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

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