DaxibotulinumtoxinA for Injection (RT002)
Investigational Product for the
Treatment of Cervical Dystonia

Interim Results for Phase 2 Open-Label Study

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Disclosures

• Editorial board of *Clinical Neuropharmacology, Sleep Medicine* and *Continuum*

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• DaxibotulinumtoxinA (RT002): novel protein complex comprised of 150Kd botulinumtoxinA molecule and a proprietary peptide designed to be a long-lasting, injectable neurotoxin with no animal-derived components or human albumin.

• RT002 demonstrated 23.6 week duration of effect in treatment of glabellar lines:
  – Phase 2 double blind, active and placebo controlled study (n=268) showed 6-month median duration of $\geq$ 1-point improvement on investigator assessment with RT002 40U (23.6 weeks) vs. onabotulinumtoxinA 20U (18.8 weeks), $p=0.030^*$.  
    * First data presentation at AAD, March 2016

• Currently available treatments for cervical dystonia call for injection of botulinum toxin about every 3 months, or 4 times per year, to provide patients with an improved quality of life.

**Study Objectives**
  – To assess the safety and preliminary efficacy of RT002 in isolated CD
  – To evaluate the duration of effect of RT002 in the treatment of isolated CD
Methods

- 14 participating sites in the US (8 sites with enrolled subjects)
- Isolated CD
  - Either denovo or ≥ 6 months from last injection of any BoNT
  - No significant dystonia except CD
  - Total TWSTRS ≥ 20; Severity ≥ 15
- Injected per clinical practice of injector
  - Number of muscles
  - Dose per muscle (total dose limited by cohort)
  - Use of EMG/ultrasound
- Evaluated at baseline and 2, 4, 6, 9, 12, 16, 20 and 24 weeks
  - Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)
  - Cervical Dystonia Impact Profile (CDIP-58)
  - Clinical Global Impression of Change (CGIC)
  - Patient Global Impression of Change (PGIC)
  - Safety (e.g., adverse events prior to each visit)
Cervical Dystonia (CD) Phase 2 Study Objectives and Study Schema

Dose-Escalation Design

- **RT002** up to 200 U
- **RT002** 200 to 300 U
- **RT002** 300 to 450 U

**Cohort 1** (n=12) Completed 24 Weeks

**Cohort 2** (n=12) Completed 16 Weeks @ IA

**Cohort 3** (n=13) Completed 4 Weeks @ IA

Cohorts enrolled consecutively
DMC review at 4 weeks prior to enrolling next cohort
Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)

- TWSTRS-Total score (0-85) = sum of TWSTRS-Severity, TWSTRS-Disability and TWSTRS-Pain scores \(^1,2\)
  - TWSTRS-Severity score (0-35) – Clinician rated *(weighted sum of 6 items)*
  - TWSTRS-Disability score (0-30) – Patient rated *(sum of 6 items)*
  - TWSTRS-Pain score (0-20) – Patient rated *(weighted sum of 5 items)*

Phase 2 Study of RT002 in isolated CD:

- Primary efficacy endpoint
  - Reduction from baseline in TWSTRS-Total score at Week 4
- Endpoint for duration
  - Maintaining ≥20% benefit as measured by the reduction in TWSTRS-Total score at Week 4.

Results: Subject Disposition

n=56 subjects screened

n=19 screen failures

n=37 subjects enrolled

Cohort 1 (n=12)
Completed Week 4 (n=12)
Subjects expressed the need for retreatment (n=3)
Completed Week 24 (n=9)

Cohort 2 (n=12)
Completed Week 4 (n=12)
Completed at Week 9 due to no improvement at Week 4 (n=1)
Withdrawn by subject (n=1)
Completed Week 16 (n=9)
Withdrawn by subject (n=1)
Completed Week 24 (n=3)
Ongoing (n=5)

Cohort 3 (n=13)
Completed Week 4 (n=13*)
Withdrawn by subject (n=1)
Subjects expressed the need for retreatment (n=1)
Completed Week 24 (n=3)
Ongoing (n=13)

