



## Clinical trial results:

### A Phase 2, Multi-Center, Double-Blind, Randomized, Dose-Ranging, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of CK-2127107 In Patients with Amyotrophic Lateral Sclerosis (ALS)

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2018-000586-37 |
| Trial protocol           | IE ES NL       |
| Global end of trial date | 07 March 2019  |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 14 May 2020  |
| First version publication date | 14 May 2020  |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | CY 5022 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03160898 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Cytokinetics, Inc.   |
| Sponsor organisation address | 280 East Grand Avenue, South San Francisco, California, United States, 94080         |
| Public contact               | Medical Affairs, Cytokinetics, Inc., +1 650 6242929, medicalaffairs@cytokinetics.com |
| Scientific contact           | Medical Affairs, Cytokinetics, Inc., +1 650 6242929, medicalaffairs@cytokinetics.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 07 March 2019 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 07 March 2019 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 07 March 2019 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To assess the effect of CK-2127107 (hereafter referred to as reldesemtiv) versus placebo on respiratory function in patients with ALS.

Protection of trial subjects:

The study was conducted in accordance with the United States (US) Code of Federal Regulations (CFR) governing protection of human subjects (21 CFR 50), financial disclosure by clinical investigators (21 CFR 54), institutional review boards (IRBs; 21 CFR 56), investigational new drug applications (21 CFR 312), and applications for the US Food and Drug Administration approval to market a new drug (21 CFR 314), as appropriate. The study was also conducted in accordance with applicable International Council on Harmonisation (ICH) guidelines. Both the US regulations along with the ICH guidelines are commonly known as good clinical practices (GCPs).

An independent Data Monitoring Committee (DMC) assessed patient safety in an unblinded manner periodically during the study. The DMC was chartered to make recommendations to the sponsor, as appropriate, regarding modification in study design or conduct to ensure patient safety and the integrity of the study.

Background therapy:

Concomitant use of riluzole and/or edaravone was allowed during the study if patients had been taking riluzole for at least 30 days prior to screening and if patients had completed 2 cycles of edaravone by screening. Neither drug was allowed if they had not been used for at least 30 days prior to screening.

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 16 August 2017 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | Yes            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 11    |
| Country: Number of subjects enrolled | Spain: 38          |
| Country: Number of subjects enrolled | Ireland: 4         |
| Country: Number of subjects enrolled | Australia: 20      |
| Country: Number of subjects enrolled | Canada: 100        |
| Country: Number of subjects enrolled | United States: 284 |
| Worldwide total number of subjects   | 457                |
| EEA total number of subjects         | 53                 |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 308 |
| From 65 to 84 years                       | 149 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Patients with familial or sporadic ALS were enrolled at 65 sites in Australia, Canada, Ireland, Netherlands, Spain, and the United States. The first patient was screened on 16 August 2017 and the last patient completed on 07 March 2019.

### Pre-assignment

Screening details:

Eligible patients were male or female,  $\geq 18$  to  $\leq 80$  years of age, with familial or sporadic ALS  $\leq 24$  months prior to screening. At screening, patients were to have an upright slow vital capacity (SVC)  $\geq 60\%$  of predicted; must have been able to swallow tablets and perform pulmonary function tests; had normal lab tests; and had a caregiver (if needed).

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Trial                  |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator, Monitor |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Patients in this group received placebo (to match reldesemtiv) twice daily for 12 weeks.

|  |                         |
|--|-------------------------|
| Arm type                               | Placebo                 |
| Investigational medicinal product name | Placebo for reldesemtiv |
| Investigational medicinal product code |                         |
| Other name                             |                         |
| Pharmaceutical forms                   | Tablet                  |
| Routes of administration               | Oral use                |

Dosage and administration details:

Patients were randomized 1:1:1:1 to receive reldesemtiv 150 mg, 300 mg, 450 mg, or placebo, twice daily for 12 weeks. Doses were to be taken approximately 12 hours ( $\pm 2$  hours) apart and within 2 hours following a meal.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Reldesemtiv 150 mg |
|------------------|--------------------|

Arm description:

Patients in this group received 150 mg reldesemtiv twice daily for 12 weeks.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Reldesemtiv  |
| Investigational medicinal product code | CK-2127107   |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Patients were randomized 1:1:1:1 to receive reldesemtiv 150 mg, 300 mg, 450 mg, or placebo, twice daily for 12 weeks. Doses were to be taken approximately 12 hours ( $\pm 2$  hours) apart and within 2 hours following a meal.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Reldesemtiv 300 mg |
|------------------|--------------------|

Arm description:

Patients in this group received 300 mg reldesemtiv twice daily for 12 weeks.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Reldesemtiv 300 mg |
| Investigational medicinal product code | CK-2127107         |
| Other name                             |                    |
| Pharmaceutical forms                   | Tablet             |
| Routes of administration               | Oral use           |

**Dosage and administration details:**

Patients were randomized 1:1:1:1 to receive reldesemtiv 150 mg, 300 mg, 450 mg, or placebo, twice daily for 12 weeks. Doses were to be taken approximately 12 hours ( $\pm$  2 hours) apart and within 2 hours following a meal.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Reldesemtiv 450 mg |
|------------------|--------------------|

