ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: November 27, 2024

ClinicalTrials.gov ID: NCT04944784

Study Identification

Unique Protocol ID:	CY 5031
Brief Title:	A Study to Evaluate the Efficacy and Safety of Reldesemtiv in Patients With Amyotrophic Lateral Sclerosis (ALS) (COURAGE-ALS)
Official Title:	A Phase 3, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Reldesemtiv in Patients With Amyotrophic Lateral Sclerosis (ALS)
Secondary IDs:	2020-004040-29 [EudraCT Number]

Study Status

Record Verification:	November 2024
Overall Status:	Terminated [The DMC recommended the trial be discontinued due to futility following a planned second interim analysis.]
Study Start:	August 16, 2021 [Actual]
Primary Completion:	July 18, 2023 [Actual]
Study Completion:	July 18, 2023 [Actual]

Sponsor/Collaborators

Sponsor:	Cytokinetics
Responsible Party:	Sponsor
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	Yes

U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	Yes
IND/IDE Information:	FDA Center: CDER IND/IDE Number: 134567 Serial Number: 0059 Has Expanded Access: No
Human Subjects Review:	Board Status: Approved Approval Number: SSU00136250 Board Name: Advarra Board Affiliation: Phone: Email: Address: 6940 Columbia Gateway Dr., Suite 110, Columbia, MD 21046
Data Monitoring:	Yes
FDA Regulated Intervention:	Yes
Section 801 Clinical Trial:	Yes

Study Description

Brief Summary:	The purpose of this study is to assess the effect of reldesemtiv versus placebo on functional outcomes in ALS.
Detailed Description:	COURAGE-ALS is a Phase 3, double-blind, randomized, placebo-controlled trial of reldesemtiv in patients aged 18 to 80 with ALS. The screening and qualification period for the trial will be no more than 21 days in duration. Approximately 555 eligible ALS patients will be randomized (2:1) to receive the following dose of reldesemtiv or placebo (stratified by riluzole use/non-use and edaravone use/non-use) for the first 24 weeks (double-blind, placebo-controlled period): • 300 mg reldesemtiv twice a day for a 600 mg total daily dose (TDD) • Placebo twice daily At the end of the 24-week double-blind, placebo-controlled period, patients will transition to the active drug period, where all patients will receive the following dose of reldesemtiv for the next 24 weeks: • 300 mg reldesemtiv twice a day for a 600 mg TDD for patients who were not down titrated during the 24 weeks of blinded dosing • 150 mg reldesemtiv twice a day for a 300 mg TDD for patients who were down titrated during the 24 weeks of blinded dosing

Conditions

Conditions:	Amyotrophic Lateral Sclerosis
Keywords:	Amyotrophic Lateral Sclerosis ALS CK-2127107 Reldesemtiv COURAGE-ALS

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	4
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Allocation:	Randomized
Enrollment:	489 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Reldesemtiv Group, Double-Blind Period Participants in this arm take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Day 1 until Week 24.	Drug: Reldesemtiv Reldesemtiv Oral Tablet Other Names: • Reldesemtiv
Placebo Comparator: Placebo Group, Double-Blind Period Participants in this arm take 2 placebo oral tablets twice a day from Day 1 until Week 24.	Drug: Placebo Placebo Oral Tablet Other Names: • Placebo
Experimental: Delayed Start Group, Active Drug Period Participants in this arm were those who received placebo in the double-blind period and reldesemtiv in the active drug period. Participants take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Week 24 until Week 48. Patients who were down-titrated for any	Drug: Reldesemtiv Reldesemtiv Oral Tablet Other Names: • Reldesemtiv

Arms	Assigned Interventions
reason during the 24 weeks of blinded dosing take 1 reldesemtiv 150 mg oral tablet twice a day for a 300 mg total daily dose from Week 24 until Week 48.	
Experimental: Early Start Group, Active Drug Period Participants in this arm were those who received reldesemtiv in the double-blind and active drug periods. Participants take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Week 24 until Week 48. Patients who were down-titrated for any reason during the 24 weeks of blinded dosing take 1 reldesemtiv 150 mg oral tablet twice a day for a 300 mg total daily dose from Week 24 until Week 48.	Drug: Reldesemtiv Reldesemtiv Oral Tablet Other Names: • Reldesemtiv

