COURAGE-ALS: Results of the Phase 3 Clinical Trial of *Reldesemtiv* in ALS

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on behalf of the COURAGE-ALS Study Group

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Disclosures

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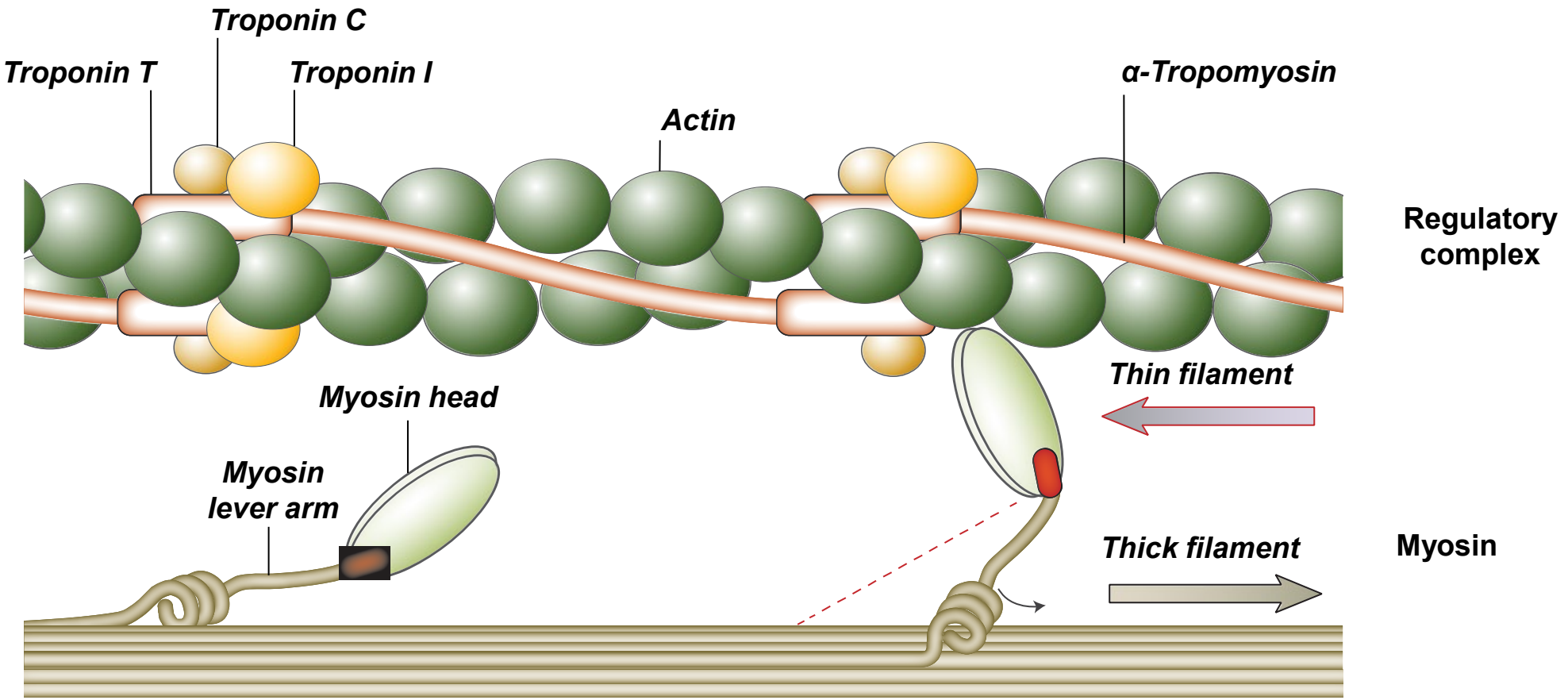
Reldesemtiv is a Selective Fast Skeletal Muscle Troponin Activator

Reldesemtiv sensitizes the sarcomere to Ca^{2+}, amplifying the response to neuromuscular input and thereby increasing muscle force



Kamisago M, et al. *N Engl J Med* 2000;343:1688-96.

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Background and Rationale

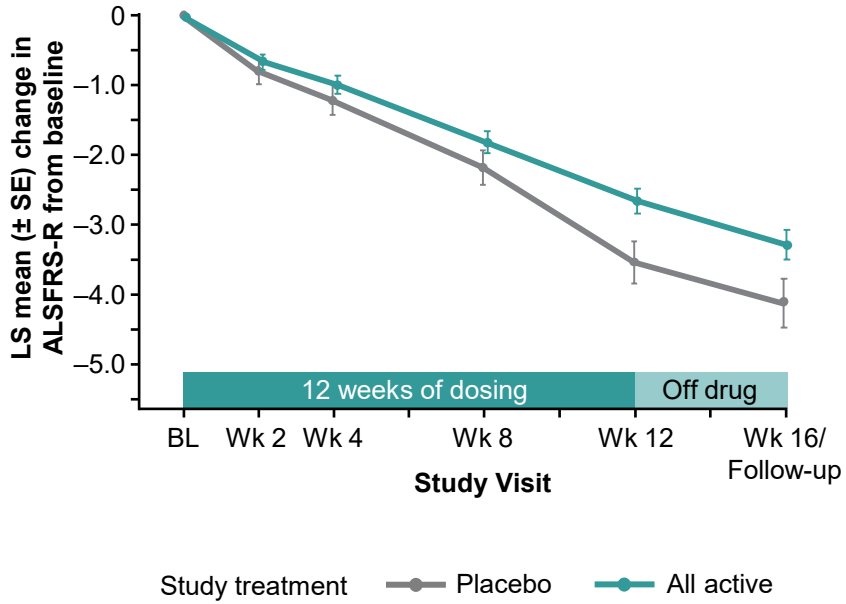
- Fast skeletal muscle troponin activators (FSTAs) increase the sensitivity of the muscle sarcomere to calcium and increase the force generated by skeletal muscle in response to submaximal rates of nerve stimulation[1]
- FSTAs increase muscle force in animal models and in normal human volunteers[1]
- In a large 3-month Phase 2 study, people living with amyotrophic lateral sclerosis (ALS) received *reldesemtiv,* a second-generation FSTA
  - *Reldesemtiv* had promising effects on ALS Functional Rating Scale-Revised (ALSFRS-R), vital capacity, and quantitative muscle strength measured with hand-held dynamometry[2]
- Although promising results were seen in the full data set and all subgroups, those participants with shorter time from onset and moderate to fast pre-study disease progression rates showed the greatest clinical signal
- For these reasons, a Phase 3 trial (NCT04944784) was deemed necessary and appropriate

1. Hwee DT, et al. *J Physiol* 2017;595:1657-70. 2. Shefner JM, et al. *Amyotroph Lateral Scler Frontotemporal Degener* 2021;22:287-99.

