# AbobotulinumtoxinA using 2-mL dilution maintains durable functional improvements across multiple treatment cycles

P2.7

Khashayar Dashtipour[a], Laxman Bahroo[b], Daniel Truong[c], Richard Trosch[d], Pascal Maisonobe[e], James F. Otto[f]

*[a]Loma Linda University School of Medicine, Loma Linda, CA, USA; [b]Georgetown University Hospital Pasquerilla Healthcare Center, Washington, DC, USA; [c]The Parkinson and Movement Disorder Institute, Fountain Valley, CA, USA; [d]Parkinson's and Movement Disorders Center, Farmington Hills, MI, USA; [e]Ipsen Pharma, Boulogne-Billancourt, France; [f]Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ, USA*

## BACKGROUND

- Cervical dystonia (CD), the most common focal dystonia, is a chronic neurological movement disorder characterized by sustained involuntary contractions of the neck muscles, leading to a disabling posture.
  - Prevalence of CD has been estimated to range from 20 to 4,100 cases per million of the population worldwide.[1]
- In the United States (US), abobotulinumtoxinA is approved for CD using 1 mL or 2 mL dilution method .
  - The subsequent approval of the 2 mL dilution method was based on studies conducted in response to feedback obtained from scientific experts and investigators in medical advisory boards and from market research studies that advocated for scientific data supporting a 2 mL dilution method, which reflected real-world off-label clinical practice in the US.
- The efficacy and safety of abobotulinumtoxinA using a 2 mL dilution method was evaluated in a 12-week, phase 3b, multicenter, randomized, double-blind, placebo-controlled trial in adults with CD (NCT01753310).[2]
  - AbobotulinumtoxinA demonstrated significant improvements in symptoms in both toxin-naïve and previously treated patients with a similar safety profile as observed with the 1 mL dilution method.
- Here, we present the results of an open-label extension (OLE) of the 12-week, double-blind study to evaluate the long-term safety and efficacy of repeat treatment cycles of abobotulinumtoxinA using 2 mL dilution method in adults with CD (NCT01753336).

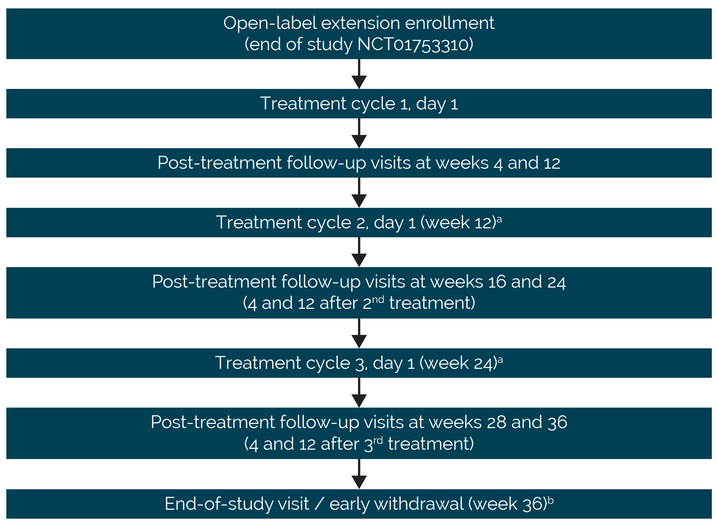
## OBJECTIVE

- To assess the long-term safety and efficacy of repeat treatment cycles of abobotulinumtoxinA using a 2 mL dilution method in adults with CD

