



## Clinical trial results: A Feasibility Study of Bezafibrate in Mitochondrial Myopathy Summary

EudraCT number	2015-000508-24
Trial protocol	GB
Global end of trial date	23 March 2017

### Results information

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

### Trial information

#### Trial identification

Sponsor protocol code	7406
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02398201
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Queen Victoria Road, Newcastle upon Tyne, United Kingdom, NE1 4LP
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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	20 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 March 2017
Global end of trial reached?	Yes
Global end of trial date	23 March 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To undertake a proof of concept study to determine whether bezafibrate can improve mitochondrial function in individuals with mitochondrial disease; to determine whether further study warranted in an RCT; and to have data to inform any power calculations for potential future studies.

Protection of trial subjects:

Two data monitoring committee meetings during the course of the study. The first of these discussed adverse events occurring within the study, and due to hypoglycaemic episodes, further monitoring of blood sugars was advised if participants were recruited to higher doses of bezafibrate. Substantial amendment submitted to reflect this.

Background therapy:

None

Evidence for comparator:

No disease modifying treatments currently available.

Actual start date of recruitment	09 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

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)	6
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants were provided with introductory information via i) routine clinic appointments; or ii) the UK mitochondrial disease cohort, inviting them to contact the study team. With further contact from participants, the participant information sheet was provided and questions answered via telephone before a screening visit was arranged.

### Pre-assignment

Screening details:

Screening was undertaken at the Clinical Research Facility, Royal Victoria Infirmary, Newcastle upon Tyne. 9 individuals were screened and 6 were recruited to the study.

### Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	Group 1
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Bezafibrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200mg TDS PO for 6/52 followed by 400mg TDS PO for 6/52

Number of subjects in period 1	Group 1
Started	6
Completed	6

### Period 2

Period 2 title	Wk 6 Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Group 1
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Bezafibrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200mg TDS PO for 6/52 followed by 400mg TDS PO for 6/52

<b>Number of subjects in period 2</b>	Group 1
Started	6
Completed	6

### Period 3

Period 3 title	Wk 12 End of Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Group 1
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Bezafibrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200mg TDS PO for 6/52 followed by 400mg TDS PO for 6/52

<b>Number of subjects in period 3</b>	Group 1
Started	6
Completed	6

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	6	6	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	6	6	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	50		
full range (min-max)	44 to 57	-	
Gender categorical			
Units: Subjects			
Female	4	4	
Male	2	2	
Complex I Respiratory Chain Enzyme Activity			
Respiratory Chain Enzyme Activity on skeletal muscle tissue homogenate taken at study baseline.			
Units: Complex I/CS			
arithmetic mean	0.073000		
standard deviation	± 0.014697	-	
Complex II Respiratory Chain Enzyme Activity			
Respiratory Chain Enzyme Activity on skeletal muscle tissue homogenate taken at study baseline.			
Units: Complex II/CS			
arithmetic mean	0.203000		
standard deviation	±	-	
Complex III Respiratory Chain Enzyme Activity			
Respiratory Chain Enzyme Activity on skeletal muscle tissue homogenate taken at study baseline.			
Units: Complex III/CS			
arithmetic mean	1.12800		
standard deviation	± 0.188611	-	
Complex IV Respiratory Chain Enzyme Activity			
Respiratory Chain Enzyme Activity on skeletal muscle tissue homogenate taken at study baseline.			
Units: Complex IV/CS			

arithmetic mean	1.406000		
standard deviation	± 0.235151	-	
Citrate synthase			
Citrate synthase activity in muscle tissue homogenate at baseline			
Units: µmol x min <sup>-1</sup> x g tissue <sup>-1</sup>			
arithmetic mean	690		
standard deviation	± 174.404	-	
mitochondrial DNA copy number			
mitochondrial DNA copy number (muscle tissue)			
Units: Relative mtDNA CN/thousands			
arithmetic mean	3863.89		
standard deviation	± 625.9426	-	
Serum FGF-21			
Serum Fibroblast growth factor-21			
Units: pg/ml			
arithmetic mean	415.00		
standard deviation	±	-	
Serum GDF-15			
Serum Growth Differentiation Factor-15			
Units: pg/ml			
arithmetic mean	1973		
standard deviation	±	-	
Muscle PGC-1α level			
Muscle PGC-1α level determined by immunoblotting			
Units: relative to control = 1.0			
arithmetic mean	0.615		
standard deviation	±	-	
skeletal muscle τ1/2 PCr			
skeletal muscle τ1/2 PCr as determined by 31P-MRS			
Units: τ1/2 PCr seconds			
arithmetic mean	48.7		
standard deviation	± 39.1	-	
Myocardial PCr/ATP ratio			
Myocardial PCr/ATP ratio as determined by 31P-MRS			
NB - only 5 individuals had values determined at baseline due to a technical error in MR set up.			
Units: PCr/ATP ratio			
arithmetic mean	1.69		
standard deviation	± 0.2	-	
Peak cardiac left ventricular torsion			
Peak cardiac left ventricular torsion as determined by cardiac cine scanning			
Units: degrees (°)			
arithmetic mean	7.66		
standard deviation	± 1.20	-	
Mean peak VO2			
Mean peak VO2 as measured by cycle ergometry			
Units: ml/min			
arithmetic mean	1214		
standard deviation	± 225	-	
Peak power			
Peak power as determined by cycle ergometry			
Units: watts			
arithmetic mean	87.2		



