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

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Context

- 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

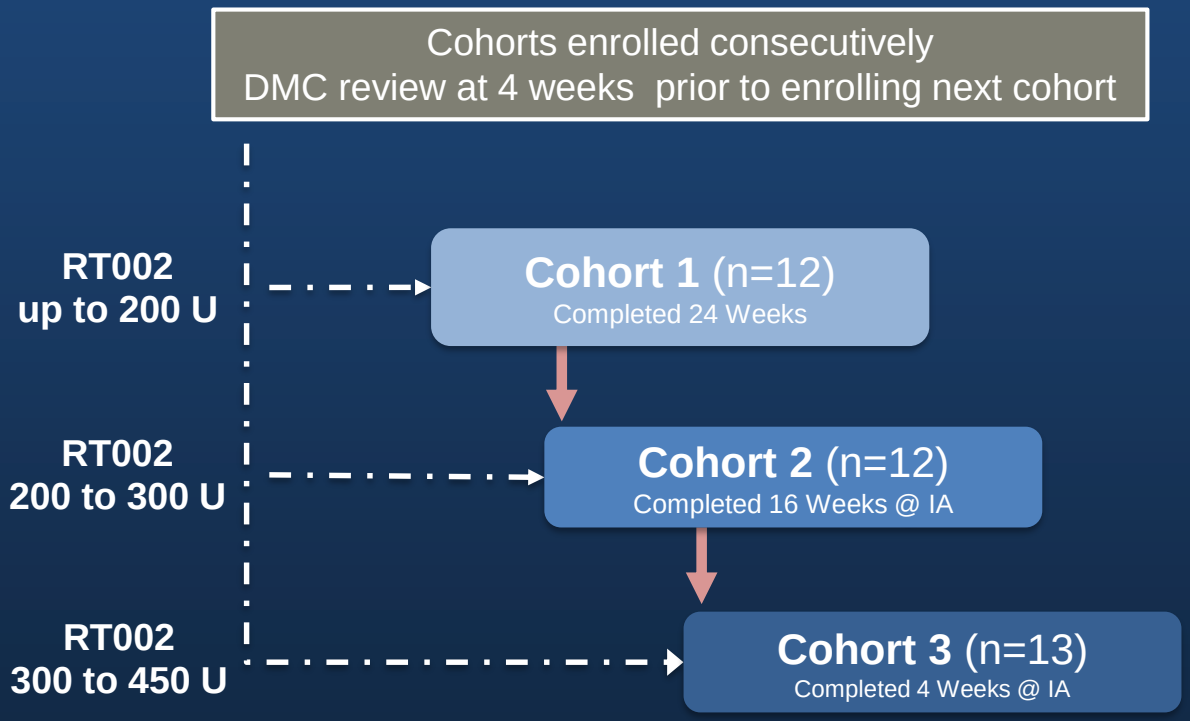
- To assess the safety and preliminary efficacy of RT002 in isolated CD
- To evaluate the duration of effect of RT002 in the treatment of isolated CD

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



Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)

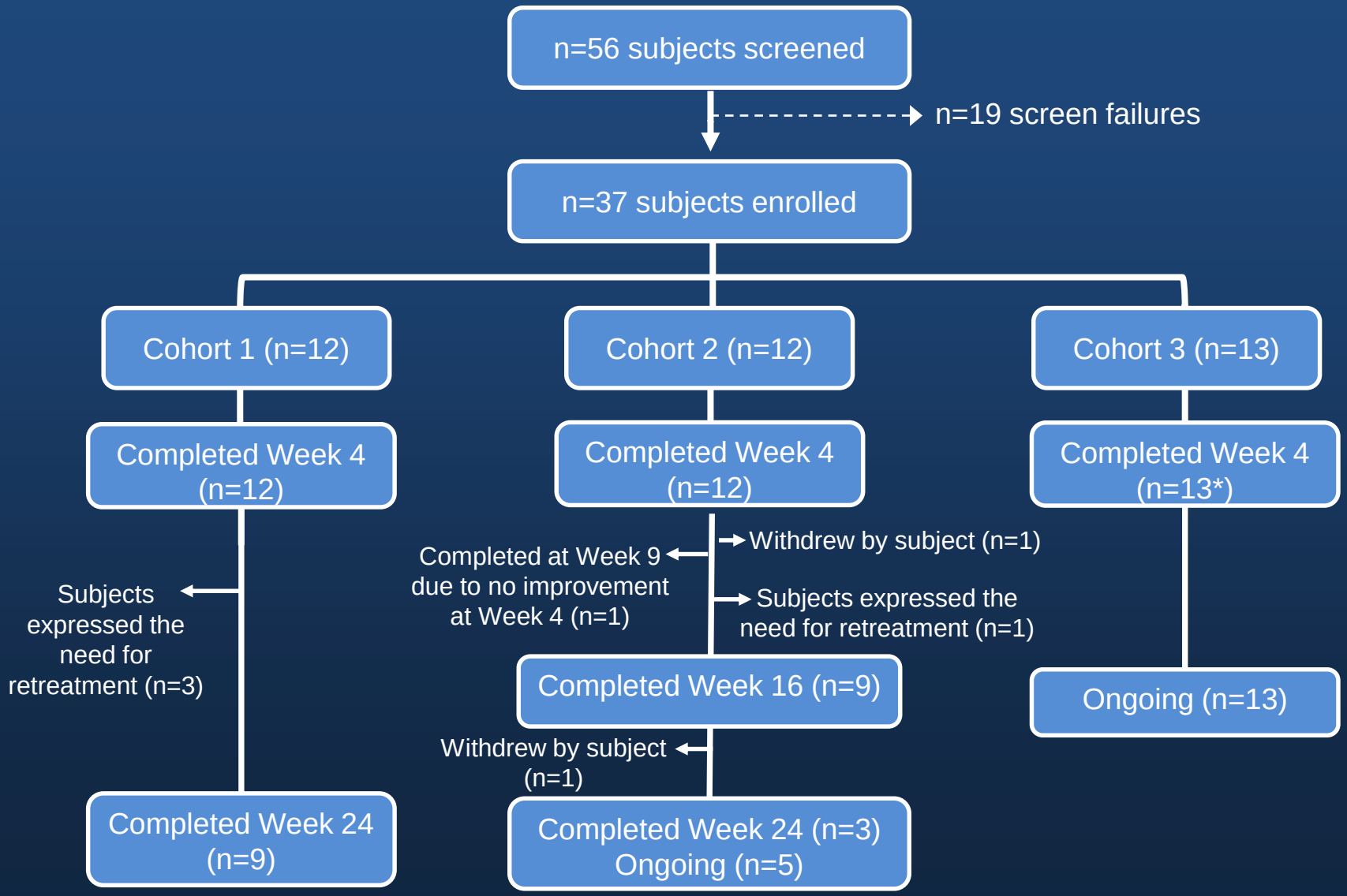
- TWSTRS-Total score (0-85) = sum of TWSTRS-Severity, TWSTRS-Disability and TWSTRS-Pain scores [1,2]
  - TWSTRS-Severity score (0-35) – Clinician rated (*weighted sum of 6 items*)
  - TWSTRS-Disability score (0-30) – Patient rated (*sum of 6 items*)
  - TWSTRS-Pain score (0-20) – Patient rated (*weighted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

[1] Consky, E, and Lang.A. Clinical assessments of patients with cervical dystonia, 1994.
[2.] Jen, M-H, et. Al. Assessing burden of illness from cervical dystonia using TWSTRS scores and health utility, 2014.

Results: Subject Disposition



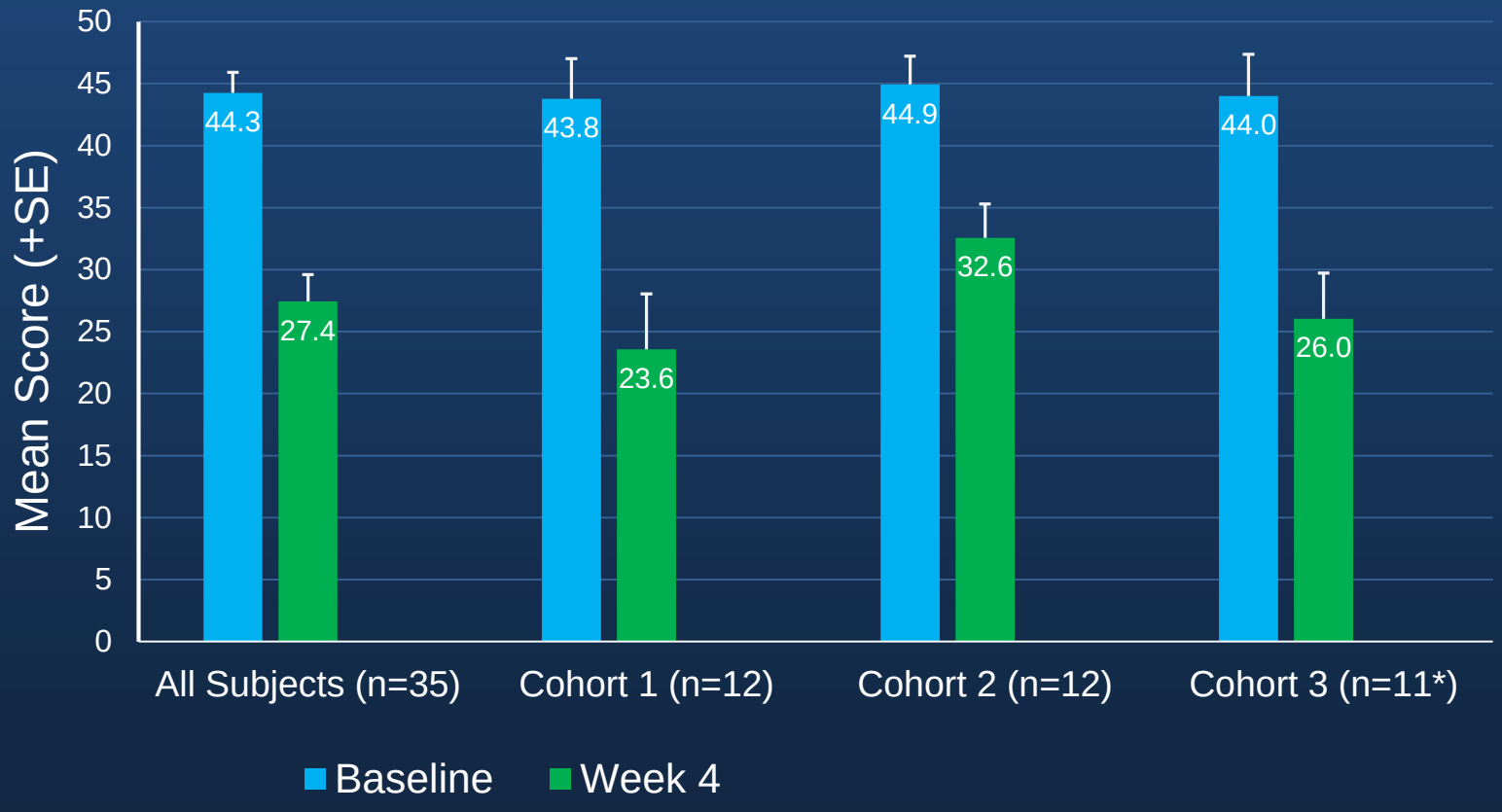
* 2 subjects missed the Week 4 visit

Demographics and Baseline Characteristics

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

