Clinical trial results:
A single-centre randomised controlled trial of propofol cardioplegia on blood and myocardial biomarkers of stress and injury in patients having isolated coronary artery bypass grafting (CABG) or aortic valve replacement (AVR) using cardiopulmonary bypass (CPB)

Summary

EudraCT number	2009-015779-28
Trial protocol	GB
Global end of trial date	31 December 2016

Results information

Result version number	v1 (current)
This version publication date	01 September 2018
First version publication date	01 September 2018

Trial information

Trial identification

Sponsor protocol code	CS/2008/3029

Additional study identifiers

ISRCTN number	ISRCTN84968882
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Bristol NHS Foundation Trust
Sponsor organisation address	Research & Innovation Dept, Level 3, UH Bristol Education Centre, Upper Maudlin Street, Bristol , United Kingdom, BS2 8AE
Public contact	Research and Development Department, University Hospitals Bristol NHS Foundation Trust, 0117 342 0233, R&DSponsorship@UHBristol.nhs.uk
Scientific contact	Clinical Trials Evaluation Unit, University of Bristol, 0117 342 3151, btc-mailbox@bristol.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2013
Global end of trial reached?	Yes
Global end of trial date	31 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the cardioprotective effect of a general anaesthetic, Propofol, when added to the cardioplegia (heart-stopping) solution used for patients undergoing isolated coronary artery bypass grafting (CABG) or aortic valve replacement (AVR) surgery using a heart-lung machine.

Protection of trial subjects:

All potential participants were sent or given an invitation letter and patient information sheet (PIS) (approved by the local Research Ethics Committee,(REC)) describing the study. The patient had time to read the PIS and to discuss their participation with others outside the research team (e.g. relatives or friends) if they wished. Most patients had at least 24 hours to consider whether to participate. Full informed consent was obtained for every trial participant. The patient's GP was informed of their participation in the trial. All members of the direct healthcare team are contractually bound to abide by standard NHS conditions of confidentiality and the need to access medical records will be explained to each patient during the process of obtaining consent.

Background therapy:

There is extensive evidence that propofol is able to protect the heart muscle from the damage that occurs when the blood supply is allowed to return to the heart after a period of low oxygen (ischaemia). Propofol has been shown to have an ability to scavenge the harmful molecules that are thought to be one of the main causes of damage and in addition, block other damaging processes.

Recent research conducted within our institute using an animal model has shown propofol used at a clinically relevant dose can indeed be cardioprotective. We therefore plan to investigate the cardioprotective action of propofol when added to the cardioplegia (heart-stopping) solution, in humans undergoing isolated coronary artery bypass grafting (CABG) or aortic valve replacement surgery (AVR) using a heart-lung machine.

Evidence for comparator:

Potential benefits to participants include the possibility of improved cardioprotection for the propofol supplementation group, which we hypothesise will lead to less injury to the heart and possibly fewer post-operative complications. Conversely, the participants randomised to the intralipid placebo group may be receiving an inferior treatment (a possible harm of participating in any trial) though this would be the same for non-trial patients receiving standard care. Patients will be randomised in a 1:1 ratio so that all will have an equal chance of being placed in either group.

Actual start date of recruitment	08 March 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 101
Worldwide total number of subjects	101
EEA total number of subjects	101

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)	32
From 65 to 84 years	69
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All potential participants received an information leaflet. Of the 159 eligible patients screened, full informed consent was taken from 101 patients who agreed to take part in the study.

Pre-assignment

Screening details:

Between March 2010 and July 2012, 203 patients were screened for inclusion in the trial, 44 of whom were ineligible.

Period 1

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

Blinding implementation details:

Randomization was carried out using a secure internet-based system (www.sealedenvelope.com) by staff not involved in data collection or patient care. The perfusionist was handed a sealed opaque envelope that contained the intervention, then prepared the cardioplegia solution (the two interventions were visually indistinguishable). All other staff remained blinded to the treatment allocation for the duration of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Propofol

Arm description:

Cardioplegia supplementation with propofol at a concentration of 6µg/ml. A propofol concentration of 6µg/ml does not exceed the level routinely observed in the circulation during induction or maintenance of anesthesia for cardiac surgery. The stock propofol (Fresenius propoven 1% emulsion: 10,000ug/ml) was diluted as recommended by the manufacturer to achieve a working solution of 2000µg/ml.

Arm type	Experimental
Investigational medicinal product name	Fresenius Propoven 1% emulsion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection/infusion
Routes of administration	Intracardiac use

Dosage and administration details:

Fresenius Propoven 1% emulsion was diluted to achieve a working solution of 2000 mg/mL. Administration via cardioplegia solution.

Arm title	Intralipid

Arm description:

Cardioplegia supplementation with intralipid. The intralipid emulsion (Fresenius 10%), was diluted in the same manner as the propofol.

Arm type	Placebo
Investigational medicinal product name	Intralipid 10%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for infusion
Routes of administration	Intracardiac use

Dosage and administration details:

Intralipid emulsion (Fresenius 10%) diluted to a working solution (equivalent to 2000 mg/mL of Fresenius Propoven 1%). administered via cardioplegia solution.

Number of subjects in period 1	Propofol	Intralipid
Started	51	50
Completed	51	50

Baseline characteristics

Reporting groups	
Reporting group title	Propofol
Reporting group description:	
Cardioplegia supplementation with propofol at a concentration of 6µg/ml. A propofol concentration of 6µg/ml does not exceed the level routinely observed in the circulation during induction or maintenance of anesthesia for cardiac surgery. The stock propofol (Fresenius propoven 1% emulsion: 10,000ug/ml) was diluted as recommended by the manufacturer to achieve a working solution of 2000µg/ml.	
Reporting group title	Intralipid
Reporting group description:	
Cardioplegia supplementation with intralipid. The intralipid emulsion (Fresenius 10%), was diluted in the same manner as the propofol.	

