Abstract #1180:

A PHASE 2, OPEN-LABEL, DOSE-ESCALATING STUDY TO EVALUATE THE SAFETY AND PRELIMINARY EFFICACY OF DAXIBOTULINUMTOXINA FOR INJECTION (RT002) IN ISOLATED CERVICAL DYSTONIA

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Introduction

- Isolated cervical dystonia (CD) is a chronic neurologic disorder characterized by involuntary patterned contractions of cervical musculature resulting in abnormal movements or postural changes of the head, neck, and shoulders.

- Currently available treatments for CD call for injection of botulinum toxin (BoNT) about every 3-4 months, or 3-4 times per year.

- DaxibotulinumtoxinA for Injection (RT002), a neuromodulator currently in clinical development, is comprised of a 150 kDa BoNT-A molecule and a proprietary peptide, with no animal-derived components or human serum albumin (HSA).

- Study Objectives:
  - To assess the safety and preliminary efficacy of RT002 for Injection in subjects with isolated CD
  - To evaluate the duration of effect of RT002 for Injection in the treatment of isolated CD
# Dose-Escalating Study Design and Subject Disposition

Patients with Moderate to Severe CD* (n=37) from 8 US Sites

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose Range</th>
<th>Subjects</th>
<th>Week 4</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>200 up to 200 U</td>
<td>n=12</td>
<td>n=12</td>
<td>n=9‡</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>200 to 300 U</td>
<td>n=12</td>
<td>n=12</td>
<td>n=7‡</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>300 to 450 U</td>
<td>n=13†</td>
<td>n=13†</td>
<td>n=9‡</td>
</tr>
</tbody>
</table>

Subjects were evaluated at 2-4 week intervals for 24-36 weeks or until loss of benefit.

*TWSTRS-Total ≥ 20, TWSTRS-Severity ≥ 15, and treatment-naïve or no BoNT within last 6 months.
†Two subjects missed the Week 4 visit. ‡Met/exceeded Target-TWSTRS at Week 24 for n=1 in Cohort 1 and n=2 in Cohort 2; at Week 20 for n=2 in Cohort 2; at Week 6 for n=1 in Cohort 3. €Added in the protocol as of January 2017. £Completed Week 36.  $Ongoing.

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RT002 is an Investigational Product
Subject Distribution by Dose

- **Low Dose Group**
  - 100U - 240U
  - n=21

- **High Dose Group**
  - 300U - 450U
  - n=16

Cohort 1 (n=12)
Cohort 2 (n=12)
Cohort 3 (n=13)
### Demographics and Baseline Characteristics
#### By Dose Group

<table>
<thead>
<tr>
<th></th>
<th>Group A 100-240 U (n=21)</th>
<th>Group B 300-450 U (n=16)</th>
<th>All (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females, n (%)</td>
<td>18 (86%)</td>
<td>10 (63%)</td>
<td>28 (76%)</td>
</tr>
<tr>
<td>Caucasians, n (%)</td>
<td>18 (86%)</td>
<td>14 (88%)</td>
<td>32 (86%)</td>
</tr>
<tr>
<td>Mean/Median CD duration (yrs) [range]</td>
<td>7.3/4.8 [0.02–24.1]</td>
<td>7.9/7.2 [0.02–23.3]</td>
<td>7.6/4.9 [0.0–24.1]</td>
</tr>
<tr>
<td>Prior treatment with BoNT</td>
<td>9 (43%)</td>
<td>8 (50%)*</td>
<td>17 (46%)</td>
</tr>
<tr>
<td>Mean RT002 dose, U</td>
<td>188</td>
<td>319</td>
<td>244</td>
</tr>
<tr>
<td>Mean TWSTRS Score:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>44.4</td>
<td>43.8</td>
<td>44.1</td>
</tr>
<tr>
<td>Severity Score</td>
<td>20.5</td>
<td>21.9</td>
<td>21.1</td>
</tr>
<tr>
<td>Disability Score</td>
<td>12.6</td>
<td>11.6</td>
<td>12.2</td>
</tr>
<tr>
<td>Pain Score</td>
<td>11.3</td>
<td>10.3</td>
<td>10.8</td>
</tr>
</tbody>
</table>