* 2 subjects missed the Week 4 visit
## Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (N=12)</th>
<th>Cohort 2 (N=12)</th>
<th>Cohort 3 (n=13)</th>
<th>All (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (range)</strong></td>
<td>57 (46–74)</td>
<td>52 (32–70)</td>
<td>58 (30–69)</td>
<td>56 (30–74)</td>
</tr>
<tr>
<td><strong>Females, n (%)</strong></td>
<td>11 (92%)</td>
<td>8 (67%)</td>
<td>9 (69%)</td>
<td>28 (76%)</td>
</tr>
<tr>
<td><strong>Caucasians, n (%)</strong></td>
<td>12 (100%)</td>
<td>9 (75%)</td>
<td>11 (85%)</td>
<td>32 (86%)</td>
</tr>
<tr>
<td><strong>Mean CD duration (range)</strong></td>
<td>8.5 (0.4–21.7)</td>
<td>5.1 (0.0–24.1)</td>
<td>9.0 (0.6–23.3)</td>
<td>7.6 (0.0–24.1)</td>
</tr>
<tr>
<td><strong>Prior BoNT treatment</strong></td>
<td>5 (42%)</td>
<td>4 (33%)</td>
<td>6 (46%)</td>
<td>15 (41%)</td>
</tr>
<tr>
<td><strong>Mean RT002 dose, U, (range)</strong></td>
<td>174 (100–200)</td>
<td>229 (200–300)</td>
<td>323 (300–450)</td>
<td>244 (100–450)</td>
</tr>
<tr>
<td><strong>Mean TWSTRS Score:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>43.8</td>
<td>44.9</td>
<td>43.7</td>
<td>44.1</td>
</tr>
<tr>
<td>Severity Score</td>
<td>20.1</td>
<td>21.4</td>
<td>21.8</td>
<td>21.1</td>
</tr>
<tr>
<td>Disability Score</td>
<td>12.8</td>
<td>12.3</td>
<td>11.5</td>
<td>12.2</td>
</tr>
<tr>
<td>Pain Score</td>
<td>11.0</td>
<td>11.2</td>
<td>10.4</td>
<td>10.8</td>
</tr>
</tbody>
</table>
Primary Endpoint:
Reduction in TWSTRS-Total Score at Week 4 by Cohort

Clinically Meaningful Reduction in TWSTRS-Total Score Observed at Week 4 across all 3 Cohorts

Mean Score (+SE)

Baseline | Week 4
---|---
44.3 ± 27.4 | 23.6 ± 32.6 | 26.0 ± 44.0 | 44.9 ± 44.0

All Subjects (n=35) | Cohort 1 (n=12) | Cohort 2 (n=12) | Cohort 3 (n=11*)

* Two subjects currently on study had missing value at Week 4
Primary Endpoint:
Reduction in TWSTRS-Total Score at Week 4 by Cohort

Clinically Meaningful Reduction in TWSTRS-Total Score Observed at Week 4 across all 3 Cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Median Score (Week 4)</th>
<th>Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>43.8</td>
<td>46%</td>
</tr>
<tr>
<td>Cohort 1</td>
<td>23.6</td>
<td>20.2</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>32.6</td>
<td>28%</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>26.0</td>
<td>41%</td>
</tr>
</tbody>
</table>

* Two subjects currently on study had missing value at Week 4
Primary & Secondary Endpoints: Reduction in TWSTRS-Total Score and Subscales at Week 4

Clinically Meaningful Reduction Observed across all 3 TWSTRS Subscales at Week 4

All Subjects with Values at both Baseline and Week 4 (n=35*)
* Excluding 2 subjects in Cohort 3 with a missing value for either Baseline or Week 4
Primary & Secondary Endpoints:
Reduction in TWSTRS-Total Score and Subscales at Week 4

Clinically Meaningful Reduction Observed across all 3 TWSTRS Subscales at Week 4

All Subjects with Values at both Baseline and Week 4 (n=35*)
* Excluding 2 subjects in Cohort 3 with a missing value for either Baseline or Week 4
Secondary Endpoints: Reduction from Baseline in CDIP-58* at Week 4