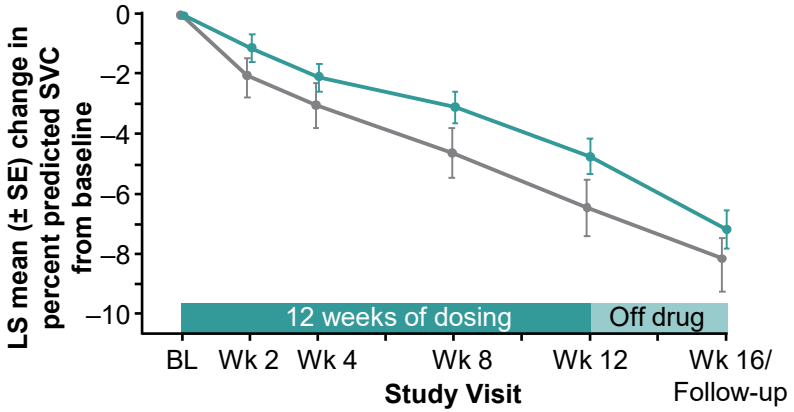
FORTITUDE-ALS

Impact of *reldesemtiv* on clinical measures: all *reldesemtiv*-treated participants compared with placebo

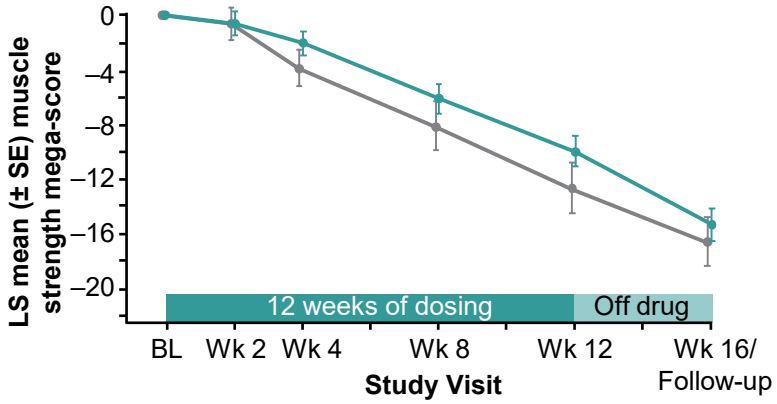
ALSFRS-R: % Change from placebo – **25%**



SVC: % Change from placebo – **27%**



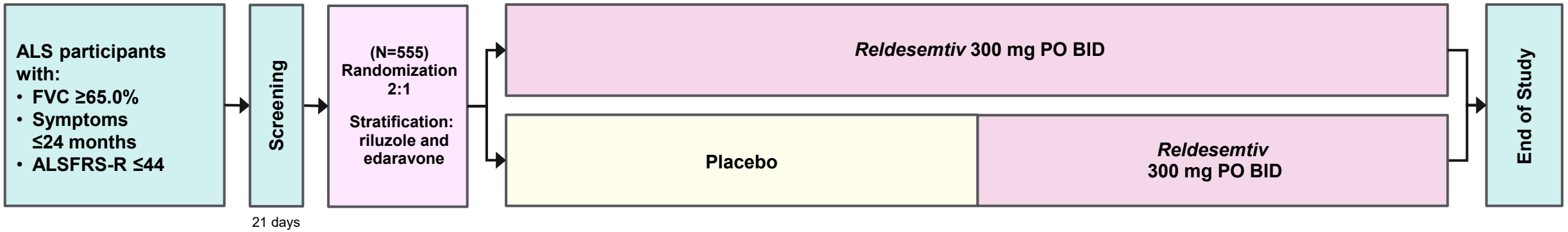
Strength: % Change from placebo – **21%**

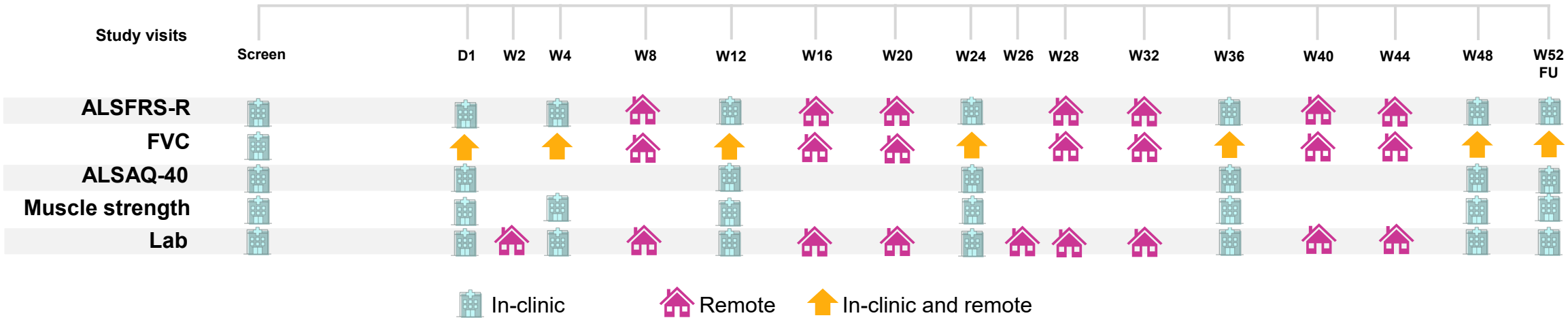


ALSFRS-R, ALS Functional Rating Scale-Revised; BL, baseline;
LS, least squares; SVC, slow vital capacity.
Shefner JM, et al. *Amyotroph Lateral Scler Frontotemporal Degener* 2021;22:287-99.

Reldesemtiv: COURAGE-ALS – Study Schematic

Global study to recruit 555 participants from 16 countries and 85 sites





ClinicalTrials.gov ID: NCT04944784.

