



## 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 |
|-----------------------|-----------------|

#### 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,<br>r.i.wadman@umcutrecht.nl |
| Scientific contact           | METC, UMC Utrecht, 31 887555555,<br>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 |
|------------------|---------|

#### 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 |
|------------------|----------------|

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 |
|-----------------------|------------------------|

|                                |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

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 |
|----------------------------|------------------------|

|                           |                    |
|---------------------------|--------------------|
| 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

| 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<br>Preterm newborn infants<br>(gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>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:<br>Crossover trial Pyridostigmine-Placebo arm<br>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:<br>Crossover trial Pyridostigmine-Placebo arm<br>Same dosing schedule as active comparator                                                                                                                                                                                                                                                                                                                            |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                              | placebo                |
| Reporting group description:<br>Crossover trial Placebo-pyridostigmine arm<br>Same schedule as comparator                                                                                                                                                                                                                                                                                                                                          |                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                              | pyridostigmine         |
| Reporting group description:<br>Crossover trial Placebo-pyridostigmine arm<br>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:<br>Placebo to crossover to pyridostigmine                                                                                                                                                                                                                                                                                                                                                                        |                        |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                         | Pyridostigmine-Placebo |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                          | Intention-to-treat     |
| Subject analysis set description:<br>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:<br>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:<br>Change in time needed to complete one round during the R9HPT                                                                                                                                                                |                                                    |
| Notes:<br>[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.<br>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**

---

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 |
|-----------------|------------|

### Dictionary used

|                 |            |
|-----------------|------------|
| Dictionary name | Systematic |
|-----------------|------------|

|                    |   |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

### Reporting groups

|                       |                                                      |
|-----------------------|------------------------------------------------------|
| Reporting group title | General disorders and administration site conditions |
|-----------------------|------------------------------------------------------|

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

---

### 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/30061431>