800 U*</td>
</tr>
</tbody>
</table>

*If a dose of 800 U was not justified for clinical or safety reasons, a lower dose of 600–800 U could be administered as an exception. TC = telephone contact; V = visit.
was assessed using the AS.26 All muscle groups on the treated
health care teams identified 2 personal, realistic goals per limb
of study visit by the same investigator for any given patient.
Efficacy assessments.

Muscle tone and REPAS. Muscle tone was assessed using the AS.24
Muscle groups on the treated body side were assessed to obtain the REPAS score for that side,
a validated summary 26-item test (16 items for upper and 10 items for lower limbs).23 Each item is rated from 0 to 4 using the
AS. Here, the 13 REPAS items for the treated body side were evaluated, resulting in a score from 0 to 52. AS and REPAS were assessed at each injection visit, 4-week control visit, and the end of study visit by the same investigator for any given patient.

Goal Attainment Scale. At each injection visit, patients and health care teams identified 2 personal, realistic goals per limb
(1 active and 1 passive allowing for up to 4 goals). Importance
of and difficulty to achieve each goal were also defined. The inves-
tigators rated the GAS score for each cycle at the next injection or
the end of study visit using a 5-point scale ranging from −2 (a lot
less than expected) to +2 (a lot better than expected).28 A score of 0 was the expected level of achievement that should be reached if
the choice of goal had been realistic.

Statistical analysis. In this exploratory trial, no distinction between primary and secondary variables was made. Safety analyses were per-
formed on the safety evaluation set (SES; all patients who received
≥1 dose of study drug). AEs were coded according to the Medical
Dictionary for Regulatory Activities version 15.0. Only treatment-
emergent AEs were analyzed, i.e., AEs with onset/worsening after
the first study drug administration up to and including 16 weeks
after the last inebotulinumtoxinA injection or the end of study
visit, whichever was later. Efficacy analyses were performed in the full
analysis set (identical to the SES in this study) using descriptive
summary statistics. Continuous variables were summarized by
number of nonmissing observations, mean, SD, median, quartiles, minimum, and maximum. For qualitative variables,
absolute and percent frequencies were calculated. Where applicable, exploratory 95% confidence intervals (CIs) were calculated.

RESULTS Patient disposition. The first patient
enrolled on May 24, 2012, and the last patient com-
pleted the study on September 12, 2014. Of 193 pa-
tients screened, 155 were eligible for participation and
received inebotulinumtoxinA; 137 patients
(88.4%) completed the study and 18 (11.6%) discon-
tinued (cycle 1, n = 3; cycle 2, n = 12; cycle 3, n = 3).
Reasons for discontinuation were: consent withdrawn (n
= 7), AEs (n = 5), predefined discontinuation criteria
met (n = 3), loss to follow-up (n = 3), noncompliance
(n = 1), and administrative reasons (n = 1). For some
patients, multiple discontinuation factors were entered.

Patient demographics and baseline characteristics. Pa-
tients’ mean (SD) age was 53.7 (13.1) years; approx-
imately two-thirds were male (67.1%) and most had
spasticity due to stroke (85.2%) or traumatic brain
injury (7.1%) (table 1).

Treatments. Most patients received the scheduled
doses: 91.0% (141/155) received 400 U in cycle 1;
90.8% (138/152) received 600 U in cycle 2; and
82.9% (116/140) received 800 U in cycle 3. In cycle 3,
93.6% (131/140) of patients received a dose of
≥700 U.

