



Clinical trial results:

Multicentre UK Study of the Acetylcholinesterase Inhibitor Donepezil in Early Dementia Associated with Parkinson's Disease (MUSTARDD-PD)

Summary

EudraCT number	2009-015170-35
Trial protocol	GB
Global end of trial date	01 September 2014

Results information

Result version number	v1 (current)
This version publication date	24 July 2016
First version publication date	24 July 2016

Trial information

Trial identification

Sponsor protocol code	5137
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Additional study identifiers

ISRCTN number	ISRCTN30151023
ClinicalTrials.gov id (NCT number)	NCT01014858
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Freeman Hospital, Freeman Road, Newcastle upon Tyne, United Kingdom, NE7 7DN
Public contact	Professor David Burn, Newcastle University, 44 0191 208 3357, david.burn@ncl.ac.uk
Scientific contact	Professor David Burn, Newcastle University, 44 0191 208 3357, david.burn@ncl.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	15 July 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 September 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Is the cholinesterase inhibitor drug donepezil hydrochloride superior to placebo in improving cognitive function, neuropsychiatric burden and functional ability in people with Parkinson's disease and mild dementia after 24 months of treatment?

Protection of trial subjects:

No actions required.

Background therapy:

Stable doses of atypical anti-psychotic medication (i.e. dose unchanged for 6 weeks prior to study entry) were permitted, as it was acknowledged that many patients with PDD experience psychotic features (especially visual hallucinations) prior to the onset of cognitive decline which may require atypical anti-psychotic medication. It was felt that it would be both impractical and unethical to exclude the use, or require the withdrawal, of these agents in a placebo-controlled study.

Patients receiving a non-selective centrally acting anticholinergic drug for control of parkinsonian motor symptoms or other indication (e.g. urinary urgency) were excluded and use of these medications were forbidden throughout the duration of the study. Previous exposure to any cholinesterase inhibitor also excluded a patient. Patients receiving the N-methyl-d-aspartate antagonist memantine were also excluded; no exposure, previous or current, was permitted.

Evidence for comparator:

This was a placebo-controlled study.

Actual start date of recruitment	30 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	7
From 65 to 84 years	52
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between February 2013 and May 2014. This typically took place in clinic or a research unit. Sites were asked to consider all subjects seen consecutively with Parkinson's disease and mild dementia as being suitable for randomisation, and to indicate in a log the reason(s) why screened patients were not randomised.

Pre-assignment

Screening details:

At the time of potential consideration for the study, the direct medical team caring for the potential participant determined if they were potentially eligible for the study with a consideration of the patient (and their records) in order to determine whether they met the inclusion criteria and if it was appropriate to approach the patient.

Pre-assignment period milestones

Number of subjects started	64 ^[1]
Number of subjects completed	62

Pre-assignment subject non-completion reasons

Reason: Number of subjects	randomised in error: 1
Reason: Number of subjects	did not attend baseline visit: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One subject was 'randomised in error' and withdrawn by site; no study data available. A second participant did not attend their baseline appointment.

Period 1

Period 1 title	Visit 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Assignment to active or placebo arm was blinded to both the participant and investigator/assessor (double-blind) through the use of matched placebo. The assessor at each visit for the Mattis DRS-2, NPI-10 and BADLS was independent, and thus blinded not only to the treatment arm, but also to reports of general symptoms, progress and adverse events, as it was acknowledged that the latter, in particular, could potentially influence the assessor as to which treatment the participant was taking.

Arms

Are arms mutually exclusive?	Yes
Arm title	Donepezil hydrochloride

Arm description:

Starting dose 5mg/day, increased to 10mg/day after 8 weeks

Arm type	Experimental
Investigational medicinal product name	Donepezil hydrochloride
Investigational medicinal product code	70676/18-12-2009, 87750/18-12-2009
Other name	Aripezil, Pridia
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Starting dose 5mg/day, increased to 10mg/day after 8 weeks

Arm title	Placebo
Arm description: Placebo was a gelatin capsule (swedish orange, size AAA) containing microcrystalline cellulose	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

One capsule daily for first 8 weeks, 2 capsules daily between weeks 9 and 26, then one capsule daily until week 104.

Number of subjects in period 1	Donepezil hydrochloride	Placebo
Started	32	30
Completed	32	30

Period 2

Period 2 title	Visit 4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Assignment to active or placebo arm was blinded to both the participant and investigator/assessor (double-blind) through the use of matched placebo. The assessor at each visit for the Mattis DRS-2, NPI-10 and BADLS was independent, and thus blinded not only to the treatment arm, but also to reports of general symptoms, progress and adverse events, as it was acknowledged that the latter, in particular, could potentially influence the assessor as to which treatment the participant was taking.

