



## Clinical trial results:

### Natural history study in adult patients with SMA types 2-3-4 and Role of neurodegenerative and neuro-inflammatory biomarkers in SMA adults treated with nusinersen.

#### Summary

EudraCT number	2019-005007-40
Trial protocol	BE
Global end of trial date	30 August 2022

#### Results information

Result version number	v1 (current)
This version publication date	03 June 2023
First version publication date	03 June 2023

#### Trial information

##### Trial identification

Sponsor protocol code	S62874
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	University Hospitals Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Department of Neurology, University Hospitals Leuven, 32 16344280, secretariaat.neuro@uzleuven.be
Scientific contact	Department of Neurology, University Hospitals Leuven, 32 16344280, secretariaat.neuro@uzleuven.be

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	30 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2022
Global end of trial reached?	Yes
Global end of trial date	30 August 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To perform a detailed clinical and functional characterization and natural history analysis in adult patients with SMA types 2-3-4 with and without nusinersen (Spinraza®) treatment.

Protection of trial subjects:

- Safety assessment of nusinersen treatment during trial (reporting of AE and SAE)
- Data handling: All data collected in this study will be coded (pseudonymized) and only the principal investigator of the study will have access to the key linking the code to the patient identification. The study nurses/investigators/ evaluators that carry out the study will be blinded to the test result.
- Ethics/Regulatory approvals: The trial will be conducted in compliance with the principles of the Declaration of Helsinki (2008), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to the Ethical Committee. The principal investigator of this study, Prof. dr. K. Claeys, obtained the GCP certificate. The Study can and will be conducted only on the basis of prior informed consent by the Patients to participate in the Study (informed consent only in those patients that are treated and are included in the prospective part of the study; not in the patients in the retrospective part of the study only). The Participating Site shall obtain a signed informed consent form (ICF) for the subjects prior to their enrollment and participation in the Study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws. The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study as confidential and shall not disclose personal identity information to any third parties or use any information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data is subject to compliance with applicable per(Directive 95/46/EC and Belgian law of 8-12-1992.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 February 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	15
From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

All 16 patients received intrathecal administrations of 12 mg of nusinersen following the standard of care dosing schedule, for a study duration of 14 months.

### Pre-assignment

Screening details:

Inclusion criteria for the prospective study evaluating treatment with nusinersen were as follows: genetically confirmed 5q SMA, adult age at the time of enrolment ( $\geq 18$  years), patients with SMA type 3 or 4, the use of an adequate contraceptive by female patients for the whole duration of the study and patients' written informed consent.

### Pre-assignment period milestones

Number of subjects started	16
Number of subjects completed	16

### Period 1

Period 1 title	overall trial period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	treated patients (all)
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Arm description:

all included patients are treated with nusinersen, therefore there is only one arm

Arm type	Experimental
Investigational medicinal product name	nusinersen (Spinraza)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

The treatment with nusinersen (Spinraza®) is done by intrathecal injection, using a standard lumbar puncture needle, in sterile conditions. Prior to injection of 5 ml nusinersen intrathecally, first 5 ml of cerebrospinal fluid (CSF) is being tapped, in order to compensate for the 5 ml of medication that will be injected, in order to keep the same total CSF volume. This is done following the normal standard-of-care procedures.

<b>Number of subjects in period 1</b>	treated patients (all)
Started	16
Completed	16



## Baseline characteristics

### Reporting groups

Reporting group title	overall trial period
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Reporting group description:

Sixteen adult SMA type 3 and 4 patients participated in a prospective, observational study to examine the effectiveness and safety of intrathecal nusinersen (Spinraza®) treatment in adult SMA patients.

Reporting group values	overall trial period	Total	
Number of subjects	16	16	
Age categorical			
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)	15	15	
From 65-84 years	1	1	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	10	10	

## End points

### End points reporting groups

Reporting group title	treated patients (all)
Reporting group description: all included patients are treated with nusinersen, therefore there is only one arm	

### Primary: Efficacy of nusinersen treatment - grip strength R hand

End point title	Efficacy of nusinersen treatment - grip strength R hand <sup>[1]</sup>
End point description:	

End point type	Primary
End point timeframe: study duration of 14 months for all patients	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: see attached document for results

End point values	treated patients (all)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: kilogram(s)				
arithmetic mean (standard deviation)	9 (± 7.76)			

<b>Attachments (see zip file)</b>	Statistics and Results published/De Wel et al Journal of
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### Statistical analyses

No statistical analyses for this end point

### Primary: Efficacy of nusinersen treatment - grip strength L hand

End point title	Efficacy of nusinersen treatment - grip strength L hand <sup>[2]</sup>
End point description:	

End point type	Primary
End point timeframe: study duration of 14 months for all patients	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: see attached document for results

<b>End point values</b>	treated patients (all)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: kilogram(s)				
arithmetic mean (standard deviation)	8.19 (± 8.78)			

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### Statistical analyses

No statistical analyses for this end point

### Primary: MRC sum score

End point title	MRC sum score <sup>[3]</sup>
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End point description:

End point type	Primary
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End point timeframe:

study duration of 14 months for all patients

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: see attached document for results

<b>End point values</b>	treated patients (all)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: sum score				
arithmetic mean (standard deviation)	39.4 (± 8.4)			

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### Statistical analyses

No statistical analyses for this end point

### Primary: 6MWD

End point title	6MWD <sup>[4]</sup>
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End point description:

End point type	Primary
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End point timeframe:

study duration of 14 months for all patients



Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: see attached document for results

End point values	treated patients (all)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: metre				
arithmetic mean (standard deviation)	303 ( $\pm$ 211)			

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### Statistical analyses

No statistical analyses for this end point

### Primary: HFMSE

End point title	HFMSE <sup>[5]</sup>
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End point description:

End point type	Primary
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End point timeframe:

study duration of 14 months for all patients

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: see attached document for results

End point values	treated patients (all)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: score				
arithmetic mean (standard deviation)	29.4 ( $\pm$ 19.9)			

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### Statistical analyses

No statistical analyses for this end point

### Primary: RULM

End point title	RULM <sup>[6]</sup>
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End point description:

End point type	Primary
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End point timeframe:

study duration of 14 months for all patients

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: see attached document for results

<b>End point values</b>	treated patients (all)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: score				
arithmetic mean (standard deviation)	28.2 ( $\pm$ 8.41)			

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### Statistical analyses

No statistical analyses for this end point

### Primary: FVC

End point title	FVC <sup>[7]</sup>
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End point description:

End point type	Primary
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End point timeframe:

study duration of 14 months for all patients

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: see attached document for results

<b>End point values</b>	treated patients (all)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: litre(s)				
arithmetic mean (standard deviation)	4.12 ( $\pm$ 1.20)			

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### Statistical analyses

No statistical analyses for this end point

### Primary: PEF

End point title	PEF <sup>[8]</sup>			
End point description:				
End point type	Primary			
End point timeframe:				
study duration of 14 months for all patients				
Notes:				
[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.				
Justification: see attached document for results				

<b>End point values</b>	treated patients (all)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: litre(s)				
arithmetic mean (standard deviation)	7.34 (± 1.94)			

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### Statistical analyses

No statistical analyses for this end point

<b>Primary: ActivLim</b>				
End point title	ActivLim <sup>[9]</sup>			
End point description:				
End point type	Primary			
End point timeframe:				
study duration of 14 months for all patients				
Notes:				
[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.				
Justification: see attached document for results				

<b>End point values</b>	treated patients (all)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: score				
arithmetic mean (standard deviation)	1.44 (± 2.59)			

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### Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

from start of the study (first visit of first included patient) until end of the study (last visit of last included patient)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23
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### Reporting groups

Reporting group title	all included patients
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Reporting group description: -

Serious adverse events	all included patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	all included patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 16 (37.50%)		
occurrences (all)	28		
Post-puncture headache			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	11		
Dizziness			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	10		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)  Agitation subjects affected / exposed occurrences (all)	8 / 16 (50.00%)  45  5 / 16 (31.25%)  22		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	3 / 16 (18.75%)  12		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	2 / 16 (12.50%)  6		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)  Myalgia subjects affected / exposed occurrences (all)	12 / 16 (75.00%)  72  7 / 16 (43.75%)  21		
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	5 / 16 (31.25%)  25		

## 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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32935160>