Clinical trial results:
Prevention by HMGCoA reductase inhibition of ALI associated with one lung ventilation following oesophagectomy by a Reduction of Pulmonary vascular dysfunction and inflammation (Prevention-HARP)

Summary

EudraCT number	2007-002454-37
Trial protocol	GB
Global end of trial date	10 November 2013

Results information

Result version number	v1 (current)
This version publication date	08 March 2020
First version publication date	08 March 2020

Trial information

Trial identification

Sponsor protocol code	RGHT000392

Additional study identifiers

ISRCTN number	ISRCTN56543987
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,
Public contact	Prof Daniel McAuley, Queen's University of Belfast, 02890 976385, d.f.mcauley@qub.ac.uk
Scientific contact	Prof Daniel McAuley, Queen's University of Belfast, 02890 976385, 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	10 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2013
Global end of trial reached?	Yes
Global end of trial date	10 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The hypothesis of the study is that treatment with simvastatin can prevent lung injury and inflammation in humans undergoing oesophagectomy as assessed by important surrogate clinical outcomes.

The primary outcome is to evaluate the efficacy of simvastatin to improve pulmonary vascular function between the simvastatin and placebo treated groups

Protection of trial subjects:

A Clinical Trials Monitor monitored study site compliance with study and CTU SOPs and provided feedback on any actual or potential problems in relation to safeguarding patients safety and wellbeing. A DMEC was appointed comprising two clinicians with experience in undertaking clinical trials / caring for critically ill patients and a statistician. The DMEC met regularly and meetings were formally minuted. The DMEC's responsibility was to safeguard the interests of the trial participants, in particular with regard to safety. The DMEC monitored recruitment and adverse events.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 August 2007
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: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

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)	22
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 102 patients, who were due to undergo esophagectomy, were assessed for eligibility between July 2007 and July 2010.
39 patients fulfilled the eligibility criteria and were enrolled into the trial.

Pre-assignment

Screening details:

Inclusion criteria
Adult patients undergoing oesophagectomy for oesophageal cancer at the Royal Victoria Hospital, Belfast (RVH) were eligible for inclusion in the study. Patients were identified prior to surgery at the oesophageal cancer multi-disciplinary meeting.

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	Investigator, Monitor, Assessor, Subject

Blinding implementation details:

Simvastatin 80 mg or placebo (1:1) were encapsulated and in identical containers to ensure blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Simvastatin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	Simvastatin
Pharmaceutical forms	Capsule
Routes of administration	Gastroenteral use

Dosage and administration details:

Simvastatin 80mg for 4 days preoperatively and for 7 days postoperatively.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Gastroenteral use

Dosage and administration details:

For 4 days pre-operatively and 7 days post-operatively.

Number of subjects in period 1	Simvastatin	Placebo
Started	19	20
Completed	15	16
Not completed	4	4
no surgery	4	4

Baseline characteristics

Reporting groups	
Reporting group title	Simvastatin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Simvastatin	Placebo	Total
Number of subjects	19	20	39
Age categorical 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)	10	12	22
From 65-84 years	9	8	17
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	64.1	64.6	
standard deviation	± 11.5	± 9.6	-
Gender categorical Units: Subjects			
Female	4	6	10
Male	15	14	29
Smoking Units: Subjects			
Yes	3	6	9
Ex-smoker	10	11	21
No	6	3	9
Preoperative chemotherapy Units: Subjects			
yes	15	14	29
no	4	6	10
BMI Units: kg/m^2			
arithmetic mean	28.2	26.6	
standard deviation	± 5.2	± 5.5	-

End points

End points reporting groups

Reporting group title	Simvastatin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: pulmonary dead space (Vd/Vt) at 6 hours

End point title	pulmonary dead space (Vd/Vt) at 6 hours
End point description:	
End point type	Primary
End point timeframe:	
at 6 hours following oesophagectomy or prior to extubation	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: Vd/Vt				
arithmetic mean (standard deviation)	0.45 (± 0.09)	0.49 (± 0.08)		

Statistical analyses

Statistical analysis title	Deadspace at 6 hours t-test
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	t-test, 2-sided

Secondary: Compliance

End point title	Compliance
End point description:	
End point type	Secondary
End point timeframe:	
at 6 hours following one lung ventilation or prior to extubation if earlier	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: mL/cm H2O				
arithmetic mean (standard deviation)	42 (± 9)	42 (± 9)		

Statistical analyses

Statistical analysis title	Compliance t-test
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	t-test, 2-sided

Secondary: PaO2/FiO2 ratio

End point title	PaO2/FiO2 ratio

End point description:

End point type	Secondary

End point timeframe:
following oesophagectomy

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: ratio				
arithmetic mean (standard deviation)	40 (± 14)	41 (± 14)		

Statistical analyses

Statistical analysis title	PaO2/FiO2 ratio t-test
Comparison groups	Simvastatin v Placebo

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	t-test, 2-sided

Secondary: Safety Profile - Aspartate aminotransferase at day 4

End point title	Safety Profile - Aspartate aminotransferase at day 4

End point description:

End point type	Secondary

End point timeframe:
at day 4

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: units/L				
arithmetic mean (standard deviation)	42 (± 6)	44 (± 6)		

Statistical analyses

Statistical analysis title	Aspartate aminotransferase Day 4 t-test
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	t-test, 2-sided

Secondary: Safety Profile - Aspartate aminotransferase at day 11

End point title	Safety Profile - Aspartate aminotransferase at day 11

End point description:

End point type	Secondary

End point timeframe:
at day 11

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: units/L				
arithmetic mean (standard deviation)	28 (± 2)	29 (± 2)		

Statistical analyses

Statistical analysis title	Aspartate aminotransferase day 11 t-test
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	t-test, 2-sided

Secondary: Safety Profile - Alanine aminotransferase day 4

End point title	Safety Profile - Alanine aminotransferase day 4
End point description:	
End point type	Secondary
End point timeframe: at day 4	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: units/L				
arithmetic mean (standard deviation)	40 (± 12)	30 (± 12)		

Statistical analyses

Statistical analysis title	Alanine aminotransferase day 4 t-test
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	t-test, 2-sided

Secondary: Safety Profile - Alanine aminotransferase day 11

End point title	Safety Profile - Alanine aminotransferase day 11

End point description:

End point type	Secondary

End point timeframe:
at day 11

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: units/L				
arithmetic mean (standard deviation)	34 (± 3)	33 (± 3)		

Statistical analyses

Statistical analysis title	Alanine aminotransferase day 11 t-test
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	t-test, 2-sided

Secondary: Safety Profile - Creatine kinase at day 4

End point title	Safety Profile - Creatine kinase at day 4

End point description:

End point type	Secondary

End point timeframe:
at day 4

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: units/L				
arithmetic mean (standard deviation)	726 (± 104)	1067 (± 104)		

Statistical analyses

Statistical analysis title	Creatine kinase day 4 t-test
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	t-test, 2-sided

Secondary: Safety Profile - Creatine kinase at day 11

End point title	Safety Profile - Creatine kinase at day 11
End point description:	

End point type	Secondary
End point timeframe: at day 11	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: units/L				
arithmetic mean (standard deviation)	161 (± 27)	162 (± 25)		

Statistical analyses

Statistical analysis title	Creatine kinase day 11 t-test
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	t-test, 2-sided

Secondary: Safety Profile - Creatinine at day 4

End point title	Safety Profile - Creatinine at day 4

End point description:

End point type	Secondary

End point timeframe:
at day 4

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: µmol/L				
arithmetic mean (standard deviation)	70 (± 3)	66 (± 3)		

Statistical analyses

Statistical analysis title	Creatinine day 4 t-test
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	t-test, 2-sided

Secondary: Safety Profile - Creatinine at day 11

End point title	Safety Profile - Creatinine at day 11

End point description:

End point type	Secondary

End point timeframe:
at day 11

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: µmol/L				
arithmetic mean (standard deviation)	61 (± 4)	62 (± 4)		

Statistical analyses

Statistical analysis title	Creatinine day 11 t-test
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	t-test, 2-sided

Other pre-specified: Plasma Rage- D0 pre-OLV

End point title	Plasma Rage- D0 pre-OLV

End point description:

End point type	Other pre-specified

End point timeframe:
D0 pre-OLV

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: (pg/mL)				
arithmetic mean (standard deviation)	1746 (± 1130)	2306 (± 2039)		

Statistical analyses

Statistical analysis title	Plasma Rage D0 pre-OLV 2-way ANOVA
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.02
Method	ANOVA

Other pre-specified: Plasma Rage D0 post-OLV	
End point title	Plasma Rage D0 post-OLV
End point description:	
End point type	Other pre-specified
End point timeframe:	
D0 post-OLV	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: (pg/mL)				
arithmetic mean (standard deviation)	1576 (± 909)	2546 (± 2465)		

Statistical analyses

Statistical analysis title	Plasma Rage D0 post-OLV 2-way ANOVA
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.02
Method	ANOVA

Other pre-specified: Plasma Rage Day 3	
End point title	Plasma Rage Day 3
End point description:	
End point type	Other pre-specified
End point timeframe:	
Day 3	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: (pg/mL)				
arithmetic mean (standard deviation)	1049 (± 845)	1541 (± 1413)		

Statistical analyses

Statistical analysis title	Plasma Rage Day 3 2-way ANOVA
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.02
Method	ANOVA

Other pre-specified: Plasma Rage Day 7

End point title	Plasma Rage Day 7

End point description:

End point type	Other pre-specified

End point timeframe:

Day 7

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: (pg/mL)				
arithmetic mean (standard deviation)	806 (± 599)	1656 (± 3069)		

Statistical analyses

Statistical analysis title	Plasma Rage Day 3 2-way ANOVA
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.02
Method	ANOVA

Other pre-specified: Hospital Outcomes - ALI

End point title	Hospital Outcomes - ALI

End point description:

End point type	Other pre-specified

End point timeframe:
until discharge

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: subjects				
Yes	0	4		
No	15	12		

Statistical analyses

Statistical analysis title	Hospital Outcome ALI Fisher exact test
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Fisher exact

Other pre-specified: Hospital Outcomes - Complications

End point title	Hospital Outcomes - Complications

End point description:

End point type	Other pre-specified

End point timeframe:
until discharge

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: subjects				
Cardiac	3	5		
Respiratory	3	8		
Infective	1	2		

Statistical analyses

Statistical analysis title	Complications Fisher exact test
Statistical analysis description: cardiac, respiratory and infective complications	
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	Fisher exact

Other pre-specified: Hospital Outcomes - ICU readmission

End point title	Hospital Outcomes - ICU readmission
End point description:	
End point type	Other pre-specified
End point timeframe: until discharge	

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: subjects				
Yes	1	4		
No	14	12		

Statistical analyses

Statistical analysis title	Hospital Outcomes- ICU readmission Fisher exact
Comparison groups	Simvastatin v Placebo

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Fisher exact

Other pre-specified: Hospital Outcome Total Ventilator Days

End point title	Hospital Outcome Total Ventilator Days

End point description:

End point type	Other pre-specified

End point timeframe:
until discharge

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: Days				
arithmetic mean (standard deviation)	1 (± 0)	5 (± 8)		

Statistical analyses

Statistical analysis title	Hospital Outcomes- Total Ventilator Days
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	t-test, 2-sided

Other pre-specified: Hospital Outcomes- Total Hospital Stay

End point title	Hospital Outcomes- Total Hospital Stay

End point description:

End point type	Other pre-specified

End point timeframe:
Until discharge

End point values	Simvastatin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: Days				
arithmetic mean (standard deviation)	22 (± 17)	33 (± 33)		

Statistical analyses

Statistical analysis title	Hospital Outcome- Total Hospital Stay t test
Comparison groups	Simvastatin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to day 7	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTC AE
Dictionary version	4

Reporting groups	
Reporting group title	Simvastatin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Simvastatin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)	6 / 16 (37.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Obstruction gastric			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute lung injury			
subjects affected / exposed	0 / 15 (0.00%)	4 / 16 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 15 (0.00%)	3 / 16 (18.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal Infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Wound infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Simvastatin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	15 / 16 (93.75%)	
Investigations			
Increased creatine phosphokinase			
subjects affected / exposed	15 / 15 (100.00%)	14 / 16 (87.50%)	
occurrences (all)	15	14	
Investigation abnormal			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 15 (13.33%)	5 / 16 (31.25%)	
occurrences (all)	2	5	
Pleural effusion			
subjects affected / exposed	1 / 15 (6.67%)	1 / 16 (6.25%)	
occurrences (all)	1	1	

Infections and infestations			
Wound infection			
subjects affected / exposed	0 / 15 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 November 2007	In the event of delay and postponement of the surgery the study medication will be stopped and then restarted 4 days prior to the new date of surgery. Above info added to intervention section 3.3 of protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23817506