standard deviation	± 8.0	-	
peak arterio-venous oxygen differential			
peak arterio-venous oxygen differential as determined by cycle ergometry			
Units: mlO2/dl			
arithmetic mean	11.4		
standard deviation	± 0.7	-	
Newcastle Mitochondrial Disease Adult Scale (NMDAS) Total			
Units: points			
arithmetic mean	24		
standard deviation	± 8.0	-	
Newcastle Mitochondrial Disease Adult Scale (NMDAS), Section I sub-total			
Units: points			
arithmetic mean	9		
standard deviation	± 5.4	-	
Newcastle Mitochondrial Disease Adult Scale (NMDAS), Section II sub-total			
Units: points			
arithmetic mean	10		
standard deviation	± 4.5	-	
Newcastle Mitochondrial Disease Adult Scale (NMDAS), Section III sub-total			
Units: points			
arithmetic mean	5.0		
standard deviation	± 2.3	-	
NMQ - mobility			
Newcastle Mitochondrial Quality of Life Scale - mobility domain			
Units: points			
arithmetic mean	60		
standard deviation	± 14.7	-	
NMQ - ADLs			
Newcastle Mitochondrial Quality of Life Scale - Activity of Daily Living domain			
Units: points			
arithmetic mean	86		
standard deviation	± 24.2	-	
NMQ - Energy			
Newcastle Mitochondrial Quality of Life Scale - energy domain			
Units: points			
arithmetic mean	45		
standard deviation	± 15.7	-	
NMQ - Vision			
Newcastle Mitochondrial Quality of Life Scale - vision domain			
Units: points			
arithmetic mean	78		
standard deviation	± 21.3	-	
NMQ - communication			
Newcastle Mitochondrial Quality of Life Scale - communication domain			
Units: points			
arithmetic mean	58.0		
standard deviation	± 19.0	-	
NMQ - memory			
Newcastle Mitochondrial Quality of Life Scale - memory domain			

Units: points			
arithmetic mean	56		
standard deviation	$\pm 12.5$	-	
NMQ - Food			
Newcastle Mitochondrial Quality of Life Scale - food domain			
Units: points			
arithmetic mean	77		
standard deviation	$\pm 17.6$	-	
NMQ - pain			
Newcastle Mitochondrial Quality of Life Scale - Pain domain			
Units: points			
arithmetic mean	66		
standard deviation	$\pm 32.3$	-	
NMQ - Muscle			
Newcastle Mitochondrial Quality of Life Scale - Muscle domain			
Units: points			
arithmetic mean	67		
standard deviation	$\pm 31.2$	-	
NMQ - Migraine			
Newcastle Mitochondrial Quality of Life Scale - Migraine domain			
Units: points			
arithmetic mean	79		
standard deviation	$\pm 25.0$	-	
NMQ - Emotion			
Newcastle Mitochondrial Quality of Life Scale - Emotion domain			
Units: points			
arithmetic mean	56		
standard deviation	$\pm 21.9$	-	
NMQ - Stigma			
Newcastle Mitochondrial Quality of Life Scale - Stigma domain			
Units: points			
arithmetic mean	69		
standard deviation	$\pm 31.5$	-	
NMQ - Family Role			
Newcastle Mitochondrial Quality of Life Scale - Family Role domain			
Units: points			
arithmetic mean	58		
standard deviation	$\pm 19.4$	-	
NMQ - Personal Relations			
Newcastle Mitochondrial Quality of Life Scale - Personal Relations domain			
Units: points			
arithmetic mean	56		
standard deviation	$\pm 26.9$	-	
NMQ - Social Role			
Newcastle Mitochondrial Quality of Life Scale - Social Role Domain			
Units: points			
arithmetic mean	48		
standard deviation	$\pm 33.5$	-	
NMQ - Diabetes			
Newcastle Mitochondrial Quality of Life Scale - Diabetes domain			
Units: points			
arithmetic mean	55		

standard deviation	± 16.8	-	
Physical Component Score			
From NMDAS - Section IV (SF12.2)			
Units: points			
arithmetic mean	37.5		
standard deviation	± 13.2	-	
Mental Component Score			
From NMDAS - Section IV (SF12.2)			
Units: points			
arithmetic mean	43.6		
standard deviation	± 7.9	-	
FIS - Total			
Fatigue Impact Scale - Total			
Units: points			
arithmetic mean	68		
standard deviation	±	-	
FIS - Physical			
Fatigue Impact Scale - Physical sub-score			
Units: points			
arithmetic mean	31.00		
standard deviation	± 12.247	-	
FIS - cognitive			
Fatigue Impact Scale - Cognitive sub-score			
Units: points			
arithmetic mean	19.00		
standard deviation	±	-	
FIS - social			
Fatigue Impact Scale - Social sub-score			
Units: points			
arithmetic mean	18.3		
standard deviation	± 9.60	-	
IPAQ score			
International Physical Activity Questionnaire (IPAQ) score			
Units: MET/mins/week			
median	1303.5		
inter-quartile range (Q1-Q3)	185.6 to 2531.25	-	
Daytime acceleration			
Activity Levels Exercise intensity & duration			
Units: milligravity			
arithmetic mean	33.56		
standard deviation	± 10.28	-	
Time in vigorous activity			
Activity Levels Exercise intensity & duration			
Units: minutes			
arithmetic mean	1.1347		
standard deviation	± 0.80121	-	
Time in Moderate activity			
Activity Levels Exercise intensity & duration			