Safety (primary study objective). Adverse events. In total,
36.1% (56/155), 37.5% (57/152), and 25.7% (36/
140) of patients reported AEs in cycles 1, 2, and 3,
respectively. There was no increased incidence
of AEs, treatment-related AEs, serious AEs, or
AESIs with increasing doses or repeated injections
(table 2).
The most frequent AEs (reported by \( \geq 5 \) [3.2%] patients overall) are summarized in table 3. The most common treatment-related AEs were pain in the extremity (n [patients] = 3; 1.9% [cycle 1, n = 1; cycle 2, n = 2]), dysphagia (n = 2; 1.3% [cycle 1, n = 1; cycle 3, n = 1]), and muscular weakness (n = 2; 1.3% [cycle 2, n = 1; cycle 3, n = 1]), i.e., weakness clearly exceeding the expected size of treatment effect (the investigator terms were left upper and lower limb weakness and muscle weakness of right leg and both patients had received treatment in the upper and lower limbs). These AEs resolved 4–6 weeks after the injection. All other treatment-related AEs were reported only by 1 patient. No serious AEs were related to incobotulinumtoxinA.

The number of patients who reported AESIs was stable across injection cycles (table 2). The AESIs recorded were dysphagia (n [patients] = 5, 3.2%), constipation (n = 2, 1.3%), dry mouth (n = 1, 0.6%), dysphonia (n = 2, 1.3%), pneumonia aspiration (n = 1, 0.6%), muscular weakness (n = 3, 1.9%), bradycardia (n = 2, 1.3%), diplopia (n = 1, 0.6%), blurred vision (n = 1, 0.6%), and dysarthria (n = 1, 0.6%). These AESIs were considered by investigators to be treatment-related for 2 patients with dysphagia, 1 patient with constipation, 1 patient with dry mouth, 2 patients with muscular weakness, 1 patient with bradycardia, and 1 patient with diplopia.

Investigator’s global assessment of tolerability. The tolerability of incobotulinumtoxinA treatment was rated as very good or good for 96.8% (150/155) of patients in cycle 1, 90.1% (137/152) in cycle 2, and 97.9% (137/140) in cycle 3. In contrast, tolerability was rated as poor for 0% (0/155), 1.3% (2/152), and 0% (0/140) of patients in cycles 1, 2, and 3, respectively.

Pulmonary function. FEV1 values were \( >50\% \) at all assessments, with mean and median values ranging from 82.5% to 85.1%. The mean and median values for MIP ranged from 46.0 to 57.2 cm H2O. No safety signal emerged from either the FEV1 or MIP results.

Anti–botulinum toxin antibodies. The antibody tests showed that no patient developed secondary non-response due to neutralizing antibodies: no patients had positive hemidiaphragm assay (HDA) results by the end of the study, and throughout the study all patients continued to respond clinically to incobotulinumtoxinA treatment, based on changes in REPAS scores (see e-Results for further detail).

Laboratory assessments and vital signs. At baseline and throughout the study, all mean and median laboratory values were within the respective normal ranges. Vital signs remained stable throughout the study (see e-Results for further detail).

Efficacy. Muscle tone and REPAS. Overall, 608 clinical patterns in 155 patients were treated in cycle 1, 743 patterns in 152 patients in cycle 2, and 811 patterns in 140 patients in cycle 3. Improvements \( \geq 1 \) point

<table>
<thead>
<tr>
<th>Table 1 Patient demographics and baseline characteristics</th>
<th>Patients (n = 155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>104 (67.1)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>53.7 (13.1)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>129 (83.2)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Missing</td>
<td>19 (12.3)</td>
</tr>
<tr>
<td>Causes of spasticity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>132 (85.2)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>87 (56.1)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>45 (29.0)</td>
</tr>
<tr>
<td>Other causes</td>
<td>23 (14.6)</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>11 (7.1)</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Other cerebral vascular disorders</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Time since diagnosis of event leading to spasticity, mo, median range</td>
<td></td>
</tr>
<tr>
<td>Right body side (n = 68)</td>
<td>46.5 (3.7-372.8)</td>
</tr>
<tr>
<td>Left body side (n = 81)</td>
<td>61.4 (2.8-428.9)</td>
</tr>
</tbody>
</table>