## METHODS

- This was a phase 3b, prospective, multicenter, open-label, repeat-treatment study that was an extension to a double-blind, placebo-controlled study that evaluated the efficacy and safety of abobotulinumtoxinA using a 2 mL dilution method in adults with CD.
- The OLE involved up to 3 treatment cycles, with re-treatment occurring every 12 to 16 weeks based on clinical judgment. The study design is outlined in **Figure 1**.
- The baseline visit (day 1 of treatment cycle 1) occurred on the same day as the last visit of the lead-in. Follow-up visits occurred at weeks 4 and 12 of each treatment cycle and at early withdrawal due to any reason.
- Eligible patients included adults (aged ≥18 years) with a primary diagnosis of idiopathic CD who completed the lead-in week 12 visit *or* whose Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score between lead-in week 4 and week 8 was reduced by ≤15% from baseline.
- For OLE cycle 1, patients who were toxin-naïve at lead-in baseline received abobotulinumtoxinA 500 U/2 mL in ≥2 affected neck muscles and non-naïve patients received 250 to 500 U/2 mL based on previous onabotulinumtoxinA dose into previously injected muscles.
- For cycles 2 and 3, dose adjustments were determined by the investigator, with increments and decrements limited to ≤250 U/cycle and maximal total dose limited to 1,000 U/cycle.
- Safety and tolerability were assessed by treatment-emergent adverse events (TEAEs), as well as through examination of vital signs, clinical laboratory assessments, and physical examinations.
  - Adverse events were assigned to a specific cycle based on the first exposure to abobotulinumtoxinA; therefore, patients who received abobotulinumtoxinA in the lead-in study had 4 cycles, whereas placebo-treated patients had 3 cycles.
- Efficacy assessments were based on TWSTRS total and subscale (severity, disability, and pain) scores.
  - Baseline was defined as day 1 of cycle 1 in the OLE.
- All analyses are descriptive in nature and were conducted using the safety population, which included all patients who received ≥1 dose of study treatment and had ≥1 safety record posttreatment.

**Figure 1. Study flow chart**




[a]This visit should occur on the same day as the last visit of the previous treatment cycle. Re-treatment was expected to occur approximately 12–16 weeks after the last treatment; however, the exact timing of treatment was determined by the investigator based on clinical need.
[b]Patients who withdrew from the study early (ie, before week 12 of cycle 3) underwent all procedures required for the week 36 visit.

## RESULTS

### Patients

- A total of 112 patients were enrolled and treated, and 92 (82.1%) completed the week 36 visit (cycle 3, week 12).
- None of the patients were excluded from the safety analysis set; 20 patients (17.9%) withdrew from the study.
  - The reasons for withdrawal were: patient's decision (n=12), lost to follow-up (n=3), investigator's decision (n=2), sponsor's decision (n=2), and other (n=1).
- Demographics and baseline characteristics are described in **Table 1**.
  - Median time since symptom onset was 10 years (range: 0–55).

**Table 1. Demographics and baseline characteristics**

| | Patients (n=112) |
|---|---|
| **Age** (years) | |
| Mean (SD) | 57.2 (11.0) |
| Range | 29–82 |
| **Gender,** n (%) | |
| Male | 42 (37.5%) |
| Female | 70 (62.5%) |
| **BMI** (kg/m²), mean (SD) | 27.0 (4.9) |
| **Race,** n (%) | |
| Caucasian or white | 106 (94.6%) |
| Asian | 3 (2.7%) |
| Black or African American | 2 (1.8%) |
| Multiple | 1 (0.9%) |
| **Ethnicity,** n (%) | |
| Hispanic or Latino | 16 (14.3%) |
| Not Hispanic or Latino | 96 (85.7%) |

BMI, body mass index; SD, standard deviation.

### Safety and tolerability

- The total dose and volume of abobotulinumtoxinA administered by treatment cycle and overall are summarized in **Table 2**.
- Mean total dose increased over treatment cycles, with toxin-naïve patients receiving higher doses on average than did non-naïve patients.