Units: minutes arithmetic mean standard deviation	70.49 ± 47.41	-	
Time in Light Activity			
Activity Levels Exercise intensity & duration			
Units: minutes arithmetic mean standard deviation	161.73 ± 40.90	-	
Muscle heteroplasmy Units: percentage arithmetic mean full range (min-max)	72 53 to 84	-	
Urine heteroplasmy Units: percentage arithmetic mean full range (min-max)	65 33 to 89	-	
Blood Heteroplasmy			
Uncorrected - raw values			
Units: percentage arithmetic mean full range (min-max)	19 11 to 27	-	
COX deficient fibres Units: percentage arithmetic mean full range (min-max)	5.0 2.0 to 10.0	-	
Timed up and go Units: seconds arithmetic mean full range (min-max)	8.9 7.13 to 11.47	-	

### Subject analysis sets

Subject analysis set title	Group 1
Subject analysis set type	Full analysis
Subject analysis set description: All recruited participants	

Reporting group values	Group 1		
Number of subjects	6		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years			

85 years and over			
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Age continuous Units: years arithmetic mean full range (min-max)			
Gender categorical Units: Subjects			
Female Male			
Complex I Respiratory Chain Enzyme Activity			
Respiratory Chain Enzyme Activity on skeletal muscle tissue homogenate taken at study baseline.			
Units: Complex I/CS arithmetic mean standard deviation	0.073000 ± 0.014697		
Complex II Respiratory Chain Enzyme Activity			
Respiratory Chain Enzyme Activity on skeletal muscle tissue homogenate taken at study baseline.			
Units: Complex II/CS arithmetic mean standard deviation	0.203000 ± 0.025965		
Complex III Respiratory Chain Enzyme Activity			
Respiratory Chain Enzyme Activity on skeletal muscle tissue homogenate taken at study baseline.			
Units: Complex III/CS arithmetic mean standard deviation	±		
Complex IV Respiratory Chain Enzyme Activity			
Respiratory Chain Enzyme Activity on skeletal muscle tissue homogenate taken at study baseline.			
Units: Complex IV/CS arithmetic mean standard deviation	1.406000 ± 0.235151		
Citrate synthase			
Citrate synthase activity in muscle tissue homogenate at baseline			
Units: µmol x min <sup>-1</sup> x g tissue <sup>-1</sup> arithmetic mean standard deviation	±		
mitochondrial DNA copy number			
mitochondrial DNA copy number (muscle tissue)			
Units: Relative mtDNA CN/thousands arithmetic mean standard deviation	3863.89 ±		
Serum FGF-21			
Serum Fibroblast growth factor-21			
Units: pg/ml arithmetic mean standard deviation	415.00 ± 193.51		
Serum GDF-15			
Serum Growth Differentiation Factor-15			
Units: pg/ml			

arithmetic mean	1973		
standard deviation	± 269.93		
Muscle PGC-1alpha level			
Muscle PGC-1alpha level determined by immunoblotting			
Units: relative to control = 1.0			
arithmetic mean	0.615		
standard deviation	± 0.197184		
skeletal muscle τ1/2 PCr			
skeletal muscle τ1/2 PCr as determined by 31P-MRS			
Units: τ1/2 PCr seconds			
arithmetic mean			
standard deviation	±		
Myocardial PCr/ATP ratio			
Myocardial PCr/ATP ratio as determined by 31P-MRS			
NB - only 5 individuals had values determined at baseline due to a technical error in MR set up.			
Units: PCr/ATP ratio			
arithmetic mean			
standard deviation	±		
Peak cardiac left ventricular torsion			
Peak cardiac left ventricular torsion as determined by cardiac cine scanning			
Units: degrees (°)			
arithmetic mean			
standard deviation	±		
Mean peak VO2			
Mean peak VO2 as measured by cycle ergometry			
Units: ml/min			
arithmetic mean			
standard deviation	±		
Peak power			
Peak power as determined by cycle ergometry			
Units: watts			
arithmetic mean			
standard deviation	±		
peak arterio-venous oxygen differential			
peak arterio-venous oxygen differential as determined by cycle ergometry			
Units: mlO2/dl			
arithmetic mean			
standard deviation	±		
Newcastle Mitochondrial Disease Adult Scale (NMDAS) Total			
Units: points			
arithmetic mean			
standard deviation	±		
Newcastle Mitochondrial Disease Adult Scale (NMDAS), Section I sub-total			
Units: points			
arithmetic mean			
standard deviation	±		
Newcastle Mitochondrial Disease Adult Scale (NMDAS), Section II sub-total			
Units: points			
arithmetic mean			
standard deviation	±		

Newcastle Mitochondrial Disease Adult Scale (NMDAS), Section III sub-total Units: points arithmetic mean standard deviation	$\pm$		
NMQ - mobility			
Newcastle Mitochondrial Quality of Life Scale - mobility domain			
Units: points arithmetic mean standard deviation	$\pm$		
NMQ - ADLs			
Newcastle Mitochondrial Quality of Life Scale - Activity of Daily Living domain			
Units: points arithmetic mean standard deviation	$\pm$		
NMQ - Energy			
Newcastle Mitochondrial Quality of Life Scale - energy domain			
Units: points arithmetic mean standard deviation	$\pm$		
NMQ - Vision			
Newcastle Mitochondrial Quality of Life Scale - vision domain			
Units: points arithmetic mean standard deviation	$\pm$		
NMQ - communication			
Newcastle Mitochondrial Quality of Life Scale - communication domain			
Units: points arithmetic mean standard deviation	$\pm$		
NMQ - memory			
Newcastle Mitochondrial Quality of Life Scale - memory domain			
Units: points arithmetic mean standard deviation	$\pm$		
NMQ - Food			
Newcastle Mitochondrial Quality of Life Scale - food domain			
Units: points arithmetic mean standard deviation	$\pm$		
NMQ - pain			
Newcastle Mitochondrial Quality of Life Scale - Pain domain			
Units: points arithmetic mean standard deviation	$\pm$		
NMQ - Muscle			
Newcastle Mitochondrial Quality of Life Scale - Muscle domain			
Units: points arithmetic mean standard deviation	$\pm$		
NMQ - Migraine			
Newcastle Mitochondrial Quality of Life Scale - Migraine domain			

Units: points			
arithmetic mean			
standard deviation	±		
NMQ - Emotion			
Newcastle Mitochondrial Quality of Life Scale - Emotion domain			
Units: points			
arithmetic mean			
standard deviation	±		
NMQ - Stigma			
Newcastle Mitochondrial Quality of Life Scale - Stigma domain			
Units: points			
arithmetic mean			
standard deviation	±		
NMQ - Family Role			
Newcastle Mitochondrial Quality of Life Scale - Family Role domain			
Units: points			
arithmetic mean			
standard deviation	±		
NMQ - Personal Relations			
Newcastle Mitochondrial Quality of Life Scale - Personal Relations domain			
Units: points			
arithmetic mean			
standard deviation	±		
NMQ - Social Role			
Newcastle Mitochondrial Quality of Life Scale - Social Role Domain			
Units: points			
arithmetic mean			
standard deviation	±		
NMQ - Diabetes			
Newcastle Mitochondrial Quality of Life Scale - Diabetes domain			
Units: points			
arithmetic mean			
standard deviation	±		
Physical Component Score			
From NMDAS - Section IV (SF12.2)			
Units: points			
arithmetic mean			
standard deviation	±		
Mental Component Score			
From NMDAS - Section IV (SF12.2)			
Units: points			
arithmetic mean			
standard deviation	±		
FIS - Total			
Fatigue Impact Scale - Total			
Units: points			
arithmetic mean	68		
standard deviation	± 28.659		
FIS - Physical			
Fatigue Impact Scale - Physical sub-score			
Units: points			
arithmetic mean			



standard deviation	±		
FIS - cognitive			
Fatigue Impact Scale - Cognitive sub-score			
Units: points			
arithmetic mean	19.00		
standard deviation	± 7.348		
FIS - social			
Fatigue Impact Scale - Social sub-score			
Units: points			
arithmetic mean	18.3		
standard deviation	± 9.60		
IPAQ score			
International Physical Activity Questionnaire (IPAQ) score			
Units: MET/mins/week			
median			
inter-quartile range (Q1-Q3)			
Daytime acceleration			
Activity Levels Exercise intensity & duration			
Units: milligravity			
arithmetic mean			
standard deviation	±		
Time in vigorous activity			
Activity Levels Exercise intensity & duration			
Units: minutes			
arithmetic mean			
standard deviation	±		
Time in Moderate activity			
Activity Levels Exercise intensity & duration			
Units: minutes			
arithmetic mean			
standard deviation	±		
Time in Light Activity			
Activity Levels Exercise intensity & duration			
Units: minutes			
arithmetic mean			
standard deviation	±		
Muscle heteroplasmy			
Units: percentage			
arithmetic mean			
full range (min-max)			
Urine heteroplasmy			
Units: percentage			
arithmetic mean			
full range (min-max)			
Blood Heteroplasmy			
Uncorrected - raw values			

Units: percentage arithmetic mean full range (min-max)			
COX deficient fibres Units: percentage arithmetic mean full range (min-max)			
Timed up and go Units: seconds arithmetic mean full range (min-max)			

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## End points

### End points reporting groups

Reporting group title	Group 1
Reporting group description: -	
Reporting group title	Group 1
Reporting group description: -	
Reporting group title	Group 1
Reporting group description: -	
Subject analysis set title	Group 1
Subject analysis set type	Full analysis
Subject analysis set description:	
All recruited participants	

### Primary: Change in Complex I Respiratory Chain Enzyme Activity between baseline & week 12

End point title	Change in Complex I Respiratory Chain Enzyme Activity between baseline & week 12
End point description:	
End point type	Primary
End point timeframe:	
Measured at weeks 0 and 12.	

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: CI/CS				
arithmetic mean (standard error)	0.073 ( $\pm$ 0.0060)	0.072 ( $\pm$ 0.0044)		

### Statistical analyses

Statistical analysis title	Change in CI between weeks 0 and 12.
Comparison groups	Group 1 v Group 1
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.7
Method	paired t test

Notes:

[1] - exploratory

### Primary: dChange in Complex II Respiratory Chain Enzyme Activity between baseline & week 12

End point title	dChange in Complex II Respiratory Chain Enzyme Activity between baseline & week 12
End point description:	
End point type	Primary
End point timeframe:	
Measured at weeks 0 and 12	

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: CII/CS				
arithmetic mean (standard error)	0.203 ( $\pm$ 0.0106)	0.227 ( $\pm$ 0.0098)		

### Statistical analyses

<b>Statistical analysis title</b>	Change in CII activity between wks 0 and 12
Comparison groups	Group 1 v Group 1
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
P-value	= 0.02
Method	paired t test

Notes:

[2] - exploratory

### Primary: Change in Complex III Respiratory Chain Enzyme Activity between baseline & week 12I

End point title	Change in Complex III Respiratory Chain Enzyme Activity between baseline & week 12I
End point description:	
End point type	Primary
End point timeframe:	
Measured at weeks 0 and 12.	

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: CIII/CS				
arithmetic mean (standard error)	1.128 ( $\pm$ 0.077)	1.129 ( $\pm$ 0.0744)		

### Statistical analyses

<b>Statistical analysis title</b>	Change in CIII activity between weeks 0 and 12
Comparison groups	Group 1 v Group 1
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	= 0.99
Method	paired t test

Notes:

[3] - exploratory

### Primary: Change in Complex IV Respiratory Chain Enzyme Activity between baseline & week 12

End point title	Change in Complex IV Respiratory Chain Enzyme Activity between baseline & week 12
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End point description:

End point type	Primary
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End point timeframe:

Measured at weeks 0 and 12.

<b>End point values</b>	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: CIVCS				
arithmetic mean (standard error)	1.406 ( $\pm$ 0.096)	1.399 ( $\pm$ 0.1189)		

### Statistical analyses

<b>Statistical analysis title</b>	Change in CIV activity between weeks 0 and 12.
Comparison groups	Group 1 v Group 1
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other <sup>[4]</sup>
P-value	= 0.96
Method	paired t test

Notes:

[4] - exploratory

### Secondary: Change in Citrate Synthase

End point title	Change in Citrate Synthase
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 and 12

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: $\mu\text{mol} \times \text{min}^{-1} \times \text{g tissue}^{-1}$				
arithmetic mean (standard error)	690 ( $\pm 71.2$ )	649 ( $\pm 73.6$ )		

### Statistical analyses

Statistical analysis title	Change in CS activity between weeks 0 and 12
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Comparison groups	Group 1 v Group 1
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Number of subjects included in analysis	12
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Analysis specification	Pre-specified
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Analysis type	other <sup>[5]</sup>
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P-value	= 0.72
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Method	paired t test
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Notes:

[5] - exploratory

### Secondary: Change in mitochondrial DNA copy number

End point title	Change in mitochondrial DNA copy number
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 and 12.

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Relative mtDNA CN/thousands				
arithmetic mean (standard error)	3863.89 ( $\pm$ 255.54)	3991.57 ( $\pm$ 314.53)		

### Statistical analyses

<b>Statistical analysis title</b>	change in mtDNA CN between weeks 0 and 12
Comparison groups	Group 1 v Group 1
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other <sup>[6]</sup>
P-value	= 0.64
Method	paired t test

Notes:

[6] - exploratory

### Secondary: Change in serum FGF-21

End point title	Change in serum FGF-21
End point description:	
End point type	Secondary
End point timeframe:	
Measured at weeks 0, 6 and 12	

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: pg/ml				
arithmetic mean (standard error)	415 ( $\pm$ 79)	1149 ( $\pm$ 128)	2173 ( $\pm$ 268)	

### Statistical analyses

<b>Statistical analysis title</b>	Change in FGF-21
Comparison groups	Group 1 v Group 1 v Group 1

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[7]</sup>
P-value	= 0.021 <sup>[8]</sup>
Method	Repeated measures ANOVA

Notes:

[7] - exploratory

[8] - a priori threshold for significance = <0.05

Greenhouse-Geisser correction

Two sided

## Secondary: Change in serum GDF-15

End point title	Change in serum GDF-15
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: pg/ml				
arithmetic mean (standard error)	1973 (± 110.2)	2432 (± 171.8)	2795 (± 160.3)	

## Statistical analyses

<b>Statistical analysis title</b>	Change in GDF-15
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[9]</sup>
P-value	= 0.007 <sup>[10]</sup>
Method	Repeated measures ANOVA

Notes:

[9] - exploratory

[10] - a priori threshold for significance = <0.05

Two sided

## Secondary: Change in muscle PGC-1alpha level

End point title	Change in muscle PGC-1alpha level
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End point description:

End point type	Secondary
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End point timeframe:

Measured at 0 and 12 weeks



End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Relative level				
arithmetic mean (standard error)	0.6150 ( $\pm$ 0.0805)	0.6681 ( $\pm$ 0.0809)		

### Statistical analyses

<b>Statistical analysis title</b>	Change in PGC1alpha level
Comparison groups	Group 1 v Group 1
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other <sup>[11]</sup>
P-value	= 0.63
Method	paired t test

Notes:

[11] - exploratory

### Secondary: Change in $\tau$ 1/2 PCr between 0 and 12 weeks

End point title	Change in $\tau$ 1/2 PCr between 0 and 12 weeks
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 and 12.

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: seconds				
arithmetic mean (standard deviation)	48.7 ( $\pm$ 39.1)	54.5 ( $\pm$ 31.7)		

### Statistical analyses

<b>Statistical analysis title</b>	Change in $\tau$ 1/2 PCr between wks 0 & 12
Comparison groups	Group 1 v Group 1

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other <sup>[12]</sup>
P-value	= 0.345 <sup>[13]</sup>
Method	paired t test

Notes:

[12] - exploratory

[13] - a priori threshold for significance = <0.05

Two sided

### Secondary: Change in Myocardial PCr/ATP ratio

End point title	Change in Myocardial PCr/ATP ratio
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 and 12

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4 <sup>[14]</sup>	4		
Units: PCr/ATP ratio				
arithmetic mean (standard deviation)	1.69 (± 0.2)	1.84 (± 0.2)		

Notes:

[14] - n=5 participants scanned at baseline due to technical error.

4 individuals had paired samples.

### Statistical analyses

<b>Statistical analysis title</b>	Change in myocardial PCr/ATP ratio
Comparison groups	Group 1 v Group 1
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other <sup>[15]</sup>
P-value	= 0.035
Method	paired t test

Notes:

[15] - exploratory

### Secondary: Change in Peak cardiac left ventricular torsion

End point title	Change in Peak cardiac left ventricular torsion
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 and 12.

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: degrees (°)				
arithmetic mean (standard deviation)	7.66 (± 1.20)	7.78 (± 1.25)		

### Statistical analyses

<b>Statistical analysis title</b>	Change in mean left ventricular torsion
Comparison groups	Group 1 v Group 1
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	other <sup>[16]</sup>
P-value	= 0.8 <sup>[17]</sup>
Method	paired t test

Notes:

[16] - exploratory

[17] - a priori threshold for significance = <0.05

Two sided

### Secondary: change in mean peak VO2

End point title	change in mean peak VO2
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 and 12.

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: ml/min				
arithmetic mean (standard deviation)	1214 (± 225)	1221 (± 221)		

### Statistical analyses

<b>Statistical analysis title</b>	Change in peak VO2
Comparison groups	Group 1 v Group 1

Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.91 <sup>[18]</sup>
Method	paired t test

Notes:

[18] - a priori threshold for significance = <0.05

Two sided

## Secondary: change in peak power

End point title	change in peak power
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End point description:

End point type	Secondary
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End point timeframe:

measured at weeks 0 and 12.

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: watts				
arithmetic mean (standard deviation)	87.2 (± 8.0)	88.2 (± 10.1)		

## Statistical analyses

<b>Statistical analysis title</b>	Change in mean peak power (W)
Comparison groups	Group 1 v Group 1
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	other <sup>[19]</sup>
P-value	= 0.87 <sup>[20]</sup>
Method	paired t test

Notes:

[19] - exploratory

[20] - a priori threshold for significance = <0.05

Two sided

## Secondary: Change in arterio-venous oxygen differential 0-12wks

End point title	Change in arterio-venous oxygen differential 0-12wks
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 and 12

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: mlO <sub>2</sub> /dl				
arithmetic mean (standard deviation)	11.4 (± 0.7)	10.4 (± 2.0)		

### Statistical analyses

<b>Statistical analysis title</b>	Change in mean peak a-VO <sub>2</sub> diff
Comparison groups	Group 1 v Group 1
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.37 <sup>[21]</sup>
Method	paired t test

Notes:

[21] - a priori threshold for significance = <0.05

Two sided

### Secondary: Change in NMDAS Total

End point title	Change in NMDAS Total
End point description:	
End point type	Secondary
End point timeframe:	
Measured at 0, 6 and 12 weeks	

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	24 (± 8.0)	24 (± 7.7)	21 (± 8.2)	

### Statistical analyses

<b>Statistical analysis title</b>	Change in NMDAS_total
Comparison groups	Group 1 v Group 1 v Group 1

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.115 <sup>[22]</sup>
Method	Repeated measures ANOVA

Notes:

[22] - a priori threshold for significance = <0.05

Two sided

### Secondary: Change in NMQ - mobility

End point title	Change in NMQ - mobility
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End point description:

End point type	Secondary
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End point timeframe:

Measured at 0,6 and 12 weeks

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	60 (± 14.7)	72 (± 25.3)	69 (± 12.5)	

### Statistical analyses

<b>Statistical analysis title</b>	change in NMQ - mobility
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[23]</sup>
P-value	= 0.127
Method	Repeated measures ANOVA

Notes:

[23] - exploratory

### Secondary: Change in NMQ - ADLs

End point title	Change in NMQ - ADLs
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End point description:

End point type	Secondary
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End point timeframe:

Measured at 0,6 and 12 weeks

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	86 ( $\pm$ 24.2)	87 ( $\pm$ 25.0)	91 ( $\pm$ 18.8)	

### Statistical analyses

Statistical analysis title	Change in NMQ - ADLs
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[24]</sup>
P-value	= 0.062
Method	Repeated measures ANOVA

Notes:

[24] - exploratory

### Secondary: Change in NMQ - Energy

End point title	Change in NMQ - Energy
End point description:	
End point type	Secondary
End point timeframe:	
Measured at 0, 6, 12 weeks	

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	45 ( $\pm$ 15.7)	46 ( $\pm$ 25.9)	49 ( $\pm$ 16.9)	

### Statistical analyses

Statistical analysis title	Change in NMQ - Energy
Comparison groups	Group 1 v Group 1 v Group 1

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[25]</sup>
P-value	= 0.127
Method	Repeated measures ANOVA

Notes:

[25] - exploratory

### Secondary: Change in NMQ - Vision

End point title	Change in NMQ - Vision
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End point description:

End point type	Secondary
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End point timeframe:

measured at Wk 0, 6 and 12 weeks

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	78 ( $\pm$ 21.3)	81 ( $\pm$ 16.1)	75 ( $\pm$ 14.3)	

### Statistical analyses

<b>Statistical analysis title</b>	Change in NMQ _ Vision
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[26]</sup>
P-value	= 0.425
Method	Repeated measures ANOVA

Notes:

[26] - exploratory

### Secondary: Change in NMQ - Communication

End point title	Change in NMQ - Communication
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.



End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	58 ( $\pm$ 19.0)	56 ( $\pm$ 14.3)	55 ( $\pm$ 13.7)	

### Statistical analyses

Statistical analysis title	Change in NMQ - Communication
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[27]</sup>
P-value	= 0.746
Method	Repeated measures ANOVA

Notes:

[27] - exploratory

### Secondary: Change in NMQ - Memory

End point title	Change in NMQ - Memory
End point description:	
End point type	Secondary
End point timeframe:	
measured at 0,6 and 12 weeks	

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	56 ( $\pm$ 12.5)	68.7 ( $\pm$ 23.9)	75 ( $\pm$ 20.4)	

### Statistical analyses

Statistical analysis title	Change in NMQ - Memory
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[28]</sup>
P-value	= 0.08
Method	Repeated measures ANOVA

Notes:

[28] - exploratory

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**Secondary: Change in NMQ - Food**

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End point title	Change in NMQ - Food
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End point description:

End point type	Secondary
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End point timeframe:

Measured at 0, 6 and 12 weeks

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End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	77 ( $\pm$ 17.6)	85.4 ( $\pm$ 13.8)	75 ( $\pm$ 20.4)	

**Statistical analyses**

<b>Statistical analysis title</b>	change in NMQ _food
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Comparison groups	Group 1 v Group 1 v Group 1
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Number of subjects included in analysis	18
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Analysis specification	Pre-specified
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Analysis type	other <sup>[29]</sup>
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P-value	= 0.094
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Method	Repeated measures ANOVA
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Notes:

[29] - exploratory

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**Secondary: Change in NMQ - Pain**

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End point title	Change in NMQ - Pain
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End point description:

End point type	Secondary
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End point timeframe:

Measured at 0, 6, 12 weeks

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End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	66 (± 32.3)	77 (± 40.4)	67.9 (± 36.8)	

### Statistical analyses

Statistical analysis title	change in NMQ - Pain
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[30]</sup>
P-value	= 0.514
Method	Repeated measures ANOVA

Notes:

[30] - exploratory

### Secondary: Change in NMQ - Muscle

End point title	Change in NMQ - Muscle
End point description:	
End point type	Secondary
End point timeframe:	
Measured at weeks 0, 6 and 12.	

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	67 (± 31.2)	73 (± 39.3)	69 (± 37.5)	

### Statistical analyses

Statistical analysis title	Change in NMQ - Muscle
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[31]</sup>
P-value	= 0.235
Method	Repeated measures ANOVA

Notes:

[31] - exploratory

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**Secondary: Change in NMQ - Migraine**

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End point title	Change in NMQ - Migraine
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.

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End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	79 ( $\pm$ 25.0)	77 ( $\pm$ 36.0)	83 ( $\pm$ 23.6)	

**Statistical analyses**

<b>Statistical analysis title</b>	change in NMQ - Migraine
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[32]</sup>
P-value	= 0.471
Method	Repeated measures ANOVA

Notes:

[32] - exploratory

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**Secondary: Change in NMQ - Emotions**

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End point title	Change in NMQ - Emotions
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.

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End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	56 ( $\pm$ 21.9)	66.5 ( $\pm$ 32.6)	66 ( $\pm$ 32.6)	

### Statistical analyses

<b>Statistical analysis title</b>	change in NMQ - Emotions
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[33]</sup>
P-value	= 0.173
Method	Repeated measures ANOVA

Notes:

[33] - exploratory

### Secondary: Change in NMQ - Stigma

End point title	Change in NMQ - Stigma
End point description:	
End point type	Secondary
End point timeframe:	
Measured at weeks 0, 6 and 12.	

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	69 ( $\pm$ 31.5)	73 ( $\pm$ 23.0)	64 ( $\pm$ 33.5)	

### Statistical analyses

<b>Statistical analysis title</b>	Change in NMQ - Stigma
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[34]</sup>
P-value	= 0.47
Method	Repeated measures ANOVA

Notes:

[34] - exploratory

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**Secondary: Change in NMQ - Family Role**

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End point title	Change in NMQ - Family Role
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.

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End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	58 (± 19.4)	62.5 (± 27.0)	56 (± 15.5)	

**Statistical analyses**

<b>Statistical analysis title</b>	Change in NMQ - Family role
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[35]</sup>
P-value	= 0.546
Method	Repeated measures ANOVA

Notes:

[35] - exploratory

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**Secondary: Change in NMQ - Personal Relations**

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End point title	Change in NMQ - Personal Relations
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.

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End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	56 ( $\pm$ 26.9)	63.5 ( $\pm$ 35.2)	64 ( $\pm$ 31.9)	

### Statistical analyses

Statistical analysis title	Change in NMQ - Personal Relations
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[36]</sup>
P-value	= 0.277
Method	Repeated measures ANOVA

Notes:

[36] - exploratory

### Secondary: Change in NMQ - Social Role

End point title	Change in NMQ - Social Role
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	48 ( $\pm$ 33.5)	60 ( $\pm$ 42.7)	54 ( $\pm$ 41.7)	

### Statistical analyses

Statistical analysis title	Change in NMQ - social role
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[37]</sup>
P-value	= 0.258
Method	Repeated measures ANOVA

Notes:

[37] - exploratory

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**Secondary: Change in Physical Component Score**

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End point title	Change in Physical Component Score
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.

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End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	37.5 (± 13.2)	34 (± 9.9)	34 (± 8.6)	

**Statistical analyses**

<b>Statistical analysis title</b>	Change in Physical Component Score
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Comparison groups	Group 1 v Group 1 v Group 1
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Number of subjects included in analysis	18
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Analysis specification	Pre-specified
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Analysis type	other <sup>[38]</sup>
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P-value	= 0.663
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Method	Repeated measures ANOVA
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Notes:

[38] - exploratory

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**Secondary: Change in Mental Component Score**

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End point title	Change in Mental Component Score
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.

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End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard deviation)	43.6 ( $\pm$ 7.9)	47 ( $\pm$ 7.4)	49 ( $\pm$ 7.6)	

### Statistical analyses

Statistical analysis title	Change in Mental Component Score
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[39]</sup>
P-value	= 0.028
Method	Repeated measures ANOVA

Notes:

[39] - exploratory

### Secondary: Change in Fatigue Impact Score\_Total

End point title	Change in Fatigue Impact Score_Total
End point description:	
End point type	Secondary
End point timeframe:	
Measured at 0, 6 and 12 weeks.	

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard error)	68 ( $\pm$ 11.7)	57 ( $\pm$ 13.9)	57 ( $\pm$ 7.7)	

### Statistical analyses

Statistical analysis title	Change in FIS - Total
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[40]</sup>
P-value	= 0.252
Method	Repeated measures ANOVA

Notes:

[40] - exploratory

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**Secondary: Change in Fatigue Impact Score\_Physical**

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End point title	Change in Fatigue Impact Score_Physical
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End point description:

End point type	Secondary
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End point timeframe:

Measured at 0, 6 and 12 weeks.

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End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard error)	31 (± 5.0)	25 (± 4.8)	26 (± 3.0)	

**Statistical analyses**

<b>Statistical analysis title</b>	Change in FIS - Physical
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[41]</sup>
P-value	= 0.127
Method	Repeated measures ANOVA

Notes:

[41] - exploratory

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**Secondary: Change in Fatigue Impact Score\_Cognitive**

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End point title	Change in Fatigue Impact Score_Cognitive
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End point description:

End point type	Secondary
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End point timeframe:

Measured at 0, 6 and 12 weeks.

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End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard error)	19 ( $\pm$ 3.0)	16 ( $\pm$ 4.1)	14 ( $\pm$ 1.1)	

## Statistical analyses

Statistical analysis title	Change in FIS - Cognitive
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[42]</sup>
P-value	= 0.289
Method	Repeated measures ANOVA

Notes:

[42] - exploratory

## Secondary: Change in Fatigue Impact Score\_Social

End point title	Change in Fatigue Impact Score_Social
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 , 6 and 12.

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: score				
arithmetic mean (standard error)	18 ( $\pm$ 3.9)	16 ( $\pm$ 5.2)	17 ( $\pm$ 3.9)	

## Statistical analyses

Statistical analysis title	Change in FIS - Social
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[43]</sup>
P-value	= 0.602
Method	Repeated measures ANOVA

Notes:

[43] - exploratory

### Secondary: Change in IPAQ Score

End point title	Change in IPAQ Score
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: MET/mins/week				
median (standard error)	1303 ( $\pm$ 531.8)	787.5 ( $\pm$ 575.3)	132.0 ( $\pm$ 324.4)	

### Statistical analyses

Statistical analysis title	Change in IPAQ score
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Comparison groups	Group 1 v Group 1 v Group 1
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Number of subjects included in analysis	18
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Analysis specification	Pre-specified
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Analysis type	other <sup>[44]</sup>
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P-value	= 0.084 <sup>[45]</sup>
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Method	Repeated measures ANOVA
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Notes:

[44] - exploratory

[45] - a priori threshold for significance = <0.05

Two sided

### Secondary: Change in Daytime Acceleration

End point title	Change in Daytime Acceleration
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 , 6 and 12.

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	6	
Units: milligravity				
arithmetic mean (standard error)	33.56 ( $\pm$ 4.6)	31.35 ( $\pm$ 5.7)	28.33 ( $\pm$ 4.7)	

### Statistical analyses

<b>Statistical analysis title</b>	Change in daytime acceleration
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other <sup>[46]</sup>
P-value	= 0.074 <sup>[47]</sup>
Method	Repeated measures ANOVA

Notes:

[46] - exploratory

[47] - a priori threshold for significance = <0.05

Two sided

### Secondary: Change in Vigorous Activity

End point title	Change in Vigorous Activity
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	6	
Units: mins				
arithmetic mean (standard error)	1.14 ( $\pm$ 0.33)	1.09 ( $\pm$ 0.31)	0.68 ( $\pm$ 0.19)	

### Statistical analyses

<b>Statistical analysis title</b>	Change in vigorous activity
Comparison groups	Group 1 v Group 1 v Group 1

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other <sup>[48]</sup>
P-value	= 0.021 <sup>[49]</sup>
Method	Repeated measures ANOVA

Notes:

[48] - exploratory

[49] - a priori threshold for significance = <0.05

Two sided

### Secondary: Change in Moderate Activity

End point title	Change in Moderate Activity
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	6	
Units: seconds				
arithmetic mean (standard error)	70.49 (± 19.35)	60.51 (± 25.41)	54.98 (± 20.45)	

### Statistical analyses

<b>Statistical analysis title</b>	Change in time in moderate activity
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other <sup>[50]</sup>
P-value	= 0.165
Method	Repeated measures ANOVA

Notes:

[50] - exploratory

### Secondary: Change in Light Activity

End point title	Change in Light Activity
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0, 6 and 12.

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	6	
Units: minutes				
arithmetic mean (standard error)	161.74 ( $\pm$ 16.7)	148.42 ( $\pm$ 20.05)	133.14 ( $\pm$ 15.07)	

### Statistical analyses

Statistical analysis title	Change in time in light activity
Comparison groups	Group 1 v Group 1 v Group 1
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other <sup>[51]</sup>
P-value	= 0.041
Method	Repeated measures