Primary Endpoint: Reduction in TWSTRS-Total Score at Week 4 by Cohort

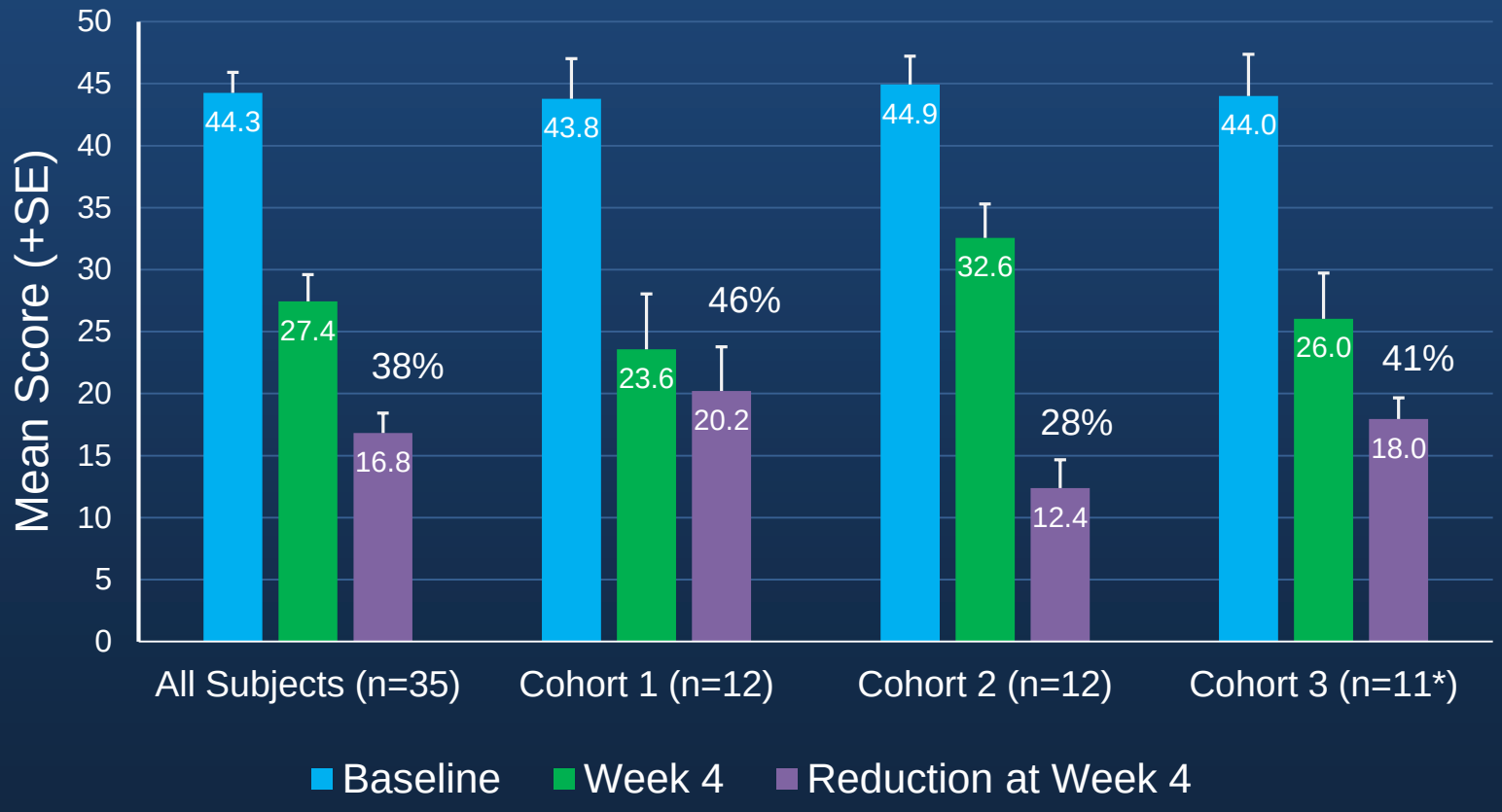
Clinically Meaningful Reduction in TWSTRS-Total Score Observed at Week 4 across all 3 Cohorts



