Clinical trial results:
Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP 2)

Summary

EudraCT number	2010-020763-20
Trial protocol	IE GB
Global end of trial date	12 May 2015

Results information

Result version number	v1 (current)
This version publication date	21 December 2017
First version publication date	21 December 2017

Trial information

Trial identification

Sponsor protocol code	10072DMcA-CS

Additional study identifiers

ISRCTN number	ISRCTN88244364
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Belfast Health & Social Care Trust (BHSCT)
Sponsor organisation address	King Edward Building, Royal Hospitals, Grosvenor Road, Belfast, United Kingdom, BT12 6BA
Public contact	Christine McNally, Northern Ireland Clinical Trials Unit (NICTU), 02890 635794, christine.mcnally@nictu.hscni.net
Scientific contact	Prof Daniel McAuley, Queen's University of Belfast, 02890 972671, d.f.mcauley@qub.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	23 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 May 2015
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 would be of therapeutic value in patients with acute lung injury (ALI). Many patients admitted to ICU need a ventilator to help them breathe and ensure that enough oxygen gets into their blood. For reasons that are unclear, when people are critically ill their lungs often fail; termed acute lung injury. There are no specific drugs to treat patients with ALI. Some small studies that have taken place over the past few years have suggested that giving patients with ALI a drug called simvastatin (usually used to treat patients with high cholesterol), might help patients to recover more quickly. We aimed to determine how long patients needed assistance with a ventilator, how fast they recovered. We measured any residual effects of their illness on their lives after one year and took blood and urine samples to determine how ALI develops and how simvastatin might alleviate this

Protection of trial subjects:

CK and liver function were closely monitored and an additional blood sample was added at day 21 to measure these. Study drug was stopped if the patient's CK or liver function was found to be out of range. To minimize the risk of causing distress to the relation of a patient who died after leaving the hospital, the Clinical Trials Unit contacted the patient's GP and the Health & Social Care Information Centre to ascertain the patient's survival status prior to sending out any follow up questionnaires.
A Clinical Trials Monitor monitored study site compliance with study and CTU SOPs and provided feedback to the Trial Management Group on any actual or potential problems in relation to safeguarding patients safety and wellbeing.
The HARP-2 DMEC was appointed comprising two clinicians with experience in undertaking clinical trials / caring for critically ill patients and a statistician who was independent of the trial. The DMEC met biannually and meetings were formally minuted. The DMEC's responsibility was to safeguard the interests of the trial participants, in particular with regard to safety and assist and advise the TSC so as to protect the validity and credibility of the trial. The DMEC monitored recruitment, adverse events and outcome data. Patient experience whilst critically ill was taken into consideration when preparing patient information leaflets and consent forms. The Chairman of CritPaL (Barry Williams) represented the patient's perspective on the TSC ensuring that the trial remained considerate of the needs of the patients and their families.
Site PIs evaluated all AEs/SAES for expectedness, causality and severity. All AEs assessed by the PI as possibly or probably related to the study drug and all SAEs that occurred during this time were followed until they were resolved or were clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). All AEs and SAEs were reviewed by the CI

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	06 December 2010
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: 510
Country: Number of subjects enrolled	Ireland: 29
Worldwide total number of subjects	539
EEA total number of subjects	539

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)	3
Adults (18-64 years)	386
From 65 to 84 years	147
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between 21st December 2010 and 13th March 2014. During the recruiting period to HARP-2 a total of 40 sites participated in the study: 5 in Ireland, 4 in Northern Ireland, 4 in Scotland and 27 in England. 1 site opened in 2010, 25 in 2011, 9 in 2012, 4 in 2013 and 1 in 2014.

Pre-assignment

Screening details:

Patients ≥ 16 years, intubated and mechanically ventilated with partial pressure of arterial oxygen to fractional inspired oxygen concentration ratio of 300 mmHg or less, with bilateral pulmonary infiltrates consistent with pulmonary oedema present on chest x-ray, and no evidence of left atrial hypertension. 5926 screened, 540 (9%) randomised.

Pre-assignment period milestones

Number of subjects started	540[1]
Number of subjects completed	539

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 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 patient withdrew consent for use of their data. So although they were enrolled in the trial we have no data available. This affects the worldwide total when compared to the age categories, so the worldwide total has been amended to 539 for submission. Likewise this affects the baseline placebo arm as technically 281 started and 280 completed but as this does not tally with the worldwide total of 539 now I have amended to 280 starting and added the justification here.