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age: 80 Years

Sex: All

Gender Based: No

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria:

- Males or Females between the ages of 18 and 80 years of age, inclusive
- Diagnosis of familial or sporadic ALS (defined as meeting the laboratory-supported probable, probable, or definite criteria for ALS according to the World Federation of Neurology El Escorial criteria). Patients who meet the possible criteria are eligible if they have lower motor neuron findings; those who have purely upper motor neuron findings are ineligible.
- First symptom of ALS ≤ 24 months prior to screening. The qualifying first symptoms of ALS are limited to manifestations of weakness in extremity, bulbar, or respiratory muscles.
- ALSFRS-R total score ≤ 44 at screening. Patients with a total score of 45 or higher may be rescreened 60±7 days following the original screening date.
- Upright FVC ≥ 65.0% of predicted for age, height, sex and ethnicity at screening according to Global Lung Initiative equation
- Must be either on riluzole for ≥ 30 days prior to screening or have not taken it for at least 30 days prior to screening
- Must have completed at least 2 cycles of edaravone at the time of screening or have not received it for at least 30 days prior to screening
- Able to swallow whole tablets

Exclusion Criteria:

- eGFRCysC < 45.0 mL/min/1.73 m2 at screening

- Urine protein/creatinine ratio > 1 mg/mg (113 mg/mmol) at screening
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3-times the upper limit of normal (ULN)
- Total bilirubin (TBL), direct or indirect bilirubin above the ULN.
- Cognitive impairment, related to ALS or otherwise that impairs the patient's ability to understand and/or comply with study procedures and provide informed consent
- Other medically significant neurological conditions that could interfere with the assessment of ALS symptoms, signs or progression.
- Has a tracheostomy

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IPDSharing

Plan to Share IPD: No

References

Citations:

Links:

Available IPD/Information:

Documents

Study Protocol
Document Date: February 24, 2023
Uploaded: 07/16/2024 00:56

Statistical Analysis Plan
Document Date: February 24, 2023
Uploaded: 07/16/2024 00:57

Study Results

Participant Flow

Pre-assignment Details	Three participants were randomized but never dosed in the study.

Reporting Groups

	Description
Reldesemtiv Group, Double-Blind Period	Participants in this arm take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Day 1 until Week 24. Reldesemtiv: Reldesemtiv Oral Tablet
Placebo Group, Double-Blind Period	Participants in this arm take 2 placebo oral tablets twice a day from Day 1 until Week 24. Placebo: Placebo Oral Tablet
Delayed Start Group, Active Drug Period	Participants in this arm were those who received placebo in the double-blind period and reldesemtiv in the active drug period. Participants take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Week 24 until Week 48. Patients who were down-titrated for any reason during the 24 weeks of blinded dosing take 1 reldesemtiv 150 mg oral tablet twice a day for a 300 mg total daily dose from Week 24 until Week 48. Reldesemtiv: Reldesemtiv Oral Tablet
Early Start Group, Active Drug Period	Participants in this arm were those who received reldesemtiv in the double-blind and active drug periods. Participants take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Week 24 until Week 48. Patients who were down-titrated for any reason during the 24 weeks of blinded dosing take 1 reldesemtiv 150 mg oral tablet twice a day for a 300 mg total daily dose from Week 24 until Week 48. Reldesemtiv: Reldesemtiv Oral Tablet

Double-blind Period

	Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period	Delayed Start Group, Active Drug Period	Early Start Group, Active Drug Period
Started	325	161	0	0
Completed	180	96	0	0
Not Completed	145	65	0	0
Study Terminated by Sponsor	96	46	0	0
Adverse Event	20	4	0	0
Withdrawal by Subject	15	4	0	0
Death	7	2	0	0
Physician Decision	2	1	0	0

	Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period	Delayed Start Group, Active Drug Period	Early Start Group, Active Drug Period
Lack of Efficacy	0	1	0	0
Sponsor Request	2	1	0	0
Planned Medical Assistance in Dying	0	3	0	0
Participant Choice	1	1	0	0
Progressive Disease	2	2	0	0

