



Clinical trial results:

Effect of MD1003 in amyotrophic lateral sclerosis: a randomized, double blind placebo controlled study

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-005810-31 |
| Trial protocol | FR |
| Global end of trial date | 24 May 2018 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 15 August 2020 |
| First version publication date | 15 August 2020 |

Trial information

Trial identification

| | |
|-----------------------|---------------------|
| Sponsor protocol code | MD1003CT2015-02-ALS |
|-----------------------|---------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03114215 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | MedDay Pharmaceuticals |
| Sponsor organisation address | 24-26 rue de la pépinière, PARIS, France, |
| Public contact | Clinical Trial Information, MEDDAY PHARMACEUTICALS, +33 181516666, |
| Scientific contact | Clinical Trial Information, MEDDAY PHARMACEUTICALS, +33 181516666, |

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 | 12 June 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 June 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 May 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Investigation of the safety of biotin in ALS

Protection of trial subjects:

signature of an ICF at the beginning of the study before any assessment.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------------------------|
| Actual start date of recruitment | 29 June 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy, Ethical reason |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | France: 30 |
| Worldwide total number of subjects | 30 |
| EEA total number of subjects | 30 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| 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) | 20 |
| From 65 to 84 years | 10 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

all patients were randomized from the June 29th 2016 to November 15th 2016 at the Principale investigator's site in Montpellier.

Pre-assignment

Screening details:

all patients screened were randomized in this study. no screen failure.

Pre-assignment period milestones

| | |
|----------------------------|----|
| Number of subjects started | 30 |
|----------------------------|----|

| | |
|------------------------------|----|
| Number of subjects completed | 30 |
|------------------------------|----|

Period 1

| | |
|----------------|-------------------------------|
| Period 1 title | Double-blind (overall period) |
|----------------|-------------------------------|

| | |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

| | |
|-------------------|-------------------------|
| Allocation method | Randomised - controlled |
|-------------------|-------------------------|

| | |
|---------------|--------------|
| Blinding used | Double blind |
|---------------|--------------|

| | |
|---------------|---|
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |
|---------------|---|

Blinding implementation details:

Each product, active or placebo will be conditioned in size one capsules having the same aspect. The capsules will contain the same quantity of white powder, with the same aspect and taste (biotin has no taste).

Placebo capsules will thus contain 100 mg more lactose in replacement of biotin.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

placebo arm

10 patients in placebo arm

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|---------|
| Investigational medicinal product name | Placebo |
|--|---------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|---------|
| Pharmaceutical forms | Capsule |
|----------------------|---------|

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

300 mg/day (100 mg tid)

| | |
|------------------|------------|
| Arm title | active arm |
|------------------|------------|

Arm description:

20 patients in the active arm

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|--------|
| Investigational medicinal product name | Biotin |
|--|--------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|---------|
| Pharmaceutical forms | Capsule |
|----------------------|---------|

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

300 mg/day (100 mg tid)

| Number of subjects in period 1 | Placebo | active arm |
|---------------------------------------|---------|------------|
| Started | 10 | 20 |
| Completed | 9 | 18 |
| Not completed | 1 | 2 |
| Adverse event, serious fatal | 1 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Double-blind |
|-----------------------|--------------|

Reporting group description: -

| Reporting group values | Double-blind | Total | |
|--|--------------|-------|--|
| Number of subjects | 30 | 30 | |
| Age categorical | | | |
| adults patients from 18 to 164 yers | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 20 | 20 | |
| From 65-84 years | 10 | 10 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | 9 | |
| Male | 21 | 21 | |

Subject analysis sets

| | |
|----------------------------|-----|
| Subject analysis set title | FAS |
|----------------------------|-----|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

This population included all randomized patients who received at least one dose of study medication and with at least one assessment at screening or baseline. In case of error in treatment allocation, the actual treatment received was used.

| | |
|----------------------------|---------------------|
| Subject analysis set title | SAFETY ANALYSIS SET |
|----------------------------|---------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

This population included all patients who received at least one dose of study medication. In case of error in treatment allocation, the actual treatment received was used. This set was used for the safety analyses.