* Two subjects currently on study had missing value at Week 4

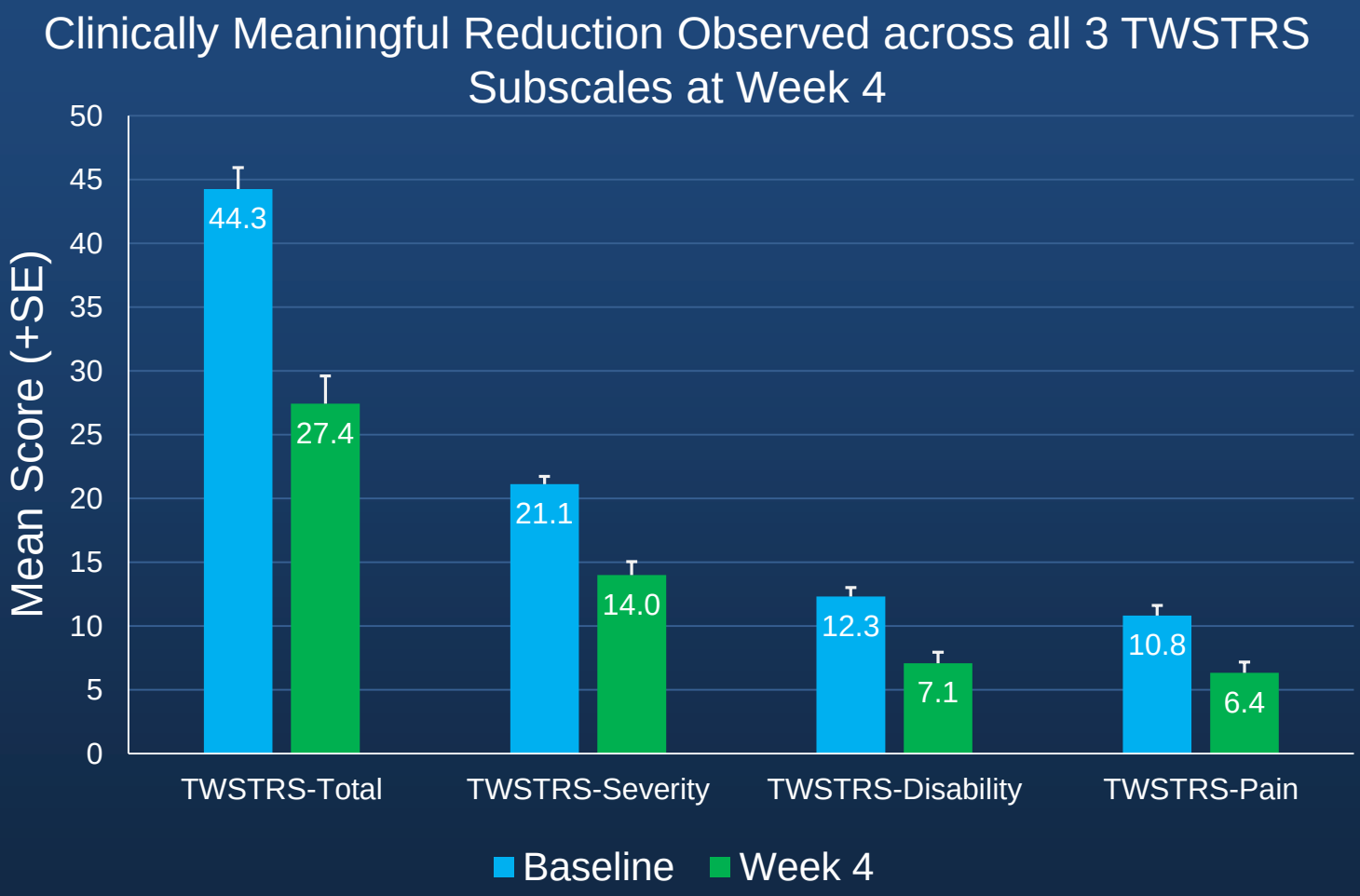
Primary Endpoint: Reduction in TWSTRS-Total Score at Week 4 by Cohort

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



* Two subjects currently on study had missing value at Week 4

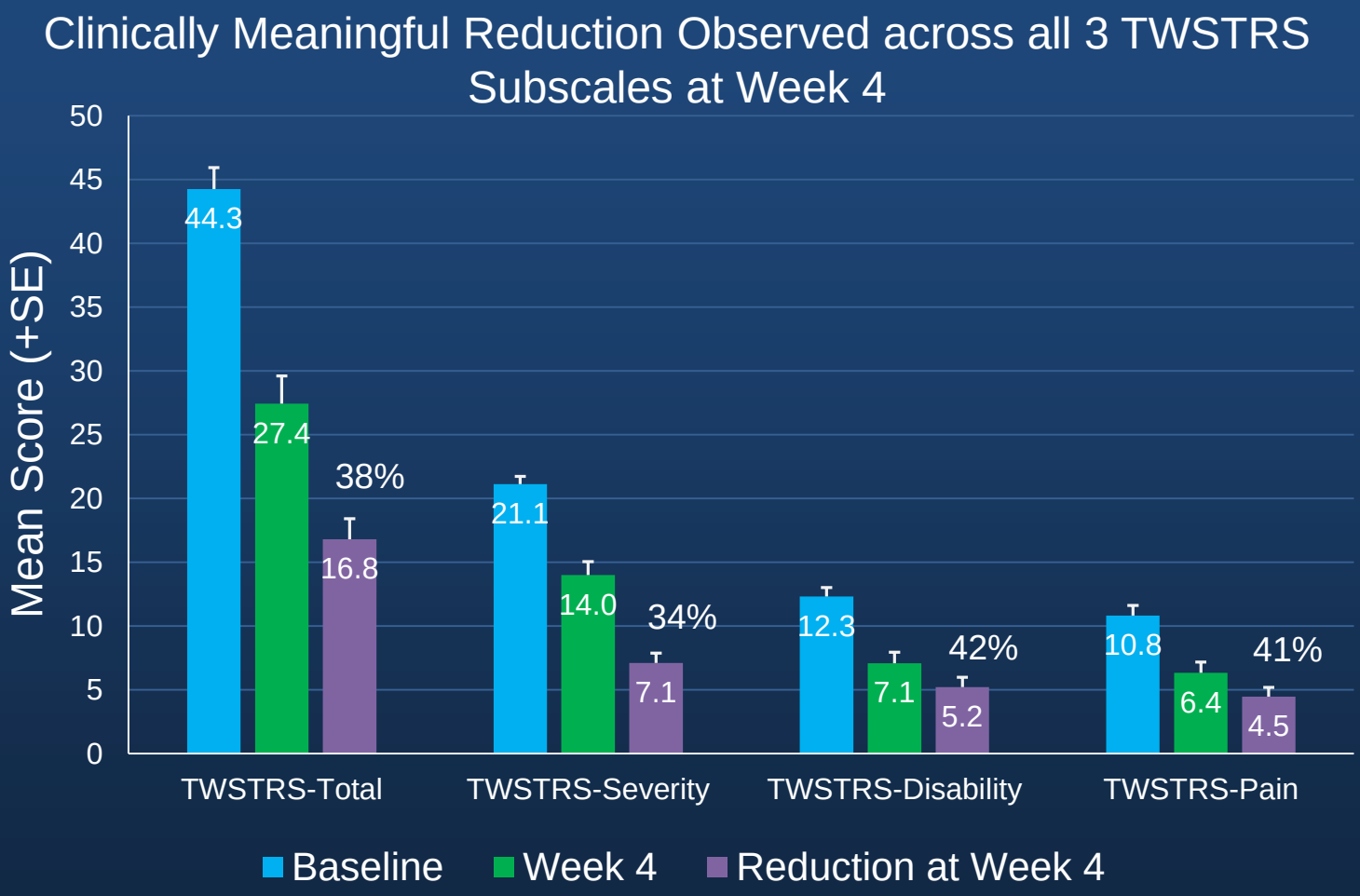
Primary & Secondary Endpoints: Reduction in TWSTRS-Total Score and Subscales at Week 4



