

**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

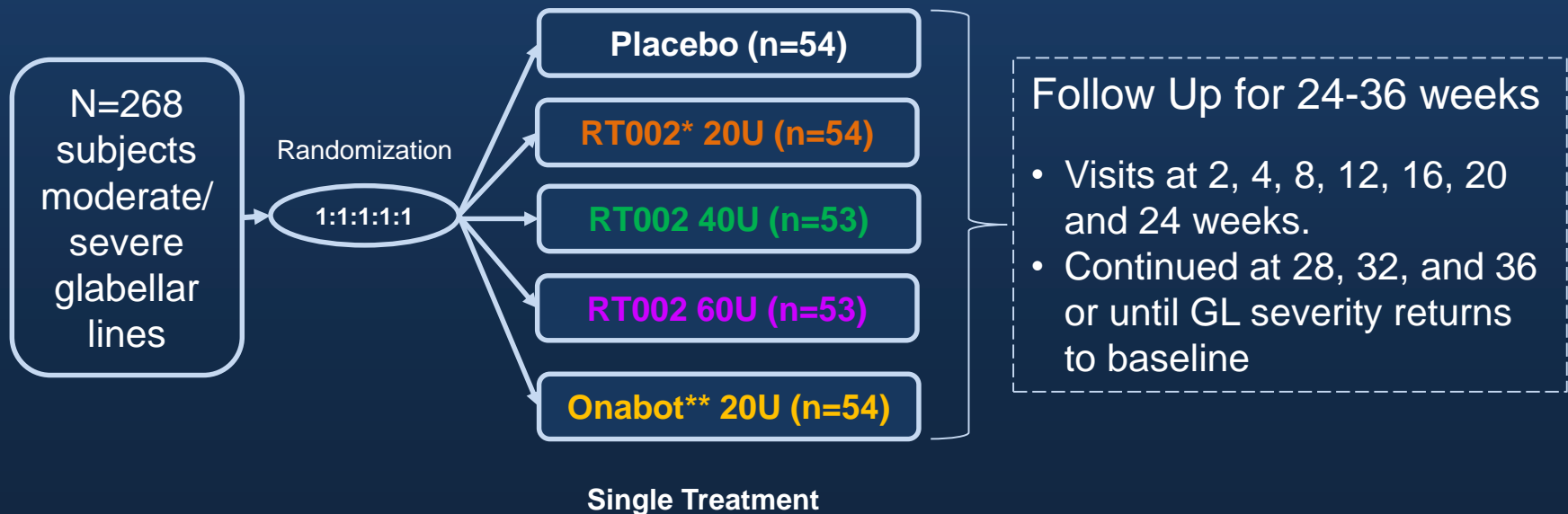
- SY to Complete

# 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



\*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	<b>Moderate</b>
3	<b>Severe</b>

Photo guide exhibiting the grades of wrinkle severity used for Investigator training and reference

- 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	<b>Moderate</b>	<b>Moderate wrinkles</b>
3	<b>Severe</b>	<b>Deep wrinkles</b>