| | |
|----------------------------|--------------|
| Subject analysis set title | PER PROTOCOL |
|----------------------------|--------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

This population included all patients of the FAS with an assessment of ALSFRS-R at baseline and at M6 and without major protocol deviations. This set was used in the sensitivity analyses to assess the impact of early death and the impact of protocol deviations.

| Reporting group values | FAS | SAFETY ANALYSIS SET | PER PROTOCOL |
|--|-----|---------------------|--------------|
| Number of subjects | 30 | 30 | 26 |
| Age categorical | | | |
| adults patients from 18 to 164 yers | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 20 | | |
| From 65-84 years | 10 | | |
| 85 years and over | 0 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | | |
| Male | 21 | | |

End points

End points reporting groups

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

Reporting group description:

placebo arm

10 patients in placebo arm

| | |
|-----------------------|------------|
| Reporting group title | active arm |
|-----------------------|------------|

Reporting group description:

20 patients in the active arm

| | |
|----------------------------|-----|
| Subject analysis set title | FAS |
|----------------------------|-----|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

This population included all randomized patients who received at least one dose of study medication and with at least one assessment at screening or baseline. In case of error in treatment allocation, the actual treatment received was used.

| | |
|----------------------------|---------------------|
| Subject analysis set title | SAFETY ANALYSIS SET |
|----------------------------|---------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

This population included all patients who received at least one dose of study medication. In case of error in treatment allocation, the actual treatment received was used. This set was used for the safety analyses.

| | |
|----------------------------|--------------|
| Subject analysis set title | PER PROTOCOL |
|----------------------------|--------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

This population included all patients of the FAS with an assessment of ALSFRS-R at baseline and at M6 and without major protocol deviations. This set was used in the sensitivity analyses to assess the impact of early death and the impact of protocol deviations.

Primary: Safety Primary Endpoint

| | |
|-----------------|-------------------------|
| End point title | Safety Primary Endpoint |
|-----------------|-------------------------|

End point description:

- Recording of adverse events in the two groups
- Laboratory testing (haematology and biochemistry panel)
 - o RBC, WBC, platelets
 - o Ferritin, CPK
 - o Electrolytes, creatinine, glycaemia
 - o AST, ALT, bilirubin, GGT, alkaline phosphatase
 - o Triglyceride, cholesterol
 - o Haemostasis: APPT, PT

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Do reported treatment-emergent adverse events (TEAEs) and serious TEAEs allow to detect a signal of safety concerns in the first 6 months of treatment?

| End point values | Placebo | active arm | SAFETY ANALYSIS SET | |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 10 | 20 | 30 | |
| Units: percent | | | | |
| number (not applicable) | 60 | 60 | 30 | |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | mann-Whitney U |
| Comparison groups | Placebo v active arm |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.493 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Motor disability: ALSFRS-R scale

| | |
|------------------------|----------------------------------|
| End point title | Motor disability: ALSFRS-R scale |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 6 months | |

| End point values | Placebo | active arm | FAS | |
|---------------------------------------|---------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 10 | 20 | 30 | |
| Units: score | | | | |
| median (inter-quartile range (Q1-Q3)) | -2.5 (-8.0 to -1.0) | -4.0 (-10.0 to -2.0) | -3.5 (-8.0 to -1.0) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease severity - Severity score

| | |
|------------------------|-----------------------------------|
| End point title | Disease severity - Severity score |
| End point description: | |
| End point type | Secondary |

End point timeframe:

6 months

| End point values | Placebo | active arm | FAS | |
|-----------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 10 | 20 | 30 | |
| Units: score | | | | |
| median (standard deviation) | -5.500 (\pm 7.990) | -7.100 (\pm 8.265) | -1.600 (\pm 7.900) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Respiratory parameters - Slow vital capacity (SVC)

| | |
|------------------------|--|
| End point title | Respiratory parameters - Slow vital capacity (SVC) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 6 Months | |

| End point values | Placebo | active arm | FAS | |
|----------------------------------|------------------|------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 0 ^[1] | 0 ^[2] | 30 | |
| Units: mean | | | | |
| arithmetic mean (standard error) | () | () | 4.24 (\pm 7.50) | |

Notes:

[1] - This analyse is not performed per reporting group (MD1003 / placebo). Only overall is available.

[2] - This analyse is not performed per reporting group (MD1003 / placebo). Only overall is available.

Statistical analyses

No statistical analyses for this end point

Secondary: Respiratory parameters - maximal inspiratory pressure (MIP)

| | |
|------------------------|---|
| End point title | Respiratory parameters - maximal inspiratory pressure (MIP) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 6 Months | |

| End point values | Placebo | active arm | FAS | |
|----------------------------------|------------------|------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 0 ^[3] | 0 ^[4] | 30 | |
| Units: MEAN | | | | |
| arithmetic mean (standard error) | () | () | 4.91 (± 8.12) | |

Notes:

[3] - This analyse is not performed per reporting group (MD1003 / placebo). Only overall is available.

[4] - This analyse is not performed per reporting group (MD1003 / placebo). Only overall is available.

Statistical analyses

No statistical analyses for this end point

Secondary: Respiratory parameters - sniff nasal inspiratory pressure (SNIP)

| | |
|-----------------|--|
| End point title | Respiratory parameters - sniff nasal inspiratory pressure (SNIP) |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

6 months

| End point values | Placebo | active arm | FAS | |
|----------------------------------|------------------|------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 0 ^[5] | 0 ^[6] | 30 | |
| Units: MEAN | | | | |
| arithmetic mean (standard error) | () | () | 12.78 (± 7.45) | |

Notes:

[5] - This analyse is not performed per reporting group (MD1003 / placebo). Only overall is available.

[6] - This analyse is not performed per reporting group (MD1003 / placebo). Only overall is available.

Statistical analyses

No statistical analyses for this end point

Secondary: Weight

| | |
|-----------------|--------|
| End point title | Weight |
|-----------------|--------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

6 months

| End point values | Placebo | active arm | FAS | |
|----------------------------------|------------------|------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 0 ^[7] | 0 ^[8] | 30 | |
| Units: mean | | | | |
| arithmetic mean (standard error) | () | () | -1.63 (± 1.29) | |

Notes:

[7] - This analyse is not performed per reporting group (MD1003 / placebo). Only overall is available.

[8] - This analyse is not performed per reporting group (MD1003 / placebo). Only overall is available.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:
at each visit

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

placebo arm

10 patients in placebo arm

| | |
|-----------------------|------------|
| Reporting group title | active arm |
|-----------------------|------------|

Reporting group description:

20 patients in the active arm

| Serious adverse events | Placebo | active arm | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 4 / 20 (20.00%) | |
| number of deaths (all causes) | 1 | 2 | |
| number of deaths resulting from adverse events | 1 | 2 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Gastrostomy | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 20 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Myocardial infarction | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Placebo | active arm | |
|--|-----------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 10 (60.00%) | 12 / 20 (60.00%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Surgical and medical procedures | | | |
| Gastrostomy | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 20 (10.00%) | |
| occurrences (all) | 0 | 2 | |
| Hip arthroplasty | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|--|---|--|
| Acute respiratory failure subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 2 / 20 (10.00%) 2 | |
| Cardiac disorders Cardiac arrest subjects affected / exposed occurrences (all) Myocardial infarction subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 | 0 / 20 (0.00%) 0 0 / 20 (0.00%) 0 | |
| Nervous system disorders Complex regional pain syndrome subjects affected / exposed occurrences (all) Restless legs syndrome subjects affected / exposed occurrences (all) Presyncope subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 1 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 | 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 0 / 20 (0.00%) 0 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Rash maculo-papular | 0 / 10 (0.00%) 0 | 1 / 20 (5.00%) 1 | |

| | | | |
|--|---|--|--|
| subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Renal and urinary disorders Urinary retention subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Musculoskeletal and connective tissue disorders Tendonitis subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 20 (0.00%) 0 | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 | 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 | |
| Metabolism and nutrition disorders Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 20 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 24 June 2016 | change of factory for the secondary packaging and labelling. |
| 14 April 2017 | addition of 12 months of open label extension |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32140672>