**Table 2. AbobotulinumtoxinA administration by treatment cycle**

| | Treatment Cycle 1 | Treatment Cycle 2 | Treatment Cycle 3 | All Treatment Cycles |
|---|---|---|---|---|
| **All patients** | | | | |
| n | 112 | 97 | 93 | 112 |
| Total dose, administered in Units, mean (SD) | 457.7 (75.3) | 507.1 (130.3) | 527.4 (166.8) | 1,334.8 (476.9) |
| Total dose <500 U, n (%) | 38 (33.9%) | 31 (32.0%) | 30 (32.3%) | |
| Total dose =500 U, n (%) | 74 (66.1%) | 41 (42.3%) | 38 (40.9%) | |
| Total dose >500 U, n (%) | 0 | 25 (25.8%) | 25 (26.9%) | |
| **Toxin-naïve patients** | | | | |
| n | 35 | 31 | 30 | |
| Total dose, administered in Units, mean (SD) | 492.9 (34.2) | 549.5 (114.6) | 596.5 (192.4) | 1,490.9 (468.6) |
| Total dose <500 U, n (%) | 2 (5.7%) | 5 (16.1%) | 5 (16.7%) | |
| Total dose =500 U, n (%) | 33 (94.3%) | 15 (48.4%) | 15 (50.0%) | |
| Total dose >500 U, n (%) | 0 | 11 (35.5%) | 10 (33.3%) | |
| **Non-naïve patients** | | | | |
| n | 77 | 66 | 63 | |
| Total dose, administered in Units, mean (SD) | 441.7 (83.2) | 487.1 (133.2) | 494.5 (143.4) | 1,263.8 (466.5) |
| Total dose <500 U, n (%) | 36 (46.8%) | 26 (39.4%) | 25 (39.7%) | |
| Total dose =500 U, n (%) | 41 (53.2%) | 26 (39.4%) | 23 (36.5%) | |
| Total dose >500 U, n (%) | 0 | 14 (21.2%) | 15 (23.8%) | |

Drug exposure for each cycle was calculated as the sum of all doses within a cycle, across all injection sites. Total cumulative drug exposure was the sum of doses across all treatment cycles. U, Unit.

- A total of 220 TEAEs were reported for 70 patients (62.5%) (**Table 3**).
- The percentages of patients reporting TEAEs in cycles 1, 2, 3, and 4 were 35.7%, 25.9%, 30.2%, and 22.8%, respectively.
- Dysphagia, muscular weakness, and neck pain were the most frequent TEAEs (10.7% each).
- Most TEAEs (n=156) were not considered by the investigators to be treatment-related.
- Seven patients reported 8 serious TEAEs.
  - There were 2 episodes of osteoarthritis and 1 of each of the following: appendicitis, cholecystitis, dysphagia, ischemic colitis, thoracic vertebral fracture, and transient ischemic attack.
  - One serious TEAE, dysphagia, which occurred during treatment cycle 1, was judged to be severe and treatment related. This event occurred in a 58-year-old, Caucasian/white female who had torticollis, laterocollis, and a history of dysphagia at enrollment to the lead-in study.

**Table 3. Summary of safety and tolerability across all treatment cycles**

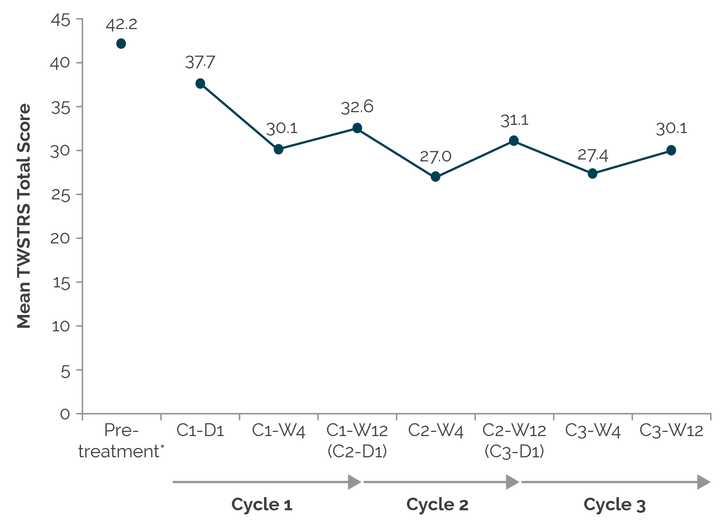
| Patients, n (%) | Patients (n=112) |
|---|---|
| **Any TEAE** | 70 (62.5%) |
| **Intensity** | |
| Severe | 10 (8.9%) |
| Moderate | 38 (33.9%) |
| Mild | 53 (47.3%) |
| **Serious adverse events** | 7 (6.3%) |
| **Relationship** | |
| Related | 33 (29.5%) |
| Not related | 56 (50.0%) |
| Missing | 1 (0.9%) |
| **Leading to study withdrawal** | 0 |
| **Leading to death** | 0 |