ALS, amyotrophic lateral sclerosis; ALSAQ-40, ALS Assessment Questionnaire 40; ALSFRS-R, ALS Functional Rating Scale-Revised; BID, twice daily; D, Day; FU, follow-up; FVC, forced vital capacity; PO, by mouth; W, Week.

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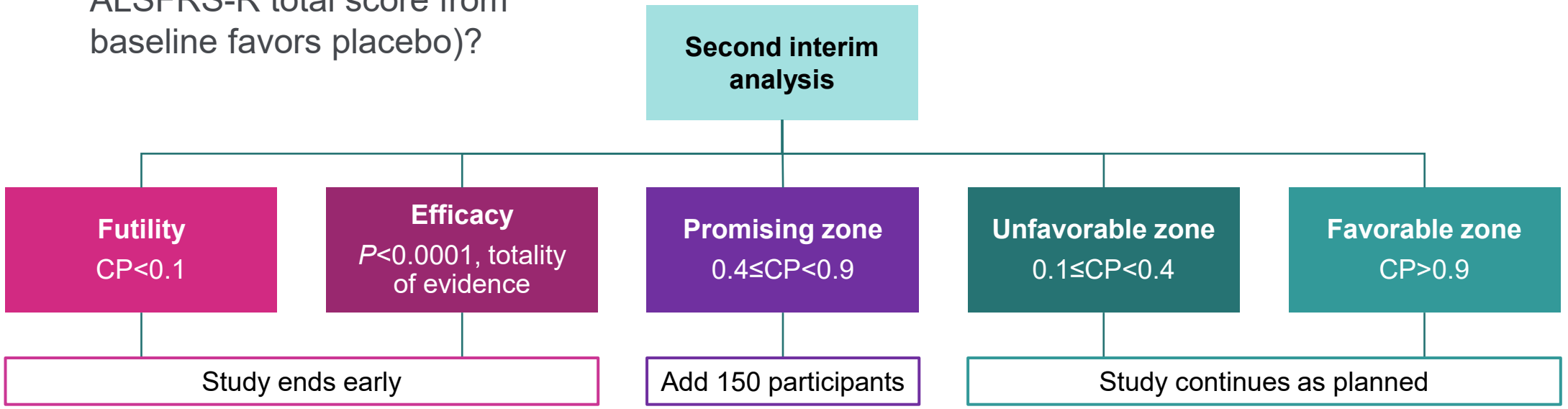
Reldesemtiv: COURAGE-ALS – Primary and Secondary Endpoints

Primary	Secondary
• Change from baseline to Week 24 in the **ALSFRS-R total score**	• **Combined assessment of ALSFRS-R total score, time to onset of respiratory insufficiency, and survival time up to Week 24 using a joint rank test**, following an algorithm that ranks each patient against the other • Participants with respiratory insufficiency are ranked lower than those with the largest drops in ALSFRS-R scores but higher than those who have died • Change from baseline to Week 24 in the **percent predicted FVC** • Change from baseline to Week 24 in the **ALSAQ-40** • Change from baseline to Week 24 in **handgrip strength** (average of both hands)

ClinicalTrials.gov ID: NCT04944784.
ALSAQ-40, ALS Assessment Questionnaire 40; ALSFRS-R, ALS Functional Rating Scale-Revised; FVC, forced vital capacity.

Reldesemtiv: COURAGE-ALS – Interim Analyses

- First interim analysis
  - Scheduled 12 weeks after at least one-third of the participants were randomized
    - Is the trial futile (estimated treatment difference of Δ in ALSFRS-R total score from baseline favors placebo)?
- Second interim analysis (results through Week 24)[1]
  - Timing of second interim analysis driven by goal to have ~40% of participants available for analysis
    - Is the trial futile?
    - Is the trial adequately powered?



CP, conditional power.

1. Joshua Chen YH, et al. *Stat Med* 2004;23:1023-38.

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After the second interim analysis, the independent Data Monitoring Committee recommended the study be stopped for futility

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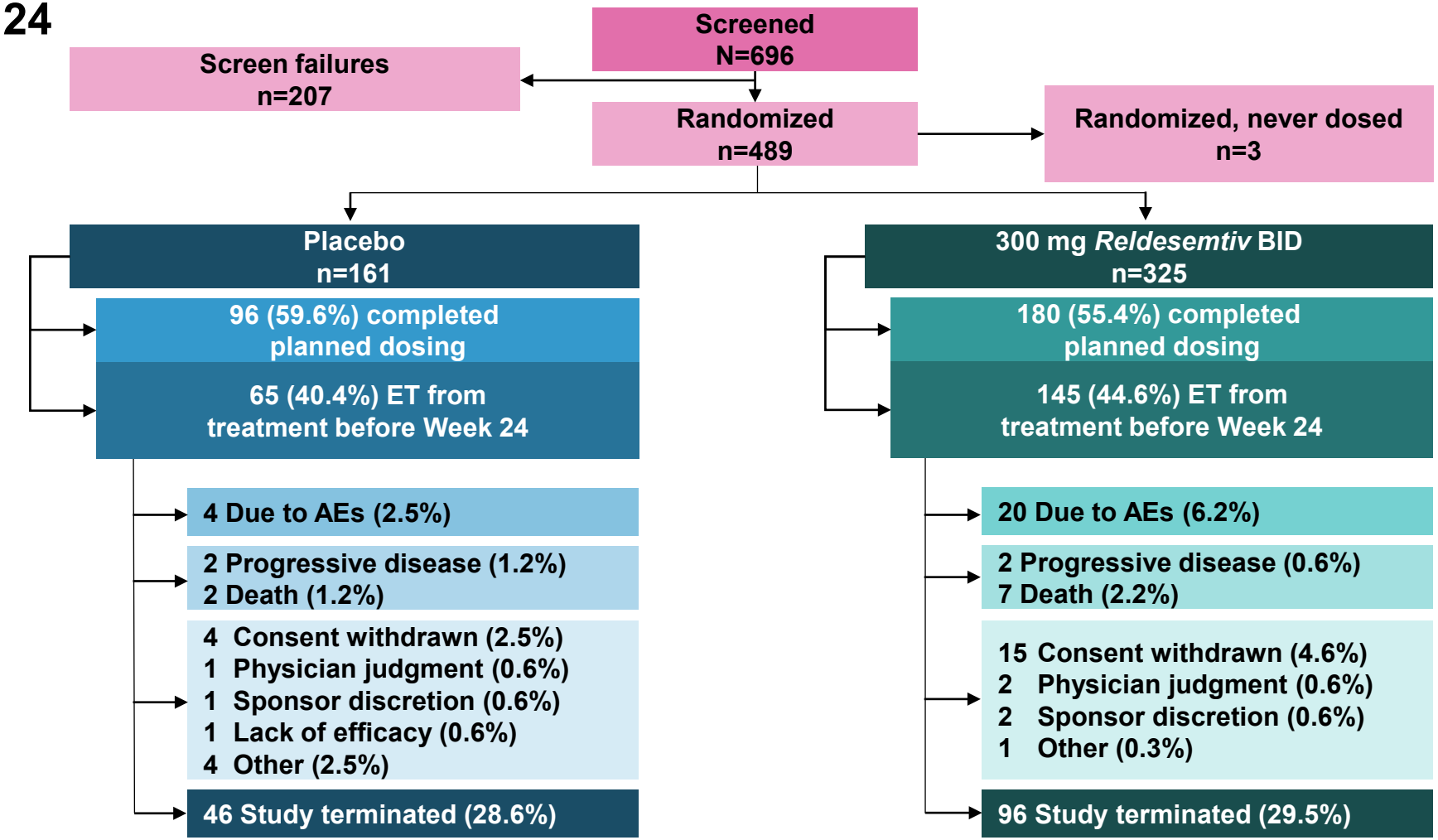
Disposition

