



## Clinical trial results: Neurophysiological assessment of the effect of Sativex (THC/CBD oromucosal spray) as add-on to treat spasticity following stroke Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2016-001034-10   |
| Trial protocol           | IT               |
| Global end of trial date | 20 February 2020 |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 26 April 2020 |
| First version publication date | 26 April 2020 |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | SativexStroke |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |                              |
|------------------------------------|------------------------------|
| ISRCTN number                      | -                            |
| ClinicalTrials.gov id (NCT number) | -                            |
| WHO universal trial number (UTN)   | -                            |
| Other trial identifiers            | SativexStroke: SativexStroke |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | IRCCS Ospedale Policlinico San Martino  |
| Sponsor organisation address | Largo Rosanna Benzi 10, Genova, Italy, 16132                                      |
| Public contact               | UO Epidemiologia Clinica, IRCCS Ospedale Policlinico San Martino, +39 0105558477, |
| Scientific contact           | UO Epidemiologia Clinica, IRCCS Ospedale Policlinico San Martino, +39 0105558477, |

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:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 31 March 2020    |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 20 February 2020 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 20 February 2020 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

To assess if Sativex is able to reduce spasticity in chronic stroke patients

Protection of trial subjects:

N/A

Background therapy:

Background therapy shall remain the same during the trial period. Other cannabinoid-derived compounds are not permitted.

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 02 May 2018 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Italy: 41 |
| Worldwide total number of subjects   | 41        |
| EEA total number of subjects         | 41        |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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)                      | 19 |
| From 65 to 84 years                       | 22 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Planned recruitment was 50 stroke survivors between May 2018 and May 2020 in Italy.

### Pre-assignment

Screening details:

Stroke survivors with spasticity in at least one muscle segment (Modified Ashworth Scale of at least 1) will be screened. Botulinum toxin treatment washout of at least 4 months is required, while concomitant antispastic drugs can be continued keeping dosage unaltered throughout the trial period.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Phase 1   |
| 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:

All subjects will be treated with both active drug and placebo with a crossover design.

### Arms

|           |              |
|-----------|--------------|
| Arm title | Experimental |
|-----------|--------------|

Arm description:

Sativex, crossover phase 1

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Sativex          |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Oromucosal spray |
| Routes of administration               | Transmucosal use |

Dosage and administration details:

Oromucosal self administration with gradual increase up to 12 sprays/day

| Number of subjects in period 1 | Experimental |
|--------------------------------|--------------|
| Started                        | 41           |
| Completed                      | 37           |
| Not completed                  | 4            |
| Consent withdrawn by subject   | 2            |
| Adverse event, non-fatal       | 2            |

**Period 2**

|                              |   |
|------------------------------|---|
| Period 2 title               | Phase 2   |
| Is this the baseline period? | No  |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

**Arms**

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Experimental 2 |
|------------------|----------------|

Arm description:

Sativex, crossover second phase

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Sativex          |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Oromucosal spray |
| Routes of administration               | Transmucosal use |

Dosage and administration details:

Oromucosal self administration with gradual increase up to 12 sprays/day

|                                       |                |
|---------------------------------------|----------------|
| <b>Number of subjects in period 2</b> | Experimental 2 |
| Started                               | 37             |
| Completed                             | 34             |
| Not completed                         | 3              |
| Consent withdrawn by subject          | 1              |
| Adverse event, non-fatal              | 2              |

## Baseline characteristics

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Phase 1 |
|-----------------------|---------|

Reporting group description:

41 stroke survivors were recruited

| Reporting group values                             | Phase 1 | Total |  |
|--|---------|-------|--|
| Number of subjects                                 | 41      | 41    |  |
| 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)                               | 19      | 19    |  |
| From 65-84 years                                   | 22      | 22    |  |
| 85 years and over                                  | 0       | 0     |  |
| Gender categorical                                 |         |       |  |
| Units: Subjects                                    |         |       |  |
| Female   | 10      | 10    |  |
| Male   | 31      | 31    |  |

### Subject analysis sets

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Intention-to-treat |
|----------------------------|--------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

94 patients were screened, 41 signed informed consent and started the trial

| Reporting group values                             | Intention-to-treat |  |  |
|--|--------------------|--|--|
| Number of subjects                                 | 41                 |  |  |
| Age categorical                                    |                    |  |  |
| 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)                               | 19                 |  |  |
| From 65-84 years                                   | 22                 |  |  |
| 85 years and over                                  | 0                  |  |  |

|                    |    |  |  |
|--------------------|----|--|--|
| Gender categorical |    |  |  |
| Units: Subjects    |    |  |  |
| Female             | 10 |  |  |
| Male               | 31 |  |  |

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## End points

### End points reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | Experimental       |
| Reporting group description:<br>Sativex, crossover phase 1   |                    |
| Reporting group title  | Experimental 2     |
| Reporting group description:<br>Sativex, crossover second phase  |                    |
| Subject analysis set title   | Intention-to-treat |
| Subject analysis set type  | Intention-to-treat |
| Subject analysis set description:<br>94 patients were screened, 41 signed informed consent and started the trial |                    |

### Primary: Spasticity assessment

|   |                       |
|---|-----------------------|
| End point title   | Spasticity assessment |
| End point description:<br>The co-primary endpoints of the study will be to assess the effect of the tested treatment on muscle spasticity assessed with the stretch reflex and the 0-10 numeric rating scale for spasticity (NRS) |                       |
| End point type  | Primary               |
| End point timeframe:<br>Primary endpoint were assessed 4 times: at baseline (T0), at the end of phase 1 (T1), at the beginning of phase 2 (T2) and at the end of phase 2 (T3)   |                       |

| End point values            | Experimental    | Experimental 2  |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 37              | 34              |  |  |
| Units: Numeric rating scale | 37              | 34              |  |  |

### Statistical analyses

|  |                                |
|--|--------------------------------|
| Statistical analysis title   | Primary endpoints analysis     |
| Statistical analysis description:<br>Primary endpoints will be compared between phase 1 baseline (T0) versus phase 1 end (T1) and phase 2 baseline (T2) versus phase 2 end (T3) with respect to experimental/placebo conditions. Quantitative endpoint (stretch reflex) will be compared using a paired t-test. Semi-quantitative data (NRS) will be compared using a non-parametric test (Wilcoxon signed rank) |                                |
| Comparison groups  | Experimental v Experimental 2  |
| Number of subjects included in analysis  | 71                             |
| Analysis specification   | Pre-specified                  |
| Analysis type  | other <sup>[1]</sup>           |
| P-value  | < 0.05                         |
| Method   | t-test, 2-sided                |
| Parameter estimate   | Mean difference (final values) |

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Notes:

[1] - In a crossover design patients taking active drug in period 1 are compared to placebo in period 2 and viceversa



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Study period (about 2 and a half months per patient)

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |      |
|-----------------|------|
| Dictionary name | none |
|-----------------|------|

|                    |   |
|--------------------|---|
| Dictionary version | 0 |
|--------------------|---|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Period 1 |
|-----------------------|----------|

Reporting group description: -

|                       |          |
|-----------------------|----------|
| Reporting group title | Period 2 |
|-----------------------|----------|

Reporting group description: -

| Serious adverse events                            | Period 1   | Period 2       |  |
|---|--|----------------|--|
| Total subjects affected by serious adverse events |  |                |  |
| subjects affected / exposed                       | 0 / 41 (0.00%)   | 2 / 37 (5.41%) |  |
| number of deaths (all causes)                     | 0  | 0              |  |
| number of deaths resulting from adverse events    | 0  | 0              |  |
| Nervous system disorders                          |  |                |  |
| Seizure   | Additional description: First epileptic seizure (probably unrelated to study drug) |                |  |
| subjects affected / exposed                       | 0 / 41 (0.00%)   | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all   | 0 / 0  | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0          |  |
| Gastrointestinal disorders                        |  |                |  |
| Nausea  |  |                |  |
| subjects affected / exposed                       | 0 / 41 (0.00%)   | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all   | 0 / 0  | 1 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 0.05 %

| Non-serious adverse events                            | Period 1         | Period 2         |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 20 / 41 (48.78%) | 21 / 37 (56.76%) |  |
| Nervous system disorders                              |                  |                  |  |

|                             |                 |                  |  |
|-----------------------------|-----------------|------------------|--|
| Dizziness                   |                 |                  |  |
| subjects affected / exposed | 8 / 41 (19.51%) | 10 / 37 (27.03%) |  |
| occurrences (all)           | 8               | 10               |  |
| Balance disorder            |                 |                  |  |
| subjects affected / exposed | 4 / 41 (9.76%)  | 8 / 37 (21.62%)  |  |
| occurrences (all)           | 4               | 8                |  |
| Gastrointestinal disorders  |                 |                  |  |
| Nausea                      |                 |                  |  |
| subjects affected / exposed | 2 / 41 (4.88%)  | 4 / 37 (10.81%)  |  |
| occurrences (all)           | 2               | 4                |  |

## 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/28882919>