TEAE, treatment-emergent adverse event

### Effectiveness

- Mean TWSTRS total score decreased from 37.7 on cycle 1, day 1 to 30.1 at cycle 3, week 12, with a total change from pretreatment baseline of –11.7 at cycle 3, week 12 (**Figure 2**).
- For each cycle, TWSTRS total and subscale scores decreased from day 1 to week 4 and increased between week 4 and week 12, although the week 12 scores remained lower than day 1 scores (**Figures 2** and **3**).
- The mean TWSTRS scores at week 4 and week 12 appeared to decrease for each successive cycle, with no return to baseline (**Figures 2** and **3**).

**Figure 2. Change from baseline in TWSTRS total score**




C, cycle; D, day; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; W, week.
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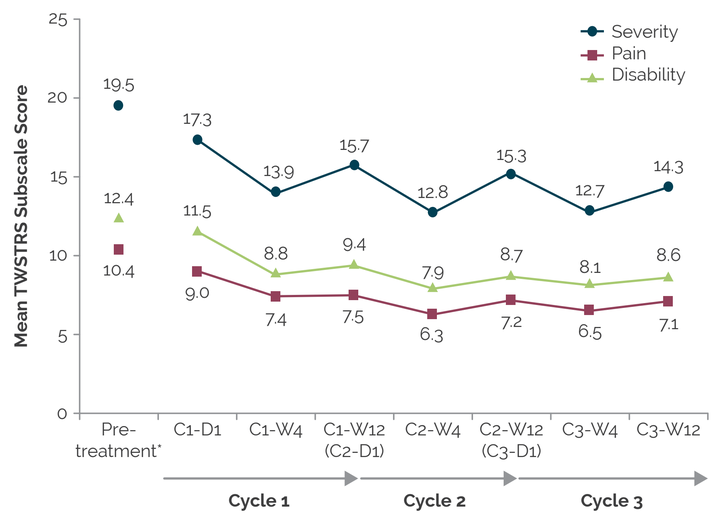


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## CONCLUSIONS

- AbobotulinumtoxinA injected at approved doses using a 2 mL dilution method provided sustained improvements within and across treatment cycles in CD patients.
- Consistent with abobotulinumtoxinA pharmacological effect, 4-week efficacy was numerically higher than 12-week efficacy for each cycle.
- Results were consistent with the lead-in double-blind study and showed that abobotulinumtoxinA using a 2 mL dilution method remained effective and well tolerated over 4 treatment cycles.
- Results with abobotulinumtoxinA using 2 mL dilution method were similar to those with 1 mL dilution method,[3,4] which allows dosing flexibility for clinicians and greater individualized patient care.

## References

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## Acknowledgements

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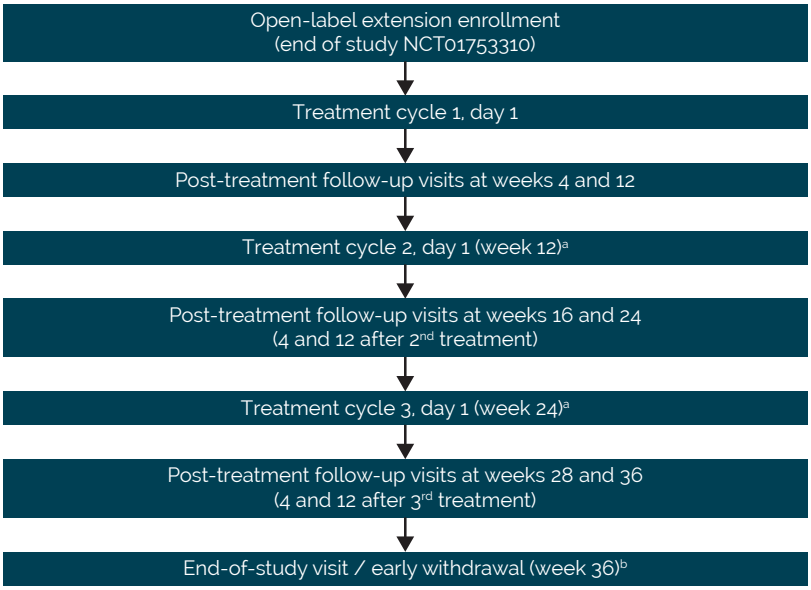