Through Week 24



AE, adverse event; BID, twice daily; ET, early termination.

Reldesemtiv: COURAGE-ALS – Key Baseline Data

	Final analysis	
	Placebo	***Reldesemtiv***
Age, years, mean	59.8	59.2
Female, %	40.3	35.0
Weight, kg, mean	78.1	79.9
BMI, kg/m^2, mean	26.4	26.9
FVC, % predicted	85.8	84.5
ALSFRS-R score	36.6	37.2
ALSAQ-40 score	31.6	29.1
No riluzole or edaravone, %	10.7	8.7
Riluzole alone, %	77.4	77.1
Edaravone alone, %	0	0.6
Both riluzole + edaravone, %	11.9	13.6
El Escorial criteria for ALS, definite, %	22.6	26.7
Time since ALS symptom onset, months	16.2	15.6
Time since ALS diagnosis, months	6.7	6.4
Pre-study disease progression rate, mean[a]	0.83	0.79

[a] =48 minus baseline ALSFRS-R total score divided by symptom duration in months.

ALS, amyotrophic lateral sclerosis; ALSAQ-40, ALS Assessment Questionnaire 40; ALSFRS-R, ALS Functional Rating Scale-Revised; BMI, body mass index; FVC, forced vital capacity.

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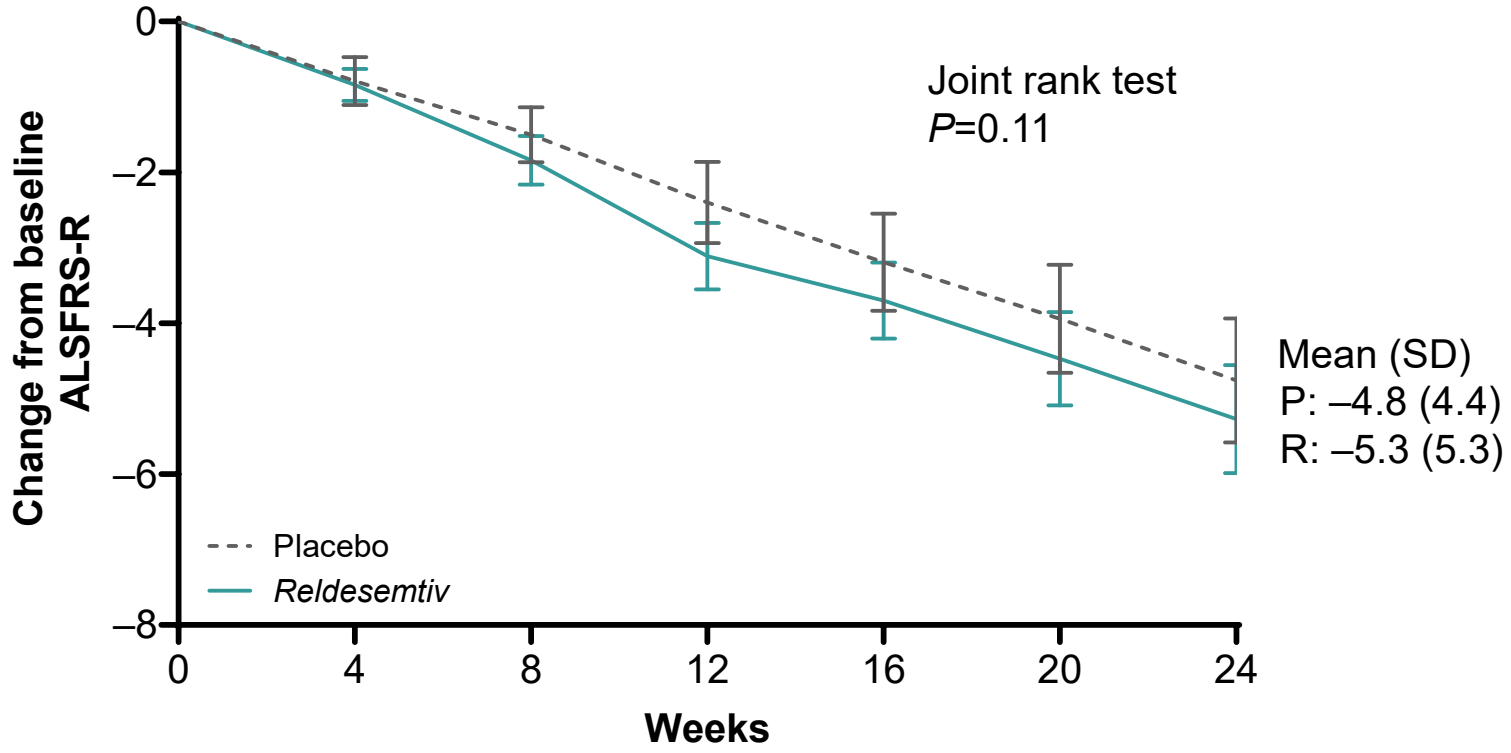
Observed Change from Baseline Through Week 24 – ALSFRS-R



Participants, n							
Placebo	159	156	152	141	123	116	113
Reldesemtiv	322	315	293	285	245	217	214

ALSFRS-R, ALS Functional Rating Scale-Revised.

