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 stufy 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'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)
  - RBC, WBC, platelets
  - Ferritin, CPK
  - Electrolytes, creatinine, glycaemia
  - AST, ALT, bilirubin, GGT, alkaline phosphatase
  - Triglyceride, cholesterol
  - 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 (± 7.990)	-7.100 (± 8.265)	-1.600 (± 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 (± 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	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 10 (10.00%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Myocardial infarction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Complex regional pain syndrome			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Restless legs syndrome			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rash maculo-papular			

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