

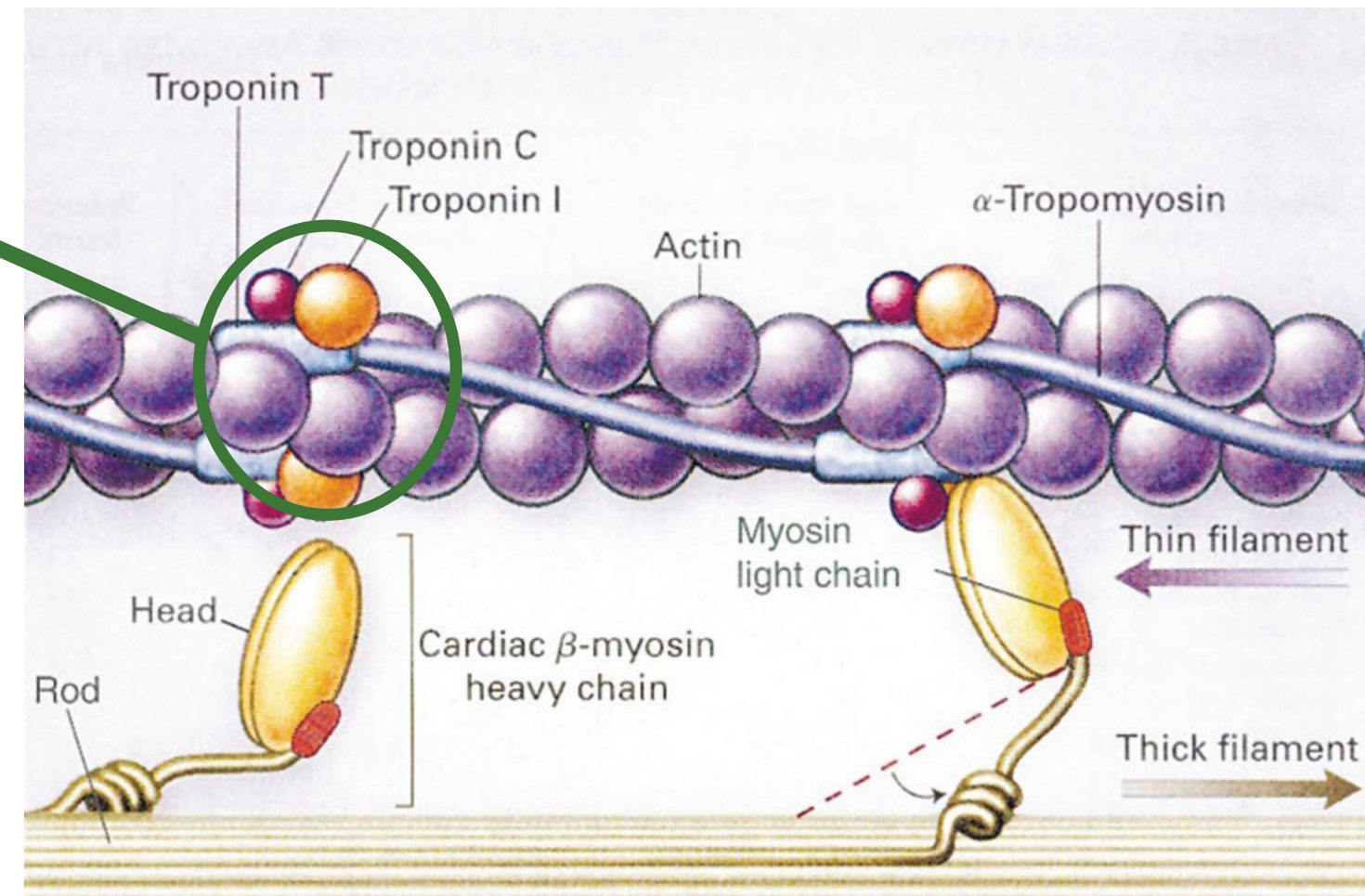
VENTILATORY INVESTIGATION OF *TIRASEMTIV* AND ASSESSMENT OF LONGITUDINAL INDICES OF TREATMENT FOR A YEAR IN ALS (VITALITY-ALS): STUDY DESIGN OF A PHASE III CLINICAL TRIAL OF *TIRASEMTIV* IN ALS

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BACKGROUND

Tirasemtiv, a fast skeletal muscle troponin activator, sensitizes the sarcomere to calcium and amplifies the muscle response to submaximal nerve stimulation. It is being developed to improve skeletal muscle function in Amyotrophic Lateral Sclerosis (ALS).