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**Table 3. Summary of safety and tolerability across all treatment cycles**

| Patients, n (%) | Patients (n=112) |
|---|---|
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| **Intensity** | |
| Severe | 10 (8.9%) |
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| Mild | 53 (47.3%) |
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TEAE, treatment-emergent adverse event

## Effectiveness

- Mean TWSTRS total score decreased from 37.7 on cycle 1, day 1 to 30.1 at cycle 3, week 12, with a total change from pretreatment baseline of –11.7 at cycle 3, week 12 (**Figure 2**).
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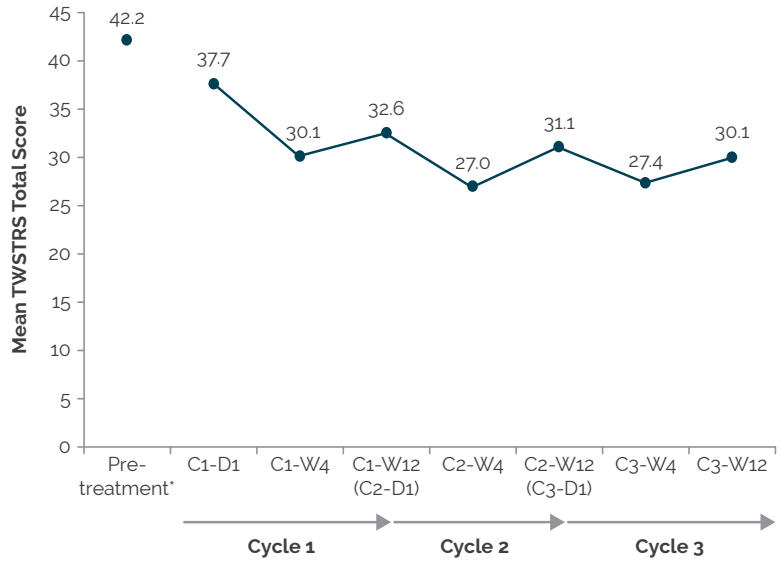


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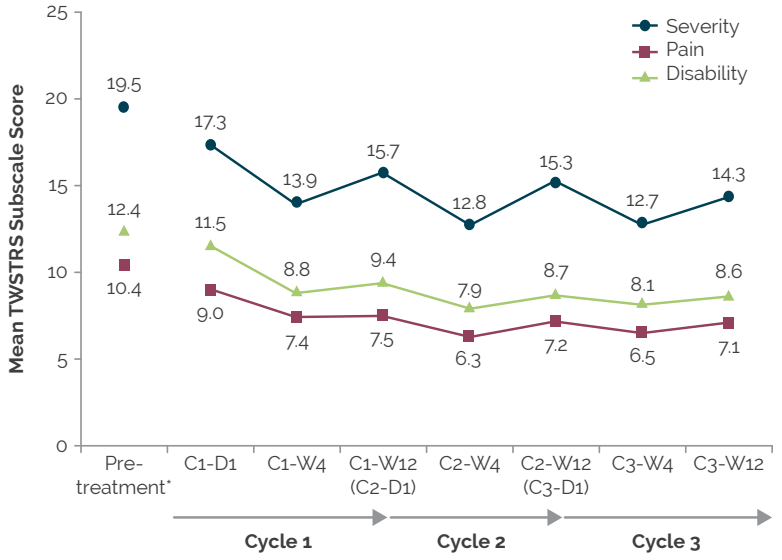


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## CONCLUSIONS

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