*Three subjects received RT002 in Cohort 1 or 2, and re-enrolled to Cohort 3.
Clinically meaningful reduction in TWSTRS-Total Score of 34% for all subjects beginning at Week 2, with the majority of this benefit maintained through Week 24 in both dose groups.
Clinically meaningful reduction in TWSTRS-Severity Score of 34% for all subjects beginning at Week 2, with the majority of this benefit maintained through Week 24 in both dose groups.
Reduction in TWSTRS-Disability Over Time
By Dose Group

Clinically meaningful reduction in TWSTRS-Disability Score of 35% for all subjects beginning at Week 2, with the majority of this benefit maintained through Week 24 in both dose groups.

Mean Change from Baseline Score

Weeks

0 2 4 6 9 12 16 20 24

100-240U (n=21)
300-450U (n=16)
All Subjects (n=37)
Clinically meaningful reduction in TWSTRS-Pain Score of 34% for all subjects beginning at Week 2, with the majority of this benefit maintained through Week 24 in both dose groups.
Duration of Effect
Defined by % Subjects Maintaining ≥ 20% of Treatment Benefit*

*Of subjects with Improvement at Week 4. Withdrawals due to need for retreatment are considered as events. Treatment benefit defined as the reduction in TWSTRS-Total score at Week 4.
97% of all subjects on CGIC† and 83% of all subjects on PGIC †† experienced an improvement in CD signs and symptoms (Score ≥ 1) at Week 4.

*Two subjects missed Week 4 visit. †Clinician Global Impression of Change; ††Patient Global Impression of Change
Quality of Life: Reduction in CDIP-58* Score Over Time
By Dose Group

Clinically meaningful reduction of 37% in CDIP-58 Score observed at Week 6 for all subjects, with the majority of this benefit maintained through Week 24.

* Cervical Dystonia Impact Profile-58 Quality of Life Measure
A clinically meaningful reduction in TWSTRS-Total Score of 37-41% was observed at Week 4, with the majority of this benefit maintained through Week 24 regardless of prior BoNT treatment.
• **Duration of Effect of > 24 Weeks:** Median duration of effect, defined as subjects maintaining ≥ 20% of the Week 4 treatment benefit (Target TWSTRS Score), was > 24 Weeks for both dose groups (Group A: 100-240U and Group B: 300-450U).

• **Improvement in Cervical Dystonia Signs and Symptoms:** A clinically significant mean reduction from baseline in the TWSTRS-Total Score of 16.8 (or 38%) was observed at Week 4 across all subjects.
  
  • Therapeutic benefit peaked at Week 6 with 50% mean reduction from baseline, and was maintained at ≥ 30% through Week 24.
  
  • Clinically meaningful reductions in TWSTRS-Severity, -Disability and -Pain Subscales were consistent and also observed at all time points.

• **Quality of Life:** Meaningful reduction in CDIP-58 score of 37% (mean reduction of 18.1) was observed at Week 6, the majority of which was maintained (26%, mean reduction of 12.6) through Week 24 across all subjects.

• A clinically meaningful improvement in TWSTRS-Total Score of ≥ 37% was observed at Week 4 regardless of whether subjects had previously received BoNT treatment.
Safety Summary

• RT002 appeared to be safe and generally well tolerated in both dose groups through Week 24, with no increase in treatment-emergent adverse events (TEAEs) upon dose escalation. All except one TEAE were mild or moderate in severity and no serious AEs were reported.

• Total of 22 treatment-related AEs in 13 of 37 subjects (35%) were reported and all resolved.
  • Reported in ≥2 cases included: dysphagia (14%), injection site erythema (8%), injection site bruising (5%), injection site pain (5%), muscle tightness (5%), and muscle weakness (5%).

• Treatment-related AEs of special interest had similar or lower incidence rates vs. prior BoNT-A studies.
  • Dysphagia: 14% (5/37; all mild); average duration 35 days.
  • Muscular weakness: 5% (2/37, 1 mild, 1 moderate), both local.
  • Neck pain: 3% (1/37; only severe TEAE reported), duration of 2 days.