



## Clinical trial results:

### Exploratory Controlled Prospective Randomized Trial to Compare the Efficacy and Safety of Two Different Pharmacology Strategies on Neurocognitive Impairment in HIV Infection. TRIANT-TE Study

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-024510-57 |
| Trial protocol           | ES             |
| Global end of trial date | 19 March 2014  |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 30 November 2016 |
| First version publication date | 30 November 2016 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | TRIAN-TE |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01348282 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Fundació Lluita Contra la SIDA  |
| Sponsor organisation address | crt. de canyet, s/n, Badalona, Spain, 08916                               |
| Public contact               | CRA, Fundació Lluita Contra la SIDA, +34 934978414 ,<br>j.toro@flsida.org |
| Scientific contact           | CRA, Fundació Lluita Contra la SIDA, +34 934978414 ,                      |

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**

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 19 March 2014 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 19 March 2014 |
| Was the trial ended prematurely?                     | No            |

Notes:

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**General information about the trial**

Main objective of the trial:

To assess the efficacy and safety of transdermal rivastigmine for the treatment of HIV-associated cognitive impairment.

Protection of trial subjects:

not specific

Background therapy: -

Evidence for comparator: -

|   |                     |
|---|---------------------|
| Actual start date of recruitment                          | 04 May 2011         |
| Long term follow-up planned                               | Yes                 |
| Long term follow-up rationale                             | Scientific research |
| Long term follow-up duration                              | 12 Months           |
| 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 | Spain: 29 |
| Worldwide total number of subjects   | 29        |
| EEA total number of subjects         | 29        |

Notes:

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**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)                      | 29 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Seventy-six subjects were screened, 29 were finally enrolled.

### Period 1

|                              |                          |
|------------------------------|--------------------------|
| Period 1 title               | overall (overall period) |
| Is this the baseline period? | Yes                      |
| Allocation method            | Randomised - controlled  |
| Blinding used                | Not blinded              |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | lithium group |
|------------------|---------------|

Arm description: -

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | oral lithium (Plenur®) |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Tablet                 |
| Routes of administration               | Oral use               |

Dosage and administration details:

400 mg twice daily and was titrated progressively to ensure plasma drug concentrations of between 0.4 and 0.8 mEq/l.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | rivastigmine group |
|------------------|--------------------|

Arm description: -

|  |                                      |
|--|--------------------------------------|
| Arm type                               | Experimental                         |
| Investigational medicinal product name | transdermal rivastigmine (Prometax®) |
| Investigational medicinal product code |                                      |
| Other name                             |                                      |
| Pharmaceutical forms                   | Tablet                               |
| Routes of administration               | Oral use                             |

Dosage and administration details:

4.6mg daily and increased to 9.5 mg daily at week 4. This second dose was maintained throughout the follow-up.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | control group |
|------------------|---------------|

Arm description: -

|   |   |
|---|---|
| Arm type  | participants who did not initiate a new treatment |
| No investigational medicinal product assigned in this arm |   |

| <b>Number of subjects in period 1</b> | lithium group | rivastigmine group | control group |
|---------------------------------------|---------------|--------------------|---------------|
| Started                               | 11            | 10                 | 8             |
| Completed                             | 6             | 5                  | 6             |
| Not completed                         | 5             | 5                  | 2             |
| Adverse event, non-fatal              | 4             | 4                  | -             |
| uncompleted assessments               | -             | -                  | 2             |
| voluntary withdrawal                  | -             | 1                  | -             |
| acute hepatitis B virus infection     | 1             | -                  | -             |

## Baseline characteristics

### Reporting groups

|                                |                    |
|--------------------------------|--------------------|
| Reporting group title          | lithium group      |
| Reporting group description: - |                    |
| Reporting group title          | rivastigmine group |
| Reporting group description: - |                    |
| Reporting group title          | control group      |
| Reporting group description: - |                    |

| Reporting group values                             | lithium group | rivastigmine group | control group |
|--|---------------|--------------------|---------------|
| Number of subjects                                 | 11            | 10                 | 8             |
| Age categorical                                    |               |                    |               |
| Age  |               |                    |               |
| Units: Subjects                                    |               |                    |               |
| In utero   | 0             | 0                  | 0             |
| Preterm newborn infants (gestational age < 37 wks) | 0             | 0                  | 0             |
| Newborns (0-27 days)                               | 0             | 0                  | 0             |
| Infants and toddlers (28 days-23 months)           | 0             | 0                  | 0             |
| Children (2-11 years)                              | 0             | 0                  | 0             |
| Adolescents (12-17 years)                          | 0             | 0                  | 0             |
| Adults (18-64 years)                               | 11            | 10                 | 8             |
| From 65-84 years                                   | 0             | 0                  | 0             |
| 85 years and over                                  | 0             | 0                  | 0             |
| Age continuous                                     |               |                    |               |
| Units: years                                       |               |                    |               |
| arithmetic mean                                    | 43            | 45                 | 45            |
| standard deviation                                 | ± 5           | ± 7                | ± 3           |
| Gender categorical                                 |               |                    |               |
| Units: Subjects                                    |               |                    |               |
| Female   | 2             | 3                  | 1             |
| Male   | 9             | 7                  | 7             |

| Reporting group values                             | Total |  |  |
|--|-------|--|--|
| Number of subjects                                 | 29    |  |  |
| Age categorical                                    |       |  |  |
| Age  |       |  |  |
| 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)                               | 29    |  |  |
| From 65-84 years                                   | 0     |  |  |

|                   |   |  |  |
|-------------------|---|--|--|
| 85 years and over | 0 |  |  |
|-------------------|---|--|--|

|   |    |  |  |
|---|----|--|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -  |  |  |
| Gender categorical<br>Units: Subjects                                   |    |  |  |
| Female  | 6  |  |  |
| Male  | 23 |  |  |

## End points

### End points reporting groups

|                                |                    |
|--------------------------------|--------------------|
| Reporting group title          | lithium group      |
| Reporting group description: - |                    |
| Reporting group title          | rivastigmine group |
| Reporting group description: - |                    |
| Reporting group title          | control group      |
| Reporting group description: - |                    |

### Primary: change in a global cognitive score (NPZ-7)

|                          |  |
|--------------------------|--|
| End point title          | change in a global cognitive score (NPZ-7) |
| End point description:   |  |
|                          |  |
| End point type           | Primary                                    |
| End point timeframe:     |  |
| From Baseline to 48 week |  |

| End point values                     | lithium group   | rivastigmine group | control group   |  |
|--------------------------------------|-----------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 6               | 5                  | 6               |  |
| Units: NPZ-7 score                   |                 |                    |                 |  |
| arithmetic mean (standard deviation) | 0.25 (± 0.4)    | 0.35 (± 0.14)      | 0.2 (± 0.44)    |  |

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title                     | Comparison between rivastigmine group and control |
| Statistical analysis description:              |   |
| Statistical significance was set at $p < 0.05$ |   |
|  |   |
| Comparison groups                              | rivastigmine group v control group                |
| Number of subjects included in analysis        | 11  |
| Analysis specification                         | Pre-specified                                     |
| Analysis type                                  | equivalence <sup>[1]</sup>                        |
| P-value  | = 0.484 <sup>[2]</sup>                            |
| Method   | t-test, 2-sided                                   |

Notes:

[1] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[2] - Cohen's effect size tests equal to 0.38

|                            |  |
|----------------------------|--|
| Statistical analysis title | Comparison between lithium group and control group |
| Comparison groups          | control group v lithium group                      |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 12                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | equivalence <sup>[3]</sup> |
| P-value                                 | = 0.849 <sup>[4]</sup>     |
| Method                                  | t-test, 2-sided            |

Notes:

[3] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[4] - Cohen's effect size tests equal to 0.12