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. A computer-generated randomisation sequence was used. Patients were randomised in a 1:1 ratio using an automated centralised 24-hour telephone or web-based randomisation service (Centre for Healthcare Randomised Trials, University of Aberdeen, UK). Randomisation was by permuted block stratified by site and by vasopressor requirement

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	Placebo

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
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
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	Placebo
Started	259	280
Completed	259	280

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	Placebo
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	Placebo	Total
Number of subjects	259	280	539
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	53.2	54.4	
standar tfee=	± 16.1	± 16.7	-

yes	21	29	50
no	238	251	489
aetiology of ARDS - near drowning Units: Subjects			
yes	0	0	0
no	259	280	539
aetiology of ARDS - thoracic trauma Units: Subjects			
yes	22	10	32
no	237	270	507
aetiology of ARDS - pneumonia Units: Subjects			
yes	161	154	315
no	98	126	224
aetiology of ARDS - other direct Units: Subjects			
yes	15	19	34
no	244	261	505
aetiology of ARDS - sepsis Units: Subjects			
yes	106	118	224
no	153	162	315
aetiology of ARDS - cardiopulmonary bypass Units: Subjects			
yes	1	0	1
no	258	280	538
aetiology of ARDS - pancreatitis Units: Subjects			
yes	5	17	22
no	254	263	517
aetiology of ARDS - non-thoracic trauma Units: Subjects			
yes	4	8	12
no	255	272	527
aetiology of ARDS - other indirect Units: Subjects			
yes	14	19	33
no	245	261	506
plateau pressure Units: cmH2O			
arithmetic mean	23.6	23.6	
standard deviation	± 6.1	± 6	-
APACHE II Units: score			
arithmetic mean	19.4	18.3	
standard deviation	± 6.9	± 6.2	-
PaO2:FiO2 ratio Units: mmHg			
arithmetic mean	16.4	17.6	
standard deviation	± 7.3	± 7.4	-

tidal volume per ideal body weight Units: mls/kg arithmetic mean standard deviation	 8.1 ± 2.8	 8.1 ± 2.6	 -
SOFA Units: score arithmetic mean standard deviation	 8.6 ± 3.2	 9 ± 2.9	 -
oxygenation index Units: cm of water/mmHg arithmetic mean standard deviation	 112.8 ± 87.3	 112 ± 89	 -
lowest mean arterial pressure Units: mmHg arithmetic mean standard deviation	 65.4 ± 9.3	 64.9 ± 8.4	 -

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	Placebo
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: ventilator-free days

End point title	ventilator-free days
End point description:	
VFDs to day 28 are defined as the number of days from the time of initiating unassisted breathing to day 28 after randomisation, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or dies prior to day 28, VFDs will be zero.	
End point type	Primary
End point timeframe:	
up to 28 days post-randomisation	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	279		
Units: days				
arithmetic mean (standard deviation)	12.6 (± 9.9)	11.5 (± 10.4)		

Statistical analyses

Statistical analysis title	VFD analysis
Comparison groups	Placebo v Intervention
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	2.8

Statistical analysis title	VFD analysis - bootstrapped
Comparison groups	Placebo v Intervention
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	2.8

Secondary: non-pulmonary organ failure free days	
End point title	non-pulmonary organ failure free days
End point description: The number of days in the first 28 days after randomisation that the patient has none of: cardiovascular support, renal support, liver support or neurological support).	
End point type	Secondary
End point timeframe: up to 28 days post-randomisation	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	279		
Units: days				
arithmetic mean (standard deviation)	19.4 (± 11.1)	17.8 (± 11.7)		

Statistical analyses

Statistical analysis title	non-pulmonary OFFDs analysis
Comparison groups	Intervention v Placebo

Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	3.5

Statistical analysis title	non-pulmonary OFFDs - bootstrapped
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	3.5

Secondary: change in oxygenation index from baseline to day 3	
End point title	change in oxygenation index from baseline to day 3
End point description: Change in oxygenation index from baseline to day 3	
End point type	Secondary
End point timeframe: day 3	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	162		
Units: cm of water/mmHg				
arithmetic mean (standard deviation)	-25.3 (± 59.7)	-8.5 (± 75.1)		

Statistical analyses

Statistical analysis title	OI day 3
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-16.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.5
upper limit	-2.1

Secondary: change in oxygenation index from baseline to day 7	
End point title	change in oxygenation index from baseline to day 7
End point description: Change in oxygenation index from baseline to day 7	
End point type	Secondary
End point timeframe: day 7	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	111		
Units: cm of water/mmHg				
arithmetic mean (standard deviation)	-33 (± 83.9)	-30.1 (± 78.5)		

Statistical analyses

Statistical analysis title	OI day 7
Comparison groups	Intervention v Placebo

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.4
upper limit	19.5

Secondary: change in oxygenation index from baseline to day 14	
End point title	change in oxygenation index from baseline to day 14
End point description: Change in oxygenation index from baseline to day 14	
End point type	Secondary
End point timeframe: day 14	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	57		
Units: cm of water/mmHg				
arithmetic mean (standard deviation)	-37.5 (± 111.3)	-24.6 (± 61.8)		

