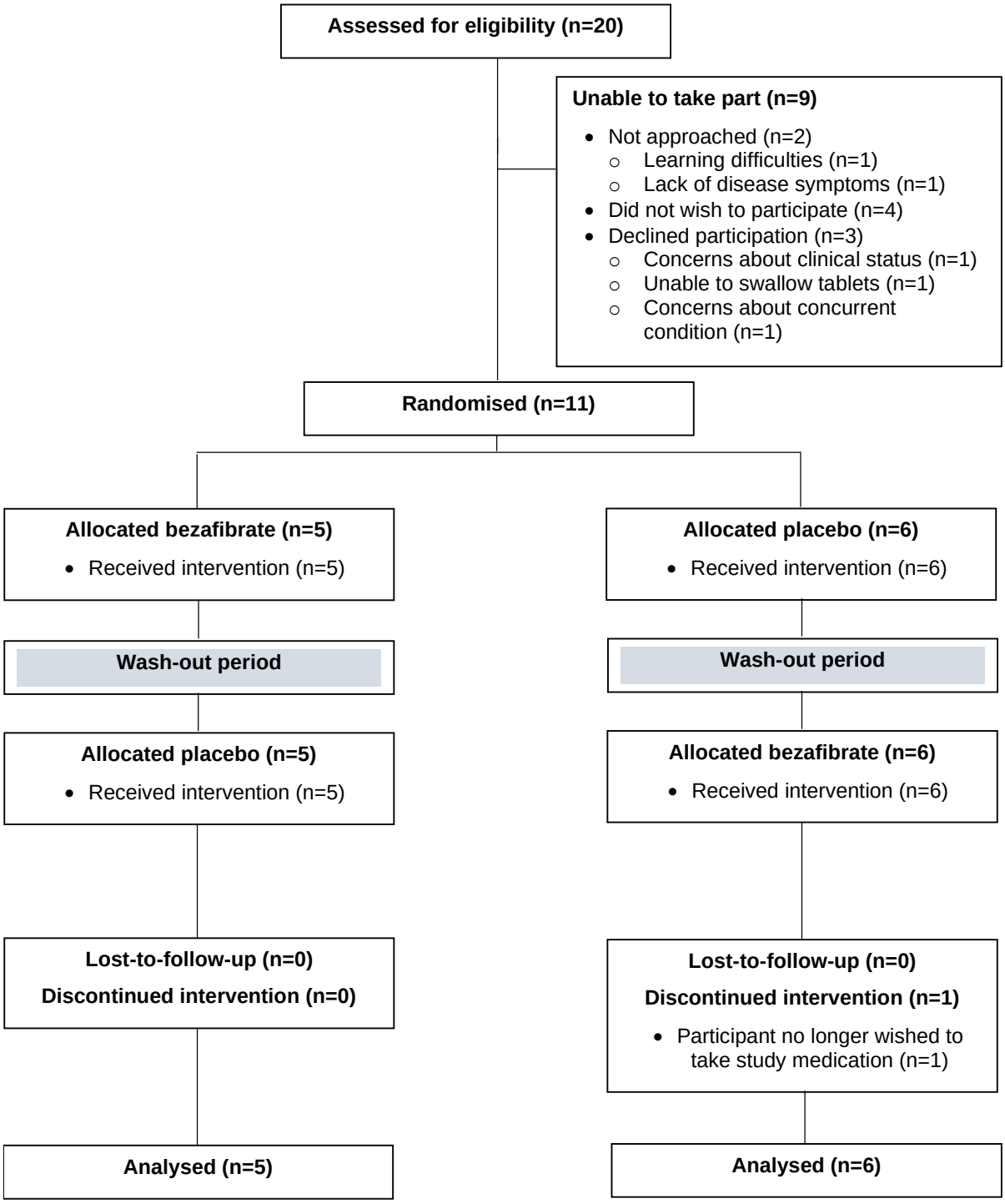
Participant Flow:



Baseline Characteristics:

Table 1 Baseline demographics by allocation order

	Bezafibrate > Placebo	Placebo > Bezafibrate
Previous cardiac transplant		
Non-Transplant	4 (80.0%)	5 (83.3%)
Transplant	1 (20.0%)	1 (16.7%)
Age (years)		
Median (range)	18 (12, 27)	13 (10, 22)
IQR	17, 21	10, 14
Age group		
<11 years	0 (0.0%)	2 (33.3%)
11-15 years	1 (20.0%)	3 (50.0%)
16+ years	4 (80.0%)	1 (16.7%)
Height (cm)		
Median (range)	173 (135, 175)	140 (118, 175)
IQR	170, 173	131, 145
Weight (kg)		
Median (range)	78 (24, 91)	34 (19, 98)
IQR	52, 91	29, 51
Bicep (mm)		
Median (range)	5 (3, 11)	10 (6, 19)
IQR	5, 9	9, 13
Tricep (mm)		
Median (range)	11 (9, 21)	12 (6, 21)
IQR	9, 17	9, 15
Subscapula (mm)		
Median (range)	13 (4, 25)	11 (8, 20)
IQR	6, 19	9, 16
Suprailiac (mm)		
Median (range)	9 (5, 23)	12 (5, 25)
IQR	6, 19	9, 21
O2 saturations (%)		
Median (range)	97 (90, 99)	97 (96, 98)
IQR	96, 99	96, 97
Heart rate (beats/minute)		
Median (range)	92 (84, 101)	93 (88, 102)
IQR	89, 94	88, 97
Respiratory rate (breaths/minute)		
Median (range)	17 (16, 19)	19 (17, 25)

	Bezafibrate > Placebo	Placebo > Bezafibrate
IQR	16, 18	18, 23
Systolic blood pressure (mmHg)		
Median (range)	120 (81, 128)	95 (83, 122)
IQR	94, 124	88, 108
Diastolic blood pressure (mmHg)		
Median (range)	60 (51, 79)	60 (48, 76)
IQR	59, 70	54, 66
Normal heart sounds		
Yes	5 (100.0%)	6 (100.0%)
Regular pulse		
Yes	5 (100.0%)	6 (100.0%)
Signs of heart failure		
No	5 (100.0%)	5 (83.3%)
Yes	0 (0.0%)	1 (16.7%)
Any episodes of fainting in the four months prior to recruitment		
No	5 (100.0%)	6 (100.0%)
Any palpitations in the four months prior to recruitment		
No	5 (100.0%)	6 (100.0%)
Any chest pain or tightness of the chest in the four months prior to recruitment		
No	5 (100.0%)	6 (100.0%)
Any unexpected decrease in exercise capacity or fitness level in the four months prior to recruitment		
No	5 (100.0%)	6 (100.0%)

Outcome Measures:

Primary outcome:

Table 1 Summary of peak VO_2 by allocation (ml/kg/min)

	Baseline	Bezafibrate	Placebo
Mean (s.d.)	18.20 (5.90)	16.93 (5.58)	17.51 (6.28)
Median (IQR)	16.0 (13.0, 25.1)	15.9 (11.9, 22.3)	14.5 (12.4, 22.1)
N	11	11	11

Table 2 Summary of peak VO_2 by period (ml/kg/min)

	Baseline	First period	Second period
Mean (s.d.)	18.20 (5.90)	16.81 (6.26)	17.63 (5.59)
Median (IQR)	16.0 (13.0, 25.1)	16.3 (11.6, 22.1)	15.5 (13.7, 22.3)
N	11	11	11

Bezafibrate and placebo were compared formally in terms of peak VO_2 using a mixed linear regression model, adjusting for period as a fixed effect and participants as random effects. The effect of period (i.e. whether peak VO_2 changed depending on whether drug or placebo was allocated first) was explored and there was no evidence of a difference (p=0.53). The interaction between treatment and period (i.e. whether the treatment effect differed depending on what period the treatment was received in) was also explored and there was also no evidence of an effect (p=0.61). Results for the final model including both treatment and period are shown in Table 4.

Table 3 Primary outcome model results[1]

Effect	Level	Estimate (95% CI)	P-value
Treatment effect	Bezafibrate vs. Placebo	-0.66 (-2.34, 1.03)	0.4266
Period effect	Second period vs. First period	0.88 (-0.81, 2.56)	0.2905

[1] Intercept (peak vo2 for placebo in the first period): 17.1 (95% CI 13.2 to 21.1), number of observations used: 33 (3 visits for 11 participants), -2 log likelihood: 161.12, within-subject s.d: 5.62

Secondary outcomes:

Monolysocardiolipin/tetralinoleoyl-cardiolipin MLCL/L4-CL ratio/cardiolipin profile in blood cells

Table 5 Summary of MLCL/L4-CL ratio by allocation

	Baseline	Bezafibrate	Placebo
Mean (s.d.)	0.797 (0.370)	1.567 (0.501)	1.604 (0.493)
Median (IQR)	0.877 (0.445, 1.027)	1.461 (1.258, 1.816)	1.618 (1.242, 1.974)
N	18	38	37

Table 6 Summary of MLCL/L4-CL ratio by period

	Baseline	First period	Second period
Mean (s.d.)	0.797 (0.370)	1.472 (0.523)	1.691 (0.447)
Median (IQR)	0.877 (0.445, 1.027)	1.369 (1.162, 1.692)	1.641 (1.371, 2.001)
N	18	36	39

There was no significant difference between bezafibrate and placebo in terms of MLCL/L4-CL (5% reduction in MLCL/L4-CL ratio for bezafibrate compared with placebo, 95% CI 19% reduction to 11% increase, p=0.53). There was evidence of a period effect on MLCL/L4-CL (20% increase in MLCL/L4-CL in second period compared with first period, 95% CI 3% increase to 40% increase, p=0.02). Results for the final model including both treatment and period are shown in Table 7.

Table 7 Model results for the effect of treatment on MLCL/L4-CL ratio[2]

Factor	Factor level	Estimate[3] (95% CI)	P-value
Treatment effect	Bezafibrate vs. Placebo	0.95 (0.81, 1.11)	0.5312
Period effect	Second period vs. First period	1.20 (1.03, 1.40)	0.0235

PCr/ATP ratio in cardiac muscle on 31P Magnetic Resonance Spectroscopy

PCr/ATP ratio was not collected due to problems with obtaining the MRS data, so this outcome was not analysed.

Skeletal muscle oxidative function on 31P Magnetic Resonance Spectroscopy

MRS was carried out only at the end of the second period for 10 participants (1 participant had missing MRS data). Table 8 summarises the Tau and Qmax by treatment for the second period.

[2] Intercept (MLCL/L4CL value for allocation in first period): 1.41 (95% CI 1.20 to 1.66), number of observations used: 30 (3 visits for 10 participants), -2 log likelihood: -68.46
[3] MLCL/L4CL was modelled on the log to base 10 scale

Table 8 Summary of MRS skeletal muscle oxidative function in the second period by allocation

	Bezafibrate	Placebo
Tau (S)		
Mean (s.d.)	99.47 (41.79)	57.71 (30.80)
Median (IQR)	91.8 (76.4, 129.4)	69.9 (38.9, 71.1)
N	5	5
Qmax (mM/s)		
Mean (s.d.)	0.19 (0.11)	0.39 (0.16)
Median (IQR)	0.2 (0.1, 0.2)	0.3 (0.3, 0.4)
N	5	5

Quality of life (QoL) assessed using age-appropriate PedsQL questionnaires

Table 9 Summary of quality of life scores, for patient and parent, for the core and fatigue domains by allocation

	Baseline	Bezafibrate	Placebo
Core: patient scores			
Mean (s.d.)	50.445 (20.069)	51.383 (20.242)	54.842 (18.589)
Median (range)	46.739 (20.455, 78.261)	55.435 (23.913, 83.696)	55.435 (28.261, 88.043)
IQR	35.870, 67.045	31.522, 63.043	35.870, 68.478
Missing	0	0	0
N	11	11	11
Core: parent scores			
Mean (s.d.)	49.832 (17.590)	50.145 (15.282)	49.333 (15.864)
Median (range)	51.087 (23.913, 76.087)	57.609 (25.000, 66.667)	51.087 (19.565, 68.478)
IQR	38.043, 61.364	40.217, 60.870	45.652, 60.870
Missing	1	1	1
N	10	10	10
Fatigue: patient scores			
Mean (s.d.)	46.361 (16.633)	49.495 (22.569)	47.601 (20.991)
Median (range)	43.056 (16.667, 75.000)	54.167 (0.000, 81.944)	48.611 (12.500, 83.333)
IQR	37.500, 58.333	33.333, 63.889	31.944, 66.667
Missing	0	0	0
N	11	11	11
Fatigue: parent scores			
Mean (s.d.)	47.500 (16.483)	49.028 (16.783)	51.315 (15.087)
Median (range)	45.833 (19.444, 69.444)	53.472 (23.611, 80.556)	55.025 (29.167, 76.389)

	Baseline	Bezafibrate	Placebo
IQR	36.111, 63.889	34.722, 56.944	36.111, 59.722
Missing	1	1	1
N	10	10	10

Table 10 Summary of quality of life scores, for patient and parent, for the core and fatigue domains by period

	Baseline	First period	Second period
Core: patient scores			
Mean (s.d.)	50.445 (20.069)	53.557 (20.807)	52.668 (18.126)
Median (range)	46.739 (20.455, 78.261)	56.522 (23.913, 88.043)	55.435 (28.261, 79.348)
IQR	35.870, 67.045	34.783, 63.043	33.696, 68.478
Missing	0	0	0
N	11	11	11
Core: parent scores			
Mean (s.d.)	49.832 (17.590)	49.261 (16.265)	50.217 (14.849)
Median (range)	51.087 (23.913, 76.087)	50.469 (19.565, 66.667)	56.522 (25.000, 68.478)
IQR	38.043, 61.364	42.391, 63.043	40.217, 60.870
Missing	1	1	1
N	10	10	10
Fatigue: patient scores			
Mean (s.d.)	46.361 (16.633)	47.475 (25.586)	49.621 (17.169)
Median (range)	43.056 (16.667, 75.000)	50.000 (0.000, 83.333)	54.167 (12.500, 69.444)
IQR	37.500, 58.333	26.389, 66.667	36.111, 63.889
Missing	0	0	0
N	11	11	11
Fatigue: parent scores			
Mean (s.d.)	47.500 (16.483)	49.894 (16.465)	50.449 (15.521)
Median (range)	45.833 (19.444, 69.444)	54.167 (29.167, 80.556)	53.472 (23.611, 76.389)
IQR	36.111, 63.889	34.722, 59.722	37.500, 56.944
Missing	1	1	1
N	10	10	10

Absolute neutrophil count

Table 11 Summary of absolute neutrophil counts by allocation

	Baseline	Bezafibrate	Placebo
Mean (s.d.)	3.95 (3.83)	5.21 (5.10)	4.89 (4.37)
Median (IQR)	2.3 (1.1, 8.4)	3.5 (1.8, 8.3)	3.8 (1.6, 7.4)
N	11	11	11

Table 12 Summary of absolute neutrophil counts by period

	Baseline	First period	Second period
Mean (s.d.)	3.95 (3.83)	3.92 (3.70)	6.19 (5.35)
Median (IQR)	2.3 (1.1, 8.4)	3.5 (1.0, 5.2)	3.8 (1.9, 11.6)
N	11	11	11

Amino acid expression (serum arginine and cysteine levels)

Table 13 Summary of plasma arginine and plasma cysteine by allocation

	Baseline	Bezafibrate	Placebo
Plasma arginine			
Mean (s.d.)	39.18 (19.02)	46.09 (20.09)	38.82 (20.78)
Median (IQR)	36.0 (24.0, 43.0)	41.0 (36.0, 46.0)	31.0 (25.0, 44.0)
N	11	11	11
Plasma cysteine			
Mean (s.d.)	29.27 (11.66)	37.18 (11.28)	27.91 (6.80)
Median (IQR)	25.0 (24.0, 29.0)	34.0 (29.0, 47.0)	30.0 (22.0, 34.0)
N	11	11	11

Table 14 Summary of plasma arginine and plasma cysteine by period

	Baseline	First period	Second period
Plasma arginine			
Mean (s.d.)	39.18 (19.02)	48.09 (26.54)	36.82 (9.50)
Median (IQR)	36.0 (24.0, 43.0)	40.0 (30.0, 73.0)	41.0 (26.0, 43.0)
N	11	11	11
Plasma cysteine			
Mean (s.d.)	29.27 (11.66)	32.82 (11.05)	32.27 (9.92)
Median (IQR)	25.0 (24.0, 29.0)	34.0 (25.0, 41.0)	30.0 (25.0, 34.0)
N	11	11	11

Cardiac function (LVEF (%) and 2D strain (%))

Table 15 Summary of ECHO at rest primary cardiac function outcomes by allocation

	Baseline	Bezafibrate	Placebo
Left ventricular ejection fraction (LVEF) (%)			
Mean (s.d.)	53.27 (7.43)	56.82 (5.60)	52.91 (6.19)
Median (IQR)	56.0 (46.0, 59.0)	57.0 (56.0, 62.0)	55.0 (49.0, 57.0)
N	11	11	11
Left ventricular systolic longitudinal strain (%)			
Mean (s.d.)	-19.58 (3.05)	-19.64 (2.11)	-18.00 (2.05)
Median (IQR)	-19.0 (-22.0, -17.4)	-19.0 (-21.0, -18.0)	-18.0 (-19.0, -17.0)
N	11	11	11
Left ventricular systolic circumferential strain (%)			
Mean (s.d.)	-22.64 (3.44)	-25.09 (5.15)	-22.55 (4.32)
Median (IQR)	-22.0 (-24.0, -20.0)	-26.0 (-29.0, -21.0)	-22.0 (-25.0, -19.0)
N	11	11	11
Diastolic ratio: MV E / LV E'			
Mean (s.d.)	6.55 (1.87)	6.82 (2.26)	6.70 (2.24)
Median (IQR)	6.0 (5.1, 8.3)	6.7 (4.9, 8.2)	6.2 (6.0, 7.0)
N	11	11	10

Table 16 Summary of MRI at rest primary cardiac function outcomes by allocation

	Baseline	Bezafibrate	Placebo
Left ventricular ejection fraction (LVEF) (%)			
Mean (s.d.)	63.68 (9.28)	66.11 (6.82)	65.96 (5.54)
Median (IQR)	62.3 (57.8, 72.7)	65.5 (61.9, 72.1)	68.0 (63.5, 69.7)
N	11	10	10
Right ventricular ejection fraction (RVEF)			
Mean (s.d.)	64.85 (6.17)	65.87 (7.27)	65.55 (6.13)
Median (IQR)	65.2 (61.3, 66.2)	66.8 (62.0, 69.0)	64.6 (61.5, 68.6)
N	11	10	10

Table 17 Summary of ECHO at peak exercise primary cardiac function outcomes by allocation

	Baseline	Bezafibrate	Placebo
Left ventricular systolic longitudinal strain (%)			
Mean (s.d.)	-23.48 (4.17)	-26.07 (3.46)	-27.32 (3.39)
Median (IQR)	-22.3 (-24.0, -20.9)	-26.6 (-28.7, -24.5)	-26.3 (-29.6, -25.3)
N	8	6	9
Left ventricular systolic circumferential strain (%)			
Mean (s.d.)	-27.34 (4.40)	-33.14 (7.26)	-32.93 (5.49)
Median (IQR)	-26.2 (-32.0, -24.7)	-32.0 (-38.5, -29.6)	-31.6 (-35.9, -29.1)
N	8	8	8
Diastolic ratio: MV E / LV E'			
Mean (s.d.)	5.20 (1.21)	4.71 (0.90)	4.83 (1.35)
Median (IQR)	5.1 (4.1, 5.7)	4.7 (4.3, 4.9)	4.7 (4.0, 5.4)
N	6	6	8

Table 18 Summary of ECHO at 2 min recovery primary cardiac function outcomes by allocation[4]

	Baseline	Bezafibrate	Placebo
Left ventricular systolic longitudinal strain (%)			
Mean (s.d.)	.	-24.60 (2.57)	-25.04 (4.57)
Median (IQR)	.	-23.4 (-26.2, -22.9)	-26.1 (-28.3, -19.8)
N	0	8	7
Left ventricular systolic circumferential strain (%)			
Mean (s.d.)	.	-31.21 (4.28)	-33.70 (7.20)
Median (IQR)	.	-31.6 (-33.6, -28.9)	-31.6 (-43.0, -26.5)
N	0	8	7
Diastolic ratio: MV E / LV E'			
Mean (s.d.)	.	5.79 (1.21)	5.17 (1.73)
Median (IQR)	.	6.0 (5.3, 6.7)	4.6 (3.7, 6.9)
N	0	9	8

Arrhythmia profile from 12 lead ECG at rest and during exercise (for potential rhythm abnormalities)

[4] No values were collected in the first period for any of the ECHO parameters at 2 min recovery.

Mitochondrial size in lymphocytes

Table 19 Summary of mitochondrial size by allocation

	Baseline	Bezafibrate	Placebo
Mean (s.d.)	0.1585 (0.1136)	0.1534 (0.1109)	0.1503 (0.1026)
Median (IQR)	0.1257 (0.0843, 0.1940)	0.1265 (0.0793, 0.1917)	0.1260 (0.0856, 0.1813)
N	883	1145	1097

Numbers of mitochondria (per lymphocyte)

Table 20 Summary of number of mitochondria per lymphocyte by allocation

	Baseline	Bezafibrate	Placebo
Mean (s.d.)	4.01 (3.23)	5.33 (4.07)	4.70 (3.12)
Median (IQR)	3.0 (2.0, 6.0)	5.0 (2.0, 7.0)	4.0 (2.0, 6.0)
N	220	215	234

Total area of mitochondria per lymphocyte

Table 21 Summary of total area of mitochondria per lymphocyte by allocation

	Baseline	Bezafibrate	Placebo
Mean (s.d.)	0.6360 (0.5496)	0.8145 (0.6355)	0.7048 (0.4748)
Median (IQR)	0.5270 (0.2045, 0.9710)	0.6750 (0.3430, 1.1890)	0.6180 (0.2890, 1.0160)
N	220	215	234

Area of mitochondria as proportion of cytoplasm

Table 22 Summary of area of mitochondria as proportion of cytoplasm by allocation

	Baseline	Bezafibrate	Placebo
Mean (s.d.)	4.9578 (3.8458)	5.9500 (4.1000)	5.7088 (3.4642)
Median (IQR)	4.2240 (2.0665, 7.5890)	5.0700 (2.9540, 8.4150)	5.3480 (2.8600, 8.1390)
N	220	215	234

Mitochondria function and cristae organisation in lymphocytes/neutrophils

Table 23 Summary of fluorescein isothiocyanate (FITC) median fluorescent intensity (MFI) in peripheral blood mononuclear cells (PBMC) using mitotracker by allocation

	Baseline	Bezafibrate	Placebo
Mean (s.d.)	135.8 (53.6)	491.4 (214.9)	302.7 (157.6)
Median (IQR)	117.0 (89.9, 198.0)	373.0 (335.0, 733.0)	273.0 (216.0, 385.0)
N	7[5]	11	11

Table 24 Summary of FITC MFI in lymphocytes using mitotracker by allocation

	Baseline	Bezafibrate	Placebo
Mean (s.d.)	140.3 (51.8)	711.6 (557.6)	645.3 (407.8)
Median (IQR)	123.0 (109.5, 171.0)	699.0 (261.0, 1053.0)	506.0 (371.0, 916.0)
N	4[6]	11	9[7]

Table 25 Summary of [TMRE MFI] - [TMRE+ carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone (FCCP) MFI] in PBMC using tetramethylrhodamine ethyl ester (TMRE) by allocation

	Baseline	Bezafibrate	Placebo
Mean (s.d.)	11128.6 (11445.9)	7860.9 (9018.9)	14025.2 (15107.5)
Median (IQR)	11792.0 (320.0, 18617.0)	3182.0 (1361.0, 12957.0)	10465.0 (117.0, 26148.0)
N	7[8]	11	11

Table 26 Summary of [TMRE MFI] - [TMRE+FCCP MFI] in lymphocytes using TMRE by allocation

	Baseline	Bezafibrate	Placebo
Mean (s.d.)	1376.3 (2052.5)	7385.0 (10575.7)	19463.1 (16561.2)
Median (IQR)	560.5 (66.0, 2686.5)	1606.6 (622.0, 12031.0)	17942.0 (1719.0, 35096.0)
N	4[9]	11	9[10]

[5] Four patients had missing values for this marker: 3 were from a different machine and could not be combined, and 1 could not be bled
[6] Seven patients had missing values for this marker: 3 were from a different machine and could not be combined, 1 could not be bled, and 3 had no lymphocytes isolated
[7] Two patients had missing values for this marker due to not having lymphocytes isolated
[8] Four patients had missing values for this marker: 3 were from a different machine and could not be combined, and 1 could not be bled
[9] Seven patients had missing values for this marker: 3 were from a different machine and could not be combined, 1 could not be bled, and 3 had no lymphocytes isolated
[10] Two patients had missing values for this marker due to not having lymphocytes isolated

Arrhythmia profile

Arrhythmia profile was assessed at rest and during exercise at the timepoints, i.e. at baseline and at the end of each period. All participants had data for all three timepoints and all participants had sinus rhythm at rest and during exercise for all three timepoints.

Adverse Events:

Table 27 Line listing of all Serious Adverse Events

Study ID[11]	Allocation	Expectedness	Description	Specification	Date of onset	Relatedness[12]	Classification
48	Bezafibrate	Expected event of bezafibrate	Muscle cramp		04/04/2019	Possibly related	Resulted in persistent or significant disability / incapacity
48	Bezafibrate	Disease related anticipated event	Neutropaenia	neutropenic chest infection	11/04/2019	Unlikely to be related	Required hospitalisation
48	Bezafibrate	Unexpected adverse event	Chest infection		11/04/2019	Unlikely to be related	Required hospitalisation
48	Bezafibrate	Unexpected adverse event	Bladder control loss		08/06/2019	Unlikely to be related	Required hospitalisation
24	Bezafibrate	Expected event of bezafibrate	Diarrhoea and vomiting		17/09/2019	Probably related	Required hospitalisation
24	Bezafibrate	Expected event of bezafibrate	Diarrhoea		03/10/2019	Probably related	Required hospitalisation
48	Wash-out period	Unexpected adverse event	Pyrexia of unknown origin		08/08/2019	Unlikely to be related	Required hospitalisation
48	Placebo	Unexpected adverse event	Viral illness		19/11/2019	Unlikely to be related	Required hospitalisation
16	Placebo	Unexpected adverse event	Tonsilitis		20/11/2019	Not related	Required hospitalisation

[11] To maintain the confidentiality of participants from other members of the study group, the study IDs used here have been changed.
[12] Assigned during the trial when investigators were blinded to the allocation

Table 28 Line listing of all non-serious adverse events

Allocation	Expectedness	Event description	Number of events
Bezafibrate	Expected event of bezafibrate	Stomach cramps	1
Bezafibrate	Expected event of bezafibrate	Nausea	1
Bezafibrate	Unexpected adverse events	Temperature	1
Bezafibrate	Unexpected adverse events	Vomiting	2
Bezafibrate	Unexpected adverse events	Abdominal pain	1
Bezafibrate	Expected event of bezafibrate	Raised creatinine	1
Bezafibrate	Expected event of bezafibrate	Raised creatine kinase	1
Bezafibrate	Expected event of bezafibrate	Leg muscle cramps	1
Bezafibrate	Unexpected adverse events	Achilles tendon injury/pain	1
Bezafibrate	Expected event of bezafibrate	Vomiting	2
Bezafibrate	Unexpected adverse events	Pulled hamstring	1
Bezafibrate	Disease related anticipated event	Fatigue	1
Placebo	Disease related anticipated event	Fatigue	1
Bezafibrate	Expected event of bezafibrate	Diarrhoea	1
Placebo	Disease related anticipated event	Diarrhoea	1
Placebo	Disease related anticipated event	Neutropenia	2
Bezafibrate	Expected event of bezafibrate	Cheek rash	1
Bezafibrate	Unexpected adverse events	Cold/puffy eyes	1
Bezafibrate	Unexpected adverse events	Pedal verruca	1
Bezafibrate	Unexpected adverse events	Urine infection	1
Bezafibrate	Expected event of bezafibrate	Abdominal pain/discomfort	1
Bezafibrate	Expected event of bezafibrate	Legs aching	1

Allocation	Expectedness	Event description	Number of events
Bezafibrate	Expected event of bezafibrate	Gastrointestinal symptoms	1
Placebo	Unexpected adverse events	Nose bleed	1