



Clinical trial results:

Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in mechanically ventilated patients at high risk of delirium

Summary

EudraCT number	2012-003114-13
Trial protocol	GB
Global end of trial date	11 January 2017

Results information

Result version number	v1 (current)
This version publication date	03 March 2018
First version publication date	03 March 2018
Summary attachment (see zip file)	MoDUS summary results (MoDUS summary results.pdf.docx)

Trial information

Trial identification

Sponsor protocol code	RD2012-134
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Additional study identifiers

ISRCTN number	ISRCTN89079989
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	West Hertfordshire Hospitals NHS Trust
Sponsor organisation address	Vicarage Road, Watford, United Kingdom, WD18 0HB
Public contact	Intensive Care, West Hertfordshire Hospitals NHS Trust, +44 1923217610, valerie.page@whht.nhs.uk
Scientific contact	Intensive Care, West Hertfordshire Hospitals NHS Trust, +44 1923217610, valerie.page@whht.nhs.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 March 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis that treatment with enteral Simvastatin 80mg once daily for a maximum of 28 days will increase the number of delirium/coma free days in mechanically ventilated patients at high risk of delirium. The study has three distinct objectives:

Objective 1: to conduct a prospective randomised double-blind, placebo-controlled phase II single-centre trial of Simvastatin for the prevention/treatment of delirium.

Objective 2: to determine any improvement in related neurocognitive sequelae coupled with standard clinical outcomes.

Objective 3: to study the biological effect of Simvastatin on systemic markers of inflammation and cholinergic activity as related to the number of delirium/coma free days and the potential of beta-amyloid as a predictor of the risk of long term cognitive impairment.

Protection of trial subjects:

Consent to continue consent interview and follow up phone assessments provided opportunities for investigators to determine pain and distress so principal investigator was able to advise on referral or to recommend GP attendance.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	07 January 2013
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: 142
Worldwide total number of subjects	142
EEA total number of subjects	142

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)	72
From 65 to 84 years	63
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between Feb 1, 2013, and July 29, 2016 at a single site, Watford General Hospital.

Pre-assignment

Screening details:

Patients receiving invasive mechanical ventilation within the first 72 h of ICU admission were screened for inclusion in the study. 1164 screened, 142 (12.2%) randomised and included in the final analysis.

Pre-assignment period milestones

Number of subjects started	142
Number of subjects completed	142

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Simvastatin 40mg or identical placebo (95% lactose) tablets were packaged identically and identified only by the unique trial identifier. The study statistician generated the randomisation schedule in advance using nQuery Advisor version 4.0, and randomisation was by variable block sizes of 2, 4, 6, and 8, without stratification.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

Once daily simvastatin 80mg (as two 40mg tablets) administered enterally via a feeding tube or orally for up to 28 days.

Arm type	Experimental
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	PL08215/0042
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Enteral use

Dosage and administration details:

Once daily simvastatin 80mg (as two 40mg tablets) administered enterally via a feeding tube or orally for up to 28 days.

Arm title	Control
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Arm description:

once daily 80mg placebo (as two 40mg tablets); identical to the Simvastatin, administered enterally via a feeding tube or orally for up to 28 days.

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Coated tablet
Routes of administration	Enteral use

Dosage and administration details:

once daily placebo 80mg, as two 40mg tablets administered enterally via a feeding tube or orally for up to 28 days.

Number of subjects in period 1	Intervention	Control
Started	71	71
Completed	71	71

Baseline characteristics

Reporting groups

Reporting group title	Intervention
Reporting group description: Once daily simvastatin 80mg (as two 40mg tablets) administered enterally via a feeding tube or orally for up to 28 days.	
Reporting group title	Control
Reporting group description: once daily 80mg placebo (as two 40mg tablets); identical to the Simvastatin, administered enterally via a feeding tube or orally for up to 28 days.	

