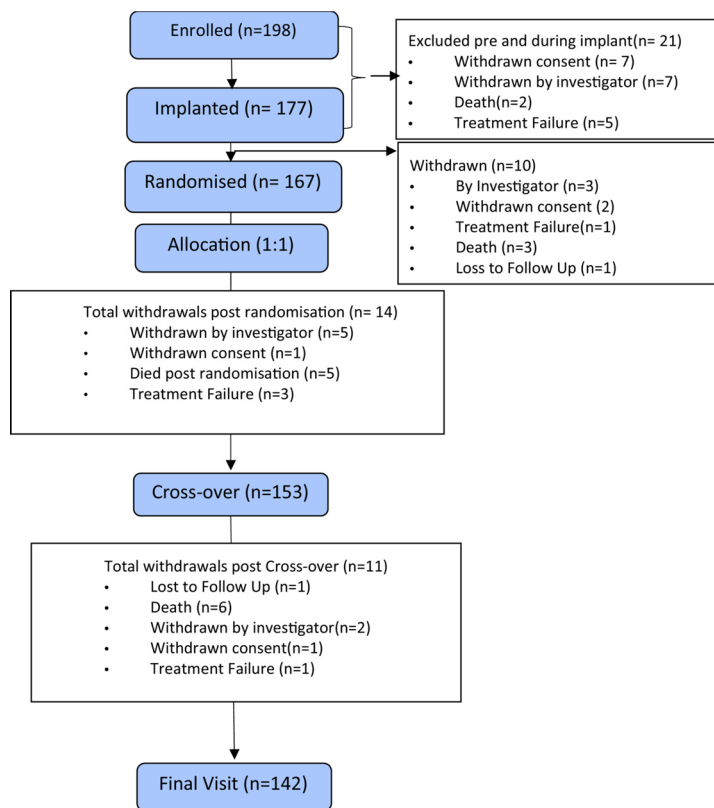


Participant flow



Baseline characteristics

Table 1. Clinical Characteristics of ITT Population at Baseline

Characteristic	All Patients (N= 167)	Arm A (N= 83)	Arm B (N= 84)
Sex (Male) [n (%)]	151 (90%)	74 (89%)	77 (92%)
Age (years)	69 ± 9.7	70 ± 9.0	68 ± 10.2
Ethnicity (Asian) [n (%)]	17 (10%)	10 (12%)	7 (8%)
Ethnicity (Black) [n (%)]	8 (5%)	3 (4%)	5 (6%)
Ethnicity (Mixed) [n (%)]	2 (1%)	0	2 (2%)
Ethnicity (Other) [n (%)]	3 (2%)	2 (2%)	1 (1%)
Ethnicity (White) [n (%)]	137 (82%)	68 (82%)	69 (82%)
Weight (kg)	87 ± 17.3	85 ± 16.8	89 ± 17.6
BMI (kg/m ²)	29 ± 5.3	28 ± 5.0	30 ± 5.5
6-minute walk test (secs)	267 ± 110	252 ± 98	282 ± 105
Peak Oxygen / MVO ₂ (mls/kg/min)	14.2 ± 4.18	13.9 ± 4.17	14.5 ± 4.19
QRS Duration (msec)	124 ± 26	126 ± 28.4	121 ± 24.0
PR Interval (msec)	249 ± 59.2	243 ± 51.2	254 ± 66.0
Right bundle-branch block (LBBB) [n (%)]	33 (20%)	20 (24%)	13 (15%)
Left vent. Ejection Fraction (%)	33.2 ± 9.02	32.6 ± 9.70	33.8 ± 8.32
Left vent. End-diastolic diameter (mm)	60.3 ± 8.41	60.3 ± 7.68	60.3 ± 9.12
Left vent. End-systolic diameter (mm)	49.8 ± 9.89	50.0 ± 9.28	49.5 ± 10.52
BNP (ng/L)	309 [145,743]	303 [151,839]	315 [129,688]
EQ5D Health State Score	68 [50, 80]	65 [50, 80]	70 [50, 80]
Minnesota LHF Score	33 [15, 81]	31 [12, 50]	34 [17, 53]
NYHA Class (I) [n (%)]	2 (1%)	2 (2%)	0
NYHA Class (II) [n (%)]	134 (80%)	66 (80%)	68 (81%)
NYHA Class (III) [n (%)]	30 (18%)	15 (18%)	15 (18%)
NYHA Class (IV) [n (%)]	1 (1%)	0	1 (1%)
HF Aetiology – DCM [n (%)]	57 (34%)	23 (25%)	34 (41%)
HF Aetiology – Chemotherapy [n (%)]	2 (1%)	0	2 (2%)
HF Aetiology – Ischemic [n (%)]	110 (66%)	60 (72%)	50 (60%)
HF Aetiology – Tachymyopathy [n (%)]	1 (1%)	1 (1%)	0
Med History – Excess Alcohol [n (%)]	13 (8%)	4 (5%)	9 (11%)

Med History – Cancer w/Chemo [n (%)]	6 (4%)	0	6 (7%)
Med History – Cor Artery Disease [n (%)]	111 (67%)	58 (70%)	53 (63%)
Med History – Diabetes [n (%)]	64 (38%)	34 (41%)	30 (36%)
Med History – Hypertension [n (%)]	76 (46%)	38 (46%)	38 (45%)
Med History – Smoking [n (%)]	37 (22%)	19 (23%)	18(21%)
Med History – Atrial Fibrillation [n (%)]	31 (19%)	18 (22%)	13 (16%)
Ace Inhibitors / A2RA's* [n (%)]	93 (56%)	43 (52%)	50 (60%)
Aldosterone Antagonists [n (%)]	84 (50%)	34 (41%)	50 (60%)
Beta Blockers [n (%)]	113 (68%)	53 (64%)	60 (71%)
Diuretics [n (%)]	77 (46%)	37 (45%)	40 (24%)
Entresto [n (%)]	12 (7%)	5 (6%)	7 (8%)
Patients on one of above meds [n (%)]	154 (92%)	73 (88%)	81 (96%)

Outcome measures

Table 2. Treatment Effects of Primary & Secondary Endpoints

Characteristic	N	No Pacing	Pacing	Δ	p-Value
MVO ₂	167	13.71 (12.84, 14.59)	13.98 (12.97, 14.96)	0.25 (-0.23, 0.73)	0.30
Minnesota Score	151	34.6 (29.8, 39.3)	30.9 (25.1, 36.7)	-3.7 (-7.1, -0.3)	0.03
EQ5D5L Health State Score	151	64.3 (60.4, 68.3)	66.3 (61.0, 71.6)	1.9 (-1.6, 5.5)	0.28
LV Ejection Fraction (%)	167	33.0 (31.0, 34.9)	33.4 (31.2, 35.7)	0.5 (-0.7, 1.6)	0.40
LVE Diastolic Diameter (mm)	167	60.0 (58.1, 61.9)	60.1 (58.0, 62.2)	0.1 (-0.9, 1.1)	0.83
LVE Systolic Diameter (mm)	167	49.9 (47.8, 51.9)	50.6 (48.2, 52.9)	0.7 (-0.4, 1.78)	0.23
BNP*	167	335 (257, 436)	323 (242, 431)	-12 (-48, 28)	0.54

Adverse events

Table 3. Overall AE/SAEs by Treatment

Treatment	(N)	No. Subjects with AEs	No. Adverse Events	No. Subjects with SAEs	No. Serious AEs
AV optimised direct His-bundle	167	97	197	44	68
No Pacing	167	93	169	37	60

Table 4. AE/SAEs by Arm, Treatment & Timepoint

Arm	Timepoint	Treatment	(N)	No. Subjects with AEs	No. Adverse Events	No. Subjects with SAEs	No. Serious AEs
1	Pre-Implant		83	11	13	4	4
	Pre-Rand.	No Pacing (Run-in)	83	38	52	14	15
	Post-Rand.	AV optimised direct His-bundle	83	51	111	27	41
	Post-Chg.	No Pacing	83	41	70	15	24
	Total		83	74	246	49	84
2	Pre-Implant		84	14	15	7	7
	Pre-Rand.	No Pacing (Run-in)	84	29	50	11	14
	Post-Rand.	No Pacing	84	52	99	22	36
	Post-Chg.	AV optimised direct His-bundle	84	46	86	17	27
	Total		84	71	250	40	84

Table 5. Overall SAEs by Treatment and Category

Treatment	N	Death	Persistently disabling	Life threatening	Hospitalisation required	Other medical important event	Total
AV optimised direct His-bundle	167	6	1	7	44	10	68
No Pacing	167	4	3	7	41	5	60

Table 6. SAEs by Arm, Treatment, Timepoint and Category

Arm	Time	Treatment	N	Death	Persistently disabling	Life threatening	Hospitalisation required	Other medical important event	Total
1	Pre-Implant		83	0	0	0	4	0	4
	Pre-Rand.	No Pacing (Run-In)	83	0	0	1	11	3	15
	Post-Rand.	AV optimised direct His-bundle	83	3	0	5	27	6	41
	Post-Chg.	No Pacing	83	2	1	5	16	0	24
	Total	Arm Total	83	5	1	11	58	9	84
2	Pre-Implant		84	0	0	0	4	3	7
	Pre-Rand.	No Pacing (Run-In)	84	1	0	0	9	4	14
	Post-Rand.	No pacing	84	2	2	2	25	5	36
	Post-Chg.	AV optimised direct His-bundle	84	3	1	2	17	4	27
	Total	Arm Total	84	6	3	4	55	16	84

Table 7: Summary of AEs (excluding events pre-implant and pre-randomisation)

organSystemName	term	AV optimised {Events}	AV optimised {SubjectsAffected}	AV optimised {SubjectsAtRisk}	No Pacing {Events}	No Pacing {SubjectsAffected}	No Pacing {SubjectsAtRisk}
Endocrine disorders	abnormal blood sugar levels	1	1	83	0	0	83
Hepatobiliary disorders	Abnormal LFTs	1	1	83	0	0	83
Injury, poisoning and procedural complications	Accidental morphine overdose	1	1	83	0	0	83
Endocrine disorders	Acute Kidney Injury	2	2	83	1	1	83
Hepatobiliary disorders	Ascites	1	1	83	0	0	83
Cardiac disorders	Atrial Fibrillation	4	4	83	5	5	83
Cardiac disorders	Atrial flutter	1	1	83	0	0	83
Cardiac disorders	Atrial tachycardia	1	1	83	0	0	83
Musculoskeletal and connective tissue disorders	Back pain	1	1	83	0	0	83
Musculoskeletal and connective tissue disorders	Baker's cyst	1	1	83	0	0	83
Musculoskeletal and connective tissue disorders	Bilateral leg cramps	1	1	83	0	0	83
Nervous system disorders	Bilateral numbness of arm when lying either side	1	1	83	0	0	83
Respiratory, thoracic and mediastinal disorders	Bilateral Pleural Effusion	1	1	83	0	0	83
Gastrointestinal disorders	Bloatedness	1	1	83	0	0	83
Renal and urinary disorders	Blocked urethral catheter	1	1	83	0	0	83
Cardiac disorders	Cardiac symptoms of palpitations and hypotension	1	1	83	0	0	83
Infections and infestations	Chest Infection	12	9	83	7	6	83
Cardiac disorders	Chest Pain	5	5	83	4	4	83

organSystemName	term	AV optimised {Events}	AV optimised {SubjectsAffected}	AV optimised {SubjectsAtRisk}	No Pacing {Events}	No Pacing {SubjectsAffected}	No Pacing {SubjectsAtRisk}
Infections and infestations	Common Colds	1	1	83	1	1	83
Gastrointestinal disorders	Constipation	2	2	83	0	0	83
Cardiac disorders	Decompensated Heart Failure	1	1	83	0	0	83
Endocrine disorders	Diabetic Left Foot Ulcer	1	1	83	0	0	83
Gastrointestinal disorders	Diarrhoea	1	1	83	1	1	83
General disorders	Dizziness	1	1	83	2	2	83
Respiratory, thoracic and mediastinal disorders	Dry persistent cough	1	1	83	0	0	83
Skin and subcutaneous tissue disorders	Eczema Skin condition	1	1	83	0	0	83
Respiratory, thoracic and mediastinal disorders	Exacerbation of asthma	1	1	83	0	0	83
Cardiac disorders	Exacerbation of HF	3	3	83	5	5	83
General disorders	Extreme tiredness and fatigue	1	1	83	1	1	83
General disorders	Fall secondary to dizziness	1	1	83	0	0	83
General disorders	Feeling of generally unwell	1	1	83	0	0	83
Infections and infestations	Fever	1	1	83	0	0	83
Skin and subcutaneous tissue disorders	Folliculitis	1	1	83	0	0	83
Musculoskeletal and connective tissue disorders	Fractured foot	1	1	83	0	0	83
Gastrointestinal disorders	Gastritis	1	1	83	0	0	83
Metabolism and nutrition disorders	Gout	4	4	83	2	2	83
Renal and urinary disorders	Haematuria secondary to NOAC	1	1	83	0	0	83
Respiratory, thoracic and mediastinal disorders	Haemoptysis	1	1	83	0	0	83
Gastrointestinal disorders	Hemorrhoids	1	1	83	0	0	83
Cardiac disorders	HIS lead threshold rise	1	1	83	0	0	83
Infections and infestations	Hospital Acquired Pneumonia	1	1	83	0	0	83
Blood and lymphatic system disorders	Hyperglycaemic Episode	1	1	83	2	2	83
Blood and lymphatic system disorders	Hyperkalaemia	1	1	83	0	0	83
Metabolism and nutrition disorders	Hypokalemia	1	1	83	0	0	83
Skin and subcutaneous tissue disorders	Idiopathic skin condition	1	1	83	0	0	83

organSystemName	term	AV optimised {Events}	AV optimised {SubjectsAffected}	AV optimised {SubjectsAtRisk}	No Pacing {Events}	No Pacing {SubjectsAffected}	No Pacing {SubjectsAtRisk}
Ear and labyrinth disorders	Impacted ear wax	1	1	83	0	0	83
Respiratory, thoracic and mediastinal disorders	Increased breathlessness	1	1	83	5	5	83
Respiratory, thoracic and mediastinal disorders	Intermittent cough	1	1	83	0	0	83
Injury, poisoning and procedural complications	Laceration to big toe	1	1	83	0	0	83
Eye disorders	Left eye vitreous haemorrhage	1	1	83	0	0	83
Renal and urinary disorders	Left Kidney Stones	1	1	83	0	0	83
Injury, poisoning and procedural complications	Mechanical Fall	1	1	83	1	1	83
Gastrointestinal disorders	mouth ulcer requiring biopsy	1	1	83	0	0	83
Endocrine disorders	New diagnosis of diabetes	1	1	83	1	1	83
General disorders	Non cardiac chest pain	1	1	83	0	0	83
Skin and subcutaneous tissue disorders	nonblanching petechial rashes on both shins	1	1	83	0	0	83
Cardiac disorders	Non-sustained VT Episodes	6	6	83	6	6	83
Musculoskeletal and connective tissue disorders	Painful bilateral knee	1	1	83	0	0	83
Musculoskeletal and connective tissue disorders	painful lower extremities	1	1	83	0	0	83
Cardiac disorders	Palpitations	1	1	83	0	0	83
Cardiac disorders	Paroxysmal Atrial Fibrillation	4	4	83	3	3	83
Gastrointestinal disorders	Polyps in colon	1	1	83	4	4	83
General disorders	Progressive weight loss	1	1	83	0	0	83
Cardiac disorders	Raised His Lead Threshold	1	1	83	0	0	83
Blood and lymphatic system disorders	Raised INR	1	1	83	0	0	83
Injury, poisoning and procedural complications	Received external electrical shock at work (works as an electrician)	1	1	83	0	0	83
Cardiac disorders	recurrence of atrial arrhythmia	1	1	83	0	0	83
Cardiac disorders	Recurrence of atrial fibrillation	1	1	83	0	0	83
Respiratory, thoracic and mediastinal disorders	Shortness of breath, Productive cough and wheeze due to lower respiratory tract infection	1	1	83	0	0	83
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	skin cancer growth L) hand	1	1	83	0	0	83
Injury, poisoning and procedural complications	Sprained wrist due to fall	1	1	83	0	0	83

organSystemName	term	AV optimised {Events}	AV optimised {SubjectsAffected}	AV optimised {SubjectsAtRisk}	No Pacing {Events}	No Pacing {SubjectsAffected}	No Pacing {SubjectsAtRisk}
Gastrointestinal disorders	stomach pain	1	1	83	0	0	83
Infections and infestations	Suspected lower respiratory tract infection	1	1	83	0	0	83
Cardiac disorders	Sustained VT treated with ATP	1	1	83	0	0	83
Hepatobiliary disorders	swollen abdomen	1	1	83	0	0	83
Cardiac disorders	swollen bilateral legs (knee to ankle)	1	1	83	0	0	83
Cardiac disorders	Swollen feet	1	1	83	0	0	83
Blood and lymphatic system disorders	Swollen left arm secondary to blood clot	1	1	83	0	0	83
Endocrine disorders	Thyroid Deficiency	1	1	83	0	0	83
Infections and infestations	Tooth infection	1	1	83	0	0	83
Renal and urinary disorders	Urinary retention	2	2	83	1	1	83
Infections and infestations	Urinary Tract Infection	3	3	83	2	2	83
Cardiac disorders	Ventricular Tachycardia Episodes	5	5	83	2	2	83
Infections and infestations	Viral Illness of unknown origin	1	1	83	0	0	83
Gastrointestinal disorders	Weight loss and dysphagia	1	1	83	0	0	83
Renal and urinary disorders	Worsening chronic kidney disease	1	1	83	0	0	83
Renal and urinary disorders	Worsening renal function	1	1	83	0	0	83
Respiratory, thoracic and mediastinal disorders	worsening shortness of breath and activity tolerance	1	1	83	0	0	83
Respiratory, thoracic and mediastinal disorders	Shortness of breath secondary to bilateral pleural effusion	1	1	83	0	0	83
Infections and infestations	LRTI	0	0	83	1	1	83
Musculoskeletal and connective tissue disorders	Anterior L1 Compression Fracture	0	0	83	1	1	83
Gastrointestinal disorders	Barrett's Oesophagus	0	0	83	1	1	83
Cardiac disorders	Bilateral swollen and painful legs	0	0	83	1	1	83
Injury, poisoning and procedural complications	Broken rib	0	0	83	1	1	83
Surgical and medical procedures	Cataracts operation on left eye	0	0	83	1	1	83
Product Issues	Coronary Sinus lead displaced	0	0	83	1	1	83
Cardiac disorders	decreased activity tolerance and increased paroxysmal nocturnal dyspnea	0	0	83	1	1	83

organSystemName	term	AV optimised {Events}	AV optimised {SubjectsAffected}	AV optimised {SubjectsAtRisk}	No Pacing {Events}	No Pacing {SubjectsAffected}	No Pacing {SubjectsAtRisk}
Musculoskeletal and connective tissue disorders	Degenerated rotator cuff and tendinopathy	0	0	83	1	1	83
Psychiatric disorders	Depression	0	0	83	1	1	83
Injury, poisoning and procedural complications	Dislocated R shoulder due to mechanical fall	0	0	83	1	1	83
Gastrointestinal disorders	Excessive intestinal gas -belching or flatulence	0	0	83	1	1	83
General disorders	Fainting spells	0	0	83	2	2	83
Injury, poisoning and procedural complications	Fall. Walking sticks slipped off.	0	0	83	1	1	83
General disorders	Fatigue	0	0	83	1	1	83
Injury, poisoning and procedural complications	Fracture in left elbow due to a fall	0	0	83	1	1	83
Gastrointestinal disorders	Heartburn	0	0	83	1	1	83
Renal and urinary disorders	Heavily trabeculated bladder with debris in urine noted during flexible cystoscopy	0	0	83	1	1	83
Metabolism and nutrition disorders	Hyponatraemia	0	0	83	1	1	83
Renal and urinary disorders	Increased urinary frequency secondary to enlarged prostate	0	0	83	1	1	83
Renal and urinary disorders	insertion of indwelling catheter	0	0	83	1	1	83
Cardiac disorders	Intermittent high impedance on His Lead with increase in His pacing threshold	0	0	83	1	1	83
Blood and lymphatic system disorders	Iron deficiency anaemia	0	0	83	1	1	83
Cardiac disorders	Late His Lead threshold rise	0	0	83	1	1	83
Skin and subcutaneous tissue disorders	Left leg cellulitis	0	0	83	1	1	83
Skin and subcutaneous tissue disorders	Left lower leg blister	0	0	83	1	1	83
Cardiac disorders	left ventricular thrombus	0	0	83	1	1	83
Gastrointestinal disorders	Lesion in caecum	0	0	83	1	1	83
Renal and urinary disorders	Marked deterioration of kidney function	0	0	83	1	1	83
Infections and infestations	Mild Infective Exacerbation of Bronchiectasis	0	0	83	1	1	83
Infections and infestations	MRSA positive nose and groin	0	0	83	1	1	83
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Non-tender pain free lump increasing in size	0	0	83	1	1	83
Gastrointestinal disorders	Nausea	0	0	83	1	1	83

organSystemName	term	AV optimised {Events}	AV optimised {SubjectsAffected}	AV optimised {SubjectsAtRisk}	No Pacing {Events}	No Pacing {SubjectsAffected}	No Pacing {SubjectsAtRisk}
Cardiac disorders	Pericardial effusion	0	0	83	1	1	83
Infections and infestations	Productive cough	0	0	83	1	1	83
Cardiac disorders	Recurrent Falls secondary to hypotension	0	0	83	1	1	83
Respiratory, thoracic and mediastinal disorders	Progressive worsening of breathlessness	0	0	83	1	1	83
General disorders	Reduced mobility	0	0	83	1	1	83
Skin and subcutaneous tissue disorders	Right leg cellulitis	0	0	83	1	1	83
Musculoskeletal and connective tissue disorders	Shoulder joint pain	0	0	83	1	1	83
Cardiac disorders	Sinus node dysfunction	0	0	83	1	1	83
Respiratory, thoracic and mediastinal disorders	Sleep Apnoea	0	0	83	1	1	83
Cardiac disorders	Slight palpitations, Chest discomfort.	0	0	83	1	1	83
Cardiac disorders	ST elevation on ECG post MVO2	0	0	83	1	1	83
Blood and lymphatic system disorders	Swollen right leg ?secondary to blood clot	0	0	83	1	1	83
Cardiac disorders	TIA	0	0	83	1	1	83
Nervous system disorders	Tingling sensation in both feet	0	0	83	1	1	83
Surgical and medical procedures	Tooth extraction	0	0	83	1	1	83
Metabolism and nutrition disorders	Vitamin D Deficiency	0	0	83	2	2	83
Respiratory, thoracic and mediastinal disorders	worsening shortness of breath	0	0	83	2	2	83

