



## Clinical trial results:

### SPACE trial

#### SMA and Pyridostigmine in Adults and Children; Efficacy trial

Phase II, mono-center, doubleblind, placebo-controlled, crossover trial to assess efficacy of pyridostigmine in patients with spinal muscular atrophy types 2, 3 and 4

### Summary

EudraCT number	2011-004369-34
Trial protocol	NL
Global end of trial date	17 January 2018

### Results information

Result version number	v1 (current)
This version publication date	20 November 2021
First version publication date	20 November 2021
Summary attachment (see zip file)	Summary of results - SPACE trial (SPACE trial.pdf)

### Trial information

#### Trial identification

Sponsor protocol code	UMC-NMZ-SMA2011
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02941328
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	UMC Utrecht
Sponsor organisation address	Heidelberglaan, 100, Utrecht, Netherlands, 3584CX
Public contact	METC, UMC Utrecht, 0031 887555555, r.i.wadman@umcutrecht.nl
Scientific contact	METC, UMC Utrecht, 31 887555555, r.i.wadman@umcutrecht.nl

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	17 January 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 January 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this placebo-controlled cross-over trial in adult patients with SMA type 2, 3 and 4 is to investigate the effect and efficacy of pyridostigmine on muscle strength and fatiguability in patients with SMA.

Protection of trial subjects:

We conducted the study according to the principles of the Declaration of Helsinki (WMA General Assembly 2013, Fortaleza, Brazil) and in accordance with the Medical Research Involving Human Subjects Act.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2014
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	Netherlands: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	4
Adults (18-64 years)	31
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

#### Recruitment details:

We conducted an investigator-initiated, phase II, monocentre, placebo-controlled, double-blind cross-over trial at the SMA Centre at the University Medical Centre Utrecht, a tertiary referral centre for patients with SMA in the Netherlands.

We enrolled the first patient in this study on November 24, 2015. Study was ended in January 2018.

### Pre-assignment

#### Screening details:

We published the trial design and procedures previously, including detailed in- and exclusion criteria (Stam M et al. Protocol for a phase II, monocentre, double-blind, placebo-controlled, cross-over trial to assess efficacy of pyridostigmine in patients with spinal muscular atrophy types 2-4 (SPACE trial). *BMJ Open*. 2018;8(7):e019932.)

### Period 1

Period 1 title	Pyridostigmine-placebo
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

#### Blinding implementation details:

An independent pharmacist, who was not part of the study team, randomised eligible patients in a permuted four-block design. Both patients and investigators were blinded for treatment allocation.

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	pyridostigmine

#### Arm description:

Crossover trial Pyridostigmine-Placebo arm

Patients administered the study medication four times daily because of the short half-life of pyridostigmine, leading to an effect duration of approximately 4-6 hours. In order to minimize side-effects, we increased the dosage from 2 mg/kg/day to 4 mg/kg/day and finally to the targeted 6 mg/kg/day in the course of the first week of each treatment period.

Arm type	Cross-over
Investigational medicinal product name	pyridostigmine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

#### Dosage and administration details:

The study medication was administered four times daily because of the short half-life of pyridostigmine, leading to an effect duration of approximately 4-6 hours. In order to minimize side-effects, dosage was increased from 2 mg/kg/day to 4 mg/kg/day and finally to the targeted 6 mg/kg/day in the course of the first week of each treatment period. If side-effects after a dosage increase were not acceptable for the patient, the treatment period was continued with the highest tolerated dose.

<b>Arm title</b>	placebo
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#### Arm description:

Crossover trial Pyridostigmine-Placebo arm

Same dosing schedule as active comparator

Arm type	Cross-over
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	pyridostigmine	placebo
Started	17	17
Completed	17	17

## Period 2

Period 2 title	Placebo-Pyridostigmine
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

An independent pharmacist, who was not part of the study team, randomised eligible patients in a permuted four-block design. Both patients and investigators were blinded for treatment allocation.

## Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	placebo

Arm description:

Crossover trial Placebo-pyridostigmine arm

Same schedule as comparator

Arm type	Cross-over
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The study medication was administered four times daily because of the short half-life of pyridostigmine, leading to an effect duration of approximately 4-6 hours. In order to minimize side-effects, dosage was increased from 2 mg/kg/day to 4 mg/kg/day and finally to the targeted 6 mg/kg/day in the course of the first week of each treatment period. If side-effects after a dosage increase were not acceptable for the patient, the treatment period was continued with the highest tolerated dose.

Investigational medicinal product name	pyridostigmine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The study medication was administered four times daily because of the short half-life of pyridostigmine, leading to an effect duration of approximately 4-6 hours. In order to minimize side-effects, dosage was increased from 2 mg/kg/day to 4 mg/kg/day and finally to the targeted 6 mg/kg/day in the course of the first week of each treatment period. If side-effects after a dosage increase were not acceptable for the patient, the treatment period was continued with the highest tolerated dose.