Reporting group values	Intervention	Control	Total
Number of subjects	71	71	142
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			
arithmetic mean	61.9	62.1	
standard deviation	± 15.3	± 17.3	-
Gender categorical Units: Subjects			
Female	26	34	60
Male	45	37	82
Diagnosis_ARDS Units: Subjects			
Yes	23	18	41
No	48	53	101
Diagnosis_Pneumonia Units: Subjects			
Yes	33	30	63
No	38	41	79
Diagnosis_MIorCCF Units: Subjects			
Yes	2	3	5
No	69	68	137
Diagnosis_RenalorHepFailure Units: Subjects			
Yes	4	4	8

No	67	67	134
Diagnosis_COPD			
Units: Subjects			
Yes	7	3	10
No	64	68	132
Diagnosis_Haemorrhage			
Units: Subjects			
Yes	1	1	2
No	70	70	140
Diagnosis_Drug Overdose			
Units: Subjects			
Yes	3	6	9
No	68	65	133
Diagnosis_Trauma			
Units: Subjects			
Yes	0	0	0
No	71	71	142
Diagnosis_Other			
Units: Subjects			
Yes	19	17	36
No	52	54	106
CAM-ICU Status			
Units: Subjects			
Positive	56	56	112
Negative	0	4	4
Unable to assess	15	11	26
Organ failure Free			
Units: Subjects			
Yes	0	1	1
No	71	70	141
Predeliric Diagnose Group			
Units: Subjects			
Surgical	19	17	36
Medical	48	50	98
Trauma	0	1	1
Neurology/Neurosurgical	4	3	7
Alcohol Abuse Present			
Units: Subjects			
Yes	13	15	28
No	58	56	114
IQCODE			
N=67 in Intervention arm and N=60 in Placebo arm only			
Units: Score			
arithmetic mean	3.2	3.1	
standard deviation	± 0.4	± 0.3	-
Lowest RASS Score			
Units: Score			
median	-4	-4	
inter-quartile range (Q1-Q3)	-4 to -3	-4 to -3	-
Highest RASS Score			
Units: Score			

median inter-quartile range (Q1-Q3)	1 -1 to 2	1 -1 to 2	-
Highest Creatinine Units: Umol/L arithmetic mean standard deviation	111.6 ± 73.7	118.5 ± 104.9	-
Highest Bilirubin Units: Umol/L arithmetic mean standard deviation	31.0 ± 68.6	20.5 ± 25.6	-
CRP Units: mg/L arithmetic mean standard deviation	208.0 ± 169.0	212.7 ± 155.6	-
Fentanyl Total Dose Units: mgs arithmetic mean standard deviation	0.6 ± 0.7	0.6 ± 0.7	-
Propofol Total Dose Units: mgs arithmetic mean standard deviation	700.6 ± 778.8	821.5 ± 936.9	-
Apache II Score Units: Score arithmetic mean standard deviation	17.2 ± 5.3	16.7 ± 6.4	-
Chance of delirium development Units: percent arithmetic mean standard deviation	70.9 ± 26.9	70.9 ± 24.5	-
Total SOFA Score			
n=70 in Intervention and n=71 in Control arms			
Units: Score arithmetic mean standard deviation	8.8 ± 3.7	8.9 ± 3.1	-
CK Units: U/L arithmetic mean standard deviation	240.4 ± 294.7	219.7 ± 250.0	-
ALT Units: U/L arithmetic mean standard deviation	65.0 ± 63.8	62.6 ± 64.4	-

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description: Once daily simvastatin 80mg (as two 40mg tablets) administered enterally via a feeding tube or orally for up to 28 days.	
Reporting group title	Control
Reporting group description: once daily 80mg placebo (as two 40mg tablets); identical to the Simvastatin, administered enterally via a feeding tube or orally for up to 28 days.	

Primary: Delirium/Coma free at 14 days post randomisation

End point title	Delirium/Coma free at 14 days post randomisation
End point description: The primary outcome is the number of days in the first 14 days following randomisation during which the patient is alive and free from delirium and coma where days are counted as calendar days i.e. from 00:00 to 23:59.	
End point type	Primary
End point timeframe: Until 14 days post randomisation	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: Days				
arithmetic mean (standard deviation)	5.7 (\pm 5.1)	6.1 (\pm 5.2)		

Statistical analyses

Statistical analysis title	DCF Days Analysis
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	2.09

Statistical analysis title	DCF Analysis Bootstrapped
Statistical analysis description: Bootstrap t-test (bias corrected CI)	
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	2.02

Statistical analysis title	DCF Days Mann Whitney
Statistical analysis description: Two-sample Mann Whitney test	
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	DCF Days Adjusted
Statistical analysis description: Adjusted for baseline SOFA and chance of delirium development	
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	2.02

Statistical analysis title	DCF Days Joint Modelling_Recurrences
Statistical analysis description: Joint modelling approach via the R statistical package frailty pack. This approach will combine two survival models: one for the repeated daily indicator of delirium and another for the terminating event of ICU discharge or death.	
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	joint frailty modelling
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.23

Statistical analysis title	DCF Days Joint Modelling_Assignment(Simvastatin)
Statistical analysis description: Joint modelling approach via the R statistical package frailty pack. This approach will combine two survival models: one for the repeated daily indicator of delirium and another for the terminating event of ICU discharge or death.	
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	joint frailty modelling
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	2.04

Statistical analysis title	DCF Days Joint Modelling_Type(Death)
Statistical analysis description: Joint modelling approach via the R statistical package frailty pack. This approach will combine two survival models: one for the repeated daily indicator of delirium and another for the terminating event of ICU discharge or death.	
Comparison groups	Intervention v Control

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	joint frailty modelling
Parameter estimate	Hazard ratio (HR)
Point estimate	3.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.12
upper limit	11.81

Statistical analysis title	DCF Days Joint Modelling_Assignment*Type
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Statistical analysis description:

Joint modelling approach via the R statistical package frailty pack. This approach will combine two survival models: one for the repeated daily indicator of delirium and another for the terminating event of ICU discharge or death.

Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	joint frailty modelling
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	3.29

Secondary: Delirium/Coma free at 28 days post randomisation

End point title	Delirium/Coma free at 28 days post randomisation
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End point description:

The number of days in the first 28 days following randomisation during which the patient is alive and free from delirium and coma where days are counted as calendar days i.e. from 00:00 to 23:59.

End point type	Secondary
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End point timeframe:

Until 28 days post randomisation

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: Days				
arithmetic mean (standard deviation)	14.3 (\pm 11.2)	15.4 (\pm 10.9)		

Statistical analyses

Statistical analysis title	DCF 28 days t-test
Statistical analysis description: Two-sample t-test	
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.59
upper limit	4.74

Statistical analysis title	DCF 28 days bootstrap t-test
Statistical analysis description: Bootstrap t-test (bias corrected CI)	
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	5.13

Statistical analysis title	DCF 28 days Mann-Whitney
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Statistical analysis description:	
Two-sample Mann-Whitney test	
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	Wilcoxon (Mann-Whitney)

Secondary: Incidence of Delirium

End point title	Incidence of Delirium
End point description:	
End point type	Secondary
End point timeframe:	
Up to 28 days post randomisation	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: Subjects	66	67		

Statistical analyses

Statistical analysis title	Test of Proportions
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	two-sample test of proportions
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.07

Secondary: Days in coma to 14 days

End point title	Days in coma to 14 days
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End point description:

End point type	Secondary
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End point timeframe:
up to 14 days

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: Days				
arithmetic mean (standard deviation)	1.0 (\pm 1.4)	0.9 (\pm 1.5)		

Statistical analyses

Statistical analysis title	Days in coma 14
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	0.44

Secondary: Days in coma to 28 days

End point title	Days in coma to 28 days
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End point description:

End point type	Secondary
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End point timeframe:
up to 28 days

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: days				
arithmetic mean (standard deviation)	1.1 (\pm 1.7)	1.1 (\pm 1.8)		

Statistical analyses

Statistical analysis title	Days in coma 28
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.58