**Arm description:**

Patients in this group received 450 mg reldesemtiv twice daily for 12 weeks.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Reldesemtiv  |
| Investigational medicinal product code | CK-2127107   |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Other use    |

**Dosage and administration details:**

Patients were randomized 1:1:1:1 to receive reldesemtiv 150 mg, 300 mg, 450 mg, or placebo, twice daily for 12 weeks. Doses were to be taken approximately 12 hours ( $\pm$  2 hours) apart and within 2 hours following a meal.

| <b>Number of subjects in period 1</b> | Placebo | Reldesemtiv 150 mg | Reldesemtiv 300 mg |
|---------------------------------------|---------|--------------------|--------------------|
| Started                               | 115     | 112                | 113                |
| Completed                             | 95      | 100                | 97                 |
| Not completed                         | 20      | 12                 | 16                 |
| Adverse event, serious fatal          | 1       | -                  | -                  |
| Consent withdrawn by subject          | 1       | 2                  | 2                  |
| Physician decision                    | 1       | -                  | -                  |
| Adverse event, non-fatal              | 4       | 8                  | 7                  |
| Unspecified                           | 2       | -                  | 2                  |
| Lost to follow-up                     | 1       | 1                  | 1                  |
| Progressive disease                   | 4       | 1                  | 2                  |
| Sponsor decision                      | 2       | -                  | -                  |
| Difficulty traveling to clinic visits | 3       | -                  | -                  |
| Protocol deviation                    | 1       | -                  | 2                  |

| <b>Number of subjects in period 1</b> | Reldesemtiv 450 mg |
|---------------------------------------|--------------------|
| Started                               | 117                |
| Completed                             | 98                 |
| Not completed                         | 19                 |
| Adverse event, serious fatal          | 1                  |
| Consent withdrawn by subject          | 1                  |

|                                       |    |
|---------------------------------------|----|
| Physician decision                    | 1  |
| Adverse event, non-fatal              | 10 |
| Unspecified                           | 2  |
| Lost to follow-up                     | 2  |
| Progressive disease                   | 1  |
| Sponsor decision                      | -  |
| Difficulty traveling to clinic visits | 1  |
| Protocol deviation                    | -  |

## Period 2

|                              |                   |
|------------------------------|-------------------|
| Period 2 title               | Efficacy Analyses |
| Is this the baseline period? | No                |
| Allocation method            | Not applicable    |
| Blinding used                | Not blinded       |

## Arms

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Reldesemtiv 300 mg & 450 mg (pooled) |
|------------------|--------------------------------------|

Arm description:

Patients from the reldesemtiv 300 mg and 450 mg groups were pooled for analysis purposes only.

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Pooled for analysis purposes only |
| Investigational medicinal product name | Reldesemtiv                       |
| Investigational medicinal product code | CK-2127107                        |
| Other name                             |                                   |
| Pharmaceutical forms                   | Tablet                            |
| Routes of administration               | Oral use                          |

Dosage and administration details:

For analysis purposes only, patients from the reldesemtiv 300 mg and 450 mg groups were pooled to evaluate the efficacy responses of the pooled group compared with those of the placebo group.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Reldesemtiv 300 mg & 450 mg (pooled) |
|---|--------------------------------------|
| Started   | 230                                  |
| Completed   | 195                                  |
| Not completed                                       | 35                                   |
| Adverse event, serious fatal                        | 1                                    |
| Consent withdrawn by subject                        | 3                                    |
| Physician decision                                  | 1                                    |
| Adverse event, non-fatal                            | 17                                   |
| Unspecified   | 4                                    |
| Lost to follow-up                                   | 3                                    |

|                                       |   |
|---------------------------------------|---|
| Progressive disease                   | 3 |
| Difficulty traveling to clinic visits | 1 |
| Protocol deviation                    | 2 |

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Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The Reldesemtiv 300 mg & 450 mg (pooled) arm was added for efficacy analysis purposes only. A prespecified efficacy analysis was to compare this pooled group to placebo for each efficacy endpoint. All data from this arm (disposition and efficacy) derives from both the reldesemtiv 300 mg arm and the reldesemtiv 450 mg arm.

## Baseline characteristics

### Reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | Placebo            |
| Reporting group description:   |                    |
| Patients in this group received placebo (to match reldesemtiv) twice daily for 12 weeks. |                    |
| Reporting group title  | Reldesemtiv 150 mg |
| Reporting group description:   |                    |
| Patients in this group received 150 mg reldesemtiv twice daily for 12 weeks.             |                    |
| Reporting group title  | Reldesemtiv 300 mg |
| Reporting group description:   |                    |
| Patients in this group received 300 mg reldesemtiv twice daily for 12 weeks.             |                    |
| Reporting group title  | Reldesemtiv 450 mg |
| Reporting group description:   |                    |
| Patients in this group received 450 mg reldesemtiv twice daily for 12 weeks.             |                    |

| Reporting group values                | Placebo | Reldesemtiv 150 mg | Reldesemtiv 300 mg |
|---------------------------------------|---------|--------------------|--------------------|
| Number of subjects                    | 115     | 112                | 113                |
| Age categorical<br>Units: Subjects    |         |                    |                    |
| Adults (18-64 years)                  | 74      | 81                 | 80                 |
| From 65-84 years                      | 41      | 31                 | 33                 |
| Gender categorical<br>Units: Subjects |         |                    |                    |
| Female                                | 47      | 41                 | 42                 |
| Male                                  | 68      | 71                 | 71                 |

| Reporting group values                | Reldesemtiv 450 mg | Total |  |
|---------------------------------------|--------------------|-------|--|
| Number of subjects                    | 117                | 457   |  |
| Age categorical<br>Units: Subjects    |                    |       |  |
| Adults (18-64 years)                  | 73                 | 308   |  |
| From 65-84 years                      | 44                 | 149   |  |
| Gender categorical<br>Units: Subjects |                    |       |  |
| Female                                | 50                 | 180   |  |
| Male                                  | 67                 | 277   |  |



## End points

### End points reporting groups

|   |                                      |
|---|--------------------------------------|
| Reporting group title   | Placebo                              |
| Reporting group description:<br>Patients in this group received placebo (to match reldesemtiv) twice daily for 12 weeks.  |                                      |
| Reporting group title   | Reldesemtiv 150 mg                   |
| Reporting group description:<br>Patients in this group received 150 mg reldesemtiv twice daily for 12 weeks.  |                                      |
| Reporting group title   | Reldesemtiv 300 mg                   |
| Reporting group description:<br>Patients in this group received 300 mg reldesemtiv twice daily for 12 weeks.  |                                      |
| Reporting group title   | Reldesemtiv 450 mg                   |
| Reporting group description:<br>Patients in this group received 450 mg reldesemtiv twice daily for 12 weeks.  |                                      |
| Reporting group title   | Reldesemtiv 300 mg & 450 mg (pooled) |
| Reporting group description:<br>Patients from the reldesemtiv 300 mg and 450 mg groups were pooled for analysis purposes only.  |                                      |
| Subject analysis set title  | Full Analysis Set                    |
| Subject analysis set type   | Full analysis                        |
| Subject analysis set description:<br>The Full Analysis Set consisted of all randomized patients who received any amount of study drug and had a baseline and at least 1 postbaseline efficacy assessment. |                                      |

### Primary: Change from Baseline to Week 12 in Percent Predicted Slow Vital Capacity

|   |  |
|---|--|
| End point title   | Change from Baseline to Week 12 in Percent Predicted Slow Vital Capacity |
| End point description:<br>Slow vital capacity was measured using a spirometer (in units of liters). Following 3 to 5 breaths at rest, patients were instructed to take as deep an inspiration as possible followed by a maximum exhalation (blowing out all the air in their lungs). Values obtained were converted to percent predicted values (ie, the test result as a percent of predicted values for the patients of similar demographic and baseline characteristics [eg, height, age, sex]). |  |
| End point type  | Primary  |
| End point timeframe:<br>Baseline to Week 12   |  |

| End point values                    | Placebo         | Reldesemtiv 150 mg | Reldesemtiv 300 mg | Reldesemtiv 450 mg |
|-------------------------------------|-----------------|--------------------|--------------------|--------------------|
| Subject group type                  | Reporting group | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed         | 114             | 112                | 113                | 117                |
| Units: percent                      |                 |                    |                    |                    |
| least squares mean (standard error) | -6.46 (± 0.964) | -4.97 (± 0.952)    | -4.62 (± 0.963)    | -4.58 (± 0.927)    |

|                  |                                      |  |  |  |
|------------------|--------------------------------------|--|--|--|
| End point values | Reldesemtiv 300 mg & 450 mg (pooled) |  |  |  |
|------------------|--------------------------------------|--|--|--|

|                                     |                      |  |  |  |
|-------------------------------------|----------------------|--|--|--|
| Subject group type                  | Reporting group      |  |  |  |
| Number of subjects analysed         | 230                  |  |  |  |
| Units: percent                      |                      |  |  |  |
| least squares mean (standard error) | -4.60 ( $\pm$ 0.701) |  |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Reldesemtiv 150 mg - placebo comparison of change |
| Statistical analysis description:   |   |
| Difference in LS mean changes from baseline: reldesemtiv 150 mg minus placebo |   |
| Comparison groups   | Placebo v Reldesemtiv 150 mg                      |
| Number of subjects included in analysis                                       | 226   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | superiority                                       |
| P-value   | = 0.2501  |
| Method  | Mixed models analysis                             |
| Parameter estimate  | LS mean difference                                |
| Point estimate  | 1.49  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -1.05   |
| upper limit   | 4.03  |
| Variability estimate  | Standard error of the mean                        |
| Dispersion value  | 1.291   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Reldesemtiv 300 mg - placebo comparison of change |
| Statistical analysis description:   |   |
| Difference in LS mean changes from baseline: reldesemtiv 300 mg minus placebo |   |
| Comparison groups   | Placebo v Reldesemtiv 300 mg                      |
| Number of subjects included in analysis                                       | 227   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | superiority                                       |
| P-value   | = 0.1549  |
| Method  | Mixed models analysis                             |
| Parameter estimate  | LS mean difference                                |
| Point estimate  | 1.84  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -0.7  |
| upper limit   | 4.38  |
| Variability estimate  | Standard error of the mean                        |
| Dispersion value  | 1.29  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Reldesemtiv 450 mg - placebo comparison of change |
| Statistical analysis description:   |   |
| Difference in LS mean changes from baseline: reldesemtiv 450 mg minus placebo |   |
| Comparison groups   | Placebo v Reldesemtiv 450 mg                      |
| Number of subjects included in analysis                                       | 231   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | superiority                                       |
| P-value   | = 0.1417  |
| Method  | Mixed models analysis                             |
| Parameter estimate  | LS mean difference                                |
| Point estimate  | 1.88  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -0.63   |
| upper limit   | 4.38  |
| Variability estimate  | Standard error of the mean                        |
| Dispersion value  | 1.274   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Reldesemtiv 300&450 mg (pooled)-placebo comparison |
| Statistical analysis description:   |  |
| Difference in LS mean changes from baseline: reldesemtiv 300 mg & 450 mg (pooled) minus placebo |  |
| Comparison groups   | Placebo v Reldesemtiv 300 mg & 450 mg (pooled)     |
| Number of subjects included in analysis   | 344  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | superiority  |
| P-value   | = 0.0964   |
| Method  | Mixed models analysis                              |
| Parameter estimate  | LS mean difference                                 |
| Point estimate  | 1.86   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | -0.33  |
| upper limit   | 4.05   |
| Variability estimate  | Standard error of the mean                         |
| Dispersion value  | 1.115  |

## Secondary: Slope from Baseline to Week 12 in Muscle Strength Mega-Score

|                 |  |
|-----------------|--|
| End point title | Slope from Baseline to Week 12 in Muscle Strength Mega-Score |
|-----------------|--|

End point description:

Muscle strength of 6 muscle groups (elbow flexion, wrist extension, first dorsal interosseous, hip flexion, knee extension, and ankle dorsiflexion) and hand grip strength were measured bilaterally using a hand-

held dynamometer. Muscle strength was measure twice for each body location; if the variability between the first 2 measures was > 15%, a third measure was obtained.

The muscle strength of each measured body location as a percent of change from baseline was determined using the equation:  $([\text{postbaseline value} - \text{baseline value}] / \text{baseline value}) \times 100$ .

The mega-score was a composite score that averaged strength across muscle groups. It was calculated as the mean of the muscle strength scores among the 6 muscle groups and hand grip strength, each measured bilaterally (totaling 14 body locations).

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline to Week 12  |           |

| End point values                    | Placebo             | Reldesemtiv 150 mg  | Reldesemtiv 300 mg  | Reldesemtiv 450 mg  |
|-------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type                  | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed         | 114                 | 112                 | 113                 | 117                 |
| Units: change/day                   |                     |                     |                     |                     |
| least squares mean (standard error) | -0.1444 (± 0.02492) | -0.1198 (± 0.02463) | -0.1299 (± 0.02474) | -0.0956 (± 0.02421) |

| End point values                    | Reldesemtiv 300 mg & 450 mg (pooled) |  |  |  |
|-------------------------------------|--------------------------------------|--|--|--|
| Subject group type                  | Reporting group                      |  |  |  |
| Number of subjects analysed         | 230                                  |  |  |  |
| Units: change/day                   |                                      |  |  |  |
| least squares mean (standard error) | -0.1127 (± 0.01731)                  |  |  |  |

## Statistical analyses

| Statistical analysis title  | Reldesemtiv 150 mg - placebo comparison of change |
|---|---|
| Statistical analysis description:   |   |
| Difference in LS mean changes from baseline: reldesemtiv 150 mg minus placebo |   |
| Comparison groups   | Reldesemtiv 150 mg v Placebo                      |
| Number of subjects included in analysis                                       | 226   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | superiority                                       |
| P-value   | = 0.4824  |
| Method  | Mixed models analysis                             |
| Parameter estimate  | LS mean difference                                |
| Point estimate  | 0.0246  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -0.0442   |
| upper limit   | 0.0935  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Reldesemtiv 300 mg - placebo comparison of change |
| Statistical analysis description:   |   |
| Difference in LS mean changes from baseline: reldesemtiv 300 mg minus placebo |   |
| Comparison groups   | Placebo v Reldesemtiv 300 mg                      |
| Number of subjects included in analysis                                       | 227   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | superiority                                       |
| P-value   | = 0.6787  |
| Method  | Mixed models analysis                             |
| Parameter estimate  | LS mean difference                                |
| Point estimate  | 0.0146  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -0.0544   |
| upper limit   | 0.0835  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Reldesemtiv 450 mg - placebo comparison of change |
| Statistical analysis description:   |   |
| Difference in LS mean changes from baseline: reldesemtiv 450 mg minus placebo |   |
| Comparison groups   | Placebo v Reldesemtiv 450 mg                      |
| Number of subjects included in analysis                                       | 231   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | superiority                                       |
| P-value   | = 0.1604  |
| Method  | Mixed models analysis                             |
| Parameter estimate  | LS mean difference                                |
| Point estimate  | 0.0488  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -0.0194   |
| upper limit   | 0.1171  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Reldesemtiv 300&450 mg (pooled)-placebo comparison |
| Statistical analysis description:   |  |
| Difference in LS mean changes from baseline: reldesemtiv 300 mg & 450 mg (pooled) minus placebo |  |
| Comparison groups   | Placebo v Reldesemtiv 300 mg & 450 mg (pooled)     |

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 344                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.2966              |
| Method                                  | Mixed models analysis |
| Parameter estimate                      | LS mean difference    |
| Point estimate                          | 0.0317                |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -0.0279               |
| upper limit                             | 0.0913                |

### Secondary: Change from Baseline to Week 12 in ALS Functional Rating Scale - Revised (ALSFRS-R) Total Score

|  |   |
|--|---|
| End point title  | Change from Baseline to Week 12 in ALS Functional Rating Scale - Revised (ALSFRS-R) Total Score |
| End point description:   |   |
| <p>The ALSFRS-R is used to measure the progression and severity of disability in patients with ALS. The ALSFRS-R consists of 12 questions, assessing a patient's capability and independence in functional activities relevant to ALS, categorized in the following 4 domains: gross motor tasks, fine motor tasks, bulbar functions, and respiratory function. Each question is scored from 0 (indicating incapable or dependent) to 4 (normal). The total score ranges from 0 to 48. Higher scores reflect more normal function and lower scores reflect more impaired function.</p> |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline to Week 12  |   |

| End point values                    | Placebo         | Reldesemtiv 150 mg | Reldesemtiv 300 mg | Reldesemtiv 450 mg |
|-------------------------------------|-----------------|--------------------|--------------------|--------------------|
| Subject group type                  | Reporting group | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed         | 114             | 112                | 113                | 117                |
| Units: ALSFRS-R Total Score         |                 |                    |                    |                    |
| least squares mean (standard error) | -3.53 (± 0.313) | -2.40 (± 0.311)    | -2.62 (± 0.317)    | -2.94 (± 0.307)    |

| End point values                    | Reldesemtiv 300 mg & 450 mg (pooled) |  |  |  |
|-------------------------------------|--------------------------------------|--|--|--|
| Subject group type                  | Reporting group                      |  |  |  |
| Number of subjects analysed         | 230                                  |  |  |  |
| Units: ALSFRS-R Total Score         |                                      |  |  |  |
| least squares mean (standard error) | -2.78 (± 0.228)                      |  |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Reldesemtiv 150 mg - placebo comparison of change |
| Statistical analysis description:   |   |
| Difference in LS mean changes from baseline: reldesemtiv 150 mg minus placebo |   |
| Comparison groups   | Placebo v Reldesemtiv 150 mg                      |
| Number of subjects included in analysis                                       | 226   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | superiority                                       |
| P-value   | = 0.0087  |
| Method  | Mixed models analysis                             |
| Parameter estimate  | LS mean difference                                |
| Point estimate  | 1.13  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.29  |
| upper limit   | 1.97  |
| Variability estimate  | Standard error of the mean                        |
| Dispersion value  | 0.427   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Reldesemtiv 300 mg - placebo comparison of change |
| Statistical analysis description:   |   |
| Difference in LS mean changes from baseline: reldesemtiv 300 mg minus placebo |   |
| Comparison groups   | Placebo v Reldesemtiv 300 mg                      |
| Number of subjects included in analysis                                       | 227   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | superiority                                       |
| P-value   | = 0.0351  |
| Method  | Mixed models analysis                             |
| Parameter estimate  | LS mean difference                                |
| Point estimate  | 0.91  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.06  |
| upper limit   | 1.75  |
| Variability estimate  | Standard error of the mean                        |
| Dispersion value  | 0.43  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Reldesemtiv 450 mg - placebo comparison of change |
| Statistical analysis description:   |   |
| Difference in LS mean changes from baseline: reldesemtiv 450 mg minus placebo |   |
| Comparison groups   | Placebo v Reldesemtiv 450 mg                      |
| Number of subjects included in analysis                                       | 231   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | superiority                                       |
| P-value   | = 0.1642  |
| Method  | Mixed models analysis                             |
| Parameter estimate  | LS mean difference                                |
| Point estimate  | 0.59  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -0.24   |
| upper limit   | 1.43  |
| Variability estimate  | Standard error of the mean                        |
| Dispersion value  | 0.425   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Reldesemtiv 300&450 mg (pooled)-placebo comparison |
| Statistical analysis description:   |  |
| Difference in LS mean changes from baseline: reldesemtiv 300 mg & 450 mg (pooled) minus placebo |  |
| Comparison groups   | Placebo v Reldesemtiv 300 mg & 450 mg (pooled)     |
| Number of subjects included in analysis   | 344  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | superiority  |
| P-value   | = 0.0435   |
| Method  | Mixed models analysis                              |
| Parameter estimate  | LS mean difference                                 |
| Point estimate  | 0.75   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.02   |
| upper limit   | 1.48   |
| Variability estimate  | Standard error of the mean                         |
| Dispersion value  | 0.371  |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from administration of the first dose of study drug through 4 weeks after the last dose of study drug

Adverse event reporting additional description:

An AE was treatment-emergent if it started or worsened (eg, increased in severity) during or after the first dose of study drug.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Patients in this group received placebo (to match reldesemtiv) twice daily for 12 weeks.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Reldesemtiv 150 mg |
|-----------------------|--------------------|

Reporting group description:

Patients in this group received 150 mg reldesemtiv twice daily for 12 weeks.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Reldesemtiv 300 mg |
|-----------------------|--------------------|

Reporting group description:

Patients in this group received 300 mg reldesemtiv twice daily for 12 weeks.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Reldesemtiv 450 mg |
|-----------------------|--------------------|

Reporting group description:

Patients in this group received 450 mg reldesemtiv twice daily for 12 weeks.

| Serious adverse events                            | Placebo          | Reldesemtiv 150 mg | Reldesemtiv 300 mg |
|---|------------------|--------------------|--------------------|
| Total subjects affected by serious adverse events |                  |                    |                    |
| subjects affected / exposed                       | 10 / 115 (8.70%) | 8 / 112 (7.14%)    | 8 / 113 (7.08%)    |
| number of deaths (all causes)                     | 2                | 0                  | 0                  |
| number of deaths resulting from adverse events    | 1                | 0                  | 0                  |
| Investigations                                    |                  |                    |                    |
| Alanine aminotransferase increased                |                  |                    |                    |
| subjects affected / exposed                       | 0 / 115 (0.00%)  | 0 / 112 (0.00%)    | 0 / 113 (0.00%)    |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 0              | 0 / 0              |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0              | 0 / 0              |
| Aspartate aminotransferase increased              |                  |                    |                    |
| subjects affected / exposed                       | 0 / 115 (0.00%)  | 0 / 112 (0.00%)    | 0 / 113 (0.00%)    |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 0              | 0 / 0              |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0              | 0 / 0              |
| Blood creatine phosphokinase                      |                  |                    |                    |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| increased                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Glomerular filtration rate decreased            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Weight decreased                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 1 / 112 (0.89%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Head injury                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Joint dislocation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 112 (0.89%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Traumatic fracture                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Jugular vein thrombosis                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subclavian vein thrombosis                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Cardiac disorders                                    |                 |                 |                 |
| Cardiac failure                                      |                 |                 |                 |
| subjects affected / exposed                          | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Palpitations   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute myocardial infarction                          |                 |                 |                 |
| subjects affected / exposed                          | 1 / 115 (0.87%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                             |                 |                 |                 |
| Amyotrophic lateral sclerosis                        |                 |                 |                 |
| subjects affected / exposed                          | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           | 0 / 0           |
| Dizziness  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Muscle contractions involuntary                      |                 |                 |                 |
| subjects affected / exposed                          | 0 / 115 (0.00%) | 1 / 112 (0.89%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient ischaemic attack                           |                 |                 |                 |
| subjects affected / exposed                          | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Pain   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 112 (0.89%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Dysphagia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 2 / 112 (1.79%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oesophagitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 112 (0.89%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal prolapse                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Prostatomegaly                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic ovarian cyst                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Dyspnoea  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 112 (0.89%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory distress                            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia aspiration                            |                 |                 |                 |
| subjects affected / exposed                     | 2 / 115 (1.74%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 2 / 115 (1.74%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Hepatotoxicity                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Urinary retention                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 1 / 112 (0.89%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 112 (0.89%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Device related sepsis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Parainfluenzae virus infection                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 0 / 112 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 112 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>                     | Reldesemtiv 450 mg |  |  |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events |                    |  |  |
| subjects affected / exposed                       | 8 / 117 (6.84%)    |  |  |
| number of deaths (all causes)                     | 1                  |  |  |
| number of deaths resulting from adverse events    | 1                  |  |  |
| Investigations                                    |                    |  |  |
| Alanine aminotransferase increased                |                    |  |  |
| subjects affected / exposed                       | 2 / 117 (1.71%)    |  |  |
| occurrences causally related to treatment / all   | 2 / 2              |  |  |
| deaths causally related to treatment / all        | 0 / 0              |  |  |
| Aspartate aminotransferase increased              |                    |  |  |
| subjects affected / exposed                       | 1 / 117 (0.85%)    |  |  |
| occurrences causally related to treatment / all   | 1 / 1              |  |  |
| deaths causally related to treatment / all        | 0 / 0              |  |  |
| Blood creatine phosphokinase increased            |                    |  |  |
| subjects affected / exposed                       | 1 / 117 (0.85%)    |  |  |
| occurrences causally related to treatment / all   | 1 / 1              |  |  |
| deaths causally related to treatment / all        | 0 / 0              |  |  |
| Glomerular filtration rate decreased              |                    |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 117 (0.85%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Weight decreased                                |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Head injury                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 117 (0.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Joint dislocation                               |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Traumatic fracture                              |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular disorders                              |                 |  |  |
| Jugular vein thrombosis                         |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subclavian vein thrombosis                      |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Cardiac failure                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| Palpitations   |                 |  |  |
| subjects affected / exposed                          | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Acute myocardial infarction                          |                 |  |  |
| subjects affected / exposed                          | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Nervous system disorders                             |                 |  |  |
| Amyotrophic lateral sclerosis                        |                 |  |  |
| subjects affected / exposed                          | 1 / 117 (0.85%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 1           |  |  |
| Dizziness  |                 |  |  |
| subjects affected / exposed                          | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Muscle contractions involuntary                      |                 |  |  |
| subjects affected / exposed                          | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Transient ischaemic attack                           |                 |  |  |
| subjects affected / exposed                          | 1 / 117 (0.85%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Pain   |                 |  |  |
| subjects affected / exposed                          | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Gastrointestinal disorders                           |                 |  |  |
| Dysphagia  |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Oesophagitis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rectal prolapse                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Reproductive system and breast disorders        |                 |  |  |
| Prostatomegaly                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 117 (0.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemorrhagic ovarian cyst                       |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Dyspnoea  |                 |  |  |
| subjects affected / exposed                     | 1 / 117 (0.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory distress                            |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia aspiration                            |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Hepatotoxicity                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 117 (0.85%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Urinary retention                               |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Urinary tract infection                         |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Appendicitis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Device related sepsis                           |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Parainfluenzae virus infection                  |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urosepsis                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 117 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Placebo           | Reldesemtiv 150 mg | Reldesemtiv 300 mg |
|---|-------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events |                   |                    |                    |
| subjects affected / exposed                           | 95 / 115 (82.61%) | 99 / 112 (88.39%)  | 97 / 113 (85.84%)  |
| Investigations  |                   |                    |                    |
| Cystatin C increased                                  |                   |                    |                    |
| subjects affected / exposed                           | 2 / 115 (1.74%)   | 7 / 112 (6.25%)    | 9 / 113 (7.96%)    |
| occurrences (all)                                     | 2                 | 7                  | 9                  |
| Glomerular filtration rate decreased                  |                   |                    |                    |
| subjects affected / exposed                           | 1 / 115 (0.87%)   | 6 / 112 (5.36%)    | 6 / 113 (5.31%)    |
| occurrences (all)                                     | 1                 | 6                  | 6                  |
| Alanine aminotransferase increased                    |                   |                    |                    |
| subjects affected / exposed                           | 1 / 115 (0.87%)   | 2 / 112 (1.79%)    | 5 / 113 (4.42%)    |
| occurrences (all)                                     | 1                 | 2                  | 6                  |
| Aspartate aminotransferase increased                  |                   |                    |                    |
| subjects affected / exposed                           | 1 / 115 (0.87%)   | 2 / 112 (1.79%)    | 3 / 113 (2.65%)    |
| occurrences (all)                                     | 1                 | 2                  | 3                  |
| Injury, poisoning and procedural complications        |                   |                    |                    |
| Contusion   |                   |                    |                    |
| subjects affected / exposed                           | 15 / 115 (13.04%) | 8 / 112 (7.14%)    | 14 / 113 (12.39%)  |
| occurrences (all)                                     | 28                | 15                 | 15                 |
| Post-traumatic pain                                   |                   |                    |                    |
| subjects affected / exposed                           | 2 / 115 (1.74%)   | 6 / 112 (5.36%)    | 8 / 113 (7.08%)    |
| occurrences (all)                                     | 2                 | 8                  | 11                 |
| Skin abrasion   |                   |                    |                    |

|   |                      |                       |                      |
|---|----------------------|-----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)        | 5 / 115 (4.35%)<br>7 | 8 / 112 (7.14%)<br>10 | 3 / 113 (2.65%)<br>4 |
| Nervous system disorders                                |                      |                       |                      |
| Headache  |                      |                       |                      |
| subjects affected / exposed                             | 15 / 115 (13.04%)    | 16 / 112 (14.29%)     | 16 / 113 (14.16%)    |
| occurrences (all)                                       | 18                   | 18                    | 19                   |
| Dizziness   |                      |                       |                      |
| subjects affected / exposed                             | 11 / 115 (9.57%)     | 8 / 112 (7.14%)       | 11 / 113 (9.73%)     |
| occurrences (all)                                       | 13                   | 12                    | 13                   |
| General disorders and administration<br>site conditions |                      |                       |                      |
| Fatigue   |                      |                       |                      |
| subjects affected / exposed                             | 12 / 115 (10.43%)    | 14 / 112 (12.50%)     | 19 / 113 (16.81%)    |
| occurrences (all)                                       | 14                   | 14                    | 20                   |
| Gastrointestinal disorders                              |                      |                       |                      |
| Nausea  |                      |                       |                      |
| subjects affected / exposed                             | 14 / 115 (12.17%)    | 10 / 112 (8.93%)      | 13 / 113 (11.50%)    |
| occurrences (all)                                       | 16                   | 13                    | 14                   |
| Constipation  |                      |                       |                      |
| subjects affected / exposed                             | 5 / 115 (4.35%)      | 7 / 112 (6.25%)       | 13 / 113 (11.50%)    |
| occurrences (all)                                       | 5                    | 8                     | 15                   |
| Diarrhoea   |                      |                       |                      |
| subjects affected / exposed                             | 8 / 115 (6.96%)      | 12 / 112 (10.71%)     | 6 / 113 (5.31%)      |
| occurrences (all)                                       | 8                    | 15                    | 6                    |
| Dry mouth   |                      |                       |                      |
| subjects affected / exposed                             | 2 / 115 (1.74%)      | 2 / 112 (1.79%)       | 6 / 113 (5.31%)      |
| occurrences (all)                                       | 2                    | 2                     | 6                    |
| Skin and subcutaneous tissue disorders                  |                      |                       |                      |
| Pruritus  |                      |                       |                      |
| subjects affected / exposed                             | 2 / 115 (1.74%)      | 1 / 112 (0.89%)       | 2 / 113 (1.77%)      |
| occurrences (all)                                       | 4                    | 1                     | 3                    |
| Musculoskeletal and connective tissue<br>disorders      |                      |                       |                      |
| Arthralgia  |                      |                       |                      |
| subjects affected / exposed                             | 2 / 115 (1.74%)      | 8 / 112 (7.14%)       | 4 / 113 (3.54%)      |
| occurrences (all)                                       | 2                    | 9                     | 5                    |
| Pain in extremity                                       |                      |                       |                      |

|  |                      |                      |                        |
|--|----------------------|----------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)   | 5 / 115 (4.35%)<br>6 | 1 / 112 (0.89%)<br>1 | 3 / 113 (2.65%)<br>3   |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)  | 1 / 115 (0.87%)<br>1 | 6 / 112 (5.36%)<br>7 | 2 / 113 (1.77%)<br>2   |
| Infections and infestations<br>Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 9 / 115 (7.83%)<br>9 | 6 / 112 (5.36%)<br>6 | 10 / 113 (8.85%)<br>10 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)  | 8 / 115 (6.96%)<br>9 | 3 / 112 (2.68%)<br>5 | 5 / 113 (4.42%)<br>5   |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                                      | 3 / 115 (2.61%)<br>4 | 7 / 112 (6.25%)<br>7 | 1 / 113 (0.88%)<br>1   |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)               | 4 / 115 (3.48%)<br>4 | 3 / 112 (2.68%)<br>3 | 7 / 113 (6.19%)<br>7   |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)  | 0 / 115 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 | 6 / 113 (5.31%)<br>6   |

|  |                         |  |  |
|--|-------------------------|--|--|
| <b>Non-serious adverse events</b>  | Reldesemtiv 450 mg      |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed       | 107 / 117 (91.45%)      |  |  |
| Investigations<br>Cystatin C increased<br>subjects affected / exposed<br>occurrences (all) | 20 / 117 (17.09%)<br>22 |  |  |
| Glomerular filtration rate decreased<br>subjects affected / exposed<br>occurrences (all)   | 10 / 117 (8.55%)<br>11  |  |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)     | 11 / 117 (9.40%)<br>14  |  |  |
| Aspartate aminotransferase increased   |                         |  |  |

|  |                       |  |  |
|--|-----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)     | 9 / 117 (7.69%)<br>11 |  |  |
| Injury, poisoning and procedural complications       |                       |  |  |
| Contusion  |                       |  |  |
| subjects affected / exposed                          | 17 / 117 (14.53%)     |  |  |
| occurrences (all)                                    | 26                    |  |  |
| Post-traumatic pain                                  |                       |  |  |
| subjects affected / exposed                          | 6 / 117 (5.13%)       |  |  |
| occurrences (all)                                    | 6                     |  |  |
| Skin abrasion  |                       |  |  |
| subjects affected / exposed                          | 5 / 117 (4.27%)       |  |  |
| occurrences (all)                                    | 7                     |  |  |
| Nervous system disorders                             |                       |  |  |
| Headache   |                       |  |  |
| subjects affected / exposed                          | 12 / 117 (10.26%)     |  |  |
| occurrences (all)                                    | 13                    |  |  |
| Dizziness  |                       |  |  |
| subjects affected / exposed                          | 7 / 117 (5.98%)       |  |  |
| occurrences (all)                                    | 7                     |  |  |
| General disorders and administration site conditions |                       |  |  |
| Fatigue  |                       |  |  |
| subjects affected / exposed                          | 20 / 117 (17.09%)     |  |  |
| occurrences (all)                                    | 24                    |  |  |
| Gastrointestinal disorders                           |                       |  |  |
| Nausea   |                       |  |  |
| subjects affected / exposed                          | 22 / 117 (18.80%)     |  |  |
| occurrences (all)                                    | 23                    |  |  |
| Constipation   |                       |  |  |
| subjects affected / exposed                          | 10 / 117 (8.55%)      |  |  |
| occurrences (all)                                    | 10                    |  |  |
| Diarrhoea  |                       |  |  |
| subjects affected / exposed                          | 4 / 117 (3.42%)       |  |  |
| occurrences (all)                                    | 4                     |  |  |
| Dry mouth  |                       |  |  |
| subjects affected / exposed                          | 1 / 117 (0.85%)       |  |  |
| occurrences (all)                                    | 1                     |  |  |

|  |   |  |  |
|--|---|--|--|
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)   | 6 / 117 (5.13%)<br>6  |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all)<br><br>Muscle spasms<br>subjects affected / exposed<br>occurrences (all)                                    | 8 / 117 (6.84%)<br>10<br><br>6 / 117 (5.13%)<br>7<br><br>1 / 117 (0.85%)<br>1 |  |  |
| Infections and infestations<br>Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 9 / 117 (7.69%)<br>9<br><br>5 / 117 (4.27%)<br>7<br><br>1 / 117 (0.85%)<br>1  |  |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)<br><br>Dehydration<br>subjects affected / exposed<br>occurrences (all)  | 7 / 117 (5.98%)<br>8<br><br>6 / 117 (5.13%)<br>7                              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported