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

Single Treatment

*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

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	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

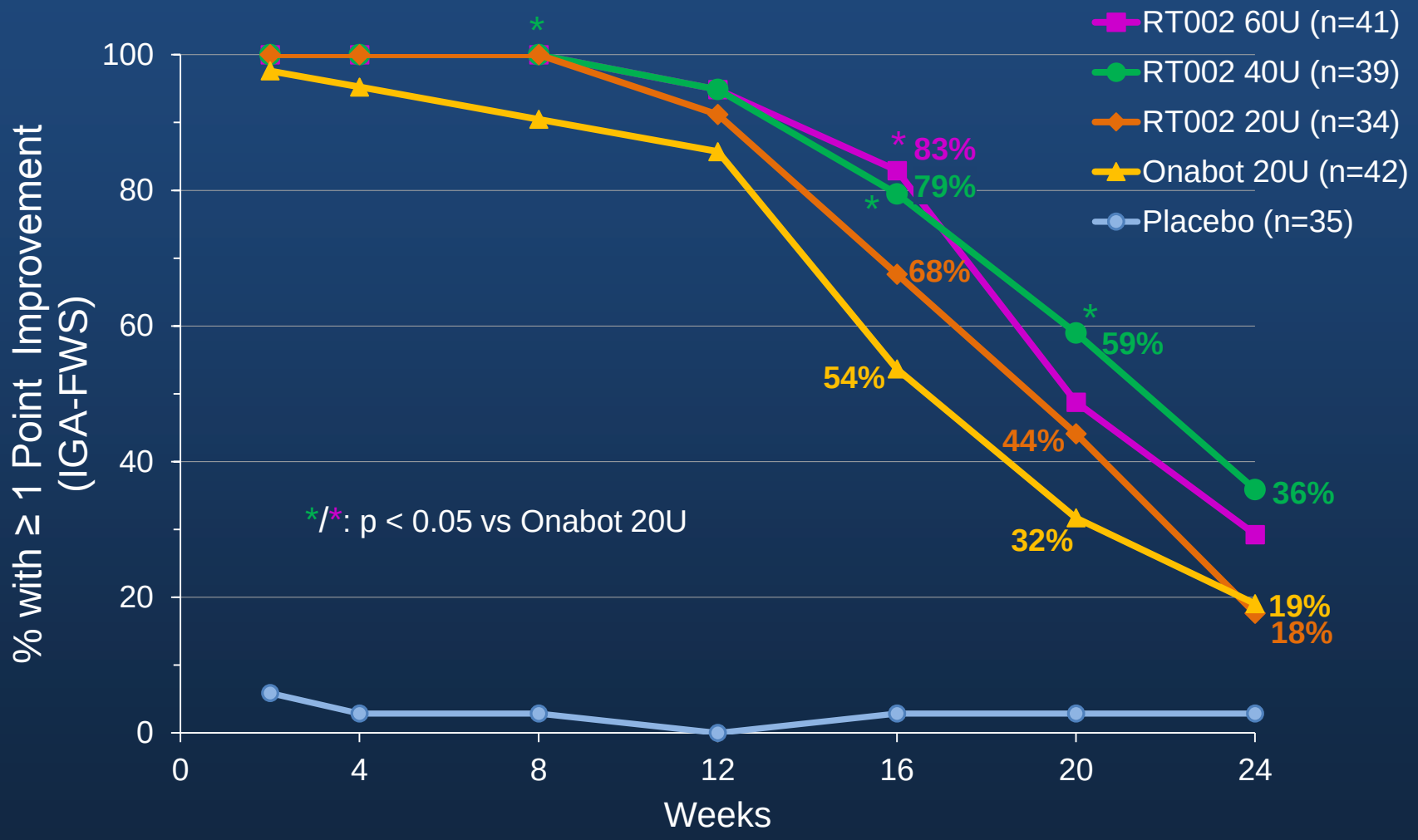
	Placebo (N=54)	RT002 20U (N=54)	RT002 40U (N=53)	RT002 60U (N=53)	Onabot 20U (N=54)
Age (years)	49.1 (32 to 64)	49.0 (30 to 64)	49.9 (30 to 63)	47.5 (30 to 64)	50.0 (36 to 63)
Male	9 (16.7%)	5 (9.3%)	7 (13.2%)	11 (20.8%)	6 (11.1%)
Female	45 (83.3%)	49 (90.7%)	46 (86.8%)	42 (79.2%)	48 (88.9%)
Race: White	46 (85.2%)	47 (87.0%)	50 (94.3%)	48 (90.6%)	47 (87.0%)
IGA-FWS: moderate	34 (63.0%)	34 (63.0%)	35 (66.0%)	30 (56.6%)	31 (57.4%)
IGA-FWS: severe	20 (37.0%)	20 (37.0%)	18 (34.0%)	23 (43.4%)	23 (42.6%)
PFWS: moderate	36 (66.7%)	36 (66.7%)	33 (62.3%)	37 (69.8%)	29 (53.7%)
PFWS: severe	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 ≥ 1 Point Improvement in IGA-FWS