Secondary: Days in delirium to 14 days

End point title	Days in delirium to 14 days
End point description:	
End point type	Secondary
End point timeframe:	
up to 14 days	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: days				
arithmetic mean (standard deviation)	5.6 (\pm 4.3)	5.5 (\pm 4.5)		

Statistical analyses

Statistical analysis title	Days in delirium 14
Comparison groups	Intervention v Control

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.53
upper limit	1.39

Secondary: Days in delirium to 28 days

End point title	Days in delirium to 28 days
End point description:	
End point type	Secondary
End point timeframe:	
up to 28 days	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: days				
arithmetic mean (standard deviation)	6.4 (± 6.0)	6.8 (± 6.6)		

Statistical analyses

Statistical analysis title	Days in delirium 28
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.82
upper limit	2.35

Secondary: VFDs to 28 days post randomisation

End point title	VFDs to 28 days post randomisation
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End point description:

End point type	Secondary
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End point timeframe:

up to 28 days

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: days				
arithmetic mean (standard deviation)	13.7 (\pm 11.9)	15.5 (\pm 11.4)		

Statistical analyses

Statistical analysis title	VFDs t-test
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.07
upper limit	5.65

Statistical analysis title	VFDs bootstrap t-test
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.37
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.79

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.96
upper limit	5.32

Notes:

[1] - Bootstrap t-test (bias corrected CI)

Statistical analysis title	VFDs Mann-whitney
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	Wilcoxon (Mann-Whitney)

Secondary: OFFDs in first 28 days

End point title	OFFDs in first 28 days
End point description:	
End point type	Secondary
End point timeframe:	
up to 28 days	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: days				
arithmetic mean (standard deviation)	14.3 (\pm 12.1)	15.7 (\pm 11.2)		

Statistical analyses

Statistical analysis title	OFFDs t-test
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.38
upper limit	5.34

Statistical analysis title	OFFDs bootstrap t-test
Statistical analysis description: Bootstrap t-test (bias corrected CI)	
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.22
upper limit	5.03

Statistical analysis title	OFFDs Mann Whitney
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Wilcoxon (Mann-Whitney)

Secondary: All cause mortality at 6 months

End point title	All cause mortality at 6 months
End point description:	
End point type	Secondary
End point timeframe: 6 months post randomisation	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: subjects	30	22		

Statistical analyses

Statistical analysis title	Mortality Risk Ratio
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	2.11

Statistical analysis title	Mortality Logrank
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2 ^[2]
Method	Logrank

Notes:

[2] - Events expected from Logrank test were 25.45 in Intervention arm and 26.55 in Control arm.

Secondary: Cognitive decline via IQCODE

End point title	Cognitive decline via IQCODE
End point description:	
End point type	Secondary
End point timeframe:	
at 6 months	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	27		
Units: score				
arithmetic mean (standard deviation)	3.0 (\pm 0.5)	3.1 (\pm 0.7)		

Statistical analyses

Statistical analysis title	IQCODE ANCOVA
Statistical analysis description: ANCOVA adjusting for baseline IQCODE. n=21 in interventions arm and n=27 in the control arm	
Comparison groups	Intervention v Control
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.39

Secondary: BTACT at 6 months

End point title	BTACT at 6 months
End point description:	
End point type	Secondary
End point timeframe: at 6 months	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	24		
Units: standardised scores				
arithmetic mean (standard deviation)	-0.2 (\pm 0.5)	0.1 (\pm 0.5)		

Statistical analyses

Statistical analysis title	BTACT t-test
Statistical analysis description: BTACT composite is an average of the standardized scores and was calculated on the basis of no. of tasks completed.	
Comparison groups	Intervention v Control
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.6

Secondary: Duration of hospital stay until death or discharge

End point title	Duration of hospital stay until death or discharge
End point description:	
End point type	Secondary
End point timeframe: randomisation until death or discharge	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: days				
arithmetic mean (standard deviation)	20.3 (± 22.1)	20.4 (± 16.6)		

Statistical analyses

Statistical analysis title	hospital stay cox regression
Comparison groups	Intervention v Control