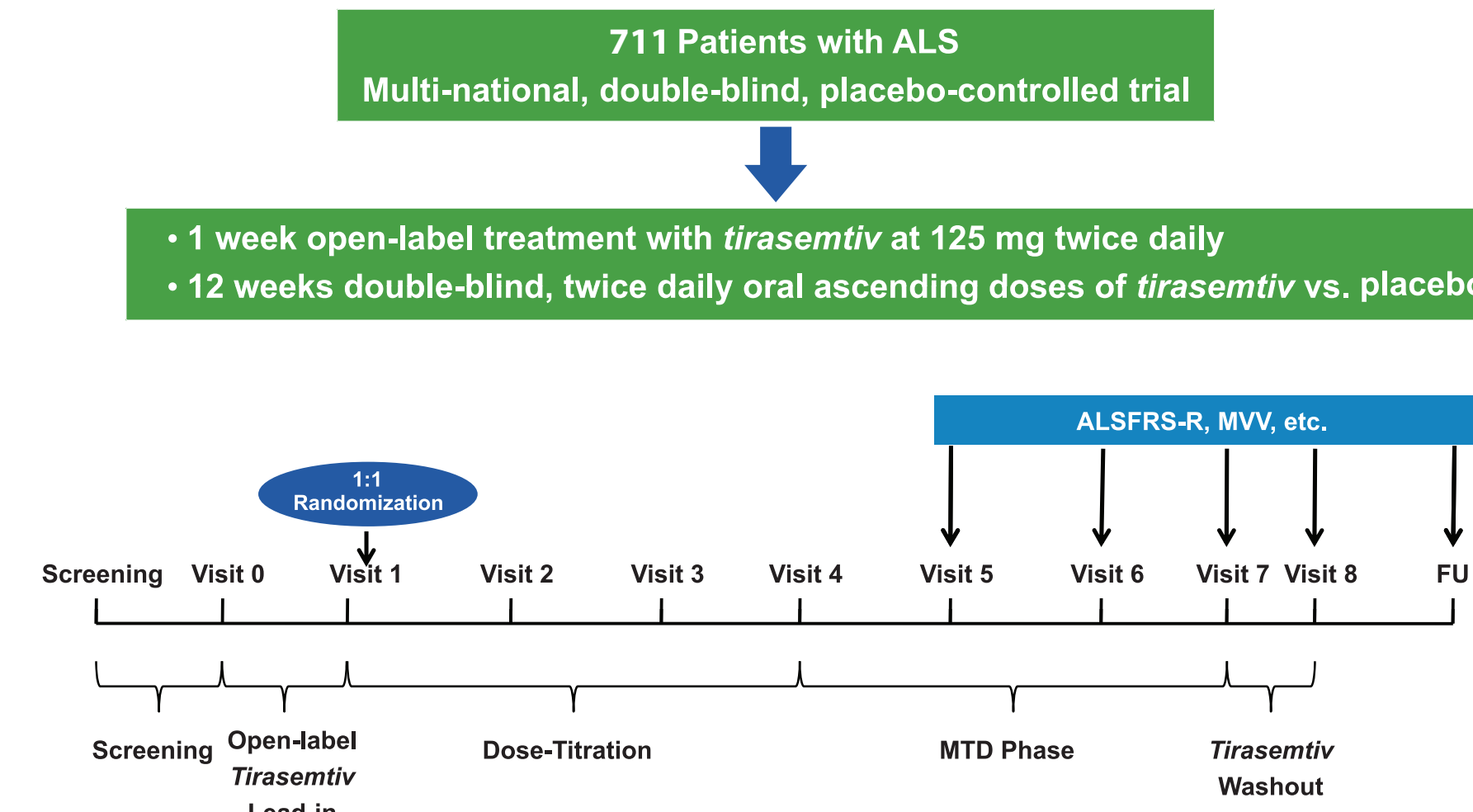
Tirasemtiv activates the troponin complex of fast skeletal muscle



***Tirasemtiv* is a Small Molecule Activator of the Skeletal Sarcomere**

METHODS

Based on observations from three small phase IIa clinical trials with *tirasemtiv*, a larger phase IIb clinical trial, BENEFIT-ALS, was conducted in patients with ALS. BENEFIT-ALS (n=711) was an international, randomized, double-blind, placebo-controlled, parallel group study with *tirasemtiv* administered twice daily at each patient's maximum tolerated dose, up to 500 mg daily for 12 weeks.



LEADERSHIP

Lead Investigator: Jeremy Shefner, MD, PhD, Barrow Neurological Institute, Phoenix, AZ

Study Director, Cytokinetics: Jinsy Andrews, MD, MSc

RESULTS

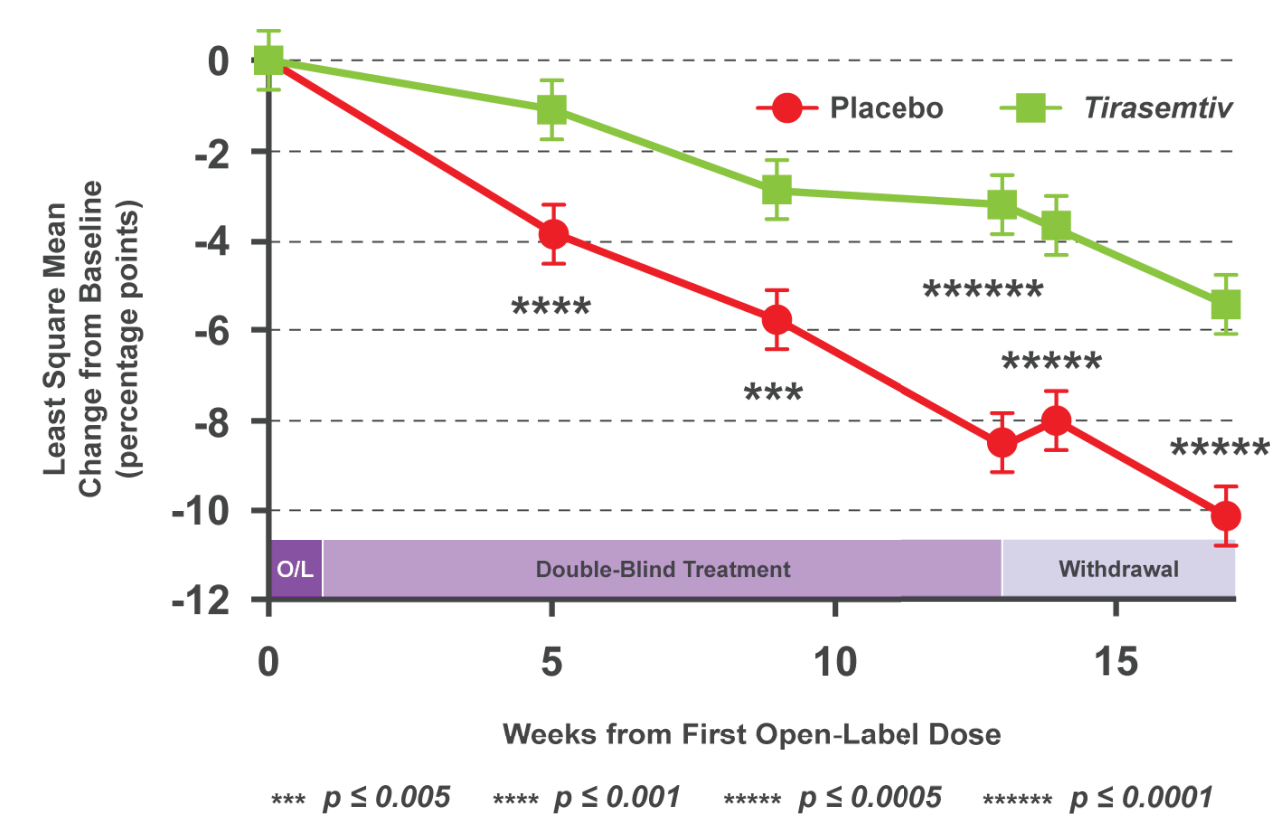
- In all completed studies, *tirasemtiv* appeared generally safe and well tolerated

- In BENEFIT-ALS

- Percent predicted slow vital capacity (SVC)
 - Declined more slowly over 12 weeks on *tirasemtiv* versus placebo (-3.12 ± 0.90 versus -8.66 ± 0.80 percentage points, p < 0.0001)
 - This difference (4.91 percentage points, p = 0.0002) persisted for at least 28 days after the last dose of double-blind treatment.
- The Muscle Strength Mega-Score (percent change from baseline) also declined more slowly on *tirasemtiv* versus placebo (p=0.016 for the difference in slope of decline).

BENEFIT-ALS

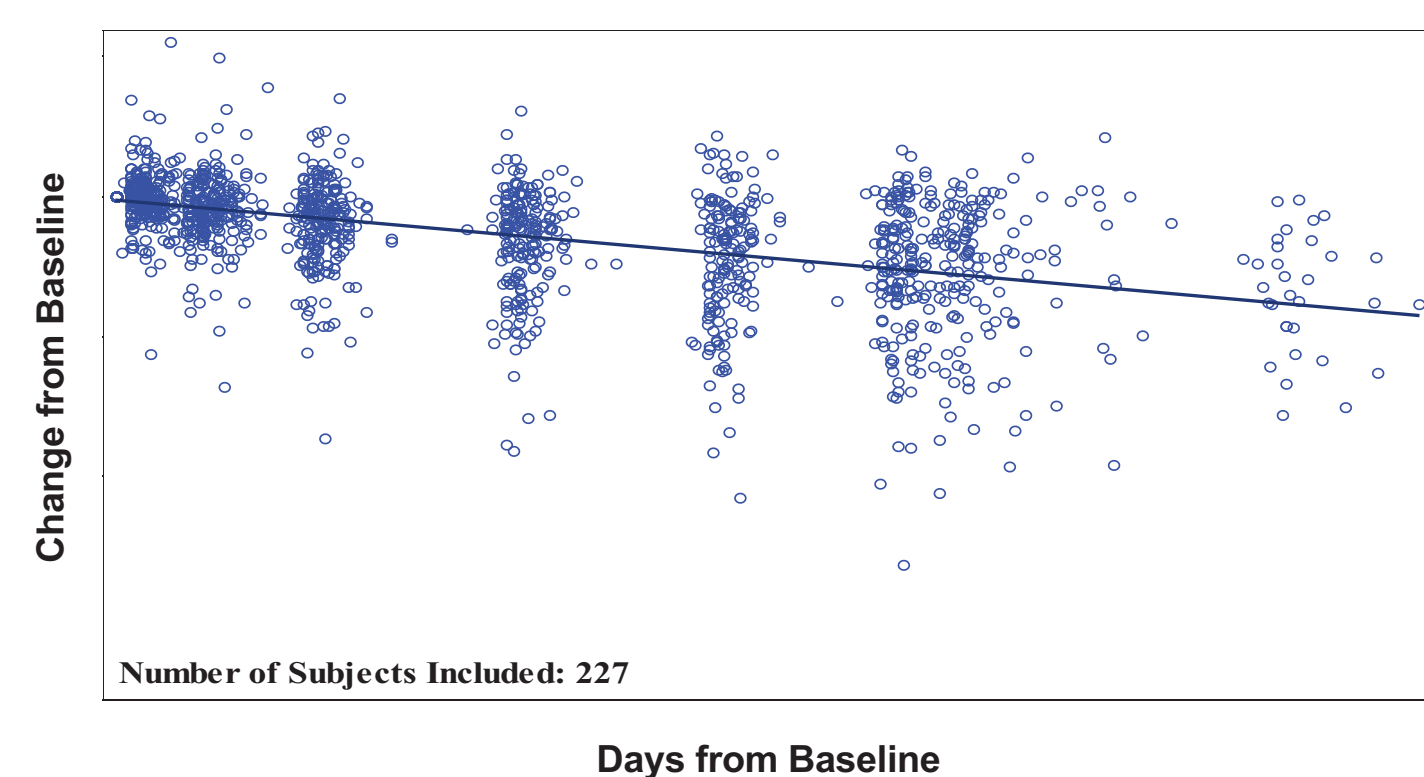
Slow Vital Capacity (% Predicted) in BENEFIT-ALS



Change in % Predicted SVC by Subgroup in BENEFIT-ALS

Subgroup	% Predicted SVC - Primary Analysis (n)	Placebo	Tirasemtiv	Difference	P-value
Age ≥ 65	198	-4.12	-3.16	0.96	0.0359
Age 65	198	-4.87	-3.16	1.71	0.0002
Female	358	-4.84	-3.16	1.68	0.0016
Male	270	-3.38	-3.16	0.22	0.9013
Europe	133	-2.24	-3.16	0.92	0.1488
North America	255	-5.27	-3.16	2.11	0.0001
Rhizole Use	251	-3.16	-3.16	0.00	0.8126
Rhizole Non Use	132	-6.85	-3.16	3.69	0.0000
Without Onset	192	-4.73	-3.16	1.57	0.2563
Limb Onset	232	-3.85	-3.16	0.69	0.0002
% Predicted SVC > Median	192	-2.83	-3.16	0.33	0.1891
% Predicted SVC ≤ Median	192	-6.02	-3.16	2.86	0.0001
SNP-Median	173	-5.43	-3.16	2.27	0.0049
SNP-Non-Median	119	-3.11	-3.16	0.05	0.9011
Weight-Median	177	-5.44	-3.16	2.28	0.0018
Weight-Non-Median	205	-3.25	-3.16	0.09	0.8880
BMI-Median	213	-4.37	-3.16	1.21	0.0117
BMI-Non-Median	189	-4.96	-3.16	1.80	0.0020

Natural History of Decline of % Predicted SVC

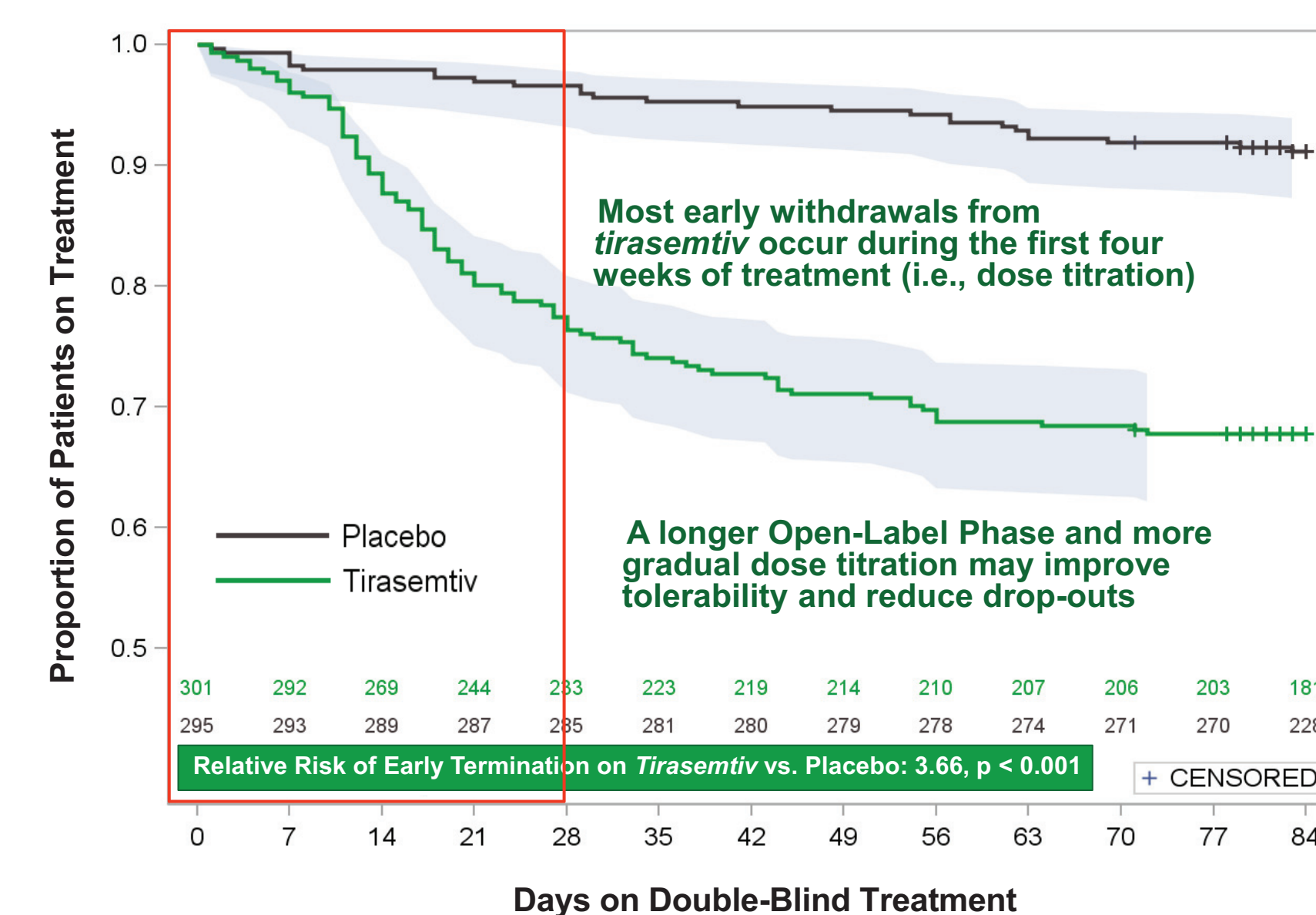


The rate of decline of SVC in the PROACT database (-0.096 percentage points/day), similar to that in the BENEFIT-ALS placebo group (-0.091 percentage points/day).

Preferred Term	Overall (N=596)	Placebo (n=295) %	<i>Tirasemtiv</i> (n=301) %	% on <i>Tirasemtiv</i> - % on Placebo
Any Adverse Event	549	87.5%	96.7%	9.2%
Dizziness	211	19.7%	50.8%	31.2%
Fatigue	142	14.2%	33.2%	19.0%
Nausea	89	7.8%	21.9%	14.1%
Headache	87	11.2%	17.9%	6.8%
Asthenia	85	12.5%	15.9%	3.4%
Muscle spasms	61	5.4%	15.0%	9.5%
Muscular weakness	54	6.8%	11.3%	4.5%
Somnolence	50	3.7%	13.0%	9.2%
Contusion	47	8.5%	7.3%	-1.2%
Insomnia	43	4.1%	10.3%	6.2%
Diarrrhea	39	5.8%	7.3%	1.5%
Decreased appetite	39	3.1%	10.0%	6.9%
Nasopharyngitis	38	6.4%	6.3%	-0.1%
Respiratory failure	36	5.8%	6.3%	0.5%
Confusional state	36	1.0%	11.0%	9.9%
Constipation	36	5.8%	6.3%	0.5%

Duration of Dizziness in BENEFIT-ALS

- Dizziness that began during the Open-Label Phase resolved in ...
 - 20.0 ± 27.70 days (0 - 113.6 days) on double-blind *tirasemtiv*
 - 14.2 ± 25.47 days (0 - 121.4 days) on double-blind placebo
- The means and ranges of the duration of dizziness beginning during open-label *tirasemtiv* are similar and overlap between double-blind *tirasemtiv* and placebo
- The open-label lead-in likely succeeded in preventing dizziness that began during the Open-Label Phase from unblinding the double-blind treatment



SVC by Maximum Tolerated Dose in BENEFIT-ALS

SVC Change from Baseline (percentage points)	Placebo	<i>Tirasemtiv</i> Total Daily Dose		
		250 mg	375 mg	500 mg
n	189	30	38	68
Mean (SD) Average	0	7.97 (2.68)	10.85 (4.54)	12.86 (4.06)
<i>Tirasemtiv</i> Concentration				
LSM (SE)	-8.66 (0.80)	-1.48 (1.94)	-3.06 (1.78)	-3.58 (1.36)
LSM (SE) Difference from Placebo		7.14 (2.10)	5.52 (1.96)	5.07 (1.58)
p-value		0.0008	0.0054	0.0015

Dose response cannot be interpreted because patients were not randomized to these *tirasemtiv* dose levels, but adjusted according to tolerability. To better understand the relationship between dose and the effect of *tirasemtiv* on SVC, patients must be randomized to specific target dose levels.

Major Lessons Learned from BENEFIT-ALS

- BENEFIT-ALS is the first clinical trial of size to demonstrate a positive and potentially clinically meaningful effect on measures of respiratory and skeletal muscle function
- The effect of *tirasemtiv* on SVC in BENEFIT-ALS is robust and should be confirmed and extended in a longer trial
 - Similar in magnitude across all subgroups evaluated (but numerically larger in patients with higher SVC values at baseline)
 - Statistically significant within the majority of subgroups evaluated
- The open-label lead-in period succeeded in preserving the blind after randomization but did not succeed in minimizing drop-outs after randomization
- *Tirasemtiv* may have cumulative and longer term pharmacologic effects

VITALITY-ALS

VITALITY-ALS: Phase III Clinical Trial of *Tirasemtiv*

Ventilatory Investigation of *Tirasemtiv* and Assessment of Longitudinal Indices after Treatment for a Year in ALS

Primary Objective

The primary objective is to assess the effect of *tirasemtiv* versus placebo on respiratory function in patients with ALS.

Secondary Objectives

Secondary objectives include:

- Evaluation of alternative methods to assess the effect of *tirasemtiv* versus placebo on percent predicted SVC in patients with ALS
- Assessment of the effect of *tirasemtiv* versus placebo on other clinical measures related to the progressive decline in respiratory function in patients with ALS
- Assessment of the effect of *tirasemtiv* versus placebo on measures of skeletal muscle function in patients with ALS

Key Design Elements in VITALITY-ALS Compared with BENEFIT-ALS

- Attempts to improve tolerability and decrease early terminations
 - Longer open-label lead-in (2 weeks vs. 1 week)
 - Slower dose titration (every 2 weeks vs. every week)
 - More flexibility regarding dose titration
- Randomization to target dose levels (vs. titration to MTD)
- Study Design
 - Open-label lead in (2 weeks)
 - Double-blind, placebo-controlled treatment (48 weeks)
 - Double-blind, placebo-controlled *tirasemtiv* withdrawal (4 weeks)
- SVC inclusion criterion increased to 70 percent predicted
- More attention to weight loss during VITALITY-ALS

VITALITY-ALS: Study Overview

- Multi-national, double-blind, randomized, placebo-controlled, stratified, parallel group study of 48 weeks of double-blind dosing of *tirasemtiv* in ALS patients who tolerate two weeks of *tirasemtiv* 125 mg BID

- Primary Endpoint:

- The change from baseline to Week 24 of the double-blind, placebo-controlled phase in percent predicted Slow Vital Capacity (SVC)