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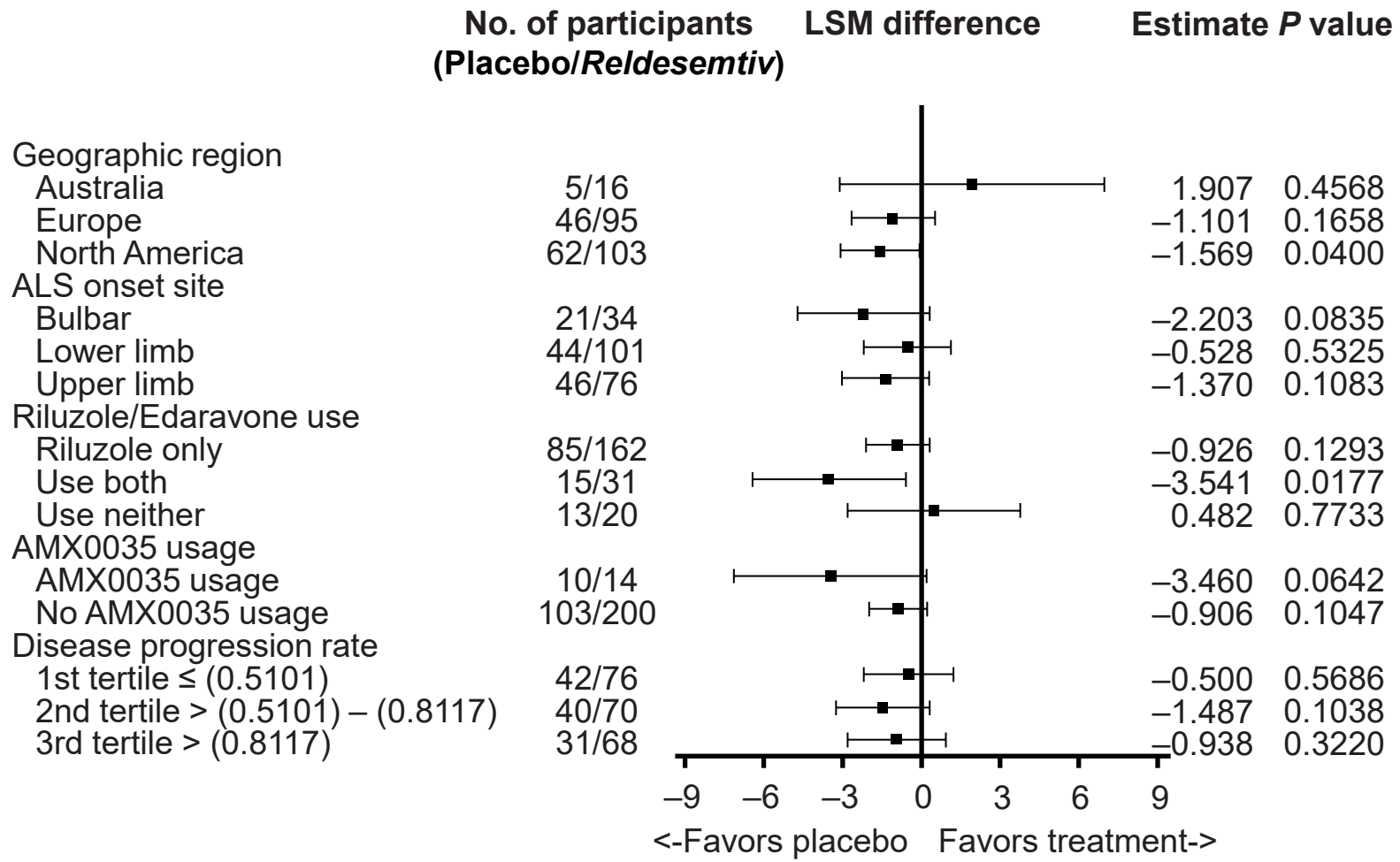
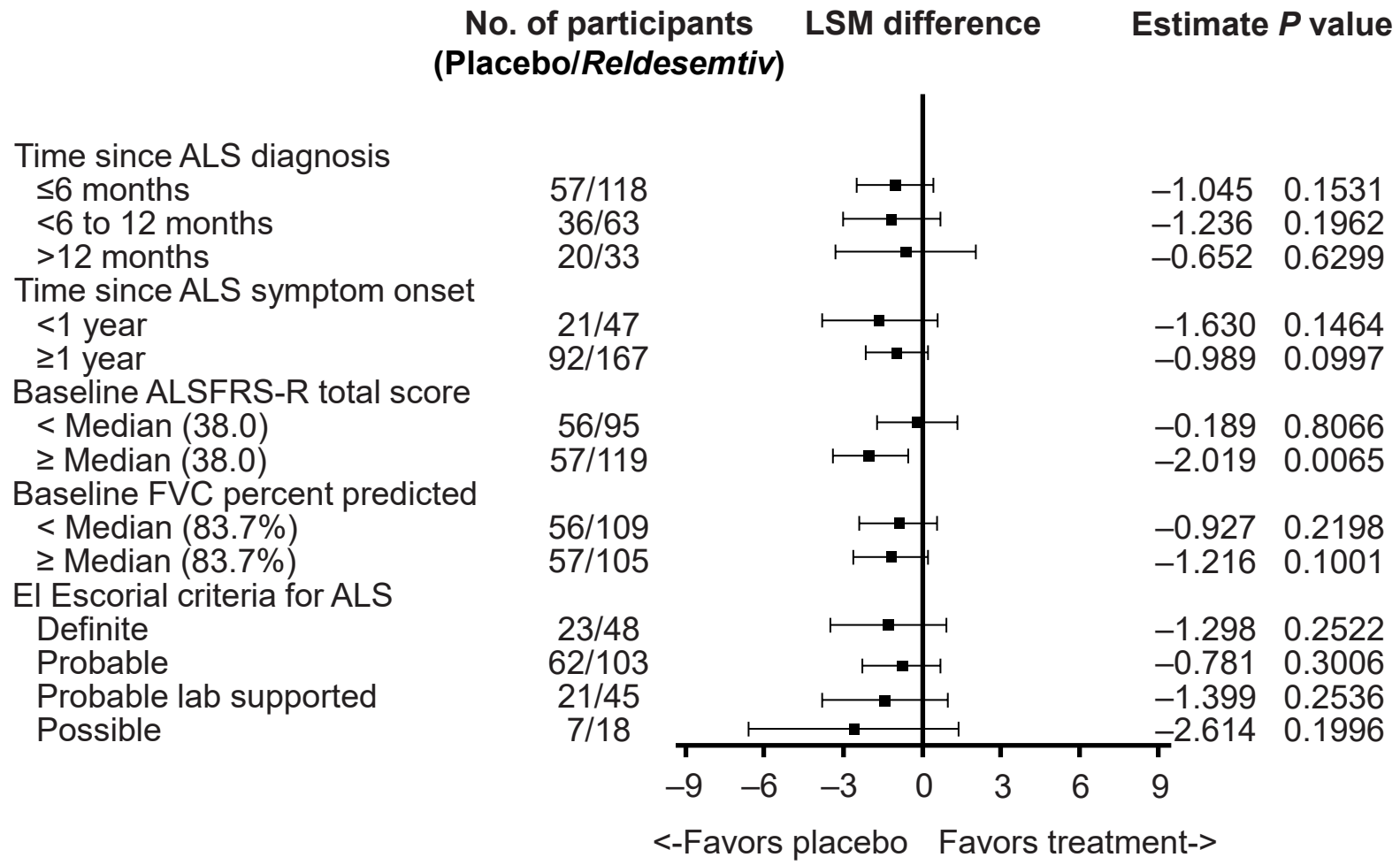
Change in ALSFRS-R by Subgroup



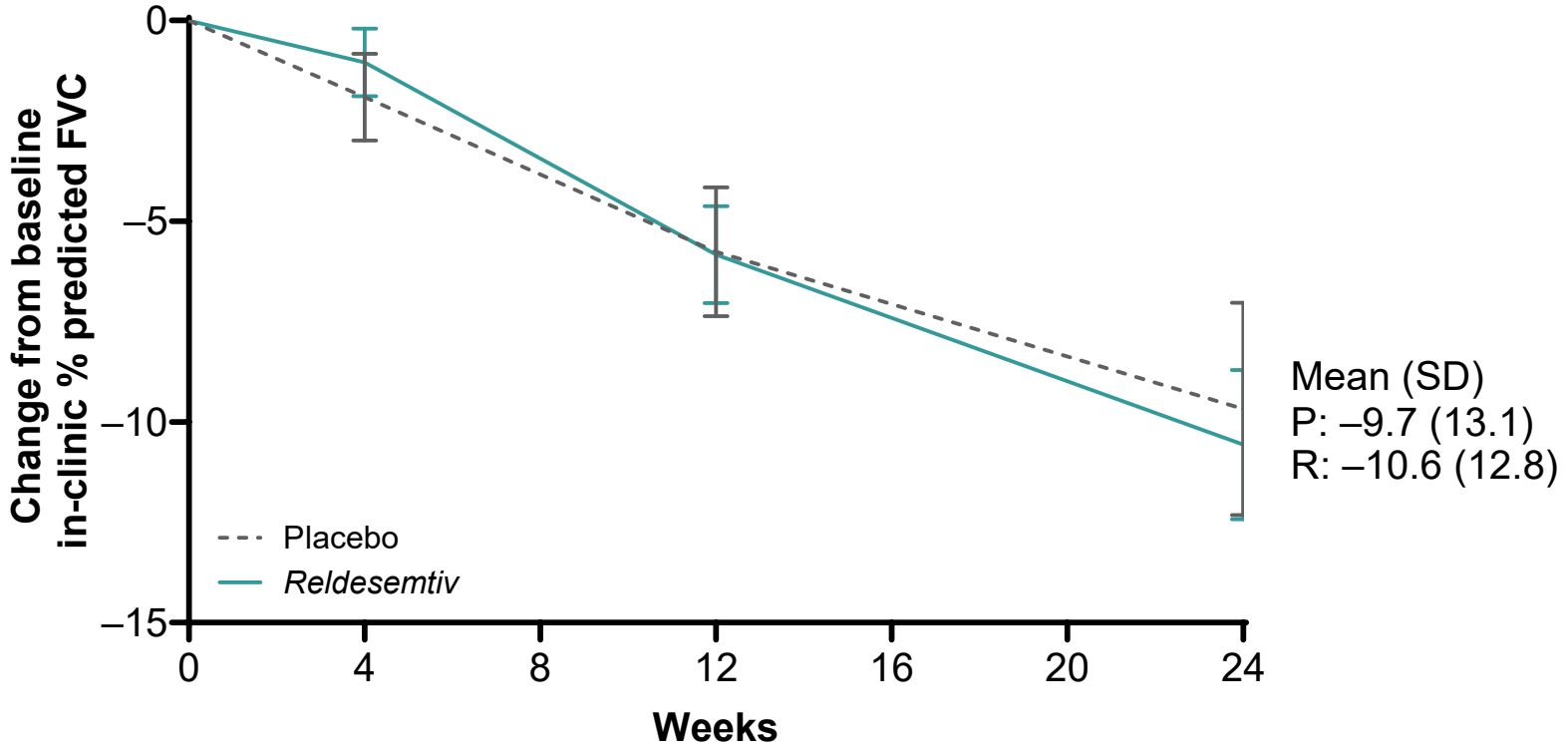
ALS, amyotrophic lateral sclerosis; LSM, least squares mean.

Change in ALSFRS-R by Subgroup



ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; FVC, forced vital capacity; LSM, least squares mean.