Meaningful Improvement from Baseline in Patient Rated Quality of Life Observed at Week 4 for all cohorts

* Cervical Dystonia Impact Profile-58 Quality of Life Measure
** Excluding 3 subjects in Cohort 3 with a missing value for at Week 4
Secondary Endpoint: Change from Baseline in TWSTRS-Total Score over Time

Clinically Meaningful Reduction in TWSTRS-Total Score Observed by Week 2 and Maintained to Week 24 for Cohort 1*

Secondary Endpoint: Change from Baseline in TWSTRS-Total Score over Time

Clinically Meaningful Reduction in TWSTRS-Total Score Observed by Week 2 and Maintained to Week 24 for Cohort 1*

Duration of Effect as defined by Weeks in Maintaining ≥ 20% Benefit

Note: Based on observed data only and n’s varied at each time point. Later-enrolled subjects in the second and third cohorts have yet to complete the trial’s 24-week protocol.
# Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Preferred Term (≥ 2 events)</th>
<th>Cohort 1 (N=12)</th>
<th>Cohort 2 (N=12)</th>
<th>Cohort 3 (n=13)</th>
<th>All (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with treatment-related AEs, n (%)</td>
<td>6 (50%)</td>
<td>5 (41.7%)</td>
<td>2 (15.4%)</td>
<td>13 (35.1%)</td>
</tr>
<tr>
<td>Total number of Treatment-related AEs*</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1 (8.3%)</td>
<td>2 (16.7%)</td>
<td>1 (7.7%)</td>
<td>4 (10.8%)†</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>2 (16.7%)</td>
<td>0</td>
<td>1 (7.7%)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>0</td>
<td>1 (8.3%)</td>
<td>1 (7.7%)</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Muscle tightness</td>
<td>0</td>
<td>1 (8.3%)</td>
<td>1 (7.7%)</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Muscular weakness (Neck)</td>
<td>2 (16.7%)</td>
<td>0</td>
<td>0</td>
<td>2 (5.4%)‡</td>
</tr>
</tbody>
</table>

* Including AEs in only 1 event (e.g., Cohort 1: Injection site bruising, and neck pain [severe]; Cohort 2: Fatigue, Muscle spasms, and Trismus)

† All events mild in severity
‡1 mild, 1 moderate in severity
Efficacy Summary

• RT002 demonstrated an improvement in TWSTRS-Total Score, with a mean reduction from baseline of 16.8 (or 38%) for all subjects at Week 4
  • Clinically meaningful reduction at Week 4 also observed across all three TWSTRS Subscales: Severity, Disability, and Pain

• CDIP-58: A meaningful improvement from baseline was observed on CDIP-58 quality of life measure at Week 4 in all 3 cohorts, with benefit maintained in Cohort 1 through Week 24

• Duration of Effect: For Cohort 1, which completed the 24 week observation period, median duration of effect, defined as subjects maintaining at least 20% of treatment benefit in TWSTRS-Total score, was > 24 weeks

• Clinician Global Impression of Change: At least 70% of subjects in Cohorts 1 and 2 demonstrated improvement on CGIC at Week 16; majority of Cohort 1 subjects maintained an improvement in CD symptoms through Week 24
Safety Summary

RT002 appeared to be generally safe and well tolerated in all 3 cohorts with an average follow-up time of 14.4 weeks

• No serious adverse events (AEs) were observed

• All AE’s were mild to moderate, except for a case of severe neck pain (onset at day 10, duration 2 days)
  – Most common treatment-related AE’s included dysphagia (10.8%), injection site erythema (8.1%), injection site pain (5.4%), muscle tightness (5.4%) and muscular weakness (5.4%)

• No increase in treatment-related AE’s occurred upon dose escalation
Acknowledgement

• Patients who participated

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  – Daniel Truong, MD, The Parkinson's and Movement Disorder Institute
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