



Clinical trial results:

A randomised, double blind, placebo controlled trial to evaluate the effect of Rivastigmine on gait in people with Parkinson's disease who have fallen.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2011-003053-25 |
| Trial protocol | GB |
| Global end of trial date | 10 September 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 07 July 2018 |
| First version publication date | 07 July 2018 |

Trial information

Trial identification

| | |
|-----------------------|------|
| Sponsor protocol code | 1466 |
|-----------------------|------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | ISRCTN19880883 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | U1111-1124-0244 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University of Bristol |
| Sponsor organisation address | Senate House, Tyndall Ave, Bristol , United Kingdom, BS8 1TH |
| Public contact | N/A, Parkinson's UK , +44 0808 800 0303, |
| Scientific contact | Dr Emily Henderson , University of Bristol , the-respond-trial@bristol.ac.uk |

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 | 02 December 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 10 September 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 September 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This study sought to assess the benefit of rivastigmine (a drug which augments mental function) on gait (walking) dysfunction in patients with Parkinson's disease (PD) with a past history of a fall. The primary aim was to determine the effect of the cholinesterase inhibitor (ChEi) rivastigmine on step time variability in patients with PD. Step time variability is a marker of how stable an individual's walking is and a prognostic marker for future falls risk.

Protection of trial subjects:

Ethics approval was granted from the South West Research Ethics Committee on 28th September 2011 and a Clinical Trial Authorisation (CTA) granted from the Medicines and Healthcare Regulatory Agency (MHRA) on 18th June 2012. The trial was performed in accordance with the UK 2004 Medicines for Human Use (Clinical Trials) Regulations and its subsequent amendments

Background therapy:

Usual dopaminergic Parkinson's medication.

Evidence for comparator:

We searched PubMed for randomized control trials (RCTs), limited only to humans using "Parkinson disease" and "Cholinesterase inhibitors" as MeSH terms. This identified twenty studies, of which, 5 reported a falls outcome. Only one randomised crossover trial sought primarily to determine the effect of a cholinesterase inhibitor – donepezil, on falls in PD. In this trial 23 subjects who reported falling or near falling more than two times a week were given donepezil for 6 weeks. Donepezil treatment was associated with a reduction in fall rate from 0.25 falls/day (SEM=0.08) on placebo to 0.13 falls/day (SEM 0.03) on donepezil (p=0.05). However, frequent fallers drove the observed benefit and the finding was reported using a per-protocol, as opposed to an intention-to-treat, analysis. The study was small and of short duration. Two RCT's of rivastigmine versus placebo reported falls as adverse events. Both reported lower proportions of falls occurring in the cholinesterase inhibitor groups (7/211 (3.3%) versus 9/123 (7.3%) and 21/362 (5.8%) versus 11/179 (6.1%)) although in both cases the absolute numbers were small. One study reported that galantamine was associated with a decrease in falls, freezing and gait domains of the UPDRS. The fifth trial stated that 'increased number of falls' contributed to withdrawal of a participant. No other gait outcome measures were reported in any of the trials.

| | |
|---|---------------------|
| Actual start date of recruitment | 04 October 2012 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Scientific research |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 130 |
| Worldwide total number of subjects | 130 |
| EEA total number of subjects | 130 |

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) | 0 |
| Adults (18-64 years) | 31 |
| From 65 to 84 years | 94 |
| 85 years and over | 5 |

Subject disposition

Recruitment

Recruitment details:

Participants were identified from community and hospital settings. Patient Identification Centres (PICs) were set-up to identify patients in other local centres and DeNDRoN (Dementias and Neurodegenerative Diseases Research Network) nurses performed pre-screening of potential participants in hospital clinics. We also recruited participants from the

Pre-assignment

Screening details:

931 were assessed for eligibility. 500 were ineligible (did not meet inclusion criteria) and 301 declined to participate.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Baseline period |
| 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:

Patients were randomly assigned (1:1) to rivastigmine (acetylcholinesterase inhibitor) or identically matched placebo capsules. Participants were enrolled and tested by an investigator (EH) who had no access to the randomisation sequence that was generated by Bristol Randomised Trials Collaboration (BRTC) clinical trials unit using a web-based program. A treatment pack number was issued via a secure website that matched a drug pack held in the pharmacy to ensure concealment of allocation.