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

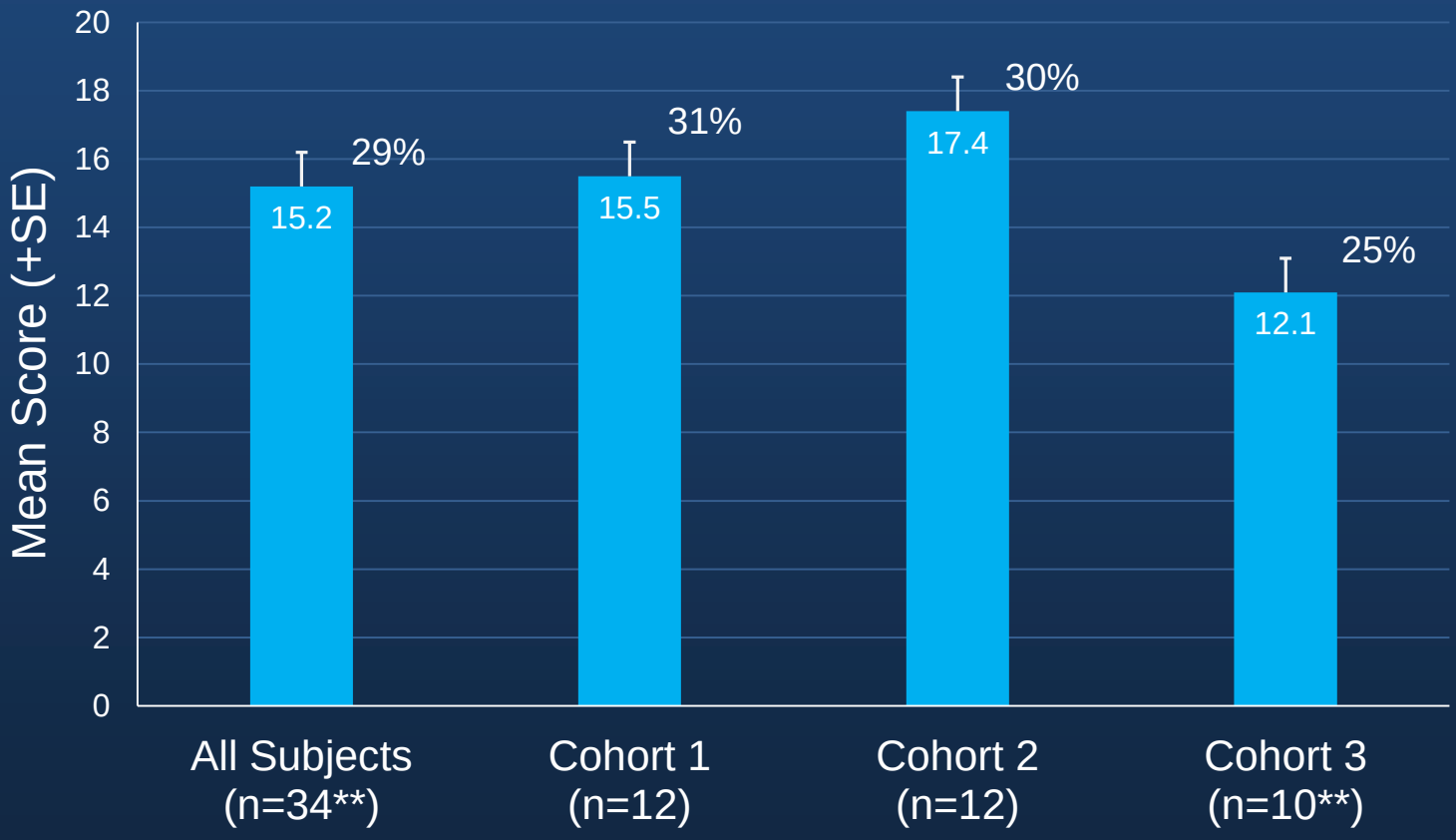


All Subjects with Values at both Baseline and Week 4 (n=35*)