Reporting group values	Propofol	Intralipid	Total
Number of subjects	51	50	101
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			
The median age of participants was 67.9 years (IQR, 63.9- 73.7 years)			
Units: years			
median	66.5	70.6	
inter-quartile range (Q1-Q3)	62.5 to 72.1	65 to 76.4	-
Gender categorical Units: Subjects			
Female	10	14	24
Male	41	36	77
Operation Units: Subjects			
CABG	31	30	61
AVR	20	20	40
Diabetic Units: Subjects			
Diabetic	11	10	21
Non-diabetic	40	40	80
Number of diseased vessels			
One participant in the intralipid group had AVR and CABG (planned AVR surgery, decision to perform CABG made intra-operatively), therefore only 19 patients with no diseased vessels.			
Units: Subjects			
None	20	19	39

Single	1	2	3
Double	6	12	18
Triple	24	17	41
>50% disease in left main stem Units: Subjects			
Yes	9	5	14
No	42	45	87
Smoking status Units: Subjects			
Smoker	5	5	10
Non-smoker	17	24	41
Ex-smoker >1 month	29	21	50
Family history Units: Subjects			
Yes	24	31	55
No	27	19	46
Previous stroke (CVA) or transient ischemic attack (TIA) Units: Subjects			
Yes	2	4	6
No	49	46	95
Operative priority Units: Subjects			
Elective	47	46	93
Urgent	4	4	8
Number of grafts (intra-operative, CABG patients only)			
Number of grafts (therefore post-intervention but not a study end point).			
Units: Subjects			
1 graft	1	0	1
2 grafts	8	7	15
3 grafts	16	18	34
4 grafts	6	5	11
AVR participants	20	20	40
NYHA class Units: Subjects			
I/Asymptomatic	14	10	24
II	20	26	46
III	16	14	30
IV	1	0	1
CCS class Units: Subjects			
Asymptomatic	11	16	27
I.	8	6	14
II	20	17	37
III	11	8	19
IV	1	3	4
Previous myocardial infarction Units: Subjects			
Yes	10	13	23
No	41	37	78

Hypercholesterolaemia Units: Subjects			
Yes	37	39	76
No	14	11	25
Hypothyroidism Units: Subjects			
Yes	4	5	9
No	47	45	92
Pre-operative aspirin Units: Subjects			
Yes	35	35	70
No	16	15	31
Pre-operative clopidogrel Units: Subjects			
Yes	16	11	27
No	35	39	74
Pre-operative warfarin Units: Subjects			
Yes	4	3	7
No	47	47	94
Pre-operative heparin/clexane Units: Subjects			
Yes	1	2	3
No	50	48	98
Pre-operative beta blockers Units: Subjects			
Yes	28	24	52
No	23	26	49
Pre-operative calcium antagonists Units: Subjects			
Yes	16	11	27
No	35	39	74
Pre-operative oral nitrates Units: Subjects			
Yes	7	9	16
No	44	41	85
Pre-operative other lipid lowering agents Units: Subjects			
Yes	2	2	4
No	49	48	97
Pre-operative statins Units: Subjects			
Yes	41	39	80
No	10	11	21
Pre-operative ACE inhibitors Units: Subjects			
Yes	27	22	49
No	24	28	52
Pre-operative angiotensin 2 blockers Units: Subjects			
Yes	5	1	6

No	46	49	95
Pre-operative diuretics Units: Subjects			
Yes	12	8	20
No	39	42	81
Pre-operative digoxin Units: Subjects			
Yes	3	3	6
No	48	47	95
Pre-operative anti-arrhythmic drugs Units: Subjects			
Yes	1	1	2
No	50	49	99
Hypertension requiring treatment Units: Subjects			
Yes	44	35	79
No	7	15	22
Myocardial infarction within the last 90 days of randomisation Units: Subjects			
Yes	3	7	10
No	47	42	89
Missing	1	1	2
Heart rhythm Units: Subjects			
Sinus	44	47	91
Atrial fibrillation/flutter	6	3	9
Missing	1	0	1
BMI Units: kg/m2			
arithmetic mean	29.3	27.1	
standard deviation	± 5.6	± 3.8	-
estimated glomerular filtration rate Units: mL/min/1.73 m2			
arithmetic mean	69.9	72.2	
standard deviation	± 20	± 14.8	-
EuroSCORE (additive) Units: N/A			
median	4	5	
inter-quartile range (Q1-Q3)	2 to 5	3 to 6	-
Operation length (intra-operative)			
Length of operation (therefore post-intervention but not a study end point)			
Units: Minutes			
arithmetic mean	191	190.1	
standard deviation	± 32.2	± 29.7	-
Cumulative cross-clamp time (intra-operative)			
Amount of time participant on cross-clamp (therefore post-intervention but not a study end point). One participant in propofol arm with cross-clamp time missing because surgery performed off-pump.			
Units: Minutes			
arithmetic mean	54	53.4	
standard deviation	± 19.7	± 16.2	-

Total bypass time (intra-operative)			
Amount of time on cardiopulmonary bypass (therefore post-intervention but not a study end point). One participant in propofol arm with cross-clamp time missing because surgery performed off-pump.			
Units: Minutes			
arithmetic mean	88.2	88.8	
standard deviation	± 22	± 19	-
Concentration of propofol in cardioplegia (intra-operative)			
Total concentration of propofol in cardioplegia (therefore post-intervention but not a study end point). Six participants with systemic propofol concentration missing, as they did not receive any intervention.			
Units: µg/ml			
arithmetic mean	9.92	4.46	
standard deviation	± 1.38	± 1.8	-
Concentration of systemic (arterial line) plasma propofol pre-cross-clamp (intra-operative)			
Concentration of systemic (arterial line) plasma propofol (therefore post-intervention but not a study end point). Six participants with systemic propofol concentration missing, as they did not receive any intervention.			
Units: µg/ml			
arithmetic mean	3.92	4.34	
standard deviation	± 1.38	± 1.36	-
Concentration of systemic (arterial line) plasma propofol during cross-clamp (intra-operative)			
Concentration of systemic (arterial line) plasma propofol (therefore post-intervention but not a study end point). Six participants with systemic propofol concentration missing, as they did not receive any intervention.			
Units: µg/ml			
arithmetic mean	4.16	4.36	
standard deviation	± 1.2	± 1.23	-
Concentration of systemic (arterial line) plasma propofol 10mins post-cross-clamp release (intra-op)			
Concentration of systemic (arterial line) plasma propofol (therefore post-intervention but not a study end point). Six participants with systemic propofol concentration missing, as they did not receive any intervention.			
Units: µg/ml			
arithmetic mean	4.07	4.51	
standard deviation	± 1.1	± 1.18	-
Estimated volume of cardioplegia given (intra-operative, CABG participants only)			
Estimated volume of cardioplegia given in CABG participants (therefore post-intervention but not a study end point)			
Units: ml			
arithmetic mean	1207	1197	
standard deviation	± 355	± 333	-
Total volume of cold blood cardioplegia (intra-operative, AVR participants only)			
Total volume of cold blood cardioplegia in AVR participants (therefore post-intervention but not a study end point).			
Units: ml			
arithmetic mean	1790.2	1782.4	
standard deviation	± 322	± 264.1	-

Haemoglobin Units: g/L			
arithmetic mean	13.7	13.5	
standard deviation	± 1.7	± 1.7	-
Platelets Units: 10^9 /L			
arithmetic mean	221.2	232.1	
standard deviation	± 53.6	± 63.9	-

End points

End points reporting groups

Reporting group title	Propofol
Reporting group description:	
Cardioplegia supplementation with propofol at a concentration of 6µg/ml. A propofol concentration of 6µg/ml does not exceed the level routinely observed in the circulation during induction or maintenance of anesthesia for cardiac surgery. The stock propofol (Fresenius propoven 1% emulsion: 10,000ug/ml) was diluted as recommended by the manufacturer to achieve a working solution of 2000µg/ml.	
Reporting group title	Intralipid
Reporting group description:	
Cardioplegia supplementation with intralipid. The intralipid emulsion (Fresenius 10%), was diluted in the same manner as the propofol.	
Subject analysis set title	CABG patients - propofol
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
CABG patients, propofol arm	
Subject analysis set title	CABG patients - intralipid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
CABG patients, intralipid arm	
Subject analysis set title	AVR patients - propofol
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
AVR patients, propofol arm	
Subject analysis set title	AVR patients - intralipid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
AVR patients, intralipid arm	
Subject analysis set title	Patients for biopsy analysis - propofol
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients with biopsy samples analysed - propofol group	
Subject analysis set title	Patients for biopsy analysis - intralipid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients with biopsy samples analysed - intralipid group	
Subject analysis set title	CABG patients for biopsy analysis - propofol
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of CABG patients with biopsy samples analysed - propofol group	
Subject analysis set title	CABG patients for biopsy analysis – intralipid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of CABG patients with biopsy samples analysed - intralipid group	
Subject analysis set title	AVR patients for biopsy analysis – propofol
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of AVR patients with biopsy samples analysed - propofol group	
Subject analysis set title	AVR patients for biopsy analysis – intralipid
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Subgroup of AVR patients with biopsy samples analysed - intralipid group

Primary: Troponin T

End point title	Troponin T

End point description:

End point type	Primary

End point timeframe:
Measured at baseline, and then at 1, 6, 12, 24 and 48 hours post chest closure

End point values	Propofol	Intralipid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	50		
Units: ng/L				
median (inter-quartile range (Q1-Q3))				
Pre-operative (number <14ng/L)	30 (30 to 30)	34 (34 to 34)		
Pre-operative (number >=14ng/L)	20 (20 to 20)	15 (15 to 15)		
Pre-operative (>=14ng/L only)	21 (15 to 24)	20 (15 to 29)		
1hr post-chest closure	393 (298 to 597)	486 (360 to 571)		
6hr post-chest closure	552 (396 to 827)	616.5 (492.5 to 704)		
12hr post-chest closure	434 (350.5 to 651.5)	497 (419 to 607)		
24hr post-chest closure	385 (263 to 448)	395 (300 to 507.3)		
48hr post-chest closure	302.7 (211 to 378)	280.5 (222 to 367)		

Statistical analyses

Statistical analysis title	Troponin T geometric mean ratio (95% CI)
Comparison groups	Intralipid v Propofol
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.051
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.01

Secondary: Lactate	
End point title	Lactate
End point description:	

End point type	Secondary
End point timeframe:	
Measured at baseline, and then at 1, 6, 12, 24 and 48 hours post chest closure	

End point values	Propofol	Intralipid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	50		
Units: mmol/L				
median (inter-quartile range (Q1-Q3))				
Pre-operative	0.8 (0.5 to 1.1)	0.8 (0.6 to 1)		
1hr post-chest closure	1.2 (0.9 to 1.4)	1 (0.7 to 1.1)		
6hr post-chest closure	1.1 (0.9 to 1.6)	1.1 (0.8 to 1.4)		
12hr post-chest closure	1.5 (1 to 1.7)	1.2 (1 to 1.5)		
24hr post-chest closure	1.3 (1.1 to 1.8)	1.2 (1 to 1.6)		
48hr post-chest closure	1.2 (0.9 to 1.5)	1.2 (1 to 1.6)		

Statistical analyses

Statistical analysis title	Lactate geometric mean ratio
Comparison groups	Propofol v Intralipid
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.18

Secondary: pH	
End point title	pH

End point description:

End point type	Secondary

End point timeframe:

Measured at baseline, and then at 1, 6, 12, 24 and 48 hours post chest closure

End point values	Propofol	Intralipid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	50		
Units: pH units				
arithmetic mean (standard deviation)				
Pre-operative	7.416 (± 0.031)	7.426 (± 0.039)		
1hr post-chest closure	7.373 (± 0.047)	7.369 (± 0.058)		
6hr post-chest closure	7.339 (± 0.046)	7.347 (± 0.054)		
12hr post-chest closure	7.339 (± 0.047)	7.351 (± 0.055)		
24hr post-chest closure	7.336 (± 0.044)	7.351 (± 0.048)		
48hr post-chest closure	7.356 (± 0.041)	7.367 (± 0.06)		

Statistical analyses

Statistical analysis title	pH mean difference
Comparison groups	Propofol v Intralipid
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.003

Secondary: Creatinine

End point title	Creatinine

End point description:

The effect of propofol supplementation on post-operative renal function differed between CABG and AVR participants - p=0.069.

End point type	Secondary

End point timeframe:

Measured at baseline, and then at 1, 6, 12, 24 and 48 hours post chest closure

End point values	CABG patients - propofol	CABG patients - intralipid	AVR patients - propofol	AVR patients - intralipid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	30	20	20
Units: µmol/L				
median (inter-quartile range (Q1-Q3))				
Pre-operative	88 (74 to 105)	88 (78 to 92)	88.5 (81.5 to 106.5)	83.5 (72 to 95.5)
1hr post-chest closure	91 (77 to 98)	84 (78 to 96)	95 (85.5 to 111.5)	83.5 (67 to 91)
6hr post-chest closure	96 (81 to 113)	90.5 (82 to 100)	101 (94 to 119)	90.5 (78 to 96)
12hr post-chest closure	98 (85 to 112)	94 (85 to 102)	115 (97 to 127)	94 (82 to 109)
24hr post-chest closure	110 (90 to 147)	97 (90.5 to 118)	129 (107 to 157)	92.5 (77 to 110)
48hr post-chest closure	112 (87 to 165)	97 (81 to 114.5)	119 (104 to 145)	88.5 (80 to 115.5)

Statistical analyses

Statistical analysis title	Creatinine geometric mean ratio - CABG patients

Statistical analysis description:

Geometric mean ratio for propofol vs. intralipid in isolated CABG patients.

Comparison groups	CABG patients - propofol v CABG patients - intralipid
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.051

Statistical analysis title	Creatinine geometric mean ratio - AVR patients

Statistical analysis description:

Geometric mean ratio for propofol vs. intralipid in isolated AVR patients

Comparison groups	AVR patients - propofol v AVR patients - intralipid

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.019
upper limit	1.125

Secondary: Length of ICU stay

End point title	Length of ICU stay

End point description:

The effect of propofol supplementation on length of ICU stay differed between CABG and AVR participants - p=0.068.

End point type	Secondary

End point timeframe:

Length of stay in intensive care unit

End point values	CABG patients - propofol	CABG patients - intralipid	AVR patients - propofol	AVR patients - intralipid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	30	20	20
Units: hours				
median (inter-quartile range (Q1-Q3))	69.3 (47.8 to 113)	87.3 (68 to 114)	89.5 (46.9 to 120.5)	47 (43 to 89.5)

Statistical analyses

Statistical analysis title	Time in ICU hazard ratio - CABG patients

Statistical analysis description:

Hazard ratio for time in intensive care unit in propofol group compared to intralipid group in isolated CABG patients

Comparison groups	CABG patients - propofol v CABG patients - intralipid
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	2.09

Statistical analysis title	Time in ICU hazard ratio - AVR patients

Statistical analysis description:

Hazard ratio for time in intensive care unit in propofol group compared to intralipid group in isolated AVR patients

Comparison groups	AVR patients - propofol v AVR patients - intralipid
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.09
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.09

Secondary: EQ5D visual analogue score

End point title	EQ5D visual analogue score

End point description:

End point type	Secondary

End point timeframe:

Collected at baseline and 3 months post-operatively

End point values	Propofol	Intralipid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	50		
Units: Scale of 0 to 100				
arithmetic mean (standard deviation)				
Pre-operative	68 (± 21)	66 (± 20.8)		
3 months post-operative	77 (± 19.2)	80 (± 12.4)		

Statistical analyses

Statistical analysis title	EQ5D VAS score mean difference
Comparison groups	Propofol v Intralipid
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.21
upper limit	2.87

Secondary: EQ5D utility score

End point title	EQ5D utility score

End point description:

End point type	Secondary

End point timeframe:

Collected at baseline and 3 months post-operatively

End point values	CABG patients - propofol	CABG patients - intralipid	AVR patients - propofol	AVR patients - intralipid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	30	20	20
Units: Possible range from -0.11 to 1.00				
median (inter-quartile range (Q1-Q3))				
Pre-operative	0.796 (0.689 to 1)	0.727 (0.62 to 0.85)	0.867 (0.638 to 1)	0.76 (0.62 to 1)
3 months post-operative	0.814 (0.727 to 1)	0.796 (0.689 to 1)	0.788 (0.586 to 0.925)	1 (0.691 to 1)

Statistical analyses

No statistical analyses for this end point

Secondary: EQ5D utility score (binary)

End point title	EQ5D utility score (binary)

End point description:

EQ5D scores dichotomised into perfect health (score of 1) vs. less than perfect health (score <1.000) for statistical analysis.

The effect of propofol supplementation on post-operative EQ5D utility score differed between CABG and AVR participants - test for interaction p=0.067.

End point type	Secondary

End point timeframe:

Collected at baseline and 3 months post-operatively

End point values	CABG patients - propofol	CABG patients - intralipid	AVR patients - propofol	AVR patients - intralipid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30[1]	29[2]	20	19[3]
Units: patients				
3 months post-operatively	12	9	5	10

Notes:

[1] - 1 patient with 3 month EQ5D utility score missing

[2] - 1 patient with 3 month EQ5D utility score missing

[3] - 1 patient with 3 month EQ5D utility score missing

Statistical analyses

Statistical analysis title	EQ5D utility score 1 vs. <1 - CABG patients

Statistical analysis description:

Odds ratio for proportion of patients with EQ5D utility score 1 vs. <1 for propofol compared to intralipid groups in CABG patients.

Comparison groups	CABG patients - propofol v CABG patients - intralipid
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	3.62

Statistical analysis title	EQ5D utility score 1 vs. <1 - AVR patients

Statistical analysis description:

Odds ratio for proportion of patients with EQ5D utility score 1 vs. <1 for propofol compared to intralipid groups in AVR patients.

Comparison groups	AVR patients - intralipid v AVR patients - propofol

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.058
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	1.05

Secondary: CROQ core score (CABG patients only)

End point title	CROQ core score (CABG patients only)

End point description:

End point type	Secondary

End point timeframe:

Collected at baseline and 3 months post-operatively

End point values	CABG patients - propofol	CABG patients - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	30		
Units: N/A				
median (inter-quartile range (Q1-Q3))				
Pre-operative	50 (44.3 to 54.8)	52.1 (44.9 to 57.7)		
3 months post-operative	51.6 (45.9 to 55.6)	52.9 (48.1 to 55)		

Statistical analyses

Statistical analysis title	CROQ core score mean difference
Comparison groups	CABG patients - propofol v CABG patients - intralipid
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.37
upper limit	2.69

Secondary: MLHFQ overall score (AVR patients only)

End point title	MLHFQ overall score (AVR patients only)
End point description:	
Overall score from Minnisota Living with Heart Failure Questionnaire	
End point type	Secondary
End point timeframe:	
Collected at baseline and 3 months post-operatively	

End point values	AVR patients - propofol	AVR patients - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: N/A				
median (inter-quartile range (Q1-Q3))				
Pre-operative	28.5 (11 to 54)	27 (11 to 35.5)		
3 months post-operative	15 (5 to 32)	12.5 (3 to 29)		

Statistical analyses

Statistical analysis title	MLHFQ overall score mean difference
Comparison groups	AVR patients - propofol v AVR patients - intralipid
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.07
upper limit	7.84

Secondary: CROQ symptoms score (CABG patients only)

End point title	CROQ symptoms score (CABG patients only)

End point description:

End point type	Secondary

End point timeframe:

Collected at baseline and 3 months post-operatively

End point values	CABG patients - propofol	CABG patients - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	30		
Units: N/A				
median (inter-quartile range (Q1-Q3))				
Pre-operative	67.9 (54.7 to 85.7)	78.6 (50 to 89.9)		
3 months post-operative	94.7 (82.1 to 100)	96.4 (91.7 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: CROQ physical functioning score (CABG patients only)

End point title	CROQ physical functioning score (CABG patients only)

End point description:

End point type	Secondary

End point timeframe:

Collected at baseline and 3 months post-operatively

End point values	CABG patients - propofol	CABG patients - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	30		
Units: N/A				
median (inter-quartile range (Q1-Q3))				
Pre-operative	75 (50 to 87.5)	68.8 (40.7 to 96.9)		
3 months post-operative	81.3 (68.8 to 100)	87.5 (75 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: CROQ cognitive functioning score (CABG patients only)

End point title	CROQ cognitive functioning score (CABG patients only)

End point description:

End point type	Secondary

End point timeframe:

Collected at baseline and 3 months post-operatively

End point values	CABG patients - propofol	CABG patients - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	30		
Units: N/A				
median (inter-quartile range (Q1-Q3))				
Pre-operative	80 (60 to 93.3)	86.7 (66.7 to 93.3)		
3 months post-operative	90 (66.7 to 100)	86.7 (73.3 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: CROQ psychosocial functioning score (CABG patients only)

End point title	CROQ psychosocial functioning score (CABG patients only)

End point description:

End point type	Secondary

End point timeframe:

Collected at baseline and 3 months post-operatively

End point values	CABG patients - propofol	CABG patients - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	30		
Units: N/A				
median (inter-quartile range (Q1-Q3))				
Pre-operative	65.9 (51.8 to 85.7)	73.2 (53.6 to 91.1)		
3 months post-operative	86.6 (67.9 to 96.4)	87.5 (75 to 94.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: CROQ satisfaction score (CABG patients only)

End point title	CROQ satisfaction score (CABG patients only)

End point description:

End point type	Secondary

End point timeframe:

Collected at 3 months post-operatively

End point values	CABG patients - propofol	CABG patients - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	30		
Units: N/A				
median (inter-quartile range (Q1-Q3))	84.7 (72.2 to 95.8)	83.3 (72.2 to 95.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: CROQ adverse events score (CABG patients only)

End point title	CROQ adverse events score (CABG patients only)

End point description:

End point type	Secondary

End point timeframe:

Collected 3 months post-operatively

End point values	CABG patients - propofol	CABG patients - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	30		
Units: N/A				
median (inter-quartile range (Q1-Q3))	89.8 (70.5 to 95.5)	87.5 (79.5 to 95.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: MLHFQ physical dimension score (AVR patients only)

End point title	MLHFQ physical dimension score (AVR patients only)

End point description:

End point type	Secondary

End point timeframe:

Collected at baseline and 3 months post-operatively

End point values	AVR patients - propofol	AVR patients - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: N/A				
median (inter-quartile range (Q1-Q3))				
Pre-operative	15.5 (5.5 to 24)	16 (8.5 to 21)		
3 months post-operative	8 (3 to 16)	6 (1 to 15)		

Statistical analyses

No statistical analyses for this end point

Secondary: MLHFQ emotional dimension score (AVR patients only)

End point title	MLHFQ emotional dimension score (AVR patients only)

End point description:

End point type	Secondary

End point timeframe:

Collected at baseline and 3 months post-operatively

End point values	AVR patients - propofol	AVR patients - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: N/A				
median (inter-quartile range (Q1-Q3))				
Pre-operative	4.5 (1.5 to 12.5)	4 (1.5 to 8)		
3 months post-operative	3 (0 to 8)	4 (0 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: ATP in left ventricle

End point title	ATP in left ventricle
End point description: Adenosine triphosphate in the left ventricle	
End point type	Secondary
End point timeframe: Measured prior to cross-clamp and 10 minutes post cross-clamp release.	

End point values	Patients for biopsy analysis - propofol	Patients for biopsy analysis - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: nmol/mg				
median (inter-quartile range (Q1-Q3))				
Prior to cross-clamp	2.74 (2.12 to 3.55)	3.44 (2.37 to 4.16)		
10 minutes post cross-clamp release	2.46 (1.58 to 3.67)	2.77 (2.11 to 3.98)		

Statistical analyses

Statistical analysis title	ATP in left ventricle geometric mean ratio
Statistical analysis description: Geometric mean ratio for comparison of ATP in left ventricle	
Comparison groups	Patients for biopsy analysis - propofol v Patients for biopsy analysis - intralipid

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.3

Secondary: ATP in right ventricle

End point title	ATP in right ventricle
End point description:	
Adenosine triphosphate in the right ventricle	
End point type	Secondary
End point timeframe:	
Measured prior to cross-clamp and 10 minutes post cross-clamp release.	

End point values	Patients for biopsy analysis - propofol	Patients for biopsy analysis - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: nmol/mg				
median (inter-quartile range (Q1-Q3))				
Prior to cross-clamp	3.13 (2.18 to 3.86)	3.29 (2.33 to 3.79)		
10 minutes post cross-clamp release	2.87 (1.87 to 3.62)	3.25 (1.89 to 4.17)		

Statistical analyses

Statistical analysis title	ATP in right ventricle geometric mean ratio
Statistical analysis description:	
Geometric mean ratio for comparison of ATP in left ventricle	
Comparison groups	Patients for biopsy analysis - propofol v Patients for biopsy analysis - intralipid

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.08

Secondary: ADP in the left ventricle

End point title	ADP in the left ventricle

End point description:

Adenosine diphosphate in the left ventricle.
P-value for test for interaction between treatment group and operation type = 0.049

End point type	Secondary

End point timeframe:

Measured prior to cross-clamp and 10 minutes post cross-clamp release.

End point values	CABG patients for biopsy analysis - propofol	CABG patients for biopsy analysis – intralipid	AVR patients for biopsy analysis – propofol	AVR patients for biopsy analysis – intralipid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	25	15	14
Units: nmol/mg				
median (inter-quartile range (Q1-Q3))				
Prior to cross-clamp	2.28 (1.63 to 2.67)	2.42 (1.72 to 2.86)	2.42 (2.01 to 2.62)	2.15 (2.02 to 2.4)
10 minutes post cross-clamp release	1.8 (1.45 to 2.15)	2.31 (1.71 to 2.94)	1.93 (1.49 to 2.93)	1.75 (1.65 to 2.24)

Statistical analyses

Statistical analysis title	ADP in left ventricle geometric mean ratio - CABG

Statistical analysis description:

Geometric mean ratio for comparison of ADP in left ventricle between propofol and intralipid groups in CABG patients only

Comparison groups	CABG patients for biopsy analysis - propofol v CABG patients for biopsy analysis – intralipid

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.95

Statistical analysis title	ADP in left ventricle geometric mean ratio - AVR
Statistical analysis description:	
Geometric mean ratio for comparison of ADP in left ventricle between propofol and intralipid groups in AVR patients only	
Comparison groups	AVR patients for biopsy analysis – intralipid v AVR patients for biopsy analysis – propofol
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.4

Secondary: AMP in the left ventricle	
End point title	AMP in the left ventricle
End point description:	
Adenosine monophosphate in the left ventricle. P-value for test for interaction between treatment group and operation type = 0.027	
End point type	Secondary
End point timeframe:	
Measured prior to cross-clamp and 10 minutes post cross-clamp release.	

End point values	CABG patients for biopsy analysis - propofol	CABG patients for biopsy analysis – intralipid	AVR patients for biopsy analysis – propofol	AVR patients for biopsy analysis – intralipid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	25	15	14
Units: nmol/mg				
median (inter-quartile range (Q1-Q3))				
Prior to cross-clamp	1.11 (0.71 to 1.44)	0.98 (0.73 to 2)	1.13 (0.94 to 1.37)	0.97 (0.77 to 1.04)
10 minutes post cross-clamp release	0.84 (0.56 to 1.17)	1.04 (0.77 to 1.65)	1.22 (0.67 to 1.58)	0.68 (0.5 to 1.07)

Statistical analyses

Statistical analysis title	AMP in left ventricle geometric mean ratio - CABG
Statistical analysis description:	
Geometric mean ratio for comparison of AMP in left ventricle between propofol and intralipid groups in CABG patients only	
Comparison groups	CABG patients for biopsy analysis - propofol v CABG patients for biopsy analysis – intralipid
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.02

Statistical analysis title	AMP in left ventricle geometric mean ratio - AVR
Statistical analysis description:	
Geometric mean ratio for comparison of AMP in left ventricle between propofol and intralipid groups in AVR patients only	
Comparison groups	AVR patients for biopsy analysis – propofol v AVR patients for biopsy analysis – intralipid
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	2

Secondary: AMP in the right ventricle

End point title	AMP in the right ventricle
End point description:	
Adenosine monophosphate in the right ventricle	
End point type	Secondary
End point timeframe:	
Measured prior to cross-clamp and 10 minutes post cross-clamp release.	

End point values	Patients for biopsy analysis - propofol	Patients for biopsy analysis - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: nmol/mg				
median (inter-quartile range (Q1-Q3))				
Prior to cross-clamp	0.85 (0.6 to 1.24)	0.95 (0.63 to 1.41)		
10 minutes post cross-clamp release	0.92 (0.66 to 1.26)	0.83 (0.52 to 1.22)		

Statistical analyses

Statistical analysis title	AMP in right ventricle geometric mean ratio
Statistical analysis description:	
Geometric mean ratio for comparison of AMP in right ventricle	
Comparison groups	Patients for biopsy analysis - propofol v Patients for biopsy analysis - intralipid
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.4

Secondary: ATP/AMP ratio in the left ventricle	
End point title	ATP/AMP ratio in the left ventricle
End point description: Ratio of ATP/AMP in the left ventricle	
End point type	Secondary
End point timeframe: Measured prior to cross-clamp and 10 minutes post cross-clamp release.	

End point values	Patients for biopsy analysis - propofol	Patients for biopsy analysis - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: ratio				
median (inter-quartile range (Q1-Q3))				
Prior to cross-clamp	2.75 (1.78 to 3.47)	3.38 (2.36 to 4.56)		
10 minutes post cross-clamp release	2.75 (1.43 to 4.48)	3.09 (1.91 to 4.85)		

Statistical analyses

Statistical analysis title	ATP/AMP ratio in left ventricle GMR
Statistical analysis description: Geometric mean ratio for comparison of ATP/AMP ratio in left ventricle	
Comparison groups	Patients for biopsy analysis - propofol v Patients for biopsy analysis - intralipid
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.43

Secondary: ATP/AMP ratio in the right ventricle	
End point title	ATP/AMP ratio in the right ventricle

End point description: Ratio of ATP/AMP in the right ventricle	
End point type	Secondary
End point timeframe: Measured prior to cross-clamp and 10 minutes post cross-clamp release.	

End point values	Patients for biopsy analysis - propofol	Patients for biopsy analysis - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: ratio				
median (inter-quartile range (Q1-Q3))				
Prior to cross-clamp	3.6 (2.55 to 6.36)	3.34 (1.92 to 4.98)		
10 minutes post cross-clamp release	3.39 (1.89 to 5.47)	3.33 (2.2 to 5.89)		

Statistical analyses

Statistical analysis title	ATP/AMP ratio in right ventricle GMR
Statistical analysis description: Geometric mean ratio for comparison of ATP/AMP ratio in right ventricle	
Comparison groups	Patients for biopsy analysis - propofol v Patients for biopsy analysis - intralipid
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.22

Secondary: ATP/ADP ratio in the left ventricle

End point title	ATP/ADP ratio in the left ventricle
End point description: Ratio of ATP/ADP in the left ventricle	
End point type	Secondary
End point timeframe: Measured prior to cross-clamp and 10 minutes post cross-clamp release.	

End point values	Patients for biopsy analysis - propofol	Patients for biopsy analysis - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: ratio				
arithmetic mean (standard deviation)				
Prior to cross-clamp	1.272 (± 0.436)	1.459 (± 0.545)		
10 minutes post cross-clamp release	1.309 (± 0.563)	1.34 (± 0.484)		

Statistical analyses

Statistical analysis title	ATP/ADP ratio in left ventricle mean difference
Statistical analysis description: Mean difference for comparison of ATP/ADP ratio in left ventricle	
Comparison groups	Patients for biopsy analysis - propofol v Patients for biopsy analysis - intralipid
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.192
upper limit	0.239

Secondary: ATP/ADP ratio in the right ventricle

End point title	ATP/ADP ratio in the right ventricle
End point description: Ratio of ATP/ADP in the right ventricle. P-value for test for interaction between treatment group and operation type = 0.062.	
End point type	Secondary
End point timeframe: Measured prior to cross-clamp and 10 minutes post cross-clamp release.	

End point values	CABG patients for biopsy analysis - propofol	CABG patients for biopsy analysis – intralipid	AVR patients for biopsy analysis – propofol	AVR patients for biopsy analysis – intralipid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	25	15	14
Units: ratio				
arithmetic mean (standard deviation)				
Prior to cross-clamp	1.58 (± 0.66)	1.545 (± 0.583)	1.654 (± 0.804)	1.443 (± 0.822)
10 minutes post cross-clamp release	1.588 (± 0.701)	1.545 (± 0.602)	1.347 (± 0.526)	1.719 (± 0.866)

Statistical analyses

Statistical analysis title	ATP/ADP ratio in right ventricle MD - CABG

Statistical analysis description:

Mean difference for comparison of ATP/ADP ratio in right ventricle between propofol and intralipid groups in CABG patients only

Comparison groups	CABG patients for biopsy analysis - propofol v CABG patients for biopsy analysis – intralipid
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.301
upper limit	0.35

Statistical analysis title	ATP/ADP ratio in right ventricle MD - AVR

Statistical analysis description:

Mean difference for comparison of ATP/ADP ratio in right ventricle between propofol and intralipid groups in AVR patients only

Comparison groups	AVR patients for biopsy analysis – propofol v AVR patients for biopsy analysis – intralipid
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.487

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.913
upper limit	-0.06

Other pre-specified: Total ventilation time

End point title	Total ventilation time

End point description:

End point type	Other pre-specified

End point timeframe:

In-hospital

End point values	Propofol	Intralipid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	50		
Units: Hours				
median (inter-quartile range (Q1-Q3))	6.8 (4.9 to 8.8)	7.2 (5.6 to 10.5)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time on ward pre-discharge

End point title	Time on ward pre-discharge

End point description:

End point type	Other pre-specified

End point timeframe:

In-hospital

End point values	Propofol	Intralipid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	47[4]		
Units: Hours				
median (inter-quartile range (Q1-Q3))	73.5 (43.2 to 115)	92.8 (51 to 139)		

Notes:
[4] - Three participants not admitted to ward from intensive care unit

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Length of hospital stay

End point title	Length of hospital stay

End point description:

End point type	Other pre-specified

End point timeframe:
In-hospital

End point values	Propofol	Intralipid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	50		
Units: Days				
median (inter-quartile range (Q1-Q3))	7 (6 to 8)	6 (5 to 9)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: ADP in the right ventricle

End point title	ADP in the right ventricle

End point description:
Adenosine diphosphate in the right ventricle

End point type	Other pre-specified

End point timeframe:
Measured prior to cross-clamp and 10 minutes post cross-clamp release.

End point values	Patients for biopsy analysis - propofol	Patients for biopsy analysis - intralipid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: nmol/mg				
median (inter-quartile range (Q1-Q3))				

Prior to cross-clamp	2.02 (1.8 to 2.54)	2.13 (1.68 to 2.61)		
10 minutes post cross-clamp release	1.87 (1.63 to 2.52)	2.2 (1.68 to 2.56)		

Statistical analyses

Statistical analysis title	ADP in right ventricle geometric mean ratio
Statistical analysis description: Geometric mean ratio for comparison of ADP in right ventricle	
Comparison groups	Patients for biopsy analysis - propofol v Patients for biopsy analysis - intralipid
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.13

Adverse events

Adverse events information

Timeframe for reporting adverse events:

In-hospital and up to 3 months post-operatively

Adverse event reporting additional description:

All expected adverse events reported as event names (not put through medical dictionary).
Unexpected adverse events reported using MedDRA dictionary.
For all events, 'non-serious adverse events' includes ALL events (serious and non-serious). This is consistent with the trial publication.

Assessment type	Systematic

Dictionary used

Dictionary name	Not used
Dictionary version	1.0

Reporting groups

Reporting group title	Propofol
Reporting group description: -	
Reporting group title	Intralipid

Reporting group description: -

Serious adverse events	Propofol	Intralipid	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 51 (21.57%)	11 / 50 (22.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Reintubation/ventilation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence requiring reoperation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peripheral ischaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Supraventricular tachycardia/atrial fibrillation requiring treatment			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
New post-operative pacing			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Permanent pacing	Additional description: Collected as the need for permanent post-operative pacing.		
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low cardiac output			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Inotropes used post-operatively			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-aortic balloon pump used			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
New haemofiltration/dialysis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Permanent stroke			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Maculopathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Peptic ulcer/GI bleed/perforation			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other GI complications			
subjects affected / exposed	2 / 51 (3.92%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (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			
Pnuemothorax or pleural effusion requiring drainage			

subjects affected / exposed	1 / 51 (1.96%)	4 / 50 (8.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective complication			
subjects affected / exposed	3 / 51 (5.88%)	4 / 50 (8.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Propofol	Intralipid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 51 (82.35%)	43 / 50 (86.00%)	
Injury, poisoning and procedural complications			
Reintubation/ventilation			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Wound dehiscence requiring reoperation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Chest reopened due to bleeding			
subjects affected / exposed	0 / 51 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	

Post procedural haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Peripheral ischaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Supraventricular tachycardia/atrial fibrillation requiring treatment	Additional description: Collected in data collection forms as supraventricular tachycardia/atrial fibrillation requiring treatment.		
subjects affected / exposed	21 / 51 (41.18%)	24 / 50 (48.00%)	
occurrences (all)	25	24	
Ventricular fibrillation/ventricular tachycardia requiring intervention			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Myocardial infarction			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
New post-operative pacing			
subjects affected / exposed	5 / 51 (9.80%)	8 / 50 (16.00%)	
occurrences (all)	5	8	
Permanent pacing	Additional description: Collected as the need for permanent post-operative pacing.		
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Low cardiac output			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Bradycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Cardiac failure congestive			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Surgical and medical procedures			
Inotropes used post-operatively			
subjects affected / exposed	16 / 51 (31.37%)	18 / 50 (36.00%)	
occurrences (all)	15	17	
Intra-aortic balloon pump used			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Vasodilator used			
subjects affected / exposed	12 / 51 (23.53%)	13 / 50 (26.00%)	
occurrences (all)	12	13	
Tracheostomy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Continuous Positive Airway Pressure Mask			
subjects affected / exposed	7 / 51 (13.73%)	4 / 50 (8.00%)	
occurrences (all)	7	5	
New haemofiltration/dialysis			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Cholecystectomy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Permanent stroke			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Paraesthesia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
General disorders and administration			

site conditions Chest pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Eye disorders Maculopathy alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Gastrointestinal disorders Peptic ulcer/GI bleed/perforation subjects affected / exposed occurrences (all) Other GI complications subjects affected / exposed occurrences (all) Diverticulum alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2 3 / 51 (5.88%) 3 1 / 51 (1.96%) 1	0 / 50 (0.00%) 0 2 / 50 (4.00%) 2 0 / 50 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Pneumothorax or pleural effusion requiring drainage subjects affected / exposed occurrences (all) Pulmonary embolism subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1 1 / 51 (1.96%) 1	7 / 50 (14.00%) 8 0 / 50 (0.00%) 0	
Renal and urinary disorders Renal failure acute alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Infections and infestations Infective complication			

subjects affected / exposed	9 / 51 (17.65%)	18 / 50 (36.00%)	
occurrences (all)	11	21	
Sepsis			
subjects affected / exposed	4 / 51 (7.84%)	11 / 50 (22.00%)	
occurrences (all)	5	13	
Respiratory infection			
subjects affected / exposed	5 / 51 (9.80%)	10 / 50 (20.00%)	
occurrences (all)	5	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2010	Amendment 1: Microparticle testing removal
15 June 2010	Amendment 2: IL-6, IL-8, IL-10, C3a, C5a, TNFα, NGAL, 8-Isoprostane testing removed. Addition of a 3 month follow up questionnaire cover letter.
04 October 2011	Amendment 3: Approaching patients in pre-assessment, Jehovah's witness to exclusion criteria chest pain as expected event, update members of CRB) PIS (v3.0) update of PALS contact details
29 March 2012	Amendment 4: Submitted to the MHRA to retract amendment 3 as REC did not approve amendment 3
29 October 2012	Amendment 5: Changed end of trial definition and end date to 30/09/2013. REC details updated in CT form

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/26256300