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Rivastigmine |

Arm description:

Participants treated with the active medication.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Rivastigmine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

1.5mg bd for 4 weeks
3mg bd for 4 weeks
4.5mg bd for 4 weeks
6mg bd for 4 weeks
Highest tolerated dose for 16 weeks.

| | |
|------------------|-------------|
| Arm title | Placebo arm |
|------------------|-------------|

Arm description:

Patients treated with placebo

| | |
|--|---------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

1.5mg bd for 4 weeks

3mg bd for 4 weeks
 4.5mg bd for 4 weeks
 6mg bd for 4 weeks
 Highest tolerated dose for further 16 weeks.

| Number of subjects in period 1 | Rivastigmine | Placebo arm |
|---------------------------------------|--------------|-------------|
| Started | 65 | 65 |
| Completed | 65 | 65 |

Period 2

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

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Rivastigmine |

Arm description:

Participants treated with the active medication.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Rivastigmine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

1.5mg bd for 4 weeks
 3mg bd for 4 weeks
 4.5mg bd for 4 weeks
 6mg bd for 4 weeks
 Highest tolerated dose for 16 weeks.

| | |
|------------------|-------------|
| Arm title | Placebo arm |
|------------------|-------------|

Arm description:

Patients treated with placebo

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|---------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

1.5mg bd for 4 weeks

3mg bd for 4 weeks

4.5mg bd for 4 weeks

6mg bd for 4 weeks

Highest tolerated dose for further 16 weeks.

| Number of subjects in period 2 | Rivastigmine | Placebo arm |
|---------------------------------------|--------------|-------------|
| Started | 65 | 65 |
| Completed | 65 | 65 |

Baseline characteristics

Reporting groups

| | |
|--|--------------|
| Reporting group title | Rivastigmine |
| Reporting group description: Participants treated with the active medication. | |
| Reporting group title | Placebo arm |
| Reporting group description: Patients treated with placebo | |

| Reporting group values | Rivastigmine | Placebo arm | Total |
|---|---------------|----------------|-------|
| Number of subjects | 65 | 65 | 130 |
| 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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous Units: years | | | |
| geometric mean | 71 | 69 | |
| full range (min-max) | 54 to 90 | 46 to 88 | - |
| Gender categorical Units: Subjects | | | |
| Female | 30 | 19 | 49 |
| Male | 35 | 46 | 81 |
| Have experienced freezing of gait in previous month Units: Subjects | | | |
| Experienced FoG | 42 | 48 | 90 |
| Not experienced FoG | 23 | 17 | 40 |
| Falls in previous year Units: Number | | | |
| median | 5 | 5.5 | |
| inter-quartile range (Q1-Q3) | 2 to 12 | 2 to 12.5 | - |
| Gait speed Units: m/s | | | |
| geometric mean | 1 | 1 | |
| standard deviation | ± 0.3 | ± 0.3 | - |
| Step time variability (normal walking) Units: sec | | | |
| median | 0.026 | 0.024 | |
| inter-quartile range (Q1-Q3) | 0.02 to 0.047 | 0.018 to 0.039 | - |

| | | | |
|---|-------------------------|-------------------------|---|
| Step time variability (walking with simple task) Units: sec median inter-quartile range (Q1-Q3) | 0.053 0.028 to 0.138 | 0.049 0.03 to 0.11 | - |
| Step time variability (walking plus complex task) Units: sec median inter-quartile range (Q1-Q3) | 0.078 0.035 to 0.167 | 0.068 0.036 to 0.149 | - |
| MoCA | | | |
| Montreal Cognitive Assessment | | | |
| Units: Units median inter-quartile range (Q1-Q3) | 24 22 to 27 | 26 23 to 27 | - |
| Frontal Assessment Battery Units: Units median inter-quartile range (Q1-Q3) | 15 12 to 16 | 14 12 to 16 | - |
| Geriatric depression Scale Units: Units median inter-quartile range (Q1-Q3) | 3 2 to 6 | 3 1 to 5 | - |
| Cognitive Failures Questionnaire Units: Units median inter-quartile range (Q1-Q3) | 41 30 to 48 | 39 30 to 47 | - |
| MDS-UPDRS Units: Units median inter-quartile range (Q1-Q3) | 87 64 to 99 | 90 74 to 106 | - |
| Levodopa equivalent dose Units: mg median inter-quartile range (Q1-Q3) | 710 450 to 1075 | 980 650 to 1298 | - |
| Duration of Parkinson's disease (years) Units: Years median inter-quartile range (Q1-Q3) | 8 5 to 13 | 9 5 to 13 | - |
| Quality-of-life EQ-5D-5L index score | | | |
| Quality-of-life EQ-5D-5L index score | | | |
| Units: Units arithmetic mean standard deviation | 0.72 ± 0.19 | 0.71 ± 0.18 | - |
| Quality-of-life EQ-5D-5L visual analogue score | | | |
| Quality-of-life EQ-5D-5L visual analogue score | | | |
| Units: units arithmetic mean standard deviation | 64 ± 17 | 65 ± 17 | - |
| ICON-FES | | | |
| (fear of falling) | | | |
| Units: Units | | | |