Active Drug Period

	Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period	Delayed Start Group, Active Drug Period	Early Start Group, Active Drug Period
Started	0	0	96	180
Completed	0	0	31	62
Not Completed	0	0	65	118
Study Terminated by Sponsor	0	0	49	92
Adverse Event	0	0	3	6
Withdrawal by Subject	0	0	4	7
Death	0	0	3	4
Lack of Efficacy	0	0	2	2
Planned Medical Assistance in Dying	0	0	0	1

	Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period	Delayed Start Group, Active Drug Period	Early Start Group, Active Drug Period
Participant Choice	0	0	0	1
Progressive Disease	0	0	4	4
Lost to Follow-up	0	0	0	1

Baseline Characteristics

Baseline Analysis Population Description

The Safety Analysis Set, which included all enrolled participants, was used for the baseline analysis population.

Reporting Groups

	Description
Reldesemtiv Group, Double-Blind Period	Participants in this arm take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Day 1 until Week 24. Reldesemtiv: Reldesemtiv Oral Tablet
Placebo Group, Double-Blind Period	Participants in this arm take 2 placebo oral tablets twice a day from Day 1 until Week 24. Placebo: Placebo Oral Tablet

Baseline Measures

		Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period	Total
Overall Number of Participants		325	161	486
Age, Continuous [1]	Number Analyzed	323 participants	159 participants	482 participants
Mean (Standard Deviation) Unit of measure: years		59.2 (11.00)	59.8 (10.79)	59.4 (10.92)
		[1] Measure Analysis Population Description: The Full Analysis Set, which was used for efficacy outcome measures, was used for the baseline measure analysis population.		

		Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period	Total
Sex: Female, Male Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	325 participants	161 participants	486 participants
	Female	113 34.77%	64 39.75%	177 36.42%
	Male	212 65.23%	97 60.25%	309 63.58%
Ethnicity (NIH/ OMB) Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	325 participants	161 participants	486 participants
	Hispanic or Latino	15 4.62%	12 7.45%	27 5.56%
	Not Hispanic or Latino	278 85.54%	132 81.99%	410 84.36%
	Unknown or Not Reported	32 9.85%	17 10.56%	49 10.08%
Race (NIH/OMB) Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	325 participants	161 participants	486 participants
	American Indian or Alaska Native	1 0.31%	0 0%	1 0.21%
	Asian	6 1.85%	3 1.86%	9 1.85%
	Native Hawaiian or Other Pacific Islander	0 0%	0 0%	0 0%
	Black or African American	1 0.31%	4 2.48%	5 1.03%
	White	308 94.77%	149 92.55%	457 94.03%
	More than one race	9 2.77%	5 3.11%	14 2.88%

		Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period	Total
	Unknown or Not Reported	0 0%	0 0%	0 0%
Region of Enrollment Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	325 participants	161 participants	486 participants
United States		97 29.85%	56 34.78%	153 31.48%
United Kingdom		0 0%	3 1.86%	3 0.62%
Switzerland		2 0.62%	0 0%	2 0.41%
Portugal		12 3.69%	3 1.86%	15 3.09%
Spain		29 8.92%	10 6.21%	39 8.02%
Canada		48 14.77%	24 14.91%	72 14.81%
Netherlands		5 1.54%	7 4.35%	12 2.47%
Sweden		8 2.46%	7 4.35%	15 3.09%
Belgium		6 1.85%	1 0.62%	7 1.44%
Ireland		6 1.85%	2 1.24%	8 1.65%
Poland		9 2.77%	7 4.35%	16 3.29%
Denmark		1 0.31%	0 0%	1 0.21%
Italy		21 6.46%	11 6.83%	32 6.58%
Australia		22 6.77%	5 3.11%	27 5.56%
France		24 7.38%	14 8.7%	38 7.82%
Germany		35 10.77%	11 6.83%	46 9.47%

		Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period	Total
Forced vital capacity (FVC) percent predicted [1] Mean (Standard Deviation) Unit of measure: percent predicted	Number Analyzed	323 participants	159 participants	482 participants
		84.5 (14.69)	85.8 (14.19)	84.9 (14.53)
		[1] Measure Analysis Population Description: Full Analysis Set was used.		
ALSFRS-R total score [1, 2] Mean (Standard Deviation) Unit of measure: score on a scale	Number Analyzed	323 participants	159 participants	482 participants
		37.2 (4.97)	36.6 (5.44)	37.0 (5.14)
		[1] Measure Description: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) total score; rating scale 0 to 48; higher scores indicate better functional [2] Measure Analysis Population Description: Full Analysis Set was used.		
Body Mass Index [1] Mean (Standard Deviation) Unit of measure: kg/m^2	Number Analyzed	323 participants	159 participants	482 participants
		26.9 (5.67)	26.4 (4.41)	26.8 (5.29)
		[1] Measure Analysis Population Description: Full Analysis Set was used.		

		Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period	Total
ALSAQ-40 Total Score [1, 2] Mean (Standard Deviation) Unit of measure: score on a scale	Number Analyzed	323 participants	159 participants	482 participants
		29.1 (15.56)	31.6 (16.80)	29.9 (16.00)
		[1] Measure Description: ALSAQ-40 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; summary scores range from 0 (best health status) to 100 (worst health status); ALSAQ-40 total score is calculated as the sum of the summary scores from the 5 domains; lower score corresponds to better health-related quality of life. [2] Measure Analysis Population Description: Full Analysis Set was used.		
Average Maximum Handgrip Strength [1] Mean (Standard Deviation) Unit of measure: pounds	Number Analyzed	323 participants	159 participants	482 participants
		40.22 (26.122)	38.28 (26.439)	39.58 (26.216)
		[1] Measure Analysis Population Description: Full Analysis Set was used.		

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Effect of Reldesemtiv Versus Placebo on Functional Outcomes in Amyotrophic Lateral Sclerosis (ALS)
Measure Description	Change from baseline to Week 24 in Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) total score using MMRM without multiple imputation; rating scale 0 to 48; higher scores indicate better functional status
Time Frame	Baseline to Week 24

Analysis Population Description
Full Analysis Set

Reporting Groups

	Description
Reldesemtiv Group, Double-Blind Period	Participants in this arm take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Day 1 until Week 24. Reldesemtiv: Reldesemtiv Oral Tablet
Placebo Group, Double-Blind Period	Participants in this arm take 2 placebo oral tablets twice a day from Day 1 until Week 24. Placebo: Placebo Oral Tablet

Measured Values

	Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period
Overall Number of Participants Analyzed	323	159
Effect of Reldesemtiv Versus Placebo on Functional Outcomes in Amyotrophic Lateral Sclerosis (ALS) Mean (Standard Deviation) Unit of measure: score on a scale	-5.57 (5.307)	-4.76 (4.420)

2. Secondary Outcome Measure:

Measure Title	Effect of Reldesemtiv Versus Placebo on Combined Functional and Survival Outcomes in Amyotrophic Lateral Sclerosis (ALS)
Measure Description	Composite Assessment of Function and Survival (CAFS) compares ranked outcomes based on change from baseline in ALS Functional Rating Scale-Revised (ALSFRS-R) score (0-48; higher scores indicate better function), time in months to dependence on assisted ventilation (DOAV) and time in months to death. Deceased participants are ranked by time-to-death; earliest deaths ranked the lowest. DOAV survivors are ranked more favorably than those who have died but lower than those alive and not DOAV. Non-DOAV survivors are ranked based on change in ALSFRS-R (largest decline in ALSFRS-R ranked lower than less decline or improvement in ALSFRS-R). Unitless ranked scores range from 1-482 (Full Analysis Set) with larger rank scores associated with a better outcome. Ranks were analyzed using stratified Wilcoxon test comparing the ranked scores between reldesemtiv and placebo, adjusting for baseline riluzole and edaravone use. The win probability and the ratio (reldesemtiv vs placebo) are presented.
Time Frame	Baseline to Week 24

Analysis Population Description
Full Analysis Set

Reporting Groups

	Description
Reldesemtiv Group, Double-Blind Period	Participants in this arm take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Day 1 until Week 24. Reldesemtiv: Reldesemtiv Oral Tablet
Placebo Group, Double-Blind Period	Participants in this arm take 2 placebo oral tablets twice a day from Day 1 until Week 24. Placebo: Placebo Oral Tablet

Measured Values

	Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period
Overall Number of Participants Analyzed	323	159
Effect of Reldesemtiv Versus Placebo on Combined Functional and Survival Outcomes in Amyotrophic Lateral Sclerosis (ALS) Median (95% Confidence Interval) Unit of measure: unitless	232.5 (211.0 to 257.0)	264.0 (209.0 to 291.0)

3. Secondary Outcome Measure:

Measure Title	Effect of Reldesemtiv Versus Placebo on Ventilatory Function
Measure Description	Change from baseline in percent predicted forced vital capacity (FVC) using an in-clinic spirometer; a negative number for change from baseline indicates respiratory function decline relative to baseline
Time Frame	Baseline to Week 24

Analysis Population Description
Full Analysis Set

Reporting Groups

	Description
Reldesemtiv Group, Double-Blind Period	Participants in this arm take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Day 1 until Week 24. Reldesemtiv: Reldesemtiv Oral Tablet

	Description
Placebo Group, Double-Blind Period	Participants in this arm take 2 placebo oral tablets twice a day from Day 1 until Week 24. Placebo: Placebo Oral Tablet

Measured Values

	Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period
Overall Number of Participants Analyzed	323	159
Effect of Reldesemtiv Versus Placebo on Ventilatory Function Mean (Standard Deviation) Unit of measure: percent predicted	-10.562 (12.8178)	-9.677 (13.1073)

4. Secondary Outcome Measure:

Measure Title	Effect of Reldesemtiv Versus Placebo on Quality of Life
Measure Description	Change from baseline in ALSAQ-40 total score. ALSAQ-40 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; summary scores range from 0 (best health status) to 100 (worst health status); ALSAQ-40 total score is calculated as the sum of the summary scores from the 5 domains; lower score corresponds to better health-related quality of life.
Time Frame	Baseline to Week 24

Analysis Population Description
Full Analysis Set

Reporting Groups

	Description
Reldesemtiv Group, Double-Blind Period	Participants in this arm take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Day 1 until Week 24. Reldesemtiv: Reldesemtiv Oral Tablet
Placebo Group, Double-Blind Period	Participants in this arm take 2 placebo oral tablets twice a day from Day 1 until Week 24. Placebo: Placebo Oral Tablet

Measured Values

	Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period
Overall Number of Participants Analyzed	323	159
Effect of Reldesemtiv Versus Placebo on Quality of Life Mean (Standard Deviation) Unit of measure: score on a scale	11.426 (12.2102)	9.766 (11.3662)

5. Secondary Outcome Measure:

Measure Title	Effect of Reldesemtiv Versus Placebo on Handgrip Strength
Measure Description	Change from baseline in maximum handgrip strength (average of both hands) measured bilaterally by an electronic hand dynamometer
Time Frame	Baseline to Week 24

Analysis Population Description
Full Analysis Set

Reporting Groups

	Description
Reldesemtiv Group, Double-Blind Period	Participants in this arm take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Day 1 until Week 24. Reldesemtiv: Reldesemtiv Oral Tablet
Placebo Group, Double-Blind Period	Participants in this arm take 2 placebo oral tablets twice a day from Day 1 until Week 24. Placebo: Placebo Oral Tablet

Measured Values

	Reldesemtiv Group, Double-Blind Period	Placebo Group, Double-Blind Period
Overall Number of Participants Analyzed	323	159
Effect of Reldesemtiv Versus Placebo on Handgrip Strength Mean (Standard Deviation) Unit of measure: pounds	-10.134 (9.6821)	-7.370 (9.7733)

Reported Adverse Events

Time Frame	up to 48 weeks
Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Reldesemtiv Group, Double-Blind Period	Participants in this arm take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Day 1 until Week 24. Reldesemtiv: Reldesemtiv Oral Tablet
Placebo Group, Double-Blind Period	Participants in this arm take 2 placebo oral tablets twice a day from Day 1 until Week 24. Placebo: Placebo Oral Tablet
Delayed Start Group, Active Drug Period	Participants in this arm were those who received placebo in the double-blind period and reldesemtiv in the active drug period. Participants take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Week 24 until Week 48. Patients who were down-titrated for any reason during the 24 weeks of blinded dosing take 1 reldesemtiv 150 mg oral tablet twice a day for a 300 mg total daily dose from Week 24 until Week 48. Reldesemtiv: Reldesemtiv Oral Tablet
Early Start Group, Active Drug Period	Participants in this arm were those who received reldesemtiv in the double-blind and active drug periods. Participants take 2 reldesemtiv 150 mg oral tablets twice a day for a 600 mg total daily dose from Week 24 until Week 48. Patients who were down-titrated for any reason during the 24 weeks of blinded dosing take 1 reldesemtiv 150 mg oral tablet twice a day for a 300 mg total daily dose from Week 24 until Week 48. Reldesemtiv: Reldesemtiv Oral Tablet

All-Cause Mortality

	Reldesemtiv Group, Double-Blind Period		Placebo Group, Double-Blind Period		Delayed Start Group, Active Drug Period		Early Start Group, Active Drug Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total All-Cause Mortality	9/325 (2.77%)		6/161 (3.73%)		5/96 (5.21%)		8/180 (4.44%)	

Serious Adverse Events

	Reldesemtiv Group, Double-Blind Period		Placebo Group, Double-Blind Period		Delayed Start Group, Active Drug Period		Early Start Group, Active Drug Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	41/325 (12.62%)		25/161 (15.53%)		14/96 (14.58%)		33/180 (18.33%)	
Cardiac disorders								
atrial tachycardia [A] †	0/325 (0%)	0	0/161 (0%)	0	1/96 (1.04%)	1	0/180 (0%)	0
cardiac arrest [A] †	1/325 (0.31%)	1	0/161 (0%)	0	1/96 (1.04%)	1	0/180 (0%)	0
myocardial infarction [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
Gastrointestinal disorders								
colitis ischaemic [A] †	0/325 (0%)	0	0/161 (0%)	0	1/96 (1.04%)	1	0/180 (0%)	0
diarrhoea [A] †	0/325 (0%)	0	0/161 (0%)	0	1/96 (1.04%)	1	0/180 (0%)	0
dysphagia [A] †	6/325 (1.85%)	6	5/161 (3.11%)	5	2/96 (2.08%)	2	8/180 (4.44%)	8
faecaloma [A] †	0/325 (0%)	0	0/161 (0%)	0	2/96 (2.08%)	2	0/180 (0%)	0
intestinal obstruction [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
intestinal pseudo-obstruction [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
lower gastrointestinal haemorrhage [A] †	0/325 (0%)	0	0/161 (0%)	0	1/96 (1.04%)	1	0/180 (0%)	0
oesophagitis [A] †	0/325 (0%)	0	0/161 (0%)	0	1/96 (1.04%)	1	0/180 (0%)	0
pancreatitis [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1

	Reldesemtiv Group, Double-Blind Period		Placebo Group, Double-Blind Period		Delayed Start Group, Active Drug Period		Early Start Group, Active Drug Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
subileus [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
vomiting [A] †	0/325 (0%)	0	0/161 (0%)	0	1/96 (1.04%)	1	0/180 (0%)	0
General disorders								
generalised oedema [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
Hepatobiliary disorders								
cholecystitis acute [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
cholelithiasis [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
hepatitis [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
hepatotoxicity [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
Infections and infestations								
COVID-19 [A] †	2/325 (0.62%)	2	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
appendicitis [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
infectious mononucleosis [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
medical device site infection [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
peritonitis [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
pneumonia [A] †	1/325 (0.31%)	1	1/161 (0.62%)	1	1/96 (1.04%)	1	4/180 (2.22%)	4