PP Population

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**

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

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

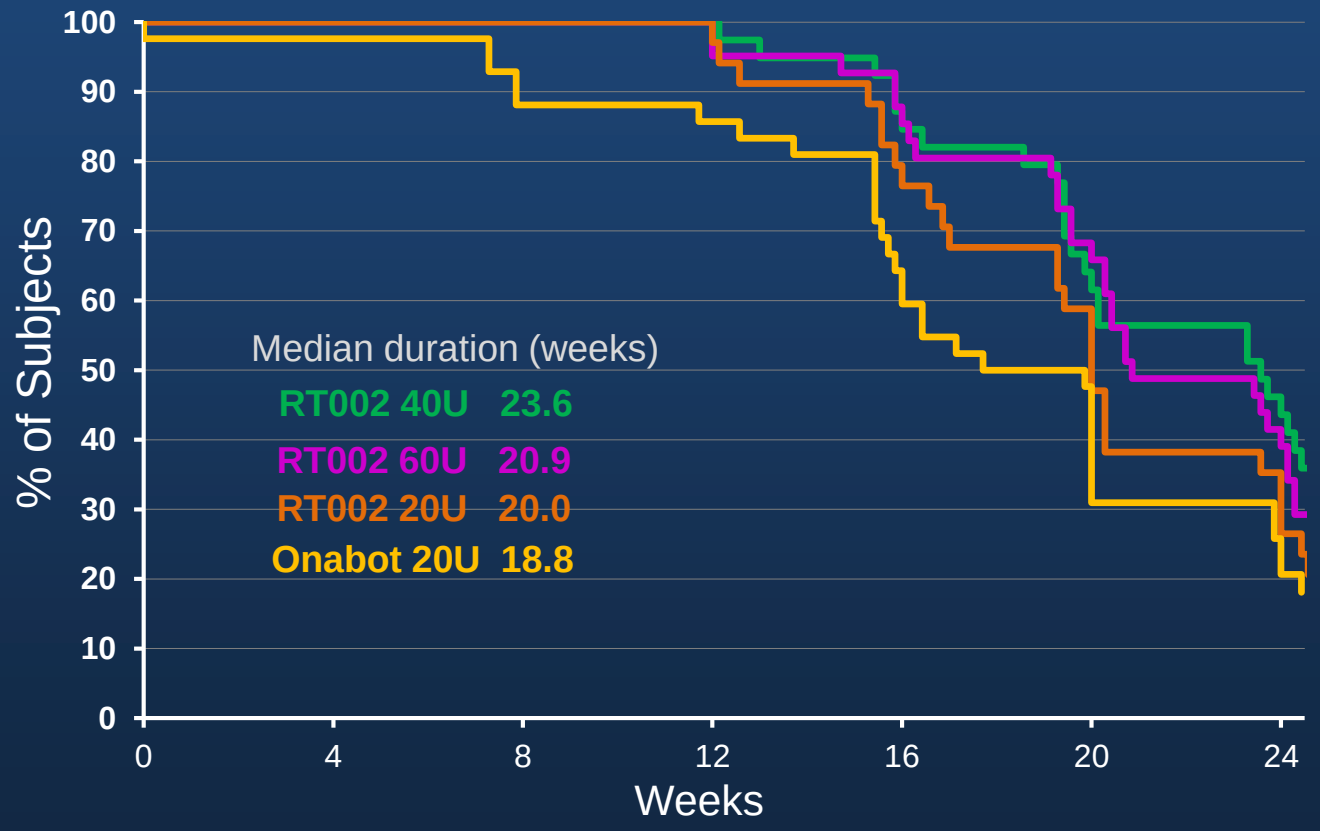
PP Population

DaxibotulinumtoxinA for Injection (RT002) is an investigational product