- 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

- $\geq 1$ -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

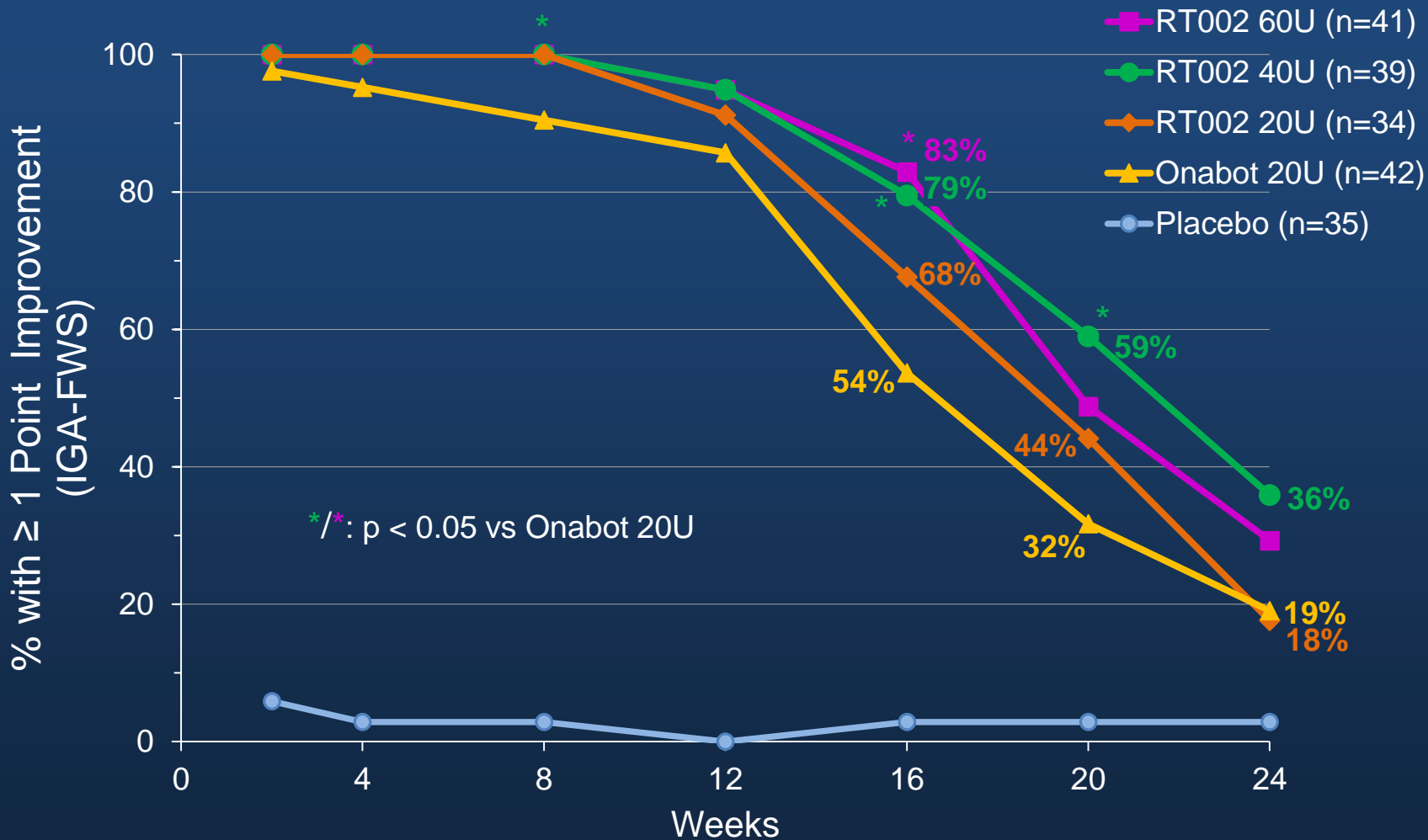
	Placebo (N=54)	RT002 20U (N=54)	RT002 40U (N=53)	RT002 60U (N=53)	Onabot 20U (N=54)
<b>Age (years)</b>	49.1 (32 to 64)	49.0 (30 to 64)	49.9 (30 to 63)	47.5 (30 to 64)	50.0 (36 to 63)
<b>Male</b>	9 (16.7%)	5 ( 9.3%)	7 (13.2%)	11 (20.8%)	6 (11.1%)
<b>Female</b>	45 (83.3%)	49 (90.7%)	46 (86.8%)	42 (79.2%)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

# 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 $\geq 1$ Point Improvement in IGA-FWS





**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**

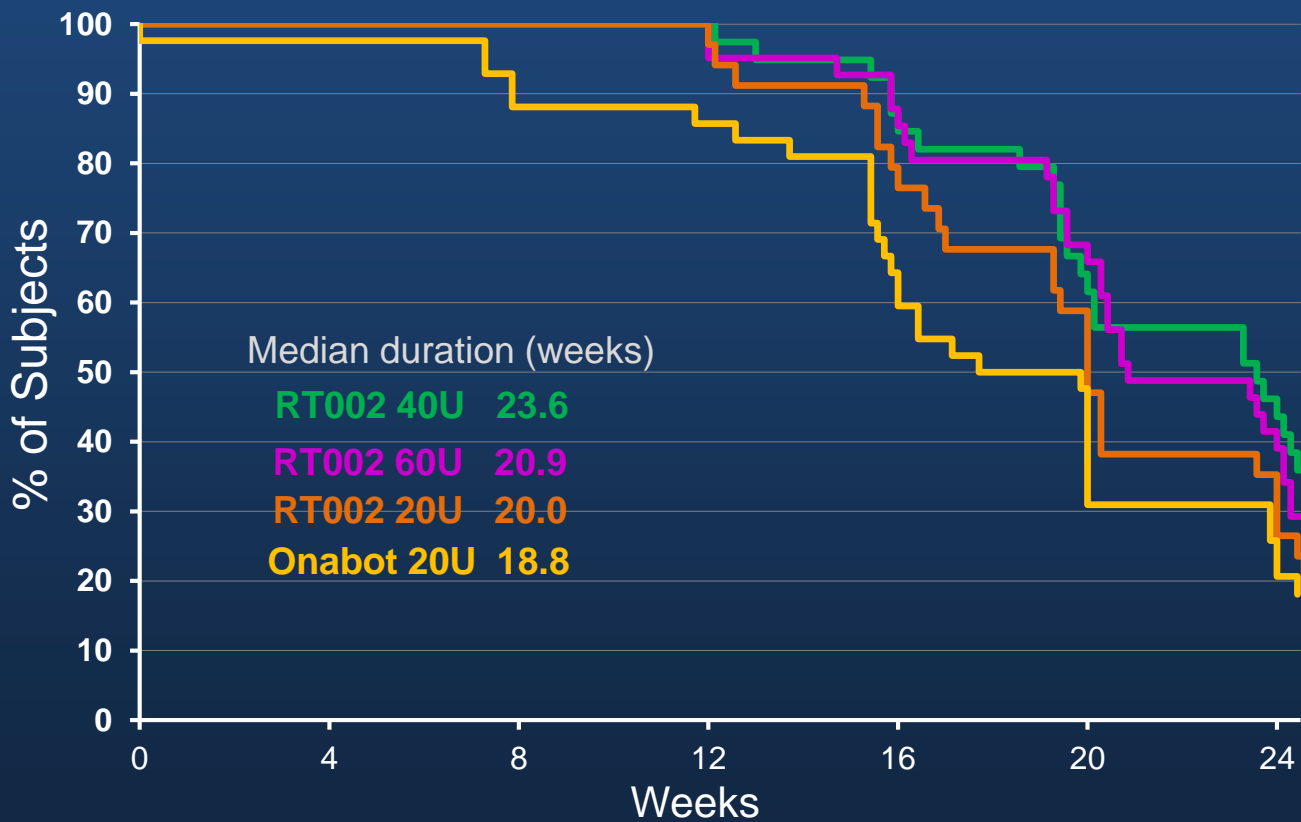
	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
<b>RT002 40U (N=39)</b>	97%	97%	97%*	85%	67%**	46%*	31%*
<b>RT002 20U (N=34)</b>	97%	97%	88%	82%	53%*	35%	12%
<b>Onabot 20U (N=42)</b>	95%	93%	83%	69%	32%	22%	12%

\* p<0.05, \*\* p<0.005 (vs Onabot 20U)

# Longer Duration of Response Observed for all Three Doses of RT002 vs. Onabot 20U: $\geq 1$ Point Improvement in IGA-FWS