Arms

Are arms mutually exclusive?	Yes
Arm title	Donepezil hydrochloride

Arm description:

Starting dose 5mg/day, increased to 10mg/day after 8 weeks

Arm type	Experimental
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Other name	Aripezil, Pridia
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Starting dose 5mg/day, increased to 10mg/day after 8 weeks

Arm title	Placebo
Arm description:	
Placebo was a gelatin capsule (swedish orange, size AAA) containing microcrystalline cellulose	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

One capsule daily for first 8 weeks, 2 capsules daily between weeks 9 and 26, then one capsule daily until week 104.

Number of subjects in period 2	Donepezil hydrochloride	Placebo
Started	32	30
Completed	14	14
Not completed	18	16
Consent withdrawn by subject	5	3
Study terminated early	13	13

Baseline characteristics

Reporting groups

Reporting group title	Donepezil hydrochloride
Reporting group description:	
Starting dose 5mg/day, increased to 10mg/day after 8 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo was a gelatin capsule (swedish orange, size AAA) containing microcrystalline cellulose	

Reporting group values	Donepezil hydrochloride	Placebo	Total
Number of subjects	32	30	62
Age categorical			
Age of participants			
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)	5	2	7
From 65-84 years	26	26	52
85 years and over	1	2	3
Age continuous			
Age			
Units: years			
arithmetic mean	73	74.6	
standard deviation	± 9	± 7	-
Gender categorical			
People with Parkinson's Disease and mild dementia residing in the UK.			
Units: Subjects			
Female	5	9	14
Male	27	21	48
MATTIS-DRS-2			
Mattis Dementia Rating Scale, Age-and-education-corrected Scaled Score			
Units: None			
arithmetic mean	7.9	7	
standard deviation	± 3	± 2.9	-
10-item NPI score			
10-item Neuropsychiatric Inventory			
Units: None			
median	2.5	4	
inter-quartile range (Q1-Q3)	0.3 to 6.8	1 to 5.8	-
NPI caregiver distress score			
Validated Questionnaire			
Units: None			

median	3	3.5	
inter-quartile range (Q1-Q3)	0 to 6	0.3 to 5	-
BADLS score			
Bristol Activities of Daily Living Scale			
Units: None			
median	5	2.5	
inter-quartile range (Q1-Q3)	3 to 11	1 to 6.5	-
MDS-UPDRS score			
Motor Subsection of the 2008 Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale			
Units: None			
median	40	34	
inter-quartile range (Q1-Q3)	34 to 49.5	29 to 42	-
ABC scale score			
Activities-specific balance confidence scale			
Units: None			
median	70	75.9	
inter-quartile range (Q1-Q3)	57.3 to 81	66.8 to 85	-
EQ5D			
Validated Quality of Life Questionnaire			
Units: None			
median	65	70	
inter-quartile range (Q1-Q3)	60 to 75	60 to 80	-
DEMQOL			
Validated Quality of Life Questionnaire			
Units: None			
median	93	95	
inter-quartile range (Q1-Q3)	84 to 98	90 to 100	-
DEMQOL-proxy			
Validated Quality of Life Questionnaire			
Units: None			
median	104	108	
inter-quartile range (Q1-Q3)	95 to 113	99 to 115	-

End points

End points reporting groups

Reporting group title	Donepezil hydrochloride
Reporting group description:	
Starting dose 5mg/day, increased to 10mg/day after 8 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo was a gelatin capsule (swedish orange, size AAA) containing microcrystalline cellulose	
Reporting group title	Donepezil hydrochloride
Reporting group description:	
Starting dose 5mg/day, increased to 10mg/day after 8 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo was a gelatin capsule (swedish orange, size AAA) containing microcrystalline cellulose	
Subject analysis set title	Donepezil hydrochloride
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
People with Parkinson's Disease and mild dementia residing in the UK. Starting dose 5mg/day, increased to 10mg/day after 8 weeks.	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
People with Parkinson's Disease and mild dementia residing in the UK. One capsule daily for first 8 weeks, 2 capsules daily between weeks 9 and 26, then one capsule daily until week 104.	

