Efficacy, Duration of Effect and Safety of DaxibotulinumtoxinA for Injection, to Treat Glabellar Lines
The Phase 2 BELMONT Study

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Financial Disclosure

• SY to Complete
BELMONT Study Design

**Objectives:**

- To determine the safety and efficacy of a single treatment of DaxibotulinumtoxinA for Injection (RT002) at three dosage levels for the treatment of glabellar lines versus OnabotulinumtoxinA or Placebo
- To assess the duration of effect of a single treatment of DaxibotulinumtoxinA at three dosage levels versus OnabotulinumtoxinA or Placebo

**Study Design:** Phase 2, Randomized, Double-Blind, Dose Ranging, Active and Placebo Controlled, Multi-Center Study conducted at 9 Canadian sites

N=268 subjects moderate/severe glabellar lines

Randomization

1:1:1:1:1

- Placebo (n=54)
- RT002* 20U (n=54)
- RT002 40U (n=53)
- RT002 60U (n=53)
- Onabot** 20U (n=54)

Follow Up for 24-36 weeks

- Visits at 2, 4, 8, 12, 16, 20 and 24 weeks.
- Continued at 28, 32, and 36 or until GL severity returns to baseline

*RT002 = DaxibotulinumtoxinA for injection (an investigational product)
**Onabot = OnabotulinumtoxinA, BOTOX®
Study Population & Wrinkle Scales
Subjects with moderate to severe glabellar lines

- At entry, subjects required to have **moderate or severe** glabellar lines (GL) as assessed by the Investigator and subject
  - Investigator Global Assessment-Facial Wrinkle Severity (IGA-FWS)
    - **IGA-FWS**
      | Rating Score | Facial Wrinkle Severity |
      |--------------|-------------------------|
      | 0            | None                    |
      | 1            | Mild                    |
      | 2            | Moderate                |
      | 3            | Severe                  |
    - Subject’s assessment of Patient Facial Wrinkle Severity (PFWS)
      - **PFWS**
        | Rating Score | Wrinkle Severity       | Description               |
        |--------------|------------------------|---------------------------|
        | 0            | None                   | No wrinkles               |
        | 1            | Mild                   | Very shallow wrinkles     |
        | 2            | Moderate               | Moderate wrinkles         |
        | 3            | Severe                 | Deep wrinkles             |

- Global Aesthetic Improvement Scale (GAIS) by Investigator and Subject also used as efficacy outcome measures

  - **Investigator and Subject GAIS**
    | Rating Score | Wrinkle Improvement       |
    |--------------|---------------------------|
    | -3          | Very Much Worse           |
    | -2          | Much Worse                |
    | -1          | Worse                     |
    | 0           | No Change                 |
    | 1           | Improved                  |
    | 2           | Much Improved             |
    | 3           | Very Much Improved        |
Study Assessments

Efficacy evaluations versus baseline

• Every 4 weeks for up to 36 weeks using Investigator Global Assessment-Facial Wrinkle Severity (IGA-FWS)
• All subjects were followed for at least 24 weeks

Primary Efficacy Assessments

• ≥ 1-point improvement on IGA-FWS
• Duration of Response

Secondary Efficacy Assessments

• Investigator Frown Wrinkle Severity (IGA-FWS) Scale
• Investigator/Subject Global Aesthetic Improvement Scale (GAIS)
• Patient Frown Wrinkle Severity (PFWS) Scale
## Demographics & Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=54)</th>
<th>RT002 20U (N=54)</th>
<th>RT002 40U (N=53)</th>
<th>RT002 60U (N=53)</th>
<th>Onabot 20U (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>49.1 (32 to 64)</td>
<td>49.0 (30 to 64)</td>
<td>49.9 (30 to 63)</td>
<td>47.5 (30 to 64)</td>
<td>50.0 (36 to 63)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>9 (16.7%)</td>
<td>5 (9.3%)</td>
<td>7 (13.2%)</td>
<td>11 (20.8%)</td>
<td>6 (11.1%)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>45 (83.3%)</td>
<td>49 (90.7%)</td>
<td>46 (86.8%)</td>
<td>42 (79.2%)</td>
<td>48 (88.9%)</td>
</tr>
<tr>
<td><strong>Race: White</strong></td>
<td>46 (85.2%)</td>
<td>47 (87.0%)</td>
<td>50 (94.3%)</td>
<td>48 (90.6%)</td>
<td>47 (87.0%)</td>
</tr>
<tr>
<td><strong>IGA-FWS: moderate</strong></td>
<td>34 (63.0%)</td>
<td>34 (63.0%)</td>
<td>35 (66.0%)</td>
<td>30 (56.6%)</td>
<td>31 (57.4%)</td>
</tr>
<tr>
<td><strong>IGA-FWS: severe</strong></td>
<td>20 (37.0%)</td>
<td>20 (37.0%)</td>
<td>18 (34.0%)</td>
<td>23 (43.4%)</td>
<td>23 (42.6%)</td>
</tr>
<tr>
<td><strong>PFWS: moderate</strong></td>
<td>36 (66.7%)</td>
<td>36 (66.7%)</td>
<td>33 (62.3%)</td>
<td>37 (69.8%)</td>
<td>29 (53.7%)</td>
</tr>
<tr>
<td><strong>PFWS: severe</strong></td>
<td>18 (33.3%)</td>
<td>18 (33.3%)</td>
<td>20 (37.7%)</td>
<td>16 (30.2%)</td>
<td>25 (46.3%)</td>
</tr>
</tbody>
</table>

DaxibotulinumtoxinA for Injection (RT002) is an investigational product.
Per Protocol Population for Efficacy Analyses

- 77 subjects excluded from Per Protocol (PP) population
  - 0 subjects violated inclusion/exclusion criteria
  - 2 subjects received incorrect dose/treatment
  - 14 subjects used a prohibited medication
  - 5\* subjects did not attend at the primary endpoint, Week 24 visit
  - 57 subjects attended the Week 24 visit off schedule (+/- 5 days)
    - Similar across treatment groups (12, 14, 10, 10, 11)
    - Not unusual for long term studies

\* Subjects may have more than one reason for exclusion
All Three Doses of RT002 had Higher Rate of Response vs. Onabot 20U on ≥ 1 Point Improvement in IGA-FWS

% with ≥ 1 Point Improvement (IGA-FWS)

Weeks

RT002 60U (n=41)
RT002 40U (n=39)
RT002 20U (n=34)
Onabot 20U (n=42)
Placebo (n=35)

* / *: p < 0.05 vs Onabot 20U

DaxibotulinumtoxinA for Injection (RT002) is an investigational product
Both RT002 20U and 40U Resulted in Higher Rate of Response vs. Onabot 20U on None/Mild Wrinkle Severity by IGA-FWS

Compared to Onabot 20U,
- RT002 40U had higher rate of response at all time points through 24 Weeks
- RT002 20U had higher rate of response at all time points through 20 Weeks

<table>
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</tr>
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<tr>
<td>RT002 40U (N=39)</td>
<td>97%</td>
<td>97%</td>
<td>97%*</td>
<td>85%</td>
<td>67%**</td>
<td>46%*</td>
<td>31%*</td>
</tr>
<tr>
<td>RT002 20U (N=34)</td>
<td>97%</td>
<td>97%</td>
<td>88%</td>
<td>82%</td>
<td>53%*</td>
<td>35%</td>
<td>12%</td>
</tr>
<tr>
<td>Onabot 20U (N=42)</td>
<td>95%</td>
<td>93%</td>
<td>83%</td>
<td>69%</td>
<td>32%</td>
<td>22%</td>
<td>12%</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.005  (vs Onabot 20U)
Longer Duration of Response Observed for all Three Doses of RT002 vs. Onabot 20U: ≥ 1 Point Improvement in IGA-FWS

Duration of Response Kaplan-Meier Curve

≥ 1 Point Improvement on IGA-FWS

p = 0.030* for RT002 40U vs. Onabot 20U

* Log-rank test

PP Population

DaxibotulinumtoxinA for Injection (RT002) is an investigational product
RT002 40U and 60U had Higher Rate of Response vs. Onabot 20U over Time on ≥ 1 Point Improvement in PFWS

![Graph showing percentage with ≥ 1 Point Improvement over time.](image)

- RT002 60U (n=41)
- RT002 40U (n=39)
- RT002 20U (n=34)
- Onabot 20U (n=42)
- Placebo (n=35)

% with ≥ 1 Point Improvement (PFWS)

- Weeks: 0, 4, 8, 12, 16, 20, 24

* / **: p < 0.05 vs Onabot 20U

PP Population

DaxibotulinumtoxinA for Injection (RT002) is an investigational product
All Three Doses of RT002 had Higher Rate of Response vs. Onabot 20U on Investigator GAIS ≥ +1

% with GAIS ≥ 1 (Investigator)

- RT002 60U (n=41)
- RT002 40U (n=39)
- RT002 20U (n=34)
- Onabot 20U (n=42)
- Placebo (n=35)

Weeks

*/*: p < 0.05 vs Onabot 20U

DaxibotulinumtoxinA for Injection (RT002) is an investigational product
Example 2-Point Improvement by IGA-FWS & PFWS at Week 4; 1-Point Sustained Duration of Effect through Week 24

DaxibotulinumtoxinA 40 U
MAXIMUM FROWN

Pre-treatment

Week 4

Week 24

Baseline Scores:
IGA-FWS: 3
PFWS: 3

Week 4 Scores:
IGA-FWS: 0
PFWS: 0

Week 24 Scores:
IGA-FWS: 2
PFWS: 2

Photo ID RT002 003-025

DaxibotulinumtoxinA for Injection is an investigational product
Example 2-Point Improvement by IGA-FWS & PFWS at Week 4; 2-Point Sustained Duration of Effect through Week 24