	Reldesemtiv Group, Double-Blind Period		Placebo Group, Double-Blind Period		Delayed Start Group, Active Drug Period		Early Start Group, Active Drug Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
pneumonia aspiration [A] †	0/325 (0%)	0	1/161 (0.62%)	1	0/96 (0%)	0	2/180 (1.11%)	2
respiratory syncytial virus infection [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
sepsis [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	2/180 (1.11%)	2
systemic infection [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
tooth infection [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
upper respiratory tract infection [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
urinary tract infection [A] †	1/325 (0.31%)	1	1/161 (0.62%)	1	0/96 (0%)	0	3/180 (1.67%)	3
urosepsis [A] †	0/325 (0%)	0	0/161 (0%)	0	1/96 (1.04%)	1	1/180 (0.56%)	1
vascular device infection [A] †	1/325 (0.31%)	1	1/161 (0.62%)	1	0/96 (0%)	0	0/180 (0%)	0
Injury, poisoning and procedural complications								
ankle fracture [A] †	0/325 (0%)	0	1/161 (0.62%)	1	0/96 (0%)	0	0/180 (0%)	0
clavicle fracture [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
concussion [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
fall [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
hip fracture [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1

	Reldesemtiv Group, Double-Blind Period		Placebo Group, Double-Blind Period		Delayed Start Group, Active Drug Period		Early Start Group, Active Drug Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
jaw fracture [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
procedural pain [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
rib fracture [A] †	0/325 (0%)	0	1/161 (0.62%)	1	0/96 (0%)	0	0/180 (0%)	0
Investigations								
SARS-CoV-2 test positive [A] †	0/325 (0%)	0	0/161 (0%)	0	1/96 (1.04%)	1	0/180 (0%)	0
alanine aminotransferase increased [A] †	2/325 (0.62%)	2	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
aspartate aminotransferase increased [A] †	2/325 (0.62%)	2	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
blood bilirubin increased [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
hepatic enzyme increased [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
oxygen saturation decreased [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
transaminases increased [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	2/180 (1.11%)	2
vital capacity decreased [A] †	0/325 (0%)	0	1/161 (0.62%)	1	0/96 (0%)	0	0/180 (0%)	0
weight decreased [A] †	2/325 (0.62%)	2	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
Metabolism and nutrition disorders								
hypokalaemia [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
hyponatraemia [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0

	Reldesemtiv Group, Double-Blind Period		Placebo Group, Double-Blind Period		Delayed Start Group, Active Drug Period		Early Start Group, Active Drug Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
malnutrition [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
refeeding syndrome [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
Musculoskeletal and connective tissue disorders								
muscle spasms [A] †	0/325 (0%)	0	1/161 (0.62%)	1	0/96 (0%)	0	0/180 (0%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
metastases to liver [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
pancreatic carcinoma [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
Nervous system disorders								
amyotropic lateral sclerosis [A] †	1/325 (0.31%)	1	1/161 (0.62%)	1	1/96 (1.04%)	1	2/180 (1.11%)	2
cerebellar stroke [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
motor neurone disease [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	2/180 (1.11%)	2
subarachnoid haemorrhage [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
Product Issues								
device dislocation [A] †	0/325 (0%)	0	0/161 (0%)	0	1/96 (1.04%)	1	0/180 (0%)	0
device malfunction [A] †	0/325 (0%)	0	1/161 (0.62%)	1	0/96 (0%)	0	0/180 (0%)	0
Psychiatric disorders								
assisted suicide [A] †	3/325 (0.92%)	3	3/161 (1.86%)	3	0/96 (0%)	0	1/180 (0.56%)	1

	Reldesemtiv Group, Double-Blind Period		Placebo Group, Double-Blind Period		Delayed Start Group, Active Drug Period		Early Start Group, Active Drug Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Renal and urinary disorders								
nephrolithiasis [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
prerenal failure [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
Respiratory, thoracic and mediastinal disorders								
acute respiratory failure [A] †	0/325 (0%)	0	2/161 (1.24%)	2	0/96 (0%)	0	1/180 (0.56%)	1
bronchial secretion retention [A] †	1/325 (0.31%)	1	1/161 (0.62%)	1	1/96 (1.04%)	1	0/180 (0%)	0
chronic respiratory failure [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
dyspnoea [A] †	0/325 (0%)	0	2/161 (1.24%)	2	0/96 (0%)	0	0/180 (0%)	0
hypercapnia [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
pulmonary embolism [A] †	2/325 (0.62%)	2	3/161 (1.86%)	3	0/96 (0%)	0	1/180 (0.56%)	1
respiratory arrest [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
respiratory disorder [A] †	1/325 (0.31%)	1	0/161 (0%)	0	1/96 (1.04%)	1	0/180 (0%)	0
respiratory distress [A] †	1/325 (0.31%)	1	0/161 (0%)	0	0/96 (0%)	0	0/180 (0%)	0
respiratory failure [A] †	8/325 (2.46%)	8	3/161 (1.86%)	3	4/96 (4.17%)	4	7/180 (3.89%)	7
Surgical and medical procedures								
euthanasia [A] †	0/325 (0%)	0	1/161 (0.62%)	1	0/96 (0%)	0	0/180 (0%)	0

	Reldesemtiv Group, Double-Blind Period		Placebo Group, Double-Blind Period		Delayed Start Group, Active Drug Period		Early Start Group, Active Drug Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
mechanical ventilation [A] †	0/325 (0%)	0	0/161 (0%)	0	0/96 (0%)	0	1/180 (0.56%)	1
medical device change [A] †	0/325 (0%)	0	1/161 (0.62%)	1	0/96 (0%)	0	0/180 (0%)	0

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 23.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Reldesemtiv Group, Double-Blind Period		Placebo Group, Double-Blind Period		Delayed Start Group, Active Drug Period		Early Start Group, Active Drug Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	258/325 (79.38%)		125/161 (77.64%)		65/96 (67.71%)		122/180 (67.78%)	
Gastrointestinal disorders								
constipation [A] †	26/325 (8%)	26	12/161 (7.45%)	12	3/96 (3.12%)	3	10/180 (5.56%)	10
diarrhoea [A] †	22/325 (6.77%)	22	14/161 (8.7%)	14	4/96 (4.17%)	4	13/180 (7.22%)	13
dysphagia [A] †	7/325 (2.15%)	7	6/161 (3.73%)	6	2/96 (2.08%)	2	9/180 (5%)	9
nausea [A] †	24/325 (7.38%)	24	6/161 (3.73%)	6	2/96 (2.08%)	2	6/180 (3.33%)	6
General disorders								
fatigue [A] †	18/325 (5.54%)	18	10/161 (6.21%)	10	2/96 (2.08%)	2	3/180 (1.67%)	3
Infections and infestations								
COVID-19 [A] †	30/325 (9.23%)	30	13/161 (8.07%)	13	8/96 (8.33%)	8	12/180 (6.67%)	12

	Reldesemtiv Group, Double-Blind Period		Placebo Group, Double-Blind Period		Delayed Start Group, Active Drug Period		Early Start Group, Active Drug Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
nasopharyngitis [A] †	17/325 (5.23%)	17	6/161 (3.73%)	6	3/96 (3.12%)	3	2/180 (1.11%)	2
urinary tract infection [A] †	20/325 (6.15%)	20	9/161 (5.59%)	9	6/96 (6.25%)	6	13/180 (7.22%)	13
Injury, poisoning and procedural complications								
contusion [A] †	12/325 (3.69%)	12	6/161 (3.73%)	6	2/96 (2.08%)	2	11/180 (6.11%)	11
fall [A] †	58/325 (17.85%)	58	23/161 (14.29%)	23	12/96 (12.5%)	12	27/180 (15%)	27
Investigations								
alanine aminotransferase increased [A] †	21/325 (6.46%)	21	3/161 (1.86%)	3	5/96 (5.21%)	5	3/180 (1.67%)	3
aspartate aminotransferase increased [A] †	18/325 (5.54%)	18	1/161 (0.62%)	1	5/96 (5.21%)	5	2/180 (1.11%)	2
Musculoskeletal and connective tissue disorders								
arthralgia [A] †	19/325 (5.85%)	19	10/161 (6.21%)	10	3/96 (3.12%)	3	9/180 (5%)	9
Nervous system disorders								
dizziness [A] †	14/325 (4.31%)	14	8/161 (4.97%)	8	1/96 (1.04%)	1	2/180 (1.11%)	2
headache [A] †	25/325 (7.69%)	25	13/161 (8.07%)	13	7/96 (7.29%)	7	6/180 (3.33%)	6

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 23.0

Limitations and Caveats

The Data Monitoring Committee reviewed unblinded data at the second planned interim analysis and recommended discontinuation of the clinical trial due to futility.

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There is NOT an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

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