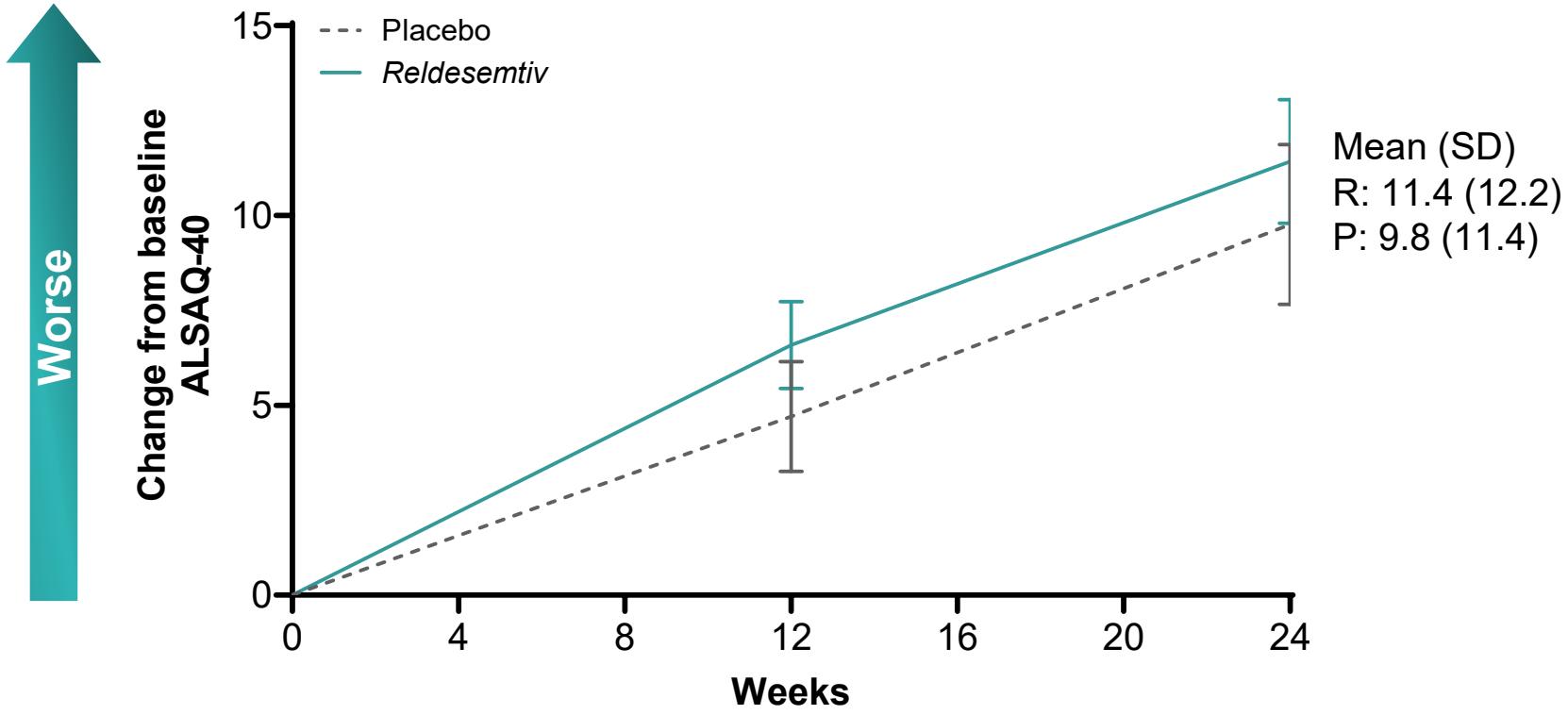
Change from Baseline Through Week 24: In-clinic % Predicted FVC



Participants, n				
Placebo	154	134	128	97
Reldesemtiv	317	271	253	185

FVC, forced vital capacity.

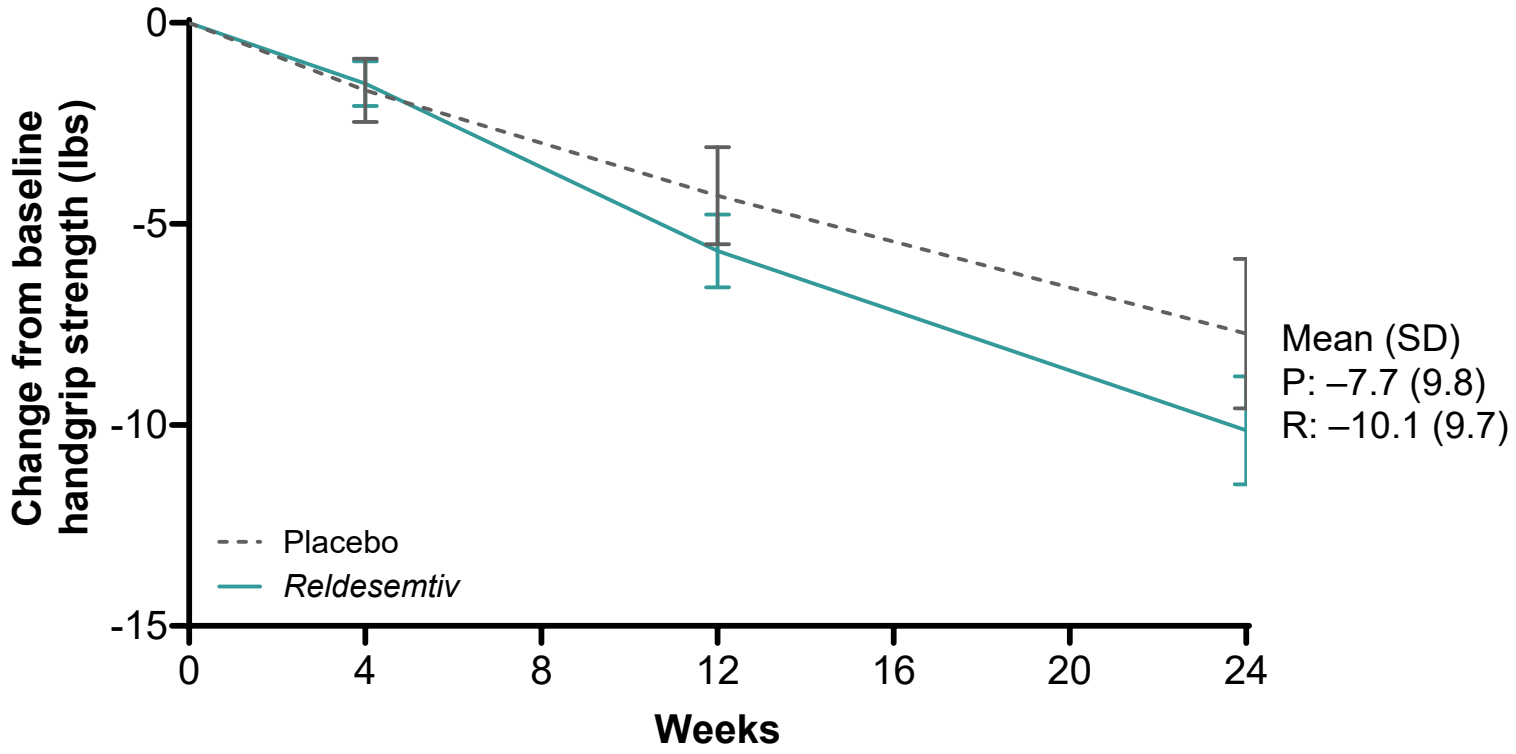
Change from Baseline Through Week 24: ALSAQ-40



Participants, n			
Placebo	158	150	114
Reldesemtiv	321	303	218

ALSAQ-40, ALS Assessment Questionnaire 40.

Change from Baseline Through Week 24: Handgrip Strength (lbs)



Participants, n				
Placebo	159	149	136	109
Reldesemtiv	321	298	276	202

Did the Modification of Inclusion Criteria Have the Intended Consequences?

Designed to enroll more rapidly progressing participants

- FORTITUDE-ALS
  - Diagnosis of ALS ≤24 months
  - No restrictions on ALSFRS-R score
- COURAGE-ALS
  - Symptoms of ALS ≤24 months
  - Maximum ALSFRS-R total score of 44

Pre-study rates of disease progression[a]					
	1st tertile	2nd tertile	3rd tertile	Mean	Median
FORTITUDE-ALS	≤0.37	0.38–0.067	>0.67	0.62	0.50
COURAGE-ALS	≤0.51	0.52–0.81	>0.81	0.81	0.64

- In COURAGE-ALS, participants with faster pre-study rates of disease progression than in FORTITUDE-ALS were enrolled

[a] =48 minus baseline ALSFRS-R total score divided by duration of ALS symptoms.

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Safety

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COURAGE-ALS: Serious Adverse Events

System Organ Class	Placebo (n=161)	*Reldesemtiv* (n=325)	Overall (N=486)
Participants with ≥1 serious TEAE	25 (15.5)	41 (12.6)	66 (13.6)
Serious TEAEs occurring in ≥2 participants in the overall population			
Respiratory, thoracic and mediastinal disorders	8 (5.0)	14 (4.3)	22 (4.5)
Gastrointestinal disorders	5 (3.1)	8 (2.5)	13 (2.7)
Infections and infestations	3 (1.9)	7 (2.2)	10 (2.1)
Investigations	1 (0.6)	5 (1.5)	6 (1.2)
Metabolism and nutrition disorders	0	3 (0.9)	3 (0.6)
Nervous system disorders	1 (0.6)	3 (0.9)	4 (0.8)
Psychiatric disorders	3 (1.9)	3 (0.9)	6 (1.2)
Injury, poisoning and procedural complications	2 (1.2)	2 (0.6)	4 (0.8)
Surgical and medical procedures	2 (1.2)	0	2 (0.4)

Data are shown as n (%) through Week 24.
TEAE, treatment-emergent adverse event.

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COURAGE-ALS: Treatment-Emergent Adverse Events

System Organ Class	Placebo (n=161)	*Reldesemtiv* (n=325)	Overall (N=486)
Participants with ≥1 TEAE	125 (77.6)	258 (79.4)	383 (78.8)
Laboratory			
Investigations[a]	19 (11.8)	61 (18.8)	80 (16.5)
Alanine aminotransferase increased	3 (1.9)	21 (6.5)	24 (4.9)
Aspartate aminotransferase increased	1 (0.6)	18 (5.5)	19 (3.9)

Data are shown as n (%) through Week 24.
[a] Only System Organ Class TEAE that differed in frequency by >5%.
TEAE, treatment-emergent adverse event.

Mortality in COURAGE-ALS (Intent-to-Treat)

Through Week 48 based upon original treatment assignment

Cause of death	Total deaths	DBPC (first 24 weeks)		Weeks 24–48	
		Placebo n=161	*Reldesemtiv* n=325	Placebo[a]	*Reldesemtiv*[a]
Respiratory failure / arrest	12 (2.5)	1 (0.6)	4 (1.2)	3 (1.9)	4 (1.2)
Assisted suicide / euthanasia	9 (1.9)	4 (2.5)	3 (0.9)	0	2 (0.6)
ALS	7 (1.4)	1 (0.6)	2 (0.6)	2 (1.2)	2 (0.6)
Cardiac arrest	2 (0.4)	0	1 (0.3)	1 (0.6)	0
Infections[b]	5 (1.0)	0	1 (0.3)	0	4 (1.2)
Unknown cause	1 (0.2)	0	1 (0.3)	0	0
Totals	36 (7.4)	6 (3.7)	9 (2.7)	6 (3.7)	15 (4.6)

All deaths were assessed as not related to study drug

Data are shown as n (%).
[a] Original treatment assignment.
[b] COVID-19, RSV, sepsis, pneumonia, infectious mononucleosis.
ALS, amyotrophic lateral sclerosis; DBPC, double-blind placebo-controlled; RSV, respiratory syncytial virus.

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Summary of Results and Conclusions

- COURAGE-ALS was stopped due to futility at the time of the second interim analysis
- *Reldesemtiv* did not alter the progression from baseline to Week 24 of the ALSFRS-R, forced vital capacity, grip strength, or ALS Assessment Questionnaire 40 in a comparison between those assigned to placebo and *reldesemtiv* in the full data set or in predefined subgroups
- There was no significant difference in the joint rank test for those taking placebo compared with *reldesemtiv*
- Changes made to the inclusion criteria from FORTITUDE-ALS resulted in enrolling participants with ALS who had faster rates of decline in pre-study disease progression
- Although the discordance between the results from the Phase 2 and Phase 3 studies of *reldesemtiv* in ALS is striking, COURAGE-ALS provides no support for the hypothesis that fast skeletal muscle troponin activation is a beneficial strategy in ALS
- Development of *reldesemtiv* for ALS has been halted

ALSAQ-40, ALS Assessment Questionnaire 40; ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; FVC, forced vital capacity.

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Backup

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Combined Assessment of Function and Survival

Combined assessment of change in ALSFRS-R total score, time to onset of dependence on assisted ventilation, and survival time up to Week 24