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.45

Statistical analysis title	hospital stay t-test
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.96
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.31
upper limit	6.65

Statistical analysis title	hospital stay hodge-lehmann
Statistical analysis description: requested by Lancet reviewer. Median (IQR) for Intervention was 13(7,25) and for Control was 16(9,28). The median difference (IQR) was 2(-2,6)	
Comparison groups	Intervention v Control
Number of subjects included in analysis	142
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.3
Method	hodge-lehmann

Secondary: Duration of hospital stay until discharge	
End point title	Duration of hospital stay until discharge
End point description:	
End point type	Secondary

End point timeframe:
randomisation until discharge

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	50		
Units: days				
arithmetic mean (standard deviation)	23.3 (\pm 24.3)	23.1 (\pm 16.9)		

Statistical analyses

Statistical analysis title	hospital stay cox regression
Comparison groups	Intervention v Control
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.925
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.53

Statistical analysis title	hospital stay t-test
Comparison groups	Intervention v Control
Number of subjects included in analysis	97
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.97
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.56
upper limit	8.21

Statistical analysis title	hospital stay hodge-lehmann
Statistical analysis description: The median (IQR) for the Intervention arm was 16(9,26) and for the Control arm was 18(12,34). The median difference(IQR) was 2(-3,7).	
Comparison groups	Intervention v Control
Number of subjects included in analysis	97
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.34
Method	hodge-lehmann

Secondary: Quality Adjusted Life Years

End point title	Quality Adjusted Life Years
End point description: QALYs calculated used baseline and 6 month EQ5D utilities on patients with complete costs and QALY data.	
End point type	Secondary
End point timeframe: over 6 months	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: QALYs				
arithmetic mean (confidence interval 95%)	0.078 (0.051 to 0.105)	0.083 (0.055 to 0.110)		

Statistical analyses

Statistical analysis title	QALY analysis
Statistical analysis description: 95% CI based on 1000 bootstrapped replicates	
Comparison groups	Intervention v Control
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.03

Secondary: Health service use costs

End point title	Health service use costs
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End point description:

Total 6 month health service costs for patients with complete costs and QALY data

End point type	Secondary
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End point timeframe:

over 6 months

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: GBP				
arithmetic mean (confidence interval 95%)	23792.37 (16109.92 to 31474.82)	22433.41 (17558.32 to 27308.51)		

Statistical analyses

Statistical analysis title	Cost analysis
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Statistical analysis description:

95% CI based on 1000 bootstrapped replicates

Comparison groups	Intervention v Control
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1358.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7286.7
upper limit	10004.61

Adverse events

Adverse events information

Timeframe for reporting adverse events:

30 days following administration of study drug.

Adverse event reporting additional description:

Events that were expected in this population (i.e. events that are in keeping with the patient's underlying medical condition) were not reported as AEs. Due to small numbers a breakdown of term is not provided for serious or non-serious AEs. For non serious adverse events, investigations is broken down into ALT>8 times ULN and CK>10 times ULN.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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Reporting groups

Reporting group title	Intervention
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Reporting group description: -

Reporting group title	Control
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Reporting group description: -

Serious adverse events	Intervention	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 71 (12.68%)	8 / 71 (11.27%)	
number of deaths (all causes)	30	22	
number of deaths resulting from adverse events	1	0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	1 / 71 (1.41%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	7 / 71 (9.86%)	7 / 71 (9.86%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Intervention	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 71 (16.90%)	7 / 71 (9.86%)	
Investigations			
Elevated CK			
subjects affected / exposed	8 / 71 (11.27%)	3 / 71 (4.23%)	
occurrences (all)	8	3	
Elevated ALT			
subjects affected / exposed	4 / 71 (5.63%)	4 / 71 (5.63%)	
occurrences (all)	4	4	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2015	3.3.2 Exclusion criteria 9. Patients with severe renal impairment (estimated creatinine clearance less than 15ml/minute) not receiving renal replacement therapy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28734823>