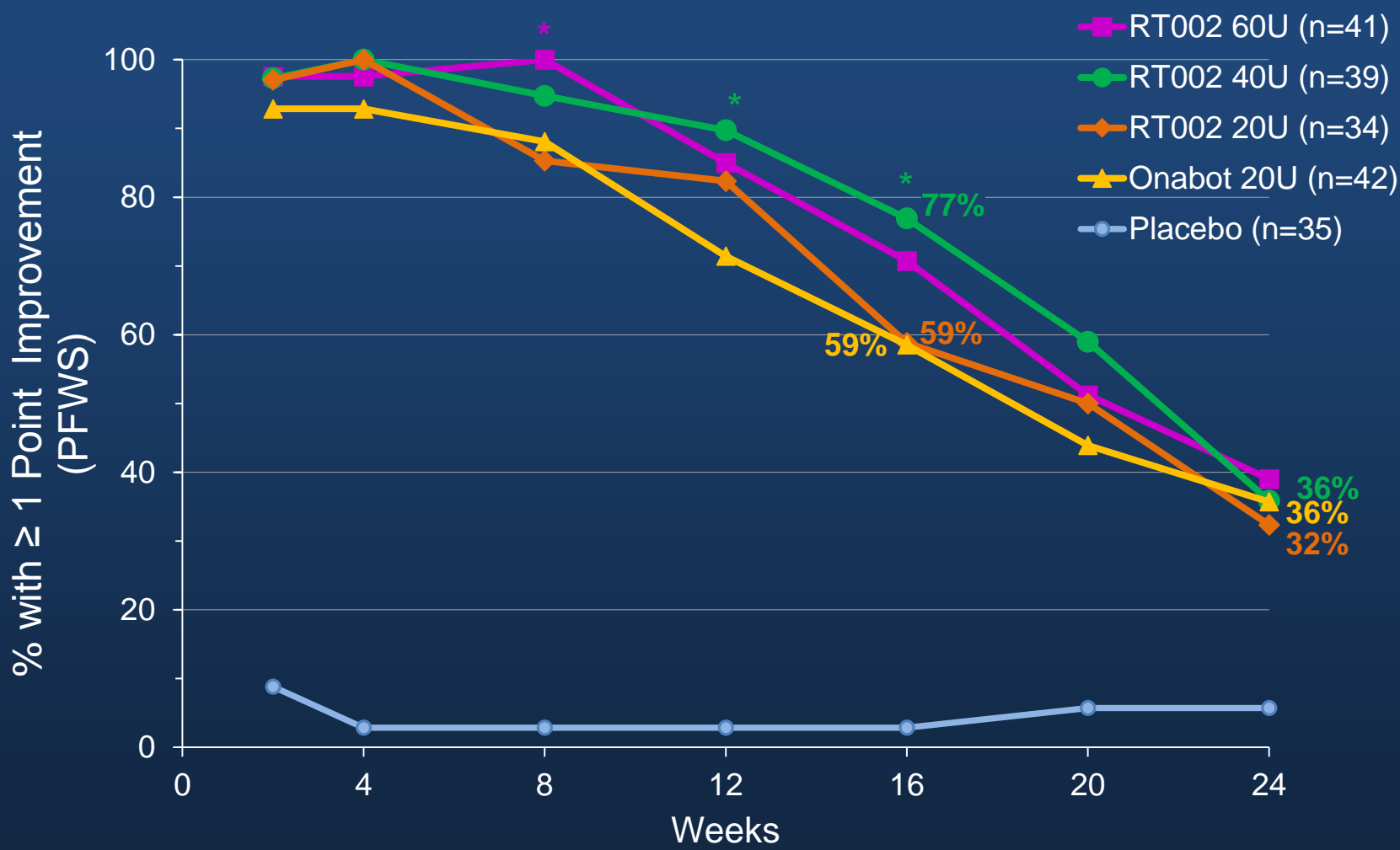
## Duration of Response Kaplan-Meier Curve $\geq 1$ Point Improvement on IGA-FWS

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



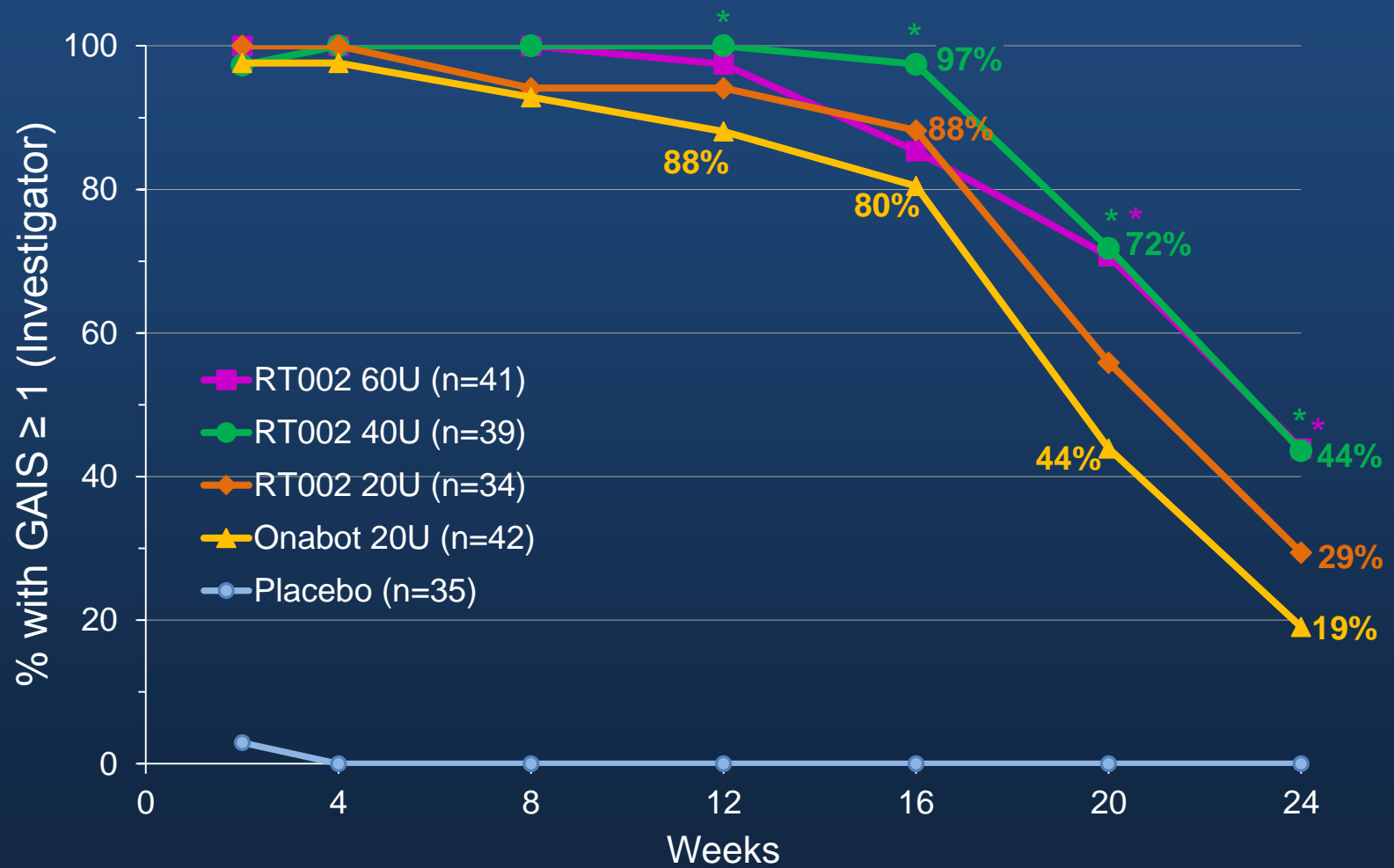
\* Log-rank test

# RT002 40U and 60U had Higher Rate of Response vs. Onabot 20U over Time on $\geq 1$ Point Improvement in PFWS



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

# All Three Doses of RT002 had Higher Rate of Response vs. Onabot 20U on Investigator GAIS $\geq +1$



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

**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

**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

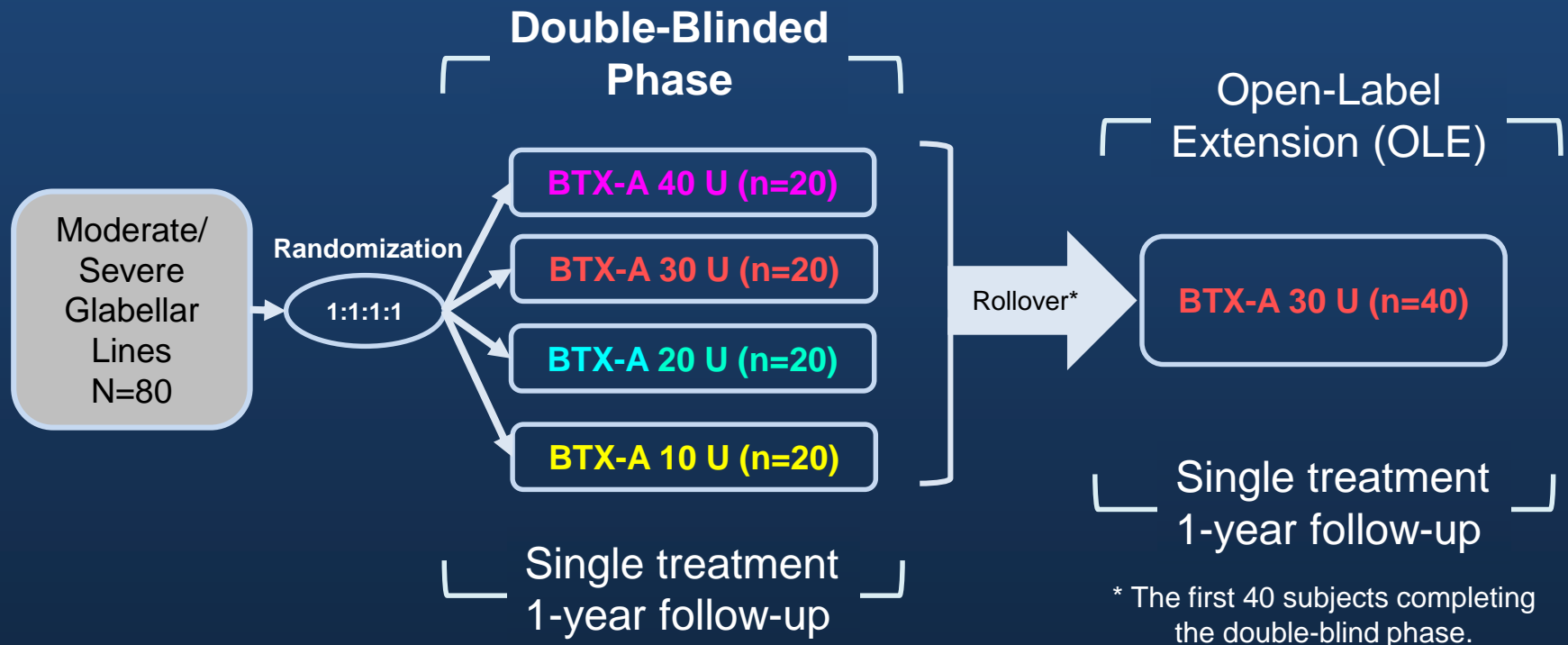
Week 4 Scores:  
IGA-FWS: 0  
PFWS: 0

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