| | | | |
|--------------------------------------|--------|--------|---|
| arithmetic mean | 22.9 | 24 | |
| standard deviation | ± 6.72 | ± 5.17 | - |
| PPA falls risk score | | | |
| PPA=Physiological Profile Assessment | | | |
| Units: Units | | | |
| arithmetic mean | 1.9 | 1.9 | |
| standard deviation | ± 1.9 | ± 1.4 | - |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Rivastigmine |
| Reporting group description: Participants treated with the active medication. | |
| Reporting group title | Placebo arm |
| Reporting group description: Patients treated with placebo | |
| Reporting group title | Rivastigmine |
| Reporting group description: Participants treated with the active medication. | |
| Reporting group title | Placebo arm |
| Reporting group description: Patients treated with placebo | |
| Subject analysis set title | Set 1 (ITT) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: ITT analysis set | |

Primary: 8 month follow-up

| | |
|----------------------------------|-------------------|
| End point title | 8 month follow-up |
| End point description: | |
| End point type | Primary |
| End point timeframe: 8 months | |

| End point values | Rivastigmine | Placebo arm | Set 1 (ITT) | |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 65 | 65 | 130 | |
| Units: number / month | | | | |
| number (not applicable) | 65 | 65 | 130 | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Falls per month |
| Statistical analysis description: Negative binomial regression | |
| Comparison groups | Rivastigmine v Placebo arm |

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | Regression, negative binomial |
| Parameter estimate | Incident rate ratio |
| Point estimate | 0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.04 |
| upper limit | 0.18 |
| Variability estimate | Standard error of the mean |

| | |
|-----------------------------------|---|
| Statistical analysis title | Primary (step time variability normal walk) |
|-----------------------------------|---|

Statistical analysis description:

Adjusted for centred age, centred baseline cognition (MoCA score), centred log baseline step time variability of condition, and previous falls categorised as (1, 2-3, 4-6, 7-19, ≥20)

| | |
|---|----------------------------|
| Comparison groups | Rivastigmine v Placebo arm |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | Regression, Linear |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.89 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.076 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Primary (step time variability simple task) |
|-----------------------------------|---|

Statistical analysis description:

Adjusted for centred age, centred baseline cognition (MoCA score), centred log baseline step time variability of condition, and previous falls categorised as (1, 2-3, 4-6, 7-19, ≥20)

| | |
|---|----------------------------|
| Comparison groups | Rivastigmine v Placebo arm |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.045 |
| Method | Regression, Linear |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 0.79 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 0.99 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.093 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Primary (step time variability complex task) |
|-----------------------------------|--|

Statistical analysis description:

Adjusted for centred age, centred baseline cognition (MoCA score), centred log baseline step time variability of condition, and previous falls categorised as (1, 2-3, 4-6, 7-19, ≥ 20)

| | |
|---|--|
| Comparison groups | Rivastigmine v Placebo arm v Set 1 (ITT) |
| Number of subjects included in analysis | 260 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.17 |
| Method | Regression, Linear |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 1.09 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.122 |

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | Gait speed (normal walking) |
|-----------------------------------|-----------------------------|

Statistical analysis description:

for baseline outcome, centred age, centred baseline cognition (MoCA score), centred baseline log step time variability during normal walking, and previous falls (categorised as 1, 2-3, 4-6, 7-19, ≥ 20).

| | |
|---|--------------------------------|
| Comparison groups | Placebo arm v Rivastigmine |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.04 |
| upper limit | 0.18 |

| | |
|---|--------------------------------|
| Statistical analysis title | Gait speed (simple task) |
| Statistical analysis description: for baseline outcome, centred age, centred baseline cognition (MoCA score), centred baseline log step time variability during normal walking, and previous falls (categorised as 1, 2-3, 4-6, 7-19, ≥ 20). | |
| Comparison groups | Rivastigmine v Placebo arm |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.037 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0.16 |

| | |
|--|--------------------------------|
| Statistical analysis title | Gait speed (complex task) |
| Statistical analysis description: adjusted for baseline outcome, centred age, centred baseline cognition (MoCA score), centred baseline log step time variability during normal walking, and previous falls (categorised as 1, 2-3, 4-6, 7-19, ≥ 20). | |
| Comparison groups | Rivastigmine v Placebo arm |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.048 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0.16 |

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | FOG episode previous month |
| Comparison groups | Rivastigmine v Placebo arm |