* 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

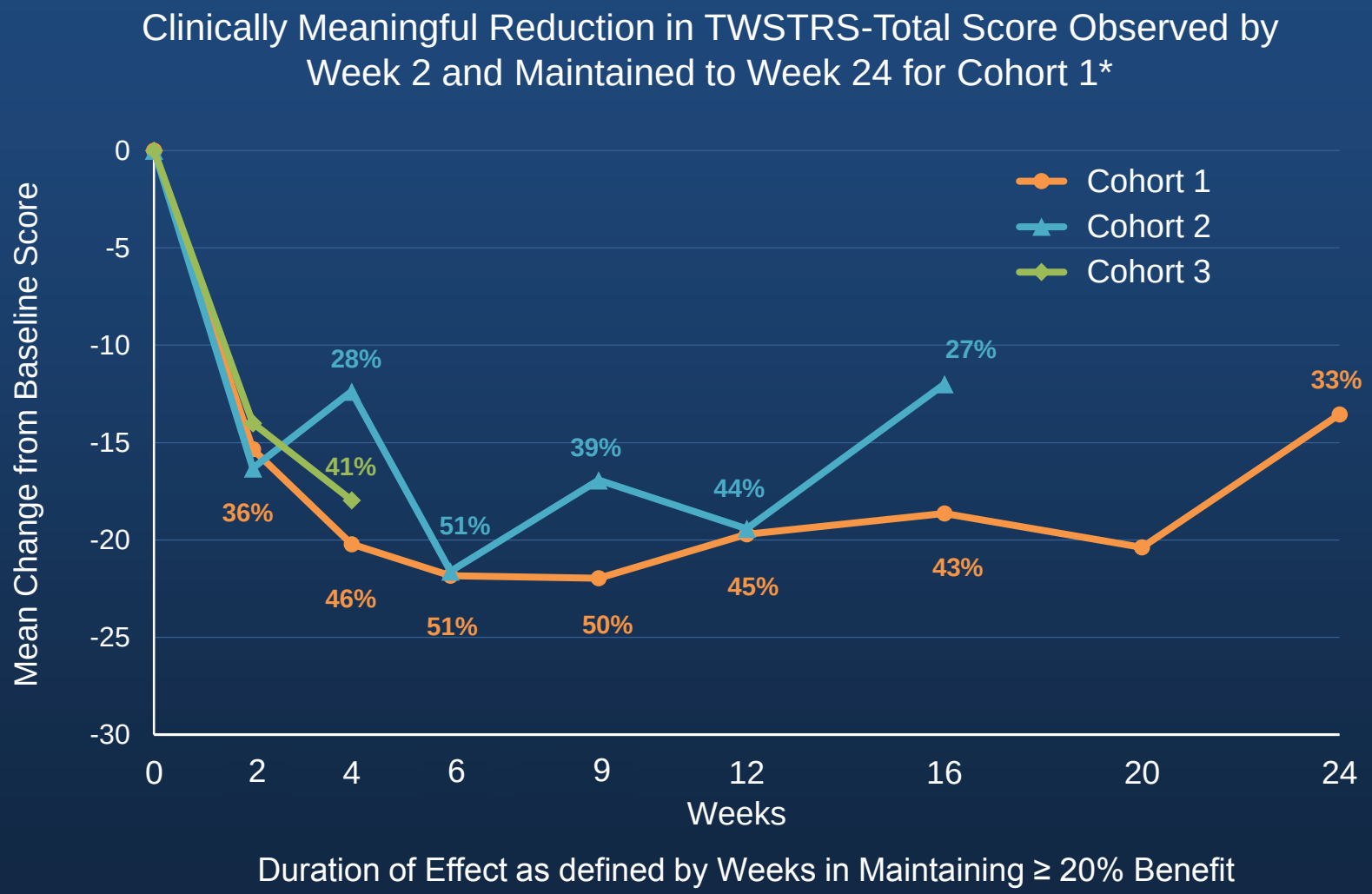
Meaningful Improvement from Baseline in Patient Rated Quality of Life Observed at Week 4 for all cohorts



* 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



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

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

* 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

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