DaxibotulinumtoxinA 40 U
MAXIMUM FROWN

Pre-treatment

Week 4

Week 24

Baseline Scores:
IGA-FWS: 2
PFWS: 2

Week 4 Scores:
IGA-FWS: 0
PFWS: 0

Week 24 Scores:
IGA-FWS: 0
PFWS: 0

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DaxibotulinumtoxinA for Injection is an investigational product
**Objective:** To compare the degree and duration of effect of onabotulinumtoxinA 10, 20, 30 and 40U in the treatment of glabellar lines

**Double-Blinded Phase**
- Randomization: 1:1:1:1
- BTX-A 10 U (n=20)
- BTX-A 20 U (n=20)
- BTX-A 30 U (n=20)
- BTX-A 40 U (n=20)

**Open-Label Extension (OLE)**
- Rollover*
  - BTX-A 30 U (n=40)

**Single treatment 1-year follow-up**
- *The first 40 subjects completing the double-blind phase.

Carruthers A, Carruthers J, Said S., Division of Dermatology, University of British Columbia, Vancouver, B.C., Canada.
Double-Blind, Randomized, Parallel Group, Dose-Ranging Study of Botulinum Toxin Type A in the Treatment of Glabellar Lines, 2005
Carruthers Study: No difference in Duration or Response Rates Observed Between Top 3 Onabot Doses (20U, 30U and 40) at Any Time Point

Carruthers A, Carruthers J, Said S., Division of Dermatology, University of British Columbia, Vancouver, B.C., Canada. Double-Blind, Randomized, Parallel Group, Dose-Ranging Study of Botulinum Toxin Type A in the Treatment of Glabellar Lines, 2005
Efficacy
- No difference in durability among top 3 doses
- No difference in response rates at any of the time points among top 3 doses (20U, 30U and 40U)

Safety
- Serious/Severe AEs: elective surgery (3) and atypical pneumonia (1); None related
- Eyebrow ptosis: 1 each in 20U and 40U; and 1 in OLE
- Other treatment-related AEs included Headache, Migraine, Tension/Pain upper nose, Tension on forehead/above the eye
- No significant differences among the four groups (double-blinded phase) in the number of AEs reported
Summary of Safety

• All five groups exhibited an excellent overall safety profile
• No serious adverse events
• Adverse events were predominantly localized, transient and mild in severity and typically injection related (erythema and pain)
• Most common adverse events by subject

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<tbody>
<tr>
<td>Headache</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Erythema</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

• DaxibotulinumtoxinA dosed at 20U and 40U exhibited NO EYELID PTOSIS
  – OnabotulinumtoxinA 20U had ptosis in 1 subject (1.9%): duration of 51 days
  – DaxibotulinumtoxinA at 60U had ptosis in 4 subjects (7.5%): mean duration of 47 days

DaxibotulinumtoxinA for Injection (RT002) is an investigational product
**Summary: RT002 Demonstrates Higher Response Rates Over Time vs. Onabot 20U with 24 Week Duration of Effect**

- **Response Rate:** RT002 40U had a higher response rate vs. Onabot 20U on ≥ 1 point improvement on IGA-FWS beginning at Week 2 through Week 24

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<td>RT002 40U</td>
<td>100%</td>
<td>100%</td>
<td>100%*</td>
<td>95%</td>
<td>79%*</td>
<td>59%*</td>
<td>36%</td>
</tr>
<tr>
<td>Onabot 20U</td>
<td>98%</td>
<td>95%</td>
<td>90%</td>
<td>86%</td>
<td>54%</td>
<td>32%</td>
<td>19%</td>
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- Consistently, RT002 40U had a higher response rate vs. Onabot 20U over time through 24 weeks on None/Mild wrinkle severity in IGA-FWS
- Similar clinically meaningful response rates observed with RT002 on GAIS & PFWS

- **Duration:** 6-month median duration of ≥ 1 point improvement on IGA-FWS with RT002 40U, with 23.6 weeks vs. 18.8 weeks for onabot 20U (p=0.030)

- **Safety:**
  - RT002 40U appears well-tolerated with no ptosis
  - RT002 40U had the most favorable risk-benefit profile in the study and was selected for the Phase 3 pivotal program
Phase 3 Program includes 2 Pivotal Trials and Open Label Safety Study

• **Design of Pivotal Trials**: two randomized, double-blind, placebo-controlled studies (n=300 each) to evaluate the safety and efficacy of a single treatment of RT002 40U for the treatment of moderate to severe glabellar lines at sites in US & Canada

  • **Primary efficacy endpoint**: composite of the proportion of subjects who achieve a score of 0 or 1 (*none or mild*) and a ≥2 point improvement from baseline in glabellar line severity on the IGA-FWS and PFWS scales, at maximum contraction (frown), at Week 4.

• **Open-label Safety Study**: designed to evaluate long-term safety of RT002 for the treatment of moderate to severe glabellar lines following single and repeat treatment administration at sites in US and Canada (n=1500)

  Topline Phase 3 results expected in Q4 2017