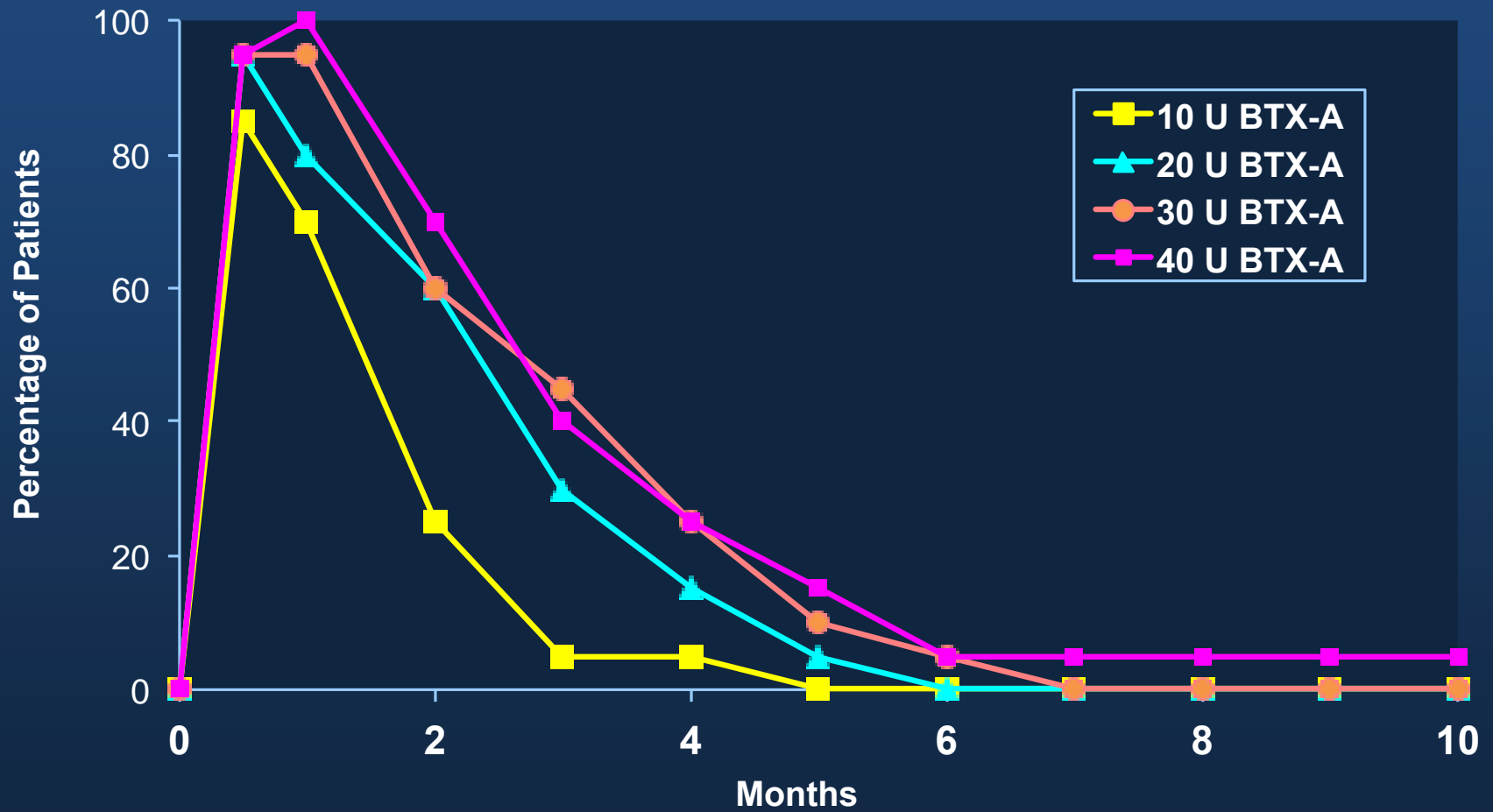
# Dose-Ranging Study of OnabotulinumtoxinA in Glabellar Lines

Carruthers et. al. (2005)

**Objective:** To compare the degree and duration of effect of onabotulinumtoxinA 10, 20, 30 and 40U in the treatment of glabellar lines



# Carruthers Study: No difference in Duration or Response Rates Observed Between Top 3 Onabot Doses (20U, 30U and 40) at Any Time Point





# Dose-Ranging Study of OnabotulinumtoxinA Summary

- **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

	Placebo N=54	RT002 20U N=54	RT002 40U N=53	RT002 60U N=53	Onabot 20U N=54
Headache	3	6	4	3	10
Erythema	4	3	4	3	5

- 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

**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  $\geq 1$  point improvement on IGA-FWS beginning at Week 2 through Week 24

	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
RT002 40U	100%	100%	100%*	95%	79%*	59%*	36%
Onabot 20U	98%	95%	90%	86%	54%	32%	19%

\* $p \leq 0.05$

- 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  $\geq 1$  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

# SAKURA Phase 3 Program with DaxibotulinumtoxinA (RT002) for the Treatment of Moderate to Severe Glabellar (Frown) Lines

## 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  $\geq 2$  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**