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

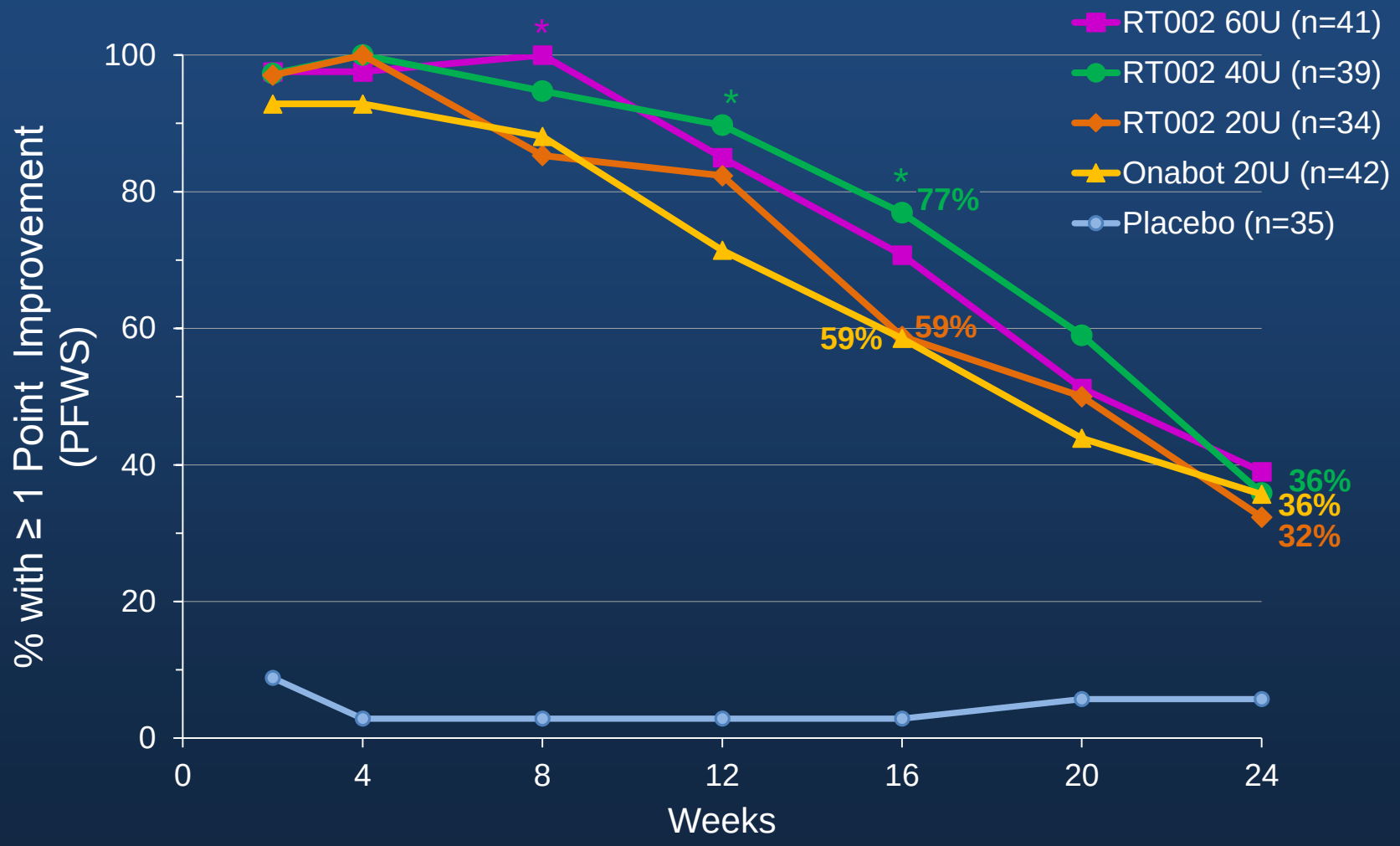


* Log-rank test

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

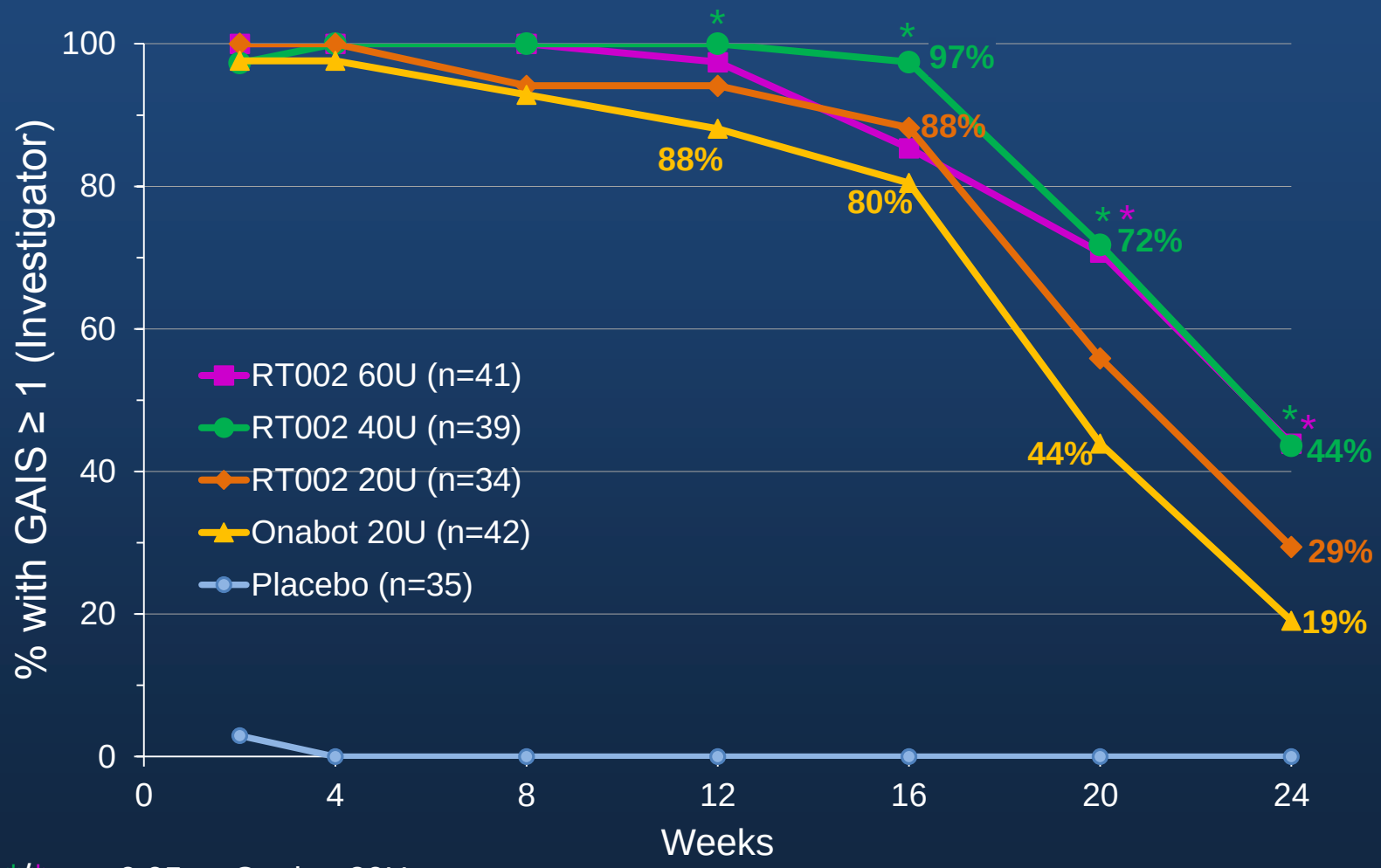


/: p < 0.05 vs Onabot 20U

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



/: p < 0.05 vs Onabot 20U

PP Population

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

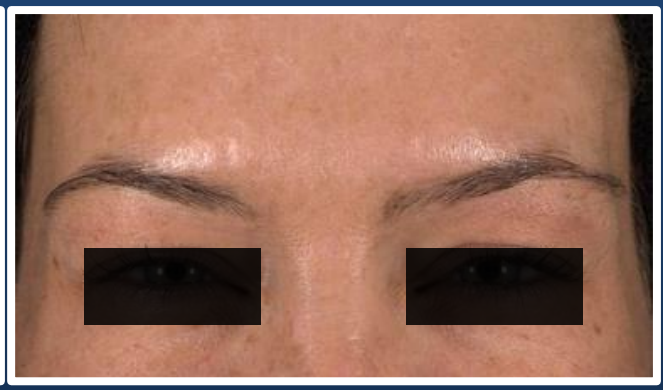
DaxibotulinumtoxinA 40 U
MAXIMUM FROWN

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

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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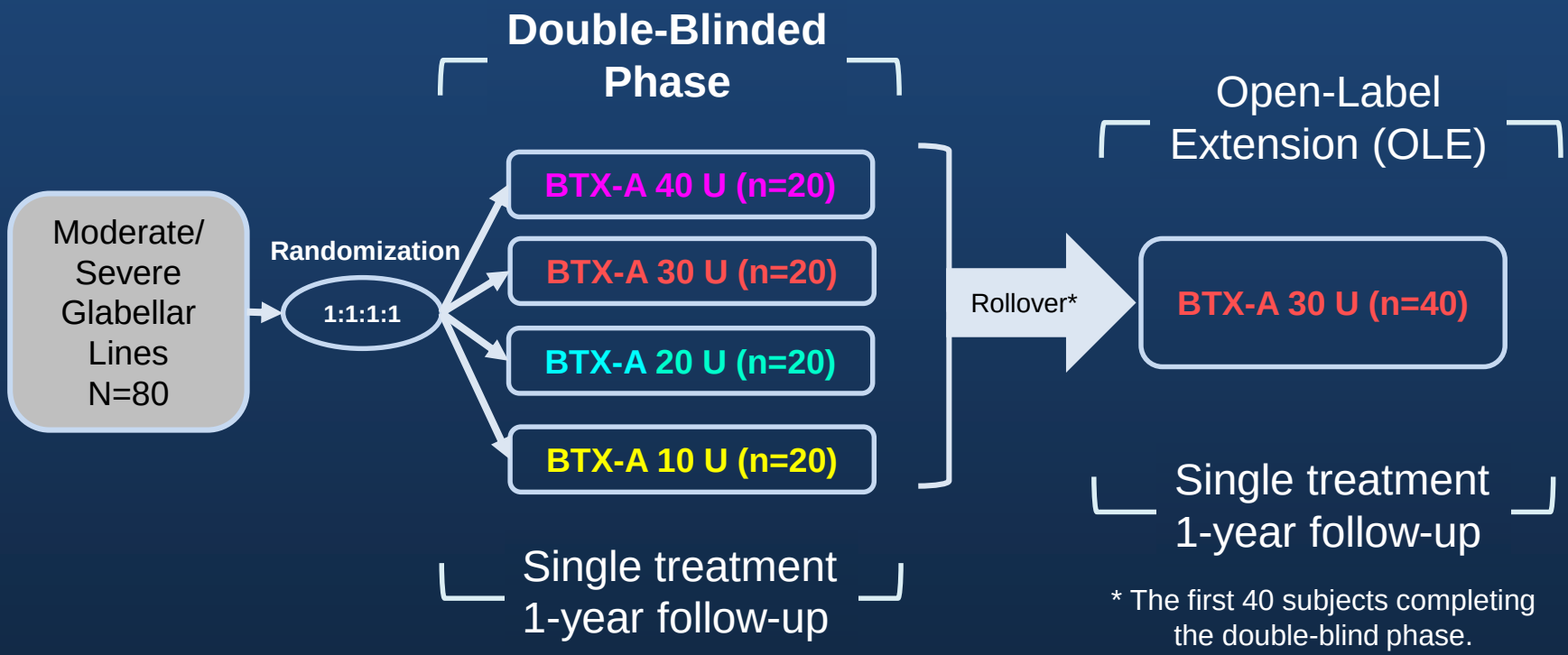