- Key Secondary Endpoints

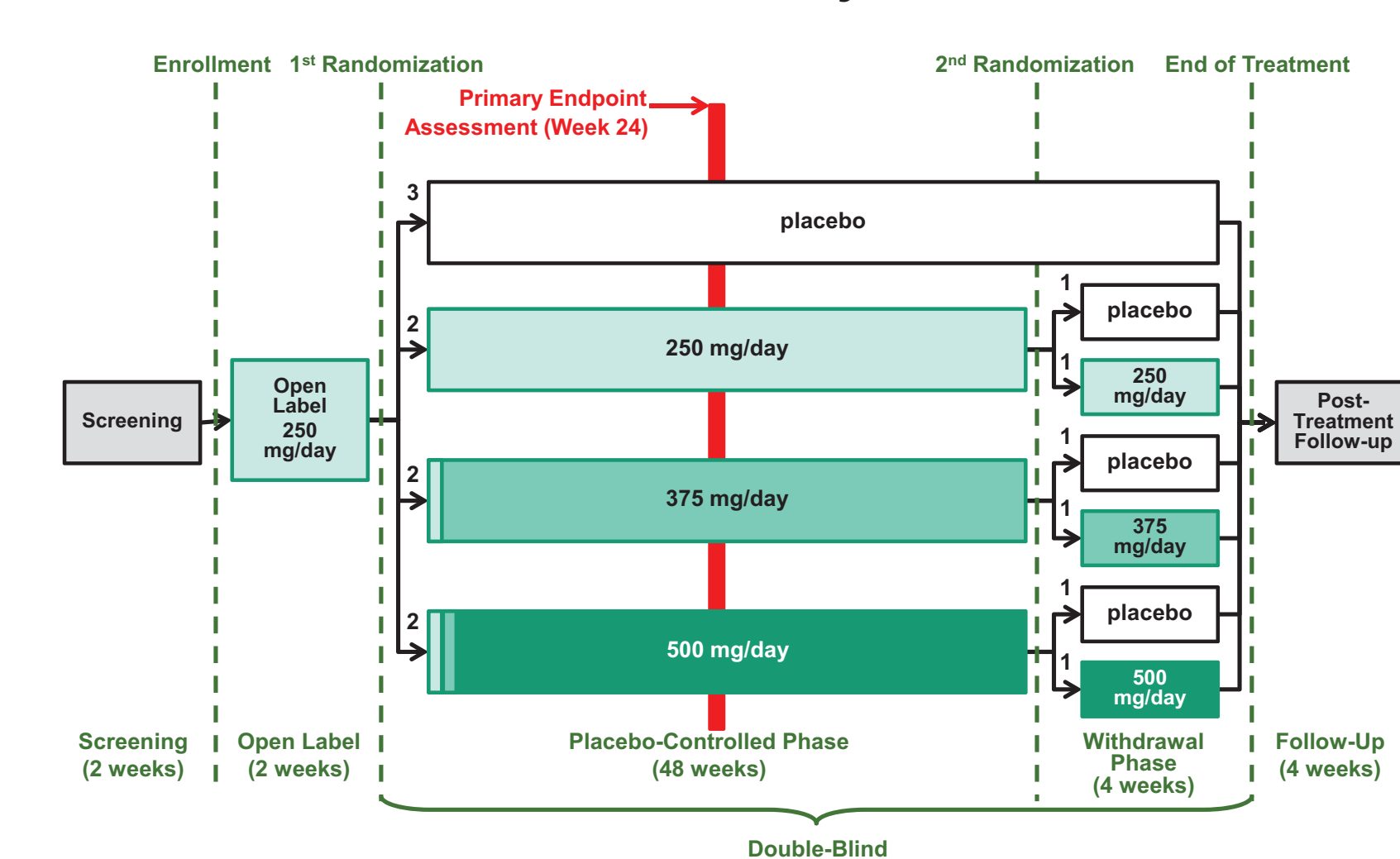
- Time to the first occurrence of a decline from baseline in percent predicted SVC ≥ 20 percentage points or the onset of respiratory insufficiency or death during all 48 weeks of double-blind, placebo-controlled treatment
- Time to the first occurrence of a decline in SVC to "50% predicted or the onset of respiratory insufficiency (defined as tracheostomy or the use of non-invasive ventilation for ≥ 22 hours per day for ≥ 10 consecutive days) or death during all 48 weeks of double-blind, placebo-controlled treatment
- Time to the first occurrence of the first use of mechanical ventilatory assistance or death during all 48 weeks of double-blind, placebo-controlled treatment
- Time to the first occurrence of a decline in the respiratory components of the ALSFRS-R (i.e., items 10, 11, and 12) or death during all 48 weeks of double-blind, placebo-controlled treatment
- Slope of the change from baseline in mega-score of muscle strength from baseline to 24 weeks of the randomized, double-blind, placebo-controlled phase

VITALITY-ALS: Study Design Overview

Three phases of the study:

- Open-label: 125 mg *tirasemtiv* twice daily for 2 weeks
- Double-Blind, Placebo Controlled:
 - Placebo: 2 placebo tablets twice daily
 - 250 mg *tirasemtiv* TDD: 125 mg twice daily
 - 375 mg *tirasemtiv* TDD: 125 mg in AM & 250 mg in PM
 - 500 mg *tirasemtiv* TDD: 250 mg in AM & 250 mg in PM
- Note: for patients randomized to 375 mg and 500 mg, dose titration will be gradual with escalation every 2 weeks
- Double-Blind, Placebo-Controlled, *Tirasemtiv* Withdrawal:
 - Placebo: maintained on placebo dose
 - *Tirasemtiv*: doubled on current *tirasemtiv* dose or crossed over to placebo

VITALITY-ALS: Study Schematic



VITALITY-ALS: Patient Journey

- Screening: 2 Weeks
- Open-Label Phase: 2 Weeks
- Double-blind, Placebo-Controlled Phase: 48 Weeks
- Double-Blind, Placebo-Controlled, *Tirasemtiv* Withdrawal Phase: 4 Weeks
- Follow-Up: 4 Weeks