Statistical analyses

Statistical analysis title	OI day 14
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.7
upper limit	21.7

Secondary: change in oxygenation index from baseline to day 28	
End point title	change in oxygenation index from baseline to day 28
End point description: Change in oxygenation index from baseline to day 28	
End point type	Secondary
End point timeframe: day 28	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	15		
Units: cm of water/mmHg				
arithmetic mean (standard deviation)	20.7 (± 125.4)	-54 (± 43.6)		

Statistical analyses

Statistical analysis title	OI day 28
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	74.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	153

Secondary: change in SOFA from baseline to day 3	
End point title	change in SOFA from baseline to day 3
End point description: Change in sequential organ failure assessment (SOFA) score from baselines to day 3	
End point type	Secondary
End point timeframe: day 3	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	225		
Units: score				
arithmetic mean (standard deviation)	-0.9 (± 2.2)	-0.8 (± 2.3)		

Statistical analyses

Statistical analysis title	SOFA day 3
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.3

Secondary: change in SOFA from baseline to day 7	
End point title	change in SOFA from baseline to day 7
End point description: Change in sequential organ failure assessment (SOFA) score from baselines to day 7	
End point type	Secondary
End point timeframe: day 7	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	155		
Units: score				
arithmetic mean (standard deviation)	-2.5 (± 3)	-2.5 (± 2.7)		

Statistical analyses

Statistical analysis title	SOFA day 7
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.6

Secondary: change in SOFA from baseline to day 14	
End point title	change in SOFA from baseline to day 14
End point description: Change in sequential organ failure assessment (SOFA) score from baselines to day 14	
End point type	Secondary
End point timeframe: day 14	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	81		
Units: score				
arithmetic mean (standard deviation)	-3.4 (± 3.3)	-2.4 (± 3.2)		

Statistical analyses

Statistical analysis title	SOFA day 14
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-0.01

Secondary: change in SOFA from baseline to day 28	
End point title	change in SOFA from baseline to day 28
End point description: Change in sequential organ failure assessment (SOFA) score from baselines to day 28	
End point type	Secondary
End point timeframe: day 28	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	23		
Units: score				
arithmetic mean (standard deviation)	-4.1 (± 3.9)	-2.7 (± 4.3)		

Statistical analyses

Statistical analysis title	SOFA day 28
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	1.3

Secondary: all cause mortality 28 days post randomisation	
End point title	all cause mortality 28 days post randomisation
End point description: All cause mortality 28 days post randomisation	

End point type	Secondary
End point timeframe: 28 days	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	280		
Units: subjects				
Alive	202	205		
Dead	57	75		

Statistical analyses

Statistical analysis title	28 day mortality
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	280		
Units: subjects				
Alive	203	210		
Dead	56	70		

Statistical analyses

Statistical analysis title	death before discharge from critical care
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.2

Secondary: death before discharge from hospital	
End point title	death before discharge from hospital
End point description: Participants who died prior to discharge from hospital	
End point type	Secondary
End point timeframe: to discharge from hospital	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	280		
Units: subjects				
Alive	192	190		
Dead	67	90		

Statistical analyses

Statistical analysis title	death before discharge from hospital
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.1

Secondary: Quality Adjusted Life Years	
End point title	Quality Adjusted Life Years
End point description: QALYs calculated used baseline, 6 and 12 month EQ5D utilities on patients with complete costs and QALY data.	
End point type	Secondary
End point timeframe: 12 months	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	153		
Units: qalys				
arithmetic mean (standard deviation)	0.136 (± 0.274)	0.072 (± 0.262)		

Statistical analyses

Statistical analysis title	QALY analysis
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.064

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.127

Secondary: Health Service Use Costs

End point title	Health Service Use Costs
End point description: Total 12 month health service costs for patients with complete costs and QALY data	
End point type	Secondary
End point timeframe: 12 months	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	153		
Units: UK pounds				
arithmetic mean (standard deviation)	24115.36 (± 17154.86)	27716.27 (± 23643.97)		

Statistical analyses

Statistical analysis title	Cost Analysis
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-3600.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8872.17
upper limit	722.79

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 days following the administration of the study drug

Adverse event reporting additional description:

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 the following terms: ALT>8 times the upper limit of normal and/or AST>8 times the upper limit of normal; CK>10 times the upper limit of normal and; Other.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Simvastatin

Reporting group description:

Patients on Simvastatin who experienced an adverse event

Reporting group title	Placebo

Reporting group description:

Patients receiving a placebo who experienced an adverse event

Serious adverse events	Simvastatin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 259 (4.25%)	14 / 280 (5.00%)	
number of deaths (all causes)	67	90	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
injury, poisoning and procedural complications			
subjects affected / exposed	1 / 259 (0.39%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	3 / 259 (1.16%)	5 / 280 (1.79%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
nervous system disorders			

subjects affected / exposed	1 / 259 (0.39%)	2 / 280 (0.71%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
gastrointestinal disorders			
subjects affected / exposed	3 / 259 (1.16%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
hepatobiliary disorders			
subjects affected / exposed	0 / 259 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	1 / 259 (0.39%)	3 / 280 (1.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
renal and urinary disorders			
subjects affected / exposed	1 / 259 (0.39%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
musculoskeletal and connective tissue disorders			
subjects affected / exposed	1 / 259 (0.39%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
infections and infestations			
subjects affected / exposed	1 / 259 (0.39%)	2 / 280 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Simvastatin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 259 (18.92%)	49 / 280 (17.50%)	
Investigations			
Elevated ALT/AST			
subjects affected / exposed	26 / 259 (10.04%)	20 / 280 (7.14%)	
occurrences (all)	32	23	
Elevated CK			
subjects affected / exposed	23 / 259 (8.88%)	15 / 280 (5.36%)	
occurrences (all)	23	15	
investigations other			
subjects affected / exposed	2 / 259 (0.77%)	2 / 280 (0.71%)	
occurrences (all)	2	2	
Injury, poisoning and procedural complications			
injury, poisoning and procedural complications			
subjects affected / exposed	0 / 259 (0.00%)	2 / 280 (0.71%)	
occurrences (all)	0	2	
Cardiac disorders			
cardiac disorders			
subjects affected / exposed	1 / 259 (0.39%)	2 / 280 (0.71%)	
occurrences (all)	2	2	
Nervous system disorders			
nervous system disorders			
subjects affected / exposed	1 / 259 (0.39%)	1 / 280 (0.36%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
blood and lymphatic system disorders			
subjects affected / exposed	1 / 259 (0.39%)	1 / 280 (0.36%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
general disorders and administration site conditions			
subjects affected / exposed	1 / 259 (0.39%)	2 / 280 (0.71%)	
occurrences (all)	1	2	

Gastrointestinal disorders gastrointestinal disorders subjects affected / exposed occurrences (all)	 3 / 259 (1.16%) 3	 4 / 280 (1.43%) 4	
Respiratory, thoracic and mediastinal disorders respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	 2 / 259 (0.77%) 2	 1 / 280 (0.36%) 1	
Skin and subcutaneous tissue disorders skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	 0 / 259 (0.00%) 0	 6 / 280 (2.14%) 6	
Renal and urinary disorders renal and urinary disorders subjects affected / exposed occurrences (all)	 1 / 259 (0.39%) 1	 2 / 280 (0.71%) 2	
Infections and infestations infections and infestations subjects affected / exposed occurrences (all)	 1 / 259 (0.39%) 1	 3 / 280 (1.07%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2011	Amendment 1 (main changes): Protocol v1.0_24.06.10 was submitted to ORECNI in the original application for Ethics approval. ORECNI requested some changes which necessitated amending the protocol to v2.0_01.09.10. The major changes included: • Amending the exclusion criteria to exclude non−english speaking patients or those who did not adequately understand verbal or written information unless an interpreter was available; • Amending the exclusion criteria to include the wording "currently" and "sustained" in relation to the use of listed concomitant medications. Amiodarone was added to the list of concomitant medications. • Clarification was given that the 80 mg dose was given as 2 x 40m tablets. • Sofa score was added to the schedule of assessments in day 14 and day 28.
27 June 2011	Protocol v2.0_01.09.10 was amended to v3.0_16.05.11. ORECNI and MHRA approved the following changes: • Change of address of the Chief Investigator (CI). • Non pulmonary organ failure free days added to secondary outcomes • An additional blood sample was added at day 21 to measure CK and liver function. • The exclusion criteria were amended to allow for patients receiving erythromycin as a prokinetic to be included in the study. • Change of address of study drug supplier. • Other changes: additional sites added.
19 September 2011	Amendment 3 (main changes): Protocol v3.0_16.05.11 was amended to v4.0_18.07.11 and was approved by ORECNI and MHRA to include the following changes: • The exclusion criteria were amended to remove clarithromycin and erythromycin. • Clarification was given that domiciliary ventilation used for sleep-disordered breathing would not be included as mechanical ventilation. • Scheduling for research samples submission was changed to allow that research samples due on bank holidays or weekends could be collected up to 2 days after the due date (with the exception of day 1).
12 March 2012	Amendment 5 (main changes): Protocol v4.0_18.07.11 was amended to v5.0_13.01.12. This amendment was approved by ORECNI and MHRA to include the following changes: • The exclusion criteria was amended to change the upper limit of normal for ALT and AST from > 5 times upper limit of normal to > 8 times upper limit of normal.

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/25268516

http://www.ncbi.nlm.nih.gov/pubmed/22985805

http://www.ncbi.nlm.nih.gov/pubmed/28511660