## Secondary: finances: Daily Functioning variables

|  |                                       |
|--|---------------------------------------|
| End point title                                  | finances: Daily Functioning variables |
| End point description:                           |                                       |
| End point type                                   | Secondary                             |
| End point timeframe:<br>from baseline to week 48 |                                       |

| End point values                     | lithium group   | rivastigmine group | control group   |  |
|--------------------------------------|-----------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 6               | 5                  | 6               |  |
| Units: numerical outcomes            |                 |                    |                 |  |
| arithmetic mean (standard deviation) | 0.16 (± 0.4)    | 0.2 (± 0.83)       | 0 (± 0)         |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>          | Comparison between rivastigmine group and control |
| Statistical analysis description:          |   |
| Statistical significance was set at p<0.05 |   |
| Comparison groups                          | rivastigmine group v control group                |
| Number of subjects included in analysis    | 11  |
| Analysis specification                     | Pre-specified                                     |
| Analysis type                              | equivalence <sup>[5]</sup>                        |
| P-value                                    | = 0.568 <sup>[6]</sup>                            |
| Method                                     | t-test, 2-sided                                   |

Notes:

[5] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[6] - Cohen's effect size tests equal to 0.36

|  |  |
|--|--|
| <b>Statistical analysis title</b>          | Comparison between lithium group and control group |
| Statistical analysis description:          |  |
| Statistical significance was set at p<0.05 |  |
| Comparison groups                          | control group v lithium group                      |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 12                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | equivalence <sup>[7]</sup> |
| P-value                                 | = 0.34 <sup>[8]</sup>      |
| Method                                  | t-test, 2-sided            |

Notes:

[7] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[8] - Cohen's effect size tests equal to 0.57

## Secondary: work: Daily Functioning variables

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | work: Daily Functioning variables |
|-----------------|-----------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

from baseline to week 48

| End point values                     | lithium group   | rivastigmine group | control group   |  |
|--------------------------------------|-----------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 6               | 5                  | 6               |  |
| Units: numerical outcomes            |                 |                    |                 |  |
| arithmetic mean (standard deviation) | 0 (± 0.63)      | -0.2 (± 0.83)      | 0.5 (± 0.83)    |  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Comparison between rivastigmine group and control |
|-----------------------------------|---|

Statistical analysis description:

Statistical significance was set at  $p < 0.05$

|   |                                    |
|---|------------------------------------|
| Comparison groups                       | rivastigmine group v control group |
| Number of subjects included in analysis | 11                                 |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | equivalence <sup>[9]</sup>         |
| P-value                                 | = 0.2 <sup>[10]</sup>              |
| Method                                  | t-test, 2-sided                    |

Notes:

[9] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[10] - Cohen's effect size tests equal to -0.84

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Comparison between lithium group and control group |
|-----------------------------------|--|

Statistical analysis description:

Statistical significance was set at  $p < 0.05$

|                   |                               |
|-------------------|-------------------------------|
| Comparison groups | control group v lithium group |
|-------------------|-------------------------------|

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 12                          |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | equivalence <sup>[11]</sup> |
| P-value                                 | = 0.27 <sup>[12]</sup>      |
| Method                                  | t-test, 2-sided             |

Notes:

[11] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[12] - Cohen's effect size tests equal to -0.68

## Secondary: Mental dimension: Quality of life variables

|                 |   |
|-----------------|---|
| End point title | Mental dimension: Quality of life variables |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

from baseline to week 48

| End point values                     | lithium group   | rivastigmine group | control group   |  |
|--------------------------------------|-----------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 6               | 5                  | 6               |  |
| Units: numerical outcomes            |                 |                    |                 |  |
| arithmetic mean (standard deviation) | 0.16 (± 0.98)   | 0 (± 0.7)          | 0 (± 0.63)      |  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Comparison between rivastigmine group and control |
|-----------------------------------|---|

Statistical analysis description:

Statistical significance was set at  $p < 0.05$

|   |                                    |
|---|------------------------------------|
| Comparison groups                       | control group v rivastigmine group |
| Number of subjects included in analysis | 11                                 |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           |                                    |
| P-value                                 | = 1 <sup>[13]</sup>                |
| Method                                  | t-test, 2-sided                    |

Notes:

[13] - Cohen's effect size tests equal to 0

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Comparison between lithium group and control group |
|-----------------------------------|--|

Statistical analysis description:

Statistical significance was set at  $p < 0.05$

|                   |                               |
|-------------------|-------------------------------|
| Comparison groups | control group v lithium group |
|-------------------|-------------------------------|

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 12                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | = 0.734 <sup>[14]</sup> |
| Method                                  | t-test, 2-sided         |

Notes:

[14] - Cohen's effect size tests equal to 0.19

## Secondary: Global quality of life

|  |                        |
|--|------------------------|
| End point title                                  | Global quality of life |
| End point description:                           |                        |
| End point type                                   | Secondary              |
| End point timeframe:<br>from baseline to week 48 |                        |

| End point values                     | lithium group   | rivastigmine group | control group   |  |
|--------------------------------------|-----------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 6               | 5                  | 6               |  |
| Units: numerical outcomes            |                 |                    |                 |  |
| arithmetic mean (standard deviation) | 0 (± 1.26)      | -0.2 (± 0.44)      | 0 (± 0)         |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>          | Comparison between rivastigmine group and control |
| Statistical analysis description:          |   |
| Statistical significance was set at p<0.05 |   |
| Comparison groups                          | control group v rivastigmine group                |
| Number of subjects included in analysis    | 11  |
| Analysis specification                     | Pre-specified                                     |
| Analysis type                              | equivalence <sup>[15]</sup>                       |
| P-value                                    | = 0.296 <sup>[16]</sup>                           |
| Method                                     | t-test, 2-sided                                   |

Notes:

[15] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[16] - Cohen's effect size tests equal to -0.68

|  |  |
|--|--|
| <b>Statistical analysis title</b>          | Comparison between lithium group and control group |
| Statistical analysis description:          |  |
| Statistical significance was set at p<0.05 |  |
| Comparison groups                          | control group v lithium group                      |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 12                          |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | equivalence <sup>[17]</sup> |
| P-value                                 | = 1 <sup>[18]</sup>         |
| Method                                  | t-test, 2-sided             |

Notes:

[17] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[18] - Cohen's effect size tests equal to 0

## Secondary: Depressive symptoms: Emotional status variables

|                 |   |
|-----------------|---|
| End point title | Depressive symptoms: Emotional status variables |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

from baseline to week 48

| End point values                     | lithium group   | rivastigmine group | control group   |  |
|--------------------------------------|-----------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 6               | 5                  | 6               |  |
| Units: numerical outcomes            |                 |                    |                 |  |
| arithmetic mean (standard deviation) | -0.2 (± 0.83)   | -1.2 (± 4.14)      | -1.2 (± 3.83)   |  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Comparison between rivastigmine group and control |
|-----------------------------------|---|

Statistical analysis description:

Statistical significance was set at  $p < 0.05$

|   |                                    |
|---|------------------------------------|
| Comparison groups                       | rivastigmine group v control group |
| Number of subjects included in analysis | 11                                 |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | equivalence <sup>[19]</sup>        |
| P-value                                 | = 1 <sup>[20]</sup>                |
| Method                                  | t-test, 2-sided                    |

Notes:

[19] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[20] - Cohen's effect size tests equal to 0

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Comparison between lithium group and control group |
|-----------------------------------|--|

Statistical analysis description:

Statistical significance was set at  $p < 0.05$

|                   |                               |
|-------------------|-------------------------------|
| Comparison groups | control group v lithium group |
|-------------------|-------------------------------|

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 12                          |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | equivalence <sup>[21]</sup> |
| P-value                                 | = 0.584 <sup>[22]</sup>     |
| Method                                  | t-test, 2-sided             |

Notes:

[21] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[22] - Cohen's effect size tests equal to 0.36

## Secondary: Anxiety symptoms: Emotional status variables

|                 |  |
|-----------------|--|
| End point title | Anxiety symptoms: Emotional status variables |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

from baseline to week 48

| End point values                     | lithium group   | rivastigmine group | control group   |  |
|--------------------------------------|-----------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 6               | 5                  | 6               |  |
| Units: numerical outcomes            |                 |                    |                 |  |
| arithmetic mean (standard deviation) | 0.6 (± 5.31)    | -1.6 (± 2.88)      | 1.2 (± 5.54)    |  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Comparison between rivastigmine group and control |
|-----------------------------------|---|

Statistical analysis description:

Statistical significance was set at  $p < 0.05$

|   |                                    |
|---|------------------------------------|
| Comparison groups                       | rivastigmine group v control group |
| Number of subjects included in analysis | 11                                 |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | equivalence <sup>[23]</sup>        |
| P-value                                 | = 0.345 <sup>[24]</sup>            |
| Method                                  | t-test, 2-sided                    |

Notes:

[23] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[24] - Cohen's effect size tests equal to -0.61

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Comparison between lithium group and control group |
|-----------------------------------|--|

Statistical analysis description:

Statistical significance was set at  $p < 0.05$

|                   |                               |
|-------------------|-------------------------------|
| Comparison groups | control group v lithium group |
|-------------------|-------------------------------|

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 12                          |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | equivalence <sup>[25]</sup> |
| P-value                                 | = 0.865 <sup>[26]</sup>     |
| Method                                  | t-test, 2-sided             |

Notes:

[25] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[26] - Cohen's effect size tests equal to -0.11

## Secondary: Total impaired areas: Daily Functioning

|                 |   |
|-----------------|---|
| End point title | Total impaired areas: Daily Functioning |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

from baseline to week 48

| End point values                     | lithium group   | rivastigmine group | control group   |  |
|--------------------------------------|-----------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 6               | 5                  | 6               |  |
| Units: numerical outcomes            |                 |                    |                 |  |
| arithmetic mean (standard deviation) | 1 (± 4.64)      | -0.6 (± 3.71)      | 0.66 (± 3.72)   |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

48 week follow-up

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |                      |
|-----------------|----------------------|
| Dictionary name | DAIDS AE GRADING TAB |
|-----------------|----------------------|

|                    |     |
|--------------------|-----|
| Dictionary version | 2.0 |
|--------------------|-----|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | lithium group |
|-----------------------|---------------|

Reporting group description: -

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | rivastigmine group |
|-----------------------|--------------------|

Reporting group description: -

|                       |               |
|-----------------------|---------------|
| Reporting group title | control group |
|-----------------------|---------------|

Reporting group description: -

| Serious adverse events                            | lithium group  | rivastigmine group | control group |
|---|----------------|--------------------|---------------|
| Total subjects affected by serious adverse events |                |                    |               |
| subjects affected / exposed                       | 0 / 11 (0.00%) | 0 / 10 (0.00%)     | 0 / 8 (0.00%) |
| number of deaths (all causes)                     | 0              | 0                  | 0             |
| number of deaths resulting from adverse events    |                |                    |               |

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

| Non-serious adverse events                            | lithium group   | rivastigmine group | control group |
|---|-----------------|--------------------|---------------|
| Total subjects affected by non-serious adverse events |                 |                    |               |
| subjects affected / exposed                           | 5 / 11 (45.45%) | 5 / 10 (50.00%)    | 0 / 8 (0.00%) |
| Nervous system disorders                              |                 |                    |               |
| rash and tremors                                      |                 |                    |               |
| subjects affected / exposed                           | 1 / 11 (9.09%)  | 0 / 10 (0.00%)     | 0 / 8 (0.00%) |
| occurrences (all)                                     | 1               | 0                  | 0             |
| Headache  |                 |                    |               |
| subjects affected / exposed                           | 1 / 11 (9.09%)  | 0 / 10 (0.00%)     | 0 / 8 (0.00%) |
| occurrences (all)                                     | 1               | 0                  | 0             |
| Blood and lymphatic system disorders                  |                 |                    |               |
| Epistaxis   |                 |                    |               |

|   |                      |                      |                    |
|---|----------------------|----------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 | 0 / 8 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Gastrointestinal disorder<br>subjects affected / exposed<br>occurrences (all)   | 0 / 11 (0.00%)<br>0  | 1 / 10 (10.00%)<br>1 | 0 / 8 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders<br>skin irritation<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1  | 2 / 10 (20.00%)<br>2 | 0 / 8 (0.00%)<br>0 |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 11 (18.18%)<br>2 | 0 / 10 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0 |
| Hepatitis B<br>subjects affected / exposed<br>occurrences (all)   | 1 / 11 (9.09%)<br>1  | 0 / 10 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 07 February 2011 | amendment in order to ask Ethics Committee                                   |
| 01 April 2011    | Protocol and PIS modification  |
| 28 June 2011     | added week 1 follow up   |
| 02 November 2011 | added new determinations: Vitamine B12, folic acid and T. Pllidum test (RPR) |
| 17 April 2012    | exclusion criteria changed   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported