Supplementary Material

Study Investigators: trial site, trials unit, statistics, health economics, committees

Trial Site
The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, United Kingdom

Investigators
- Mr Enoch Akowuah (Chief Investigator)
- Mr Andrew Goodwin (co-Investigator)
- Professor W Andrew Owens (co-Investigator)

Research Team
- Heather Robinson
- Jonathan Broughton
- Dr Khalid Khan

Clinical Trials Unit
Durham Clinical Trials Unit, Durham University; now Newcastle Clinical Trials Unit, Newcastle University

Investigators
- Professor Helen Hancock (co-Investigator)
- Rebecca Maier (co-Investigator)

Research Team
- Andrew Thorpe
- Jennifer Wilkinson
- Dr Leanne Marsay

Statistics
Statistics Group, Wolfson Research Institute for Health and Wellbeing, Durham University

Investigator
- Dr Adetayo Kasim (co-Investigator)

Health Economics
Durham Clinical Trials Unit, Durham University; now University of Warwick

Investigator
- Professor James Mason (co-Investigator)

Committees
Data Monitoring Committee Membership
- Mr Graham Cooper (Chair)
- Mr Heyman Luckraz
- Professor Chris Rogers

Trial Steering Committee Membership
- Mr Sukumaran Nair (Chair until Sep 2014)
- Professor Gavin Murphy (Acting Chair Oct 2014 to June 2015)
- Mr Peter Braidley (Chair, from July 2015)
- Mr Paul Modi
- Mr Brendan Ellis

Table 1. Eligibility criteria

Inclusion Criteria

- Aged 18 years or older at the time of consent
- Requiring first-time, non-emergency, isolated Aortic Valve Replacement surgery
- Able and willing to provide written informed consent

Exclusion Criteria

- requiring concomitant cardiac procedure(s) including redo surgery, emergency or salvage surgery,
- only conventional median sternotomy indicated*,
- haemoglobin level < 90g/L,
- pregnant**,
- currently participating in another interventional clinical trial,
- previous cardiac surgery,
- are unable to stop currently prescribed treatment affecting clotting (e·g·, heparin, warfarin), ***
- a history of thrombophilia, thrombocytopenia or other haematological conditions that would affect participation in the trial as determined by one of the three operating surgeons,
- infective endocarditis,
- prevented from having red blood cells and blood products according to a system of beliefs (e·g· Jehovah's Witnesses),
- having any other medical, psychiatric and or social reason as determined by the consenting surgeon that precludes participation.

* patients were excluded if only conventional median sternotomy was indicated, for example in the presence of significant skeletal abnormalities like kyphosis. They were also excluded if transoesophageal echocardiography could not be performed, as this was mandatory to perform safe peripheral venous cannulation. All 3 surgeons used consistent criteria.

** in women of child bearing age (18 – 50) a pregnancy test was be performed within 14 days of surgery prior to randomisation.

***for patients in both trial arms, pre-operative antiplatelet drugs (including clopidogrel and ticagrelor), and anti-coagulants (including warfarin and heparin) were discontinued 5 days prior to surgery. These drugs were re-started following surgery at the discretion of the clinical team· The exception to this was aspirin, which was stopped 5 days prior to surgery where possible, however continuation until the day of surgery did not exclude a patient from the trial.

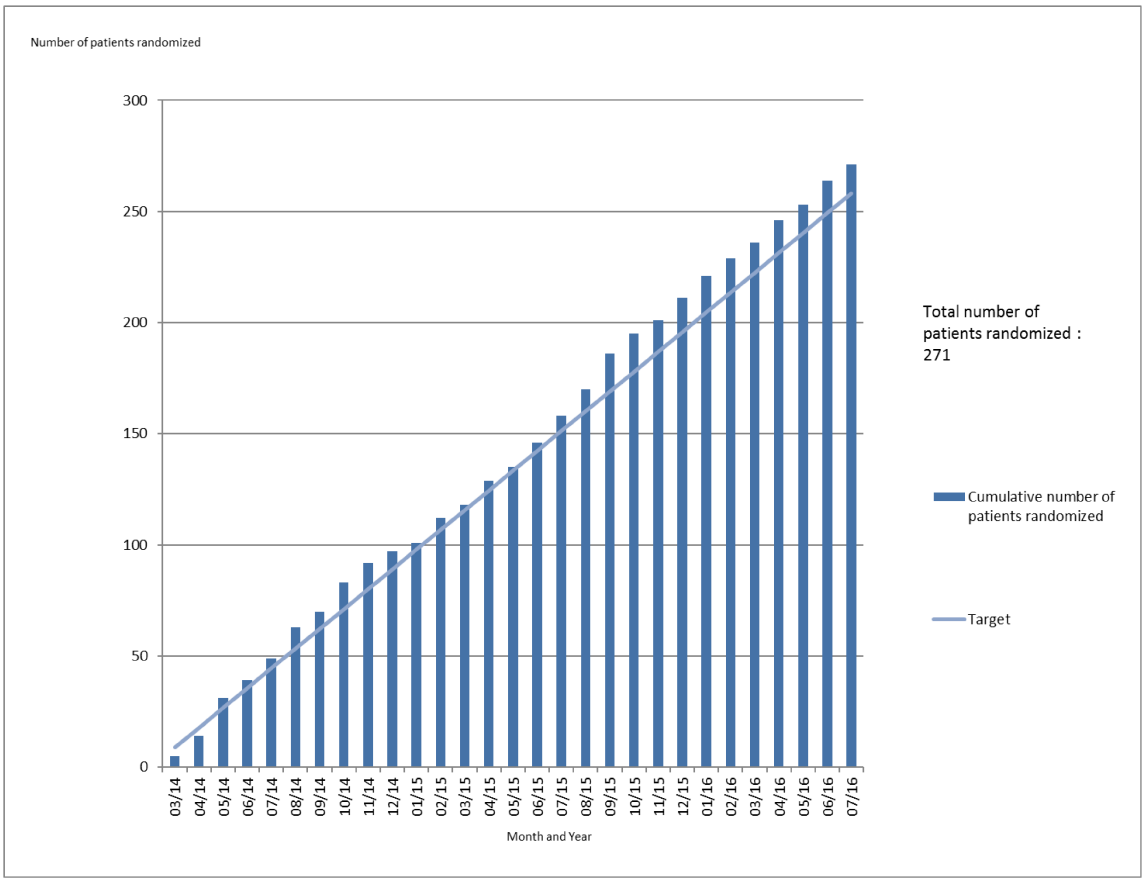

Figure 1. Trial recruitment by month.

Table 2. Conversion from mini-sternotomy to conventional sternotomy

Reason for conversion	Number of patients	Details
Anaesthetic emergency	**2**	• Patient became unstable as they were transferred into theatre and BP dropped – required conventional to re-stabilise • Anaphylactic reaction on induction needing CPR· Operation cancelled, patient taken to ITU· Widespread rash· Decision made the following morning to proceed to AVR (via full sternotomy)
Difficult vascular access (venous or arterial)	**9**	Venous • Femoral vessels unsuitable for cannulation • Poor venous drainage • Unable to pass venous dilators • Unable to insert pipe· Resistance felt, no back flow of blood· Femoral cannulation abandoned • Impossible to dilate femoral vein· Despite re-wiring, guide wire coiling within pelvic venous system Arterial • Difficulties cannulating femoral artery leading to haemodynamic instability • Poor access, unable to clamp aorta • Severe calcification of ascending aorta • Difficult access; aorta displaced to the left· Body habitus limited access
Intra-operative complications	**5**	• Bleeding from aortotomy site • Bleeding • Intra-operative decision to performed bypass graft to LAD • Post implant TOE showed small paravalvular leak and bleeding from aortotomy incision • Mild/moderate paravalvar leak on TOE· Required valve re-implant
TOTAL	**16**	

Table 3. Number of operations performed by Consultant Surgeon

	Mini-sternotomy group n=patients (%)	Conventional sternotomy group n=patients (%)	Total n=patients (%)
Consultant Surgeon A	58 (43·0)	58 (43··0)	116 (43·0)
Consultant Surgeon B	43 (31·9)	35 (25·9)	78 (28·9)
Consultant Surgeon C	34 (25·1)	42 (31·1)	76 (28·1)

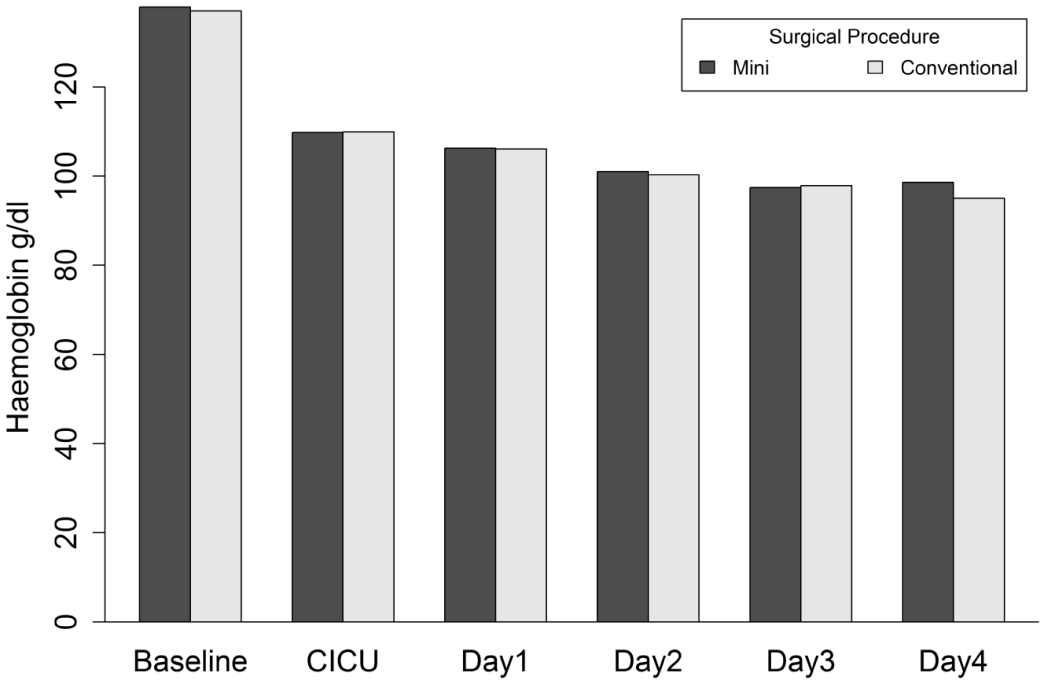

Figure 2. Haemoglobin profiles at Baseline, during CICU stay, and day 1 to day 4 post index surgery, by group

Table 4. Analgesic use and pain scores

Medication	Mini-sternotomy Group (135 patients) n = patients (%)	Conventional Sternotomy Group (135 patients) n = patients (%)	Total (270 patients) n = patients (%)
Analgesic use at baseline			
Buprenorphine patch	3 (2·2)	1 (0·7)	4 (1·5)
Codeine Phosphate	4 (3·0)	3 (0·7)	7 (2·6)
Dihydrocodeine Tartrate	0 (0·0)	1 (0·7)	1 (0·4)
Durogesic patch	0	1 (0·7)	1 (0·4)
Fentanyl	1 (0·7)	0 (0·0)	1 (0·4)
Gabapentin	1 (0·7)	0 (0·0)	1 (0·4)
Morphine Sulfate	0·0	1 (0·7)	1 (0·4)
Naxoproxen	1 (0·7)	0 (0·0)	1 (0·4)
Paracetamol	13 (9·6)	8 (5·9)	21 (7·8)
Tramadol Hydrochloride	0 (0·0)	2 (1·5)	2 (0·7)
At least one med at baseline	**16 (11·9)**	**12 (8·9)**	**28 (10·4)**
Analgesic use at day 2			
Buprenorphine patch	1 (0·7)	0 (0·0)	1 (0·4)
Codeine Phosphate	18 (13·3)	16 (11·9)	34 (12·6)
Dihydrocodeine Tartrate	4 (3·0)	6 (4·4)	10 (3·7)
Fentanyl	1 (0·7)	0 (0·0)	1 (0·4)
Gabapentin	1 (0·7)	0 (0·0)	1 (0·4)
Morphine Sulfate	13 (9·6)	13 (9·6)	26 (9·6)
Oramorph	1 (0·7)	1 (0·7)	2 (0·7)
Paracetamol	94 (69·6)	80 (59·3)	174 (64·4)
Pregabalin	1 (0·7)	0 (0·0)	1 (0·1)
Tramadol Hydrochloride	7 (5·2)	5 (3·7)	12 (4·4)
At least one med at day 2	**99 (73·3)**	**86 (63·7)**	**185 (68·5)**
Analgesic use at day 3			
Buprenorphine patch	1 (0·7)	0(0·0)	1 (0·4)
Codeine Phosphate	14 (10·4)	21 (15·6)	35 (13·0)
Dihydrocodeine Tartrate	4 (3·0)	7 (5·2)	11 (4·1)
Fentanyl	0 (0·0)	1 (0·7)	1 (0·4)
Gabapentin	1 (0·7)	1 (0·7)	2 (0·7)
Ibuprofen	0	1 (0·7)	1 (0·4)
Morphine Sulfate	6 (4·4)	1 (0·7)	7 (2·6)
Nefopam Hydrochloride	0	1 (0·7)	1 (0·4)
Oramorph	0	3 (2·2)	3 (1·1)
Paracetamol	89 (65·9)	99 (73·3)	188 (69·6)
Pregabalin	1 (0·7)	0 (0·0)	1 (0·4)
Tramadol Hydrochloride	8 (5·9)	3 (2·2)	11 (4·1)
At least one med at day 3	**90 (66·7)**	**101 (74·8)**	**191 (70·7)**
Analgesic use at Day 4			
Buprenorphine patch	1 (0·7)	0 (0·0)	1 (0·4)
Codeine Phosphate	15 (11·1)	15 (11·1)	30 (11·1)
Dihydrocodeine Tartrate	4 (3·0)	9 (6·7)	13 (4·8)
Fentanyl	1 (0·7)	1 (0·7)	2 (0·7)
Gabapentin	1 (0·7)	1 (0·7)	2 (0·7)
Ibuprofen	0 (0·0)	1 (0·7)	1 (0·4)
Paracetamol	86 (63·7)	75 (55·6)	161 (59·6)
Morphine Sulfate	1 (0·7)	2 (1·5)	3 (1·1)
Pregabalin	1 (0·7)	0 (0·0)	1 (0·4)
Tramadol Hydrochloride	3 (2·2)	3 (2·2)	6 (2·2)
At least one med at day 4	**88 (65·2)**	**81 (60·0)**	**169 (62·6)**
Analgesic use at Week 6			
Buprenorphine Patch	3(2·2)	0(0·0)	3(1·1)
Codeine Phosphate	7(5·1)	5(3·7)	12(4·5)
Dihydrocodeine Tartrate	1(0·7)	3(2·2)	4(1·5)
Fentanyl	1(0·7)	0(0·0)	1(0·4)
Gabapentin	2(1·5)	1(0·7)	3(1·1)
Ibuprofen	0(0·0)	1(0·7)	1(0·4)
Morphine Sulfate	0(0·0)	1(0·7)	1(0·4)
Paracetamol	35(25·9)	38(28·1)	73(27·0)
Pregabalin	1(0·7)	0(0·0)	1(0·4)
Tramadol Hydrochloride	2(1·5)	2(1·5)	4(1·5)
At least one med at week 6	**41(30·4)**	**41(30·4)**	**82(30·4)**
Analgesic use at Week 12			
Buprenorphine Patch	3(2·2)	0(0·0)	3(1·1)
Codeine Phosphate	7(5·2)	4(3·0)	11(4·1)

Dihyrocodeine Tartrate	0(0·0)	1(0·7)	1(0·4)
Gabapentin	2(1·5)	0(0·0)	2(0·7)
Ibuprofen	1(0·7)	0(0·0)	1(0·4)
Morphine Sulfate	1(0·7)	1(0·7)	2(0·7)
Naproxen	1(0·7)	0(0·0)	1(0·4)
Paracetamol	19(14·1)	20(14·8)	39(14·4)
Tramadol Hydrochloride	1(0·7)	1(0·7)	2(0·7)
At least one med at week 12	**23(17·0)**	**22(16·3)**	**45(16·7)**

	Mini-sternotomy Group (n=135 patients)	**Conventional sternotomy group (n=135)**
Baseline pain score		
n	128*	130*
Mean± SD	1·3 ± 2·1	0·9 ± 1·9
(min-max)	0 - 10	0 - 8
Day 2 pain score**		
n	123*	126*
Mean± SD	3·4 ± 2·4	3·7 ± 2·7
(min-max)	0 - 10	0 - 10
Day 3 pain score		
n	120*	129*
Mean± SD	2·8 ± 2·5	2·7 ± 2·3
(min-max)	0 - 9	0 - 8
Day 4 pain score		
n	116*	120*
Mean± SD	2·5 ± 2·2	2·1 ± 2·3
(min-max)	0 - 8	0 - 10
6 week pain score		
n	112*	118*
Mean± SD	1·5 ± 1·9	1·2 ± 1·8
(min-max)	0 - 8	0 - 8
12 week pain score		
n	128*	122*
Mean± SD	1·1 ± 1·9	1·0 ± 1·7
(min-max)	0 - 8	0 – 6

*Pain scores were assessed wherever possible
**Assessment on Day 2 was conducted with the patient blinded to their surgical allocation

Table 5. Adverse Events

Adverse Event	Mini-sternotomy Group n = patients (%)	Conventional Sternotomy Group n = patients (%)	Total n = patients (%)
Death			
In hospital	0/135 (0·0)	0/135 (0·0)	0/270 (0·0)
12 weeks	2/135 (1·5)	2/135 (1·5)	4/270 (1·5)
Stroke			
In hospital	3/135 (3·0)	1/135 (0·7)	4/270 (1·5)
12 weeks	4/135 (3·0)	1/135 (0·7)	5/270 (1·9)
Transient Ischaemic Attack			
In hospital	0/135 (0·0)	1/135 (0·7)	1/270 (0·4)
12 weeks	3/135 (2·2)	1/135 (0·7)	4/270 (1·5)
Renal failure			
In hospital	4/135 (2·3)	0/135 (0·0)	4/270 (1·5)
12 weeks	4/135 (2·3)	1/135 (0·7)	5/270 (1·9)
Atrial Arrhythmias			
In hospital	51/135 (37·8)	42/135 (31·1)	93/270 (34·4)
12 weeks	61/135 (45·2)	51/135 (37·8)	112/270 (41·5)
Ventricular Arrhythmias			
In hospital	2/135 (1·5)	2/135 (1·5)	4/270 (1·5)
12 weeks	2/135 (1·5)	2/135 (1·5)	4/270 (1·5)
Pericardial Effusion			
In hospital	4/135 (2·3)	1/135 (0·7)	5/270 (1·9)
12 weeks	9/135 (6·7)	6/135 (4·4)	15/270 (5·6)
Pulmonary Embolism			
In hospital	0/135 (0·0)	0/135 (0·0)	0/270 (0·0)
12 weeks	0/135 (0·0)	2/135 (1·5)	2/270 (0·7)
Chest Infection			
In hospital	7/135 (5·2)	10/135 (7·4)	17/270 (6·3)
12 weeks	18/135 (13·3)	26/135 (19·3)	44/270 (16·3)
Sternal wound infection			
In hospital	3/135 (2·2)	1/135 (0·7)	4/270 (1·5)
12 weeks	11/135 (8·1)	3/135 (2·2)	14/270 (5·2)
Re-operation for bleeding	3/135 (2·2)	5/135 (3·7)	8/270 (3·0)

Table 6. Health status, resource use and cost (complete cases)

	Conventional [C]			Mini-sternotomy [M]			[M]-[C][1]	
	mean	**(SD)**	**N**	**mean**	**(SD)**	**N**	**mean**	**(95%CI)**
Health status[2]								
EQ-5D Baseline	0·764	0·245	130	0·763	0·235	128	-0·001	(-0·060 to 0·057)
EQ-5D 2 days	0·349	0·349	133	0·353	0·291	128	0·004	(-0·074 to 0·082)
EQ-5D 6 weeks	0·798	0·194	118	0·751	0·221	112	-0·048	(-0·101 to 0·006)
EQ-5D 12 weeks	0·838	0·207	124	0·782	0·248	127	-0·056	(-0·112 to 0·001)
EQ-5D AUC (0-12 weeks)	0·162	0·041	105	0·153	0·040	98	-0·009	(-0·020 to 0·002)
Resource use								
Index Admission								
Length of stay (d)[3]	8·26	4·28	135	9·29	7·88	135	1·03	(-0·48 to 2·54)
CICU (d)	1·21	0·99	135	1·61	5·52	135	0·39	(-0·55 to 1·34)
HDU (d)	1·27	1·52	135	1·60	1·75	135	0·33	(-0·07 to 0·72)
Cardiac ward (d)	5·67	3·52	135	5·70	3·18	135	0·03	(-0·77 to 0·83)
Stroke ward (d)	0·03	0·34	135	0·11	1·00	135	0·08	(-0·10 to 0·26)
Time in first surgery (h)	2·24	0·51	135	2·98	0·69	135	0·74	(0·60 to 0·89)
Time in further surgery (h)[4]	0·08	0·34	135	0·03	0·17	135	-0·05	(-0·11 to 0·02)
Time in surgery (h)[4]	2·32	0·63	135	3·01	0·71	135	0·69	(0·53 to 0·85)
RBC (u)[4]	0·59	1·45	135	0·55	1·28	135	-0·04	(-0·37 to 0·28)
FFP (u)[4]	0·57	1·43	135	0·34	1·21	135	-0·23	(-0·55 to 0·09)
Platelets (u)[4]	0·22	0·64	135	0·12	0·46	135	-0·10	(-0·24 to 0·03)
Cryoprecipitate (u)[4]	0·01	0·09	135	0·00	0·00	135	-0·01	(-0·02 to 0·01)
Post discharge contacts								
GP surgery	1·47	1·52	129	1·40	1·32	131	-0·07	(-0·41 to 0·28)
GP home	0·09	0·32	129	0·19	0·56	131	0·10	(-0·01 to 0·21)
GP telephone	0·12	0·45	129	0·15	0·63	131	0·03	(-0·10 to 0·16)
Nurse surgery	1·38	2·56	129	2·07	3·54	131	0·69	(-0·06 to 1·44)
Nurse home	0·43	1·30	129	0·56	1·87	131	0·12	(-0·27 to 0·51)
Nurse telephone	0·05	0·25	129	0·04	0·26	131	-0·01	(-0·07 to 0·05)
Outpatient hospital	0·40	0·78	129	0·57	1·98	131	0·17	(-0·20 to 0·53)
Inpatient hospital	0·30	0·68	129	0·27	0·60	131	-0·03	(-0·18 to 0·13)
Inpatient hospital (d)	2·09	7·79	129	1·09	2·69	131	-1·00	(-2·42 to 0·42)
Total Contacts	4·29	3·53	129	5·47	4·90	131	1·18	(0·14 to 2·22)
Cost[5]								
Cost of index admission	7674	2055	135	8815	4517	135	1140	(303 to 1977)
Cost post discharge	824	2485	129	547	925	131	-277	(-734 to 180)
Cost	8527	3558	129	9274	4542	131	746	(-245 to 1737)

1 OLS regression-estimated means and 95% confidence intervals
2 EQ-5D-3L index score
3 Length stay by ward does not sum to length of stay due to theatre and transit time, and rounding
4 Item includes index and post-discharge usage
5 Resource items were costed using national reference costs except for the index procedures which were costed by South Tees Hospitals NHS Foundation Trust

Table 7. ICU Length of Stay, Fitness for Discharge and Hospital Length of Stay

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)
ICU stay (days)		
n	135	135
Mean ± SD	1·9 ± 5·8	1·3 ± 1·1
Min-Max	0 - 64*	0 - 7
Fitness for discharge (days)		
n	129**	133**
Mean ± SD	6·5 ± 3·7	6·3 ± 3·2
Min - Max	3 - 36	3 - 31
Post-operative length of stay (days)		
n	135	135
Mean ± SD	7·4 ± 7·5	6·3 ± 3·1
Min - Max	3 - 79	3 - 31

*3 patients in the mini-sternotomy group were in ICU for more than 7 days· Excluding these patients, the range would have been 0-5 days for the mini-sternotomy group.

**Fitness for discharge was assessed by the surgical and physiotherapy teams. For 6 patients in the mini-sternotomy group and 2 patients in the conventional sternotomy group this was not possible due staff availability at the point of discharge.

Table 8. Pulmonary Function Tests

		Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)	Mean Difference (95% CI; p value)
FEV1				
Baseline				
	n	123*	123*	
	Mean ± SD	2196·2 ± 712·2	2207·7 ± 748·2	-15·4 (-169·2,138·4)
	Min - Max	1000- 4340	1020-4090	
Day 4				
	n	105*	110*	
	Mean ± SD	1122·6 ± 433·0	1320·7 ± 523·5	-171·3** (-265·3,-77·2; p=0·0004)
	Min - Max	99-2400	76-2910	
6 weeks				
	n	106*	97*	
	Mean ± SD	1962·0 ± 468·7	2018·1 ± 662·8	-7·3** (-104·3,89·6)
	Min - Max	650-3570	870-3570	
FVC				
Baseline				
	n	123*	123*	
	Mean ± SD	2908·5 ± 926·4	2929·2 ± 955·7	-31·6 (-238·8,175·7)
	Min - Max	1250-6060	1200-5650	
Day 4				
	n	105*	110*	
	Mean ± SD	1478·9 ± 583·3	1697·5 ± 706·8	-129·7** (-259·2,-0·1; p=0·0498)
	Min - Max	139-2910	109-3920	
6 weeks				
	n	106*	97*	
	Mean ± SD	2529·4 ± 824·0	2615·9 ± 864·0	-36·0** (-173·2,101·2)
	Min - Max	1180-4760	1000-4840	

*It was not possible for all patients to complete pulmonary function tests
**After adjusting for randomisation factors and baseline data