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|---|----------------------------|
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.22 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.13 |
| upper limit | 1.6 |

Notes:

[1] - Adjusted for baseline outcome, centred age, centred baseline cognition (MoCA score), centred baseline log step time variability during normal walking, and previous falls (categorised as 1, 2-3, 4-6, 7-19, ≥20).

| | |
|-----------------------------------|------|
| Statistical analysis title | MoCA |
|-----------------------------------|------|

Statistical analysis description:

Adjusted for baseline outcome, centred age, centred baseline cognition (MoCA score), centred baseline log step time variability during normal walking, and previous falls (categorised as 1, 2-3, 4-6, 7-19, ≥20).

| | |
|---|----------------------------|
| Comparison groups | Rivastigmine v Placebo arm |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.78 |
| Method | Regression, Linear |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.06 |

| | |
|---|----------------------------|
| Statistical analysis title | MDS-UPDRS |
| Comparison groups | Placebo arm v Rivastigmine |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (net) |
| Point estimate | -3.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.6 |
| upper limit | 3 |

| | |
|---|--------------------------------|
| Statistical analysis title | Quality of life EQ-5D score |
| Comparison groups | Rivastigmine v Placebo arm |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.82 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.007 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.051 |
| upper limit | 0.066 |

| | |
|---|----------------------------|
| Statistical analysis title | PPA falls risk score |
| Comparison groups | Rivastigmine v Placebo arm |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Geometric mean ratio. |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.39 |

| | |
|---|----------------------------|
| Statistical analysis title | Fear of falling |
| Statistical analysis description: ICON-FES Iconographical Falls Efficacy Scale | |
| Comparison groups | Rivastigmine v Placebo arm |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.78 |
| Method | Regression, Linear |
| Parameter estimate | Geometric mean ratio |
| Point estimate | -0.25 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.03 |
| upper limit | 1.53 |

| | |
|---|----------------------------------|
| Statistical analysis title | Controlled leaning balance score |
| Comparison groups | Rivastigmine v Placebo arm |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| Method | Regression, Logistic |
| Parameter estimate | Relative risk ratio |
| Point estimate | 0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.02 |
| upper limit | 0.57 |

Notes:

[2] - Logistic regression

| | |
|--|---|
| Statistical analysis title | Mood (Geriatric Depression Scale score) |
| Statistical analysis description: | |
| Adjusted for baseline outcome, centred age, centred baseline cognition (MoCA score), centred baseline log step time variability during normal walking, and previous falls (categorised as 1, 2-3, 4-6, 7-19, ≥20). | |
| Comparison groups | Rivastigmine v Placebo arm |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.83 |
| Method | Regression, Linear |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.19 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Over 8 months of treatment

Adverse event reporting additional description:

Minimum monthly phone call to participants plus falls diaries returned on a monthly basis.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Rivastigmine |
|-----------------------|--------------|

Reporting group description:

Participants treated with the active medication.

| | |
|-----------------------|-------------|
| Reporting group title | Placebo arm |
|-----------------------|-------------|

Reporting group description:

Patients treated with placebo

| Serious adverse events | Rivastigmine | Placebo arm | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 65 (21.54%) | 13 / 65 (20.00%) | |
| number of deaths (all causes) | 2 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Biopsy of cervix | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic cancer metastatic | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural | | | |

| | | | |
|---|----------------|----------------|--|
| complications | | | |
| Fall | | | |
| subjects affected / exposed | 5 / 65 (7.69%) | 4 / 65 (6.15%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Foot operation | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hernia repair | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb operation | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parkinsonism | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 65 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Thyroid disorder | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 65 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Rivastigmine | Placebo arm | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 64 / 65 (98.46%) | 62 / 65 (95.38%) | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 14 / 65 (21.54%) | 6 / 65 (9.23%) | |
| occurrences (all) | 17 | 7 | |
| Parkinsonism | | | |
| subjects affected / exposed | 26 / 65 (40.00%) | 22 / 65 (33.85%) | |
| occurrences (all) | 36 | 28 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 20 / 65 (30.77%) | 3 / 65 (4.62%) | |
| occurrences (all) | 24 | 3 | |
| Vomiting | | | |

| | | | |
|-----------------------------|------------------|----------------|--|
| subjects affected / exposed | 11 / 65 (16.92%) | 3 / 65 (4.62%) | |
| occurrences (all) | 15 | 3 | |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 4 / 65 (6.15%) | 2 / 65 (3.08%) | |
| occurrences (all) | 5 | 2 | |

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

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

Please refer to <http://www.ncbi.nlm.nih.gov/pubmed/26795874> for exact n for each outcome measure listed.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26795874>