SUPPLIMENTARY DATA

Table Titles

Figure Titles and Legends

Table S1: Exclusion Criteria

- History of any other cardiovascular disorder
- NYHA Class III / IV heart failure
- Diabetes Mellitus
- Contraindication to magnetic resonance imaging (MRI) scanning (including claustrophobia)
- Known hypersensitivity to Trientine or excipients
- Known hypersensitivity to Gadolinium-based contrast agent
- eGFR < 50ml/min/1.73m^2
- BMI > 40kg/m^2
- History of significant malabsorption
- Copper deficiency at baseline
- Iron deficiency at baseline
- Haemoglobin < 10g/dL
- Unresolved haematological disorder
- Severe hepatic impairment
- Untreated thyroid disease
- Autoimmune disorders/connective tissue disease
- Drug or alcohol abuse
- Pregnancy/breast-feeding. Women of childbearing potential (not >2 years post- menopausal and/or not surgically sterilised) must have a negative blood serum pregnancy test, performed at visit 1 prior to administration of study medication
- Any clinically significant or unstable medical or psychiatric condition that would interfere with the patient's ability to participate in the study
- Any other condition, which in the opinion of the research team, may put participants at risk during the study, or which may affect the outcome of the study
- New medication within the preceding month of the study (excluding short term prescriptions)
- Participation in another study involving an investigational product in the previous 12 weeks

Table S2: Patient Characteristics

	Intervention Group	Control Group	p-value
Age (years)	55.5 ± 8.4	54.7 ± 13.3	0.86
Male	15	7	
Body surface area (m^2)	2.06 ± 0.25	1.94 ± 0.24	0.24
Systolic blood pressure (mmHg)	130 ± 15	137 ± 13	0.24
Diastolic blood Pressure (mmHg)	81 ± 12	75 ± 15	0.28
Heart Rate	66.5 ± 16.3	65.1 ± 11.5	0.81
ACEi / ARB	1	2	
Beta-blockers	10	5	
Calcium Channel Blockers	1	0	
Spironolactone	0	0	
PCr/ATP ratio	1.27 ± 0.44	1.51 ± 0.82	0.36
NYHA I NYHA II	14 6	7 3	
EF (%)	69.0 ± 6.8	69.8 ± 8.3	0.79
Mass/BSA (g/m^2)	73.5 ± 20.0	79.8 ± 18.6	0.43

Table S3: Adverse effects leading to non-completion of study

	Gender	Length of Treatment (weeks)	Adverse Effect
1	Male	1	Abdominal bloating
2	Male	21	Oesophageal ulcer*
3	Male	20	Arthralgia†
4	Male	4	Migraine†

* Related to tablet impaction- the patient was taking multiple other prescribed and over the counter medications, and the investigational medicinal product (IMP) was not deemed the culprit at OGD.

† Pre-existing prior to study

Table S4: Summary of important risks

Adverse Event	Number of patients experiencing adverse event (Total number of patients = 20)
Gastric complaints (nausea, gastric pain, bloating, diarrhoea, dyspepsia)	5
Dizziness	2
Increased exercise capacity	2
Chest infection	3
Increased Urinary Frequency	1
Leukopenia	1
Vivid dreams	1
Appendicitis*	1
Headache	2
Influenza-like illness	1
Common Cold	1
Vivid dreams	1
Palpitations requiring admission*	1
Wrist Sprain*	1
Adhesive capsulitis of the shoulder	1

*Serious adverse event

Table S5: Laboratory and haemodynamic data at baseline and after 6 months of treatment with trientine

	Baseline	Follow-up	p-value
Laboratory data			
Haemoglobin (g/l)	145.5 ± 13.3	143.2 ± 12.5	0.40
Urea (mmol/l)	5.1 ± 1.0	4.9 ± 1.2	0.25
Creatinine (µmol/l)	75.0 ± 13.0	74.2 ± 11.7	0.71
eGFR (ml/min/1.73m^2)	82.7 ± 8.6	84.5 ± 7.2	0.30
Alk. Phos (iu/l)	73.0 ± 19.8	78.6 ± 19.1	0.03
ALT (iu/l)	20.5 ± 6.4	23.6 ± 5.0	0.07
Magnesium (mmol/l)	0.87 ± 0.08	0.81 ± 0.12	0.14
Serum Copper (µmol/l)	16.5 ± 2.3	16.6 ± 2.7	0.83
Serum Caeruloplasmin (g/l)	0.23 ± 0.03	0.24 ±0.03	0.04
Serum Zinc (µmol/l)	20.4 ± 5.4	25.3 ± 7.9	0.15
Haemodynamics			
Systolic BP (mmHg)	131 ± 15	125 ± 15	0.21
Diastolic BP (mmHg)	83 ± 14	74 ± 7	0.06
Heart Rate (bpm)	57.5 ± 10.0	58.8 ± 9.2	0.59
BSA (m^2)	2.07 ± 0.28	2.06 ± 0.28	0.43
Cardiopulmonary Exercise Testing			
Exercise time (min)	14.7 ± 3.2	14.4 ± 2.9	0.26
Anaerobic Threshold (l/mn)	1.41 ± 0.46	1.47 ± 0.36	0.89
VO2 Max (l/mn)	2.44 ± 0.81	2.41 ± 0.74	0.46
PR interval (ms)	184 ± 20	182 ± 19	0.42
QRS duration (ms)	110 ± 12	109 ± 13	0.44
QTc (ms)	432 ± 27	429 ± 20	0.75

Table S6: Echocardiographic data at baseline and after 6 months of treatment with trientine

	Baseline	Follow-up	p-value
E velocity (cm/s)	60.8 ± 16.7	61.8 ± 12.9	0.67
A velocity (cm/s)	64.4 ± 23.0	63.7 ± 20.3	0.77
E/A ratio	1.11 ± 0.67	1.10 ± 0.50	0.84
Mean S' Velocity (cm/s)	6.9 ± 2.5	8.1 ± 1.9	0.03
Mean E' Velocity (cm/s)	6.8 ± 3.4	7.0 ± 2.5	0.71
Mean A' Velocity (cm/s)	7.4 ± 3.1	8.4 ± 2.7	0.11
Mean E/E'	10.7 ± 3.3	10.1 ± 3.2	0.43
Mitral Decel. Time (ms)	295 ± 79	265 ± 47	0.11

Table S7: Cardiac MRI at baseline and after 6 months of treatment with trientine.

	Baseline	Follow-up	p-value
Cardiac MRI: Left ventricle			
LVEDV (ml)	171 ± 36	169 ± 38	0.57
LVESV (ml)	54 ± 20	52 ± 20	0.41
SV (ml)	117 ± 22	117 ± 23	0.98
EF (%)	69 ± 7	70 ± 6	0.55
LVM (g)	152 ± 54	147 ± 55	0.06
LVEDVi (ml/m^2)	84 ± 10	84 ± 12	0.84
LVESVi (ml/m^2)	26 ± 7	26 ± 8	0.62
SVi (ml/m^2)	58 ± 9	59 ± 8	0.75
LVMi (g/m^2)	73 ± 20	73 ± 22	0.48
Native septal T1 (ms)	1060 ± 47	1049 ± 42	0.06
ECV Fraction (%)	30.0 ± 4.5	29.5 ± 4.0	0.06
Total Myocardial Volume (ml)	145 ± 52	140 ± 53	0.05
ECM Volume (ml)	44 ± 18	42 ± 17	0.04
Cellular Volume (ml)	101 ± 36	99 ± 37	0.11
GLS	-18.3 ± 3.4	-19.4 ± 3.4	0.03
PCr / ATP Ratio	1.27 ± 0.44	1.4 ± 0.39	0.46
Cardiac MRI: Left atrium			
LAESV (ml)	75.8 ± 43.6	65.8 ± 40.9	0.04
LAEDV (ml)	124.4 ± 51.3	114.6 ± 47.3	0.18
Pre-atrial contraction vol (ml)	102.9 ± 46.7	93.3 ± 40.1	0.08
LAESVi (ml/m^2)	37.3 ± 17.9	32.6 ± 17.4	0.06
LAEDVi (ml/m^2)	61.7 ± 21.9	57.4 ± 20.8	0.25
Pre-atrial contraction vol i (ml/m^2)	50.9 ± 19.8	46.6 ± 17.2	0.12
Total EF (%)	41.3 ± 8.3	45.5 ± 12.2	0.07
Passive EF (%)	18.0 ± 5.8	18.7 ± 4.9	0.64
Booster EF (%)	28.4 ± 8.9	33.2 ± 13.6	0.16
LA Expansion Index	0.73 ± 0.22	0.94 ± 0.54	0.09
Total strain (%)	20.0 ± 3.9	21.5 ± 5.0	0.04
Peak systolic strain rate (-1)	0.75 ± 13	0.83 ± 0.19	0.11
Passive Strain (%)	9.47 ± 3.06	11.1 ± 5.60	0.68
Peak early negative strain rate (-1)	-0.50 ± 0.29	-0.49 ± 0.23	0.56
Active Strain (%)	10.53 ± 3.08	10.41 ± 4.20	0.76
Peak late negative strain rate (-1)	-0.68 ± 0.20	-0.66 ± 0.30	0.91

ECV fraction was calculated as ECV = (1-hematocrit) x ƛ, where ƛ is the partition coefficient. Total myocardial volume was LV Mass / 1.05. The total extracellular volume (ECM) was calculated with the formula ECM= ECV x LVM/1.05, while the cellular volume was calculated as Cellular volume (ml)=Total myocardial volume – ECM volume).

Figure 1

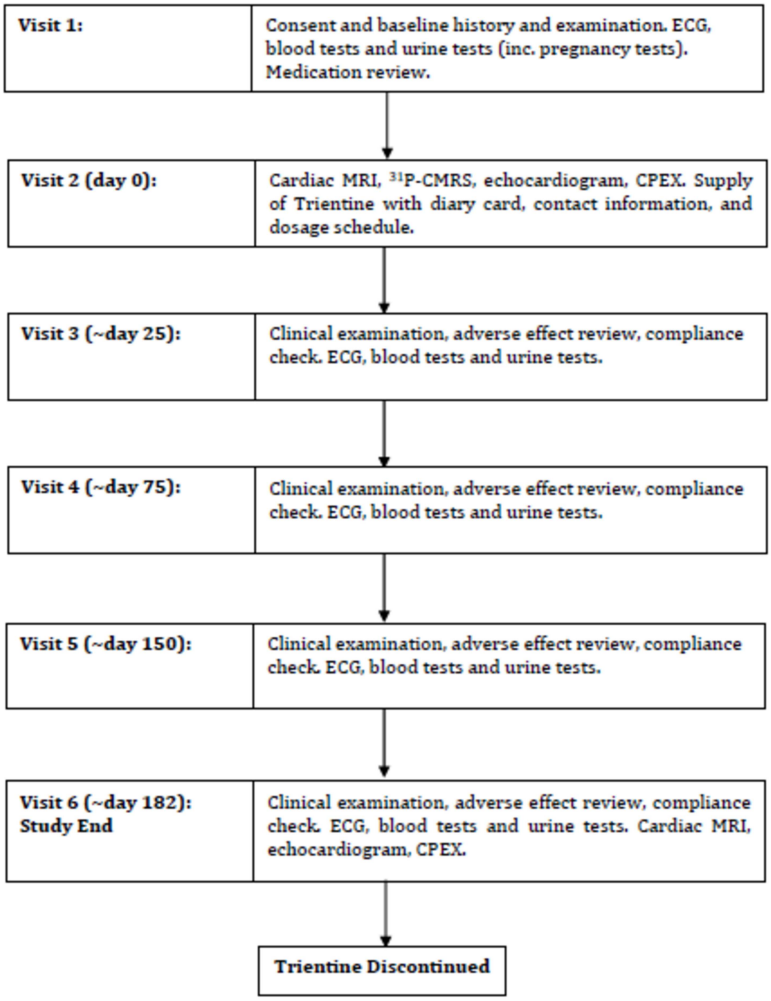
Visit 1:
Consent and baseline history and examination. ECG, blood tests and urine tests (inc. pregnancy tests). Medication review.
Visit 2 (day 0):
Cardiac MRI, ^{31}P-CMRS, echocardiogram, CPEX. Supply of Trientine with diary card, contact information, and dosage schedule.
Visit 3 (~day 25):
Clinical examination, adverse effect review, compliance check. ECG, blood tests and urine tests.
Visit 4 (~day 75):
Clinical examination, adverse effect review, compliance check. ECG, blood tests and urine tests.
Visit 5 (~day 150):
Clinical examination, adverse effect review, compliance check. ECG, blood tests and urine tests.
Visit 6 (~day 182): Study End
Clinical examination, adverse effect review, compliance check. ECG, blood tests and urine tests. Cardiac MRI, echocardiogram, CPEX.
Trientine Discontinued

Figure 2

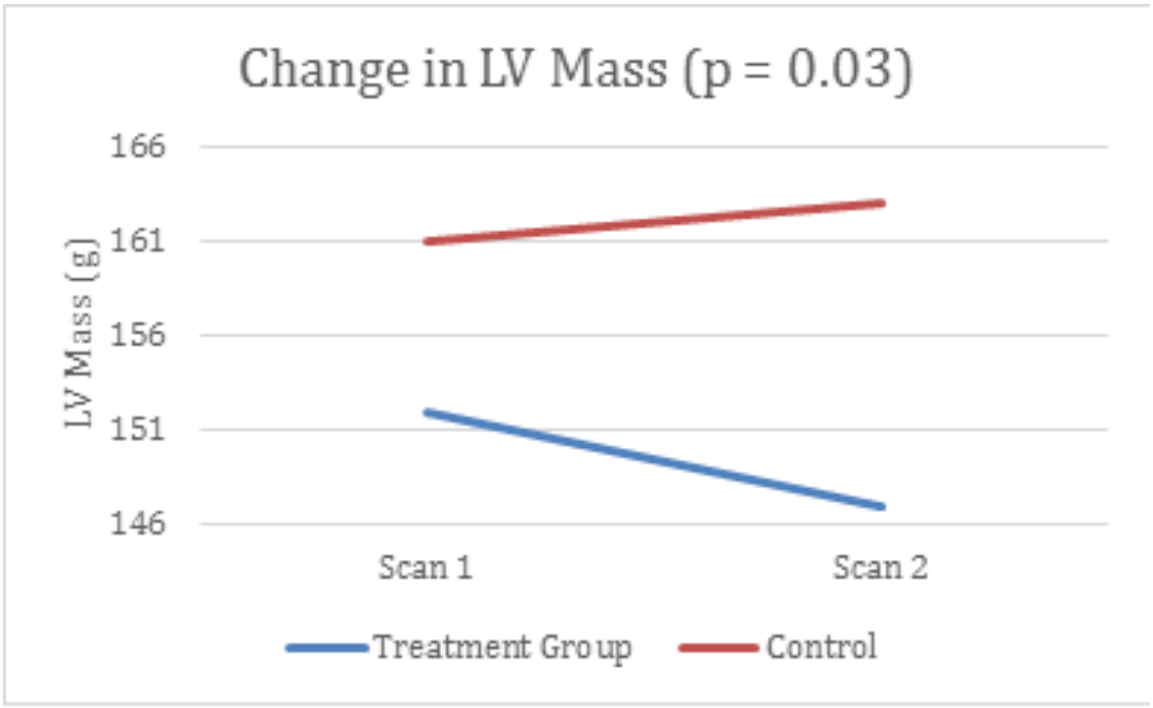
Change in LV Mass (p = 0.03)
166
161
156
151
146
LV Mass (g)
Scan 1
Scan 2
Treatment Group
Control

Figure 3

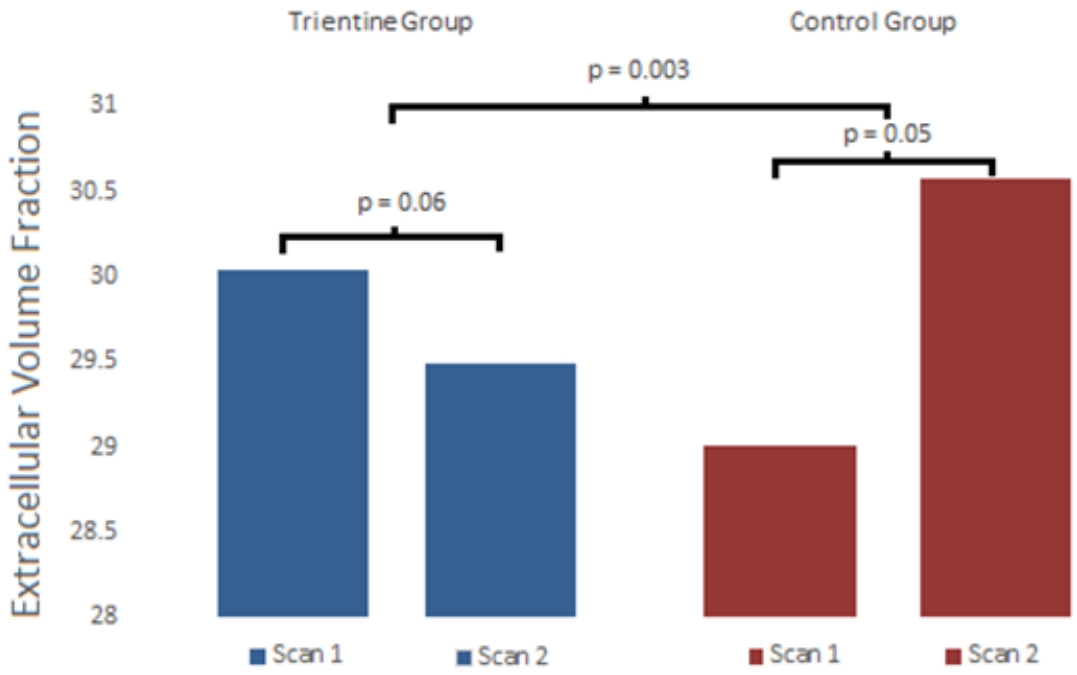
Trientine Group
Control Group
p = 0.003
p = 0.05
p = 0.06
Extracellular Volume Fraction
31
30.5
30
29.5
29
28.5
28
Scan 1
Scan 2
Scan 1
Scan 2

Figure 4