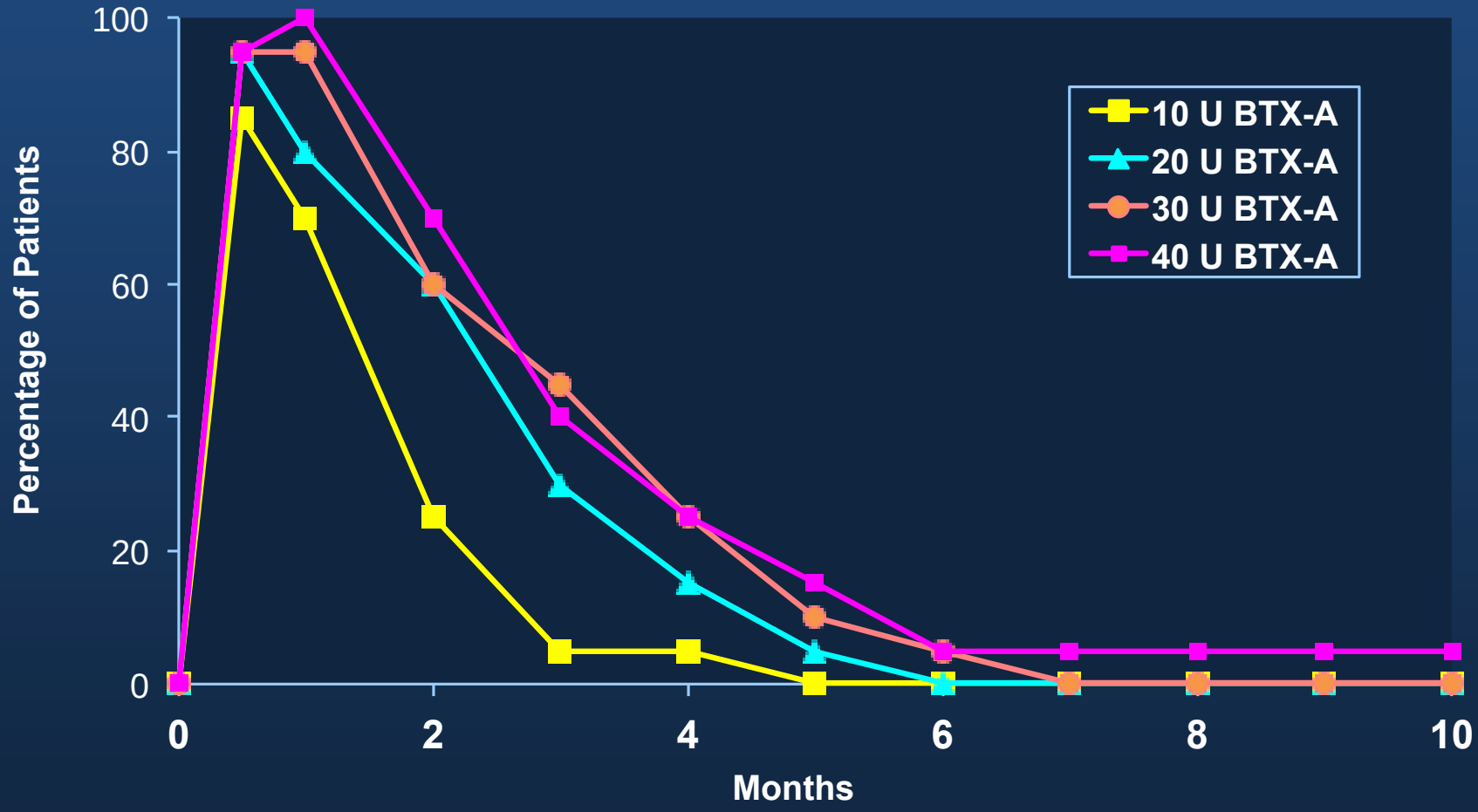
Dose-Ranging Study of OnabotulinumtoxinA in Glabellar Lines
Carruthers et. al. (2005)

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



Carruthers 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

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

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

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 ≥ 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≤ 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 ≥ 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 ≥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