<b>Arm title</b>	pyridostigmine
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Arm description:

Crossover trial Placebo-pyridostigmine arm

Patients administered the study medication four times daily because of the short half-life of

pyridostigmine, leading to an effect duration of approximately 4-6 hours. In order to minimize side-effects, we increased the dosage from 2 mg/kg/day to 4 mg/kg/day and finally to the targeted 6 mg/kg/day in the course of the first week of each treatment period.

Arm type	Cross-over
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 2</b>	placebo	pyridostigmine
Started	18	18
Completed	18	18

## Baseline characteristics

### Reporting groups<sup>[1]</sup>

Reporting group title	Pyridostigmine-placebo
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Reporting group description: -
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Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: This is a crossover trial with two different treatment periods, either pyridostigmine --> placebo (n=17) or placebo--> pyridostigmine (n=18)

Reporting group values	Pyridostigmine-placebo	Total	
Number of subjects	17	17	
Age categorical			
Mean 34 (SD 12; range 13-53)			
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	34		
standard deviation	± 12	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	8	8	

### Subject analysis sets

Subject analysis set title	Placebo-Pyridostigmine
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Placebo to crossover to pyridostigmine

Subject analysis set title	Pyridostigmine-Placebo
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Pyridostigmine to crossover to placebo

Reporting group values	Placebo-Pyridostigmine	Pyridostigmine-Placebo	
Number of subjects	18	17	

Age categorical			
Mean 34 (SD 12; range 13-53)			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Units: years			
arithmetic mean	38	34	
standard deviation	± 14	± 12	
Gender categorical			
Units: Subjects			
Female	13	9	
Male	5	8	

## End points

### End points reporting groups

Reporting group title	pyridostigmine
Reporting group description: Crossover trial Pyridostigmine-Placebo arm Patients administered the study medication four times daily because of the short half-life of pyridostigmine, leading to an effect duration of approximately 4-6 hours. In order to minimize side-effects, we increased the dosage from 2 mg/kg/day to 4 mg/kg/day and finally to the targeted 6 mg/kg/day in the course of the first week of each treatment period.	
Reporting group title	placebo
Reporting group description: Crossover trial Pyridostigmine-Placebo arm Same dosing schedule as active comparator	
Reporting group title	placebo
Reporting group description: Crossover trial Placebo-pyridostigmine arm Same schedule as comparator	
Reporting group title	pyridostigmine
Reporting group description: Crossover trial Placebo-pyridostigmine arm Patients administered the study medication four times daily because of the short half-life of pyridostigmine, leading to an effect duration of approximately 4-6 hours. In order to minimize side-effects, we increased the dosage from 2 mg/kg/day to 4 mg/kg/day and finally to the targeted 6 mg/kg/day in the course of the first week of each treatment period.	
Subject analysis set title	Placebo-Pyridostigmine
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo to crossover to pyridostigmine	
Subject analysis set title	Pyridostigmine-Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Pyridostigmine to crossover to placebo	

### Primary: repeated nine-hole peg test (R9HPT)

End point title	repeated nine-hole peg test (R9HPT) <sup>[1]</sup>
End point description: A trend was observed in the repeated nine-hole PEG test favoring pyridostigmine, with a slowing in the rate of increase in time needed over trials of -0.68s (95% CI -1.47 to 0.12, p-value = 0.09) or 44.7%.	
End point type	Primary
End point timeframe: Change in time needed to complete one round during the R9HPT	
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: crossover statistics is not possible to put in data	

End point values	pyridostigmine	placebo	placebo	pyridostigmine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	18	18
Units: time needed to complete one round				
number (not applicable)	17	17	18	18



## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

18 weeks

Adverse event reporting additional description:

Most AEs were mild, self-limiting and acceptable for patients. The most common AEs were gastro-intestinal (GI) complaints. Other related side-effects included increased saliva production and blurry sight. Participants reported muscle cramps and pain after study visits. There were four serious adverse events (SAEs), all unrelated to study medication.

Assessment type	Systematic
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### Dictionary used

Dictionary name	Systematic
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Dictionary version	1
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### Reporting groups

Reporting group title	General disorders and administration site conditions
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Reporting group description: -

Serious adverse events	General disorders and administration site conditions		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	General disorders and administration site conditions		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)		
Injury, poisoning and procedural complications			
administration site conditions			
subjects affected / exposed <sup>[1]</sup>	3 / 3 (100.00%)		
occurrences (all)	9		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The system is not accepting the actual data

## 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

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30061431>