Table 2 Summary of adverse events by injection cycle

<table>
<thead>
<tr>
<th>Cycle 3</th>
<th>Overall (n = 155)</th>
<th>Cycle 1 (n = 155)</th>
<th>Cycle 2 (n = 152)</th>
<th>All doses (n = 140)</th>
<th>800 U dose (n = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related AE</td>
<td>17 (11.0)</td>
<td>7 (4.5)</td>
<td>8 (5.3)</td>
<td>4 (2.9)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Any AESI</td>
<td>19 (12.3)</td>
<td>6 (3.9)</td>
<td>8 (5.3)</td>
<td>7 (5.0)</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>Any treatment-related AESI*</td>
<td>8 (5.2)</td>
<td>2 (1.3)</td>
<td>4 (2.6)</td>
<td>3 (2.1)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>17 (11.0)</td>
<td>4 (2.6)</td>
<td>11 (7.2)</td>
<td>3 (2.1)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Any treatment-related serious AE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any AE leading to discontinuation*</td>
<td>5 (3.2)</td>
<td>1 (0.6)</td>
<td>4 (2.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any treatment-related AE leading to discontinuation*</td>
<td>4 (2.6)</td>
<td>1 (0.6)</td>
<td>3 (2.0)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AE = adverse event; AESI = adverse event of special interest. Values represent n (%) of patients.

*AEs were classified as AESI based on a predefined list of AEs that could potentially indicate toxin spread, regardless of whether an AE was regarded as treatment-related by the investigator.

*AEs leading to discontinuation were muscular weakness (1 patient, cycle 2, related); diplopia, asthenia, and fatigue (all recorded for 1 patient, cycle 2, all related); cholecystitis (1 patient, cycle 2, not related); dysphagia (1 patient, cycle 1, related); and dry mouth (1 patient, cycle 2, related).
on the AS scale between injection and 4-week control visits were observed in 364 (59.9%) clinical patterns treated in cycle 1, 431 (58.0%) in cycle 2, and 537 (66.2%) in cycle 3.

Mean (SD) [95% CI] improvements in REPAS scores of the treated body side from each injection to the respective 4-week control visit were as follows: cycle 1, –4.6 (3.9) [−5.2, −4.0]; cycle 2, –5.9 (4.2) [−6.6, −5.2]; cycle 3, –7.1 (4.8) [−7.9, −6.3] (p < 0.0001 for all; paired sample t test).

**Goal Attainment Scale.** In cycle 1, 25.2% (39/155; 95% CI [19.0%, 32.5%]) of patients achieved ≥3 (of 4 possible) treatment goals (GAS score ≥0), compared with 50.7% (77/152; 95% CI [42.8%, 58.5%]) in cycle 2 and 68.6% (96/140; 95% CI [60.5%, 75.7%]) in cycle 3 (figure 2A). Overall, the mean (95% CI) number of goals achieved by each patient were 1.81 (1.59, 2.02) in cycle 1 (n = 155), 2.41 (2.18, 2.64) in cycle 2 (n = 152), and 3.03 (2.81, 3.24) in cycle 3 (n = 140).

**Investigators’ and patients’ global assessments of efficacy.**

The percentage of investigators assessments of very good or good increased from 55.5% (86/155; 95% CI [47.6%, 63.1%]) in cycle 1 to 72.4% (110/152; 95% CI [64.8%, 78.9%]) in cycle 2, and 89.3% (125/140; 95% CI [83.1%, 93.4%]) in cycle 3. Similarly, patient assessments of very good or good increased from 59.4% (92/155; 95% CI [51.5%, 66.8%]) in cycle 1 to 63.8% (97/152; 95% CI [55.9%, 71.0%]) in cycle 2, and 76.4% (107/140; 95% CI [68.8%, 82.7%]) in cycle 3 (figure 2B).

**DISCUSSION** Patients with multifocal spasticity may benefit from BoNT-A treatment with higher total doses than currently recommended by the prescribing information of different formulations available.23–25 However, data from prospective clinical trials with a suitable sample size to evaluate higher than labeled doses are lacking. To date, our multicenter study is the largest prospective trial designed to evaluate safety and efficacy of a comprehensive treatment approach with incobotulinumtoxinA for severe and disabling multifocal spasticity. The stepwise escalation of the total dose from 400 U up to 800 U incobotulinumtoxinA allowed physicians to increase doses per muscle within the recommended ranges and the number of muscles and spasticity patterns treated according to patients’ goals and needs.

With escalating total doses, a higher number of spasticity patterns was successfully treated, leading to increasing improvements in muscle tone, indicated by consistent decreases in REPAS score, which is the sum of the AS scores of different muscle groups. Moreover, higher incobotulinumtoxinA doses led to increased rates of goal attainment, with around two-thirds of patients achieving ≥3 of 4 predefined goals with the 600–800 U dose. Furthermore, improved global efficacy was reported by both investigators and patients, reinforcing the clinical relevance of the benefit of increasing incobotulinumtoxinA doses.

Treatment with up to 800 U incobotulinumtoxinA was well-tolerated, confirming previous reports.19,21,23 Importantly, no new safety concerns were identified for higher incobotulinumtoxinA doses of 600–800 U and few patients (n = 5) discontinued due to AEs. With prompt reporting for AEs and extensive active questioning for AESIs throughout the study, our findings revealed no meaningful increase in the incidence of AESIs or AESIs with increasing doses or repeated injections, and no cumulative effects when injected every 12–16 weeks.

A perceived risk associated with higher than labeled BoNT doses is the development of immunogenicity and resistance to treatment. No previously BoNT treatment-naive patient had a positive HDA result for neutralizing antibodies at any point. In addition, while some pretreated patients had transient positive HDA results at various points in the study, this was not associated with nonresponsiveness to incobotulinumtoxinA in any treatment cycle (defined as a lack of response based on REPAS scores), supporting the low immunogenicity of incobotulinumtoxinA.25 Some discrepancy between the identification of neutralizing antibodies and secondary nonresponse has been described previously.26 No lasting immunogenicity was recorded with increasing incobotulinumtoxinA dose across the entire study period (up to 48 weeks) and higher than labeled doses were administered in both cycles 2 and 3. Further studies are required to investigate the effect of long-term treatment with high doses.
doses of incobotulinumtoxinA on the development of immunogenicity. The dose escalation design of the study was chosen primarily to evaluate safety. A strength of this design was that this type of treatment regimen can be considered to be reflective of real-world clinical practice, i.e., physicians would progressively increase dosing based on patient need to optimize therapeutic outcomes. The open-label design and lack of a placebo control are the main limitations of the study design. A placebo arm was not included as BoNT-A injections are considered the standard of care for upper limb spasticity1–4 and the efficacy and tolerability of incobotulinumtoxinA for the treatment of upper limb spasticity at doses up to 400 U have been confirmed in previous clinical trials.6–10 Hence, ethical considerations prohibited the introduction of a placebo arm into this study. To minimize potential bias of patient-rated outcomes, patients were blinded to which dose they were receiving during which cycle.

This study addressed the previously unmet need for prospectively acquired data on the safety and efficacy of treatment with increasing incobotulinumtoxinA doses for patients with chronic upper and lower limb spasticity following brain injury. IncobotulinumtoxinA dose escalation from 400 U up to 800 U enabled treatment of a greater number of muscles and clinical spasticity patterns, resulting in increased improvements of muscle tone, goal attainment, and global efficacy, without compromising patients’ safety or tolerability. Since only incobotulinumtoxinA was investigated, our findings are specific to incobotulinumtoxinA and are not interchangeable with other BoNT formulations.

IncobotulinumtoxinA up to 800 U offers the potential for comprehensive, well-tolerated, and efficacious spasticity treatment of more clinical patterns, which allows greater focus on patients’ needs and goals compared with previously published studies on BoNT-A treatment with lower doses in chronic spasticity.

**AUTHOR CONTRIBUTIONS**

J. Wissel: study concept or design, acquisition of data, study supervision and coordination, analysis or interpretation of data, drafting the manuscript for content. D. Bensmail, J.J. Ferreira: study concept or design, acquisition of data, revising the manuscript for content. F. Molteni, L. Satkunam,
REFERENCES


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