Primary: MATTIS-DRS-2

End point title	MATTIS-DRS-2 ^[1]
End point description:	
Mattis Dementia Rating Scale, Age-and-education-corrected Scaled Score	
End point type	Primary
End point timeframe:	
26 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No inferential statistical testing carried out as study terminated early.

End point values	Donepezil hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: None				
median (inter-quartile range (Q1-Q3))	8 (5 to 12.5)	6 (5.3 to 8.8)		

Statistical analyses

No statistical analyses for this end point

Primary: MATTIS-DRS-2

End point title	MATTIS-DRS-2 ^[2]
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End point description:

Mattis Dementia Rating Scale, Raw Scores

End point type	Primary
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End point timeframe:

26 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No inferential statistical testing was able to be carried out as the study was terminated early.

End point values	Donepezil hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: None				
median (inter-quartile range (Q1-Q3))	133 (123 to 141)	130 (122 to 134)		

Statistical analyses

No statistical analyses for this end point

Primary: 10-item NPI score

End point title	10-item NPI score ^[3]
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End point description:

10-item Neuropsychiatric Inventory

End point type	Primary
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End point timeframe:

26 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No inferential statistical testing was able to be carried out as the study was terminated early.

End point values	Donepezil hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	14		
Units: None				
median (inter-quartile range (Q1-Q3))	2.5 (0.8 to 6.8)	4.5 (1.3 to 7)		

Statistical analyses

No statistical analyses for this end point

Primary: BADLS score

End point title	BADLS score ^[4]
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End point description:

Bristol Activities of Daily Living Score

End point type	Primary
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End point timeframe:

26 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No inferential statistical testing was able to be carried out as the study was terminated early.

End point values	Donepezil hydrochloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: None				
median (inter-quartile range (Q1-Q3))	5 (2.3 to 8.5)	4.5 (2 to 7.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All non-serious adverse events were reported from visit 3 until final visit. Serious adverse events were reported throughout the trial until 2 weeks after trial medication was stopped.

Assessment type	Systematic
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Dictionary used

Dictionary name	As reported
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Dictionary version	1
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Reporting groups

Reporting group title	Donepezil hydrochloride
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Reporting group description:

Starting dose 5mg/day, increased to 10mg/day after 8 weeks

Reporting group title	Placebo
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Reporting group description:

Placebo was a gelatin capsule (swedish orange, size AAA) containing microcrystalline cellulose

Serious adverse events	Donepezil hydrochloride	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 32 (12.50%)	2 / 30 (6.67%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Aortic dissection	Additional description: Death due to haemopericardium, aortic dissection and hypertension		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Acute leukaemia	Additional description: Death due to acute leukaemia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			

Confusional state	Additional description: Confused, has falls, severe offs with freezing so lost confidence walking and panicked. Refused to walk due to panic and this caused chest pain, so ambulance called.		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration	Additional description: Patient increased trial medication from 1 to 2 tablets. This caused excessive tiredness. Patient felt dehydrated, cold and faint. Patient took dioralyte to rehydrate self. Phoned 999 and taken to A&E.		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention	Additional description: Postural hypotension and urinary retention: collapsed at party, taken to A&E. Abdomen soft, suprapubic mass - bladder 999mls - catheterised.		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Donepezil hydrochloride	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 32 (59.38%)	23 / 30 (76.67%)	
Injury, poisoning and procedural complications			
Bleed post tooth extraction			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Burnt throat			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
dislocated finger when fell			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Grazed hand following fall			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Head Injury			

subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 30 (3.33%) 1	
Injury to right elbow subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 30 (0.00%) 0	
injury to left thumb subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 30 (0.00%) 0	
Laceration of scalp (due to fall) subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 30 (3.33%) 1	
Wound on left arm subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 30 (3.33%) 1	
Surgical and medical procedures Corrective surgery right middle finger subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 30 (0.00%) 0	
Surgery for skin cancer subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 30 (0.00%) 0	
Surgical procedure to right shoulder with post-operative pain subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 30 (0.00%) 0	
Cardiac disorders TIA lasting 30 minutes subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 30 (3.33%) 1	
Nervous system disorders Dyskensas subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 30 (3.33%) 1	
dystonia subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 30 (3.33%) 1	
Increased episodes of freezing			

subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
increased freezing			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
increased neuropathic pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Increased PD tremor			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Worsening of Parkinson's symptoms			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Achy legs			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Apathy			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Back ache			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Back pain increased			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Breathlessness going upstairs			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Bruising to head and shoulders			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Chestiness with cough			

subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Chesty cough		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Choked on IMP		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Confusion		
subjects affected / exposed	0 / 32 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	3
confusion/disorientation		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
coughing at night		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Dizziness		
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)
occurrences (all)	2	0
Dizziness on standing and sudden movement		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Dizziness when taking pain medication		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Drowsiness		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Excessive saliva		
subjects affected / exposed	0 / 32 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	2
face twisted		

subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Fall		
subjects affected / exposed	10 / 32 (31.25%)	12 / 30 (40.00%)
occurrences (all)	10	12
Fall/loss of consciousness		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
falls		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Fell		
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)
occurrences (all)	2	0
frequent falls		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
further deterioration in memory		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Generally unwell		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Grip in right hand weaker		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Hallucinations		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Headaches		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Hip pain		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
hypotension		

subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
increase in falls		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
increased anxiety		
subjects affected / exposed	0 / 32 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	2
Increased balance problem		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Increased confusion and drowsiness		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Increased confusion and agitation		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Increased day time somnolence		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Increased sleepiness		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
intermittent neck pain		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
intermittent tinnitus		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Itchy scalp		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Itchy skin		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Legs aching when walking		

subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
legs aching whilst walking		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Lesion on chest		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Lethargy		
subjects affected / exposed	1 / 32 (3.13%)	2 / 30 (6.67%)
occurrences (all)	1	2
Light headedness		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Loss of consciousness		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Loss of balance		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
low mood		
subjects affected / exposed	0 / 32 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	2
muddled head		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Nausea		
subjects affected / exposed	3 / 32 (9.38%)	1 / 30 (3.33%)
occurrences (all)	3	1
Nightmares		
subjects affected / exposed	1 / 32 (3.13%)	2 / 30 (6.67%)
occurrences (all)	1	2
Nose bleed		
subjects affected / exposed	1 / 32 (3.13%)	1 / 30 (3.33%)
occurrences (all)	1	1
Pain in back worsening		

subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Pain in right and left wrists worsening		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Pain in right knee on extension		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
painful right knee on exertion		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Painful right leg		
subjects affected / exposed	0 / 32 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	2
Panic attack		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Postural hypertension		
subjects affected / exposed	1 / 32 (3.13%)	1 / 30 (3.33%)
occurrences (all)	1	1
productive cough		
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)
occurrences (all)	2	0
Reduced appetite		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Reduction in semen/burning		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
right shoulder worsening		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
runny nose		
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)
occurrences (all)	2	0

Shoulder pain		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Significant behavioural changes		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
sleepiness		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
slight euphoria		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Some choking		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Sweating		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Swollen feet		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Three falls when getting out of chair		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Tiredness		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
Unable to eat or drink		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0
vaginal discharge		
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	1
Very bad nightmares		
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)
occurrences (all)	1	0

Weakness			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Weight loss			
subjects affected / exposed	2 / 32 (6.25%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
woolly head			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
worsening memory			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Worsening of back pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Worsening of confusion			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
worsening of cramps in feet			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
worsening of cramps in hands			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
worsening of cramps in legs			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
worsening of pain in left calf			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Worsening of REM/sleep disorder			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Myelodysplasia syndrome			

subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Tiredness due to reduced platelet count			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	5 / 32 (15.63%)	1 / 30 (3.33%)	
occurrences (all)	5	1	
Flatulence			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Hiatus hernia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Loose stools			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
lower abdominal cramps			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Worsening constipation			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Urinary tract infection			

subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Worsening of urinary frequency/urgency			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Infections and infestations			
Chest infection			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
infected wound			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2012	Update of protocol to version 4.0; bringing REC application up to date with MHRA/CSP applications.
01 August 2012	Update of protocol to version 5.0; removal of CT scan, DRS stratification and general protocol maintenance.
26 June 2013	Update of protocol to version 6.0 and PIS.
22 August 2013	Update to protocol version 7.0; change to DRS and removal of neurosurgery exclusion criteria.
07 March 2014	Addition of a study specific poster and leaflet.
23 April 2014	PI change at Norfolk & Norwich; PI change at Derby.
18 June 2014	Temporary halt to recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
29 May 2014	Temporary halt to recruitment.	-

Notes:

Limitations and caveats

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

Recruitment to the trial proved difficult, so the trial was terminated early. It was originally intended to recruit 500 participants, however only 62 patients were recruited over 19 months. The last results were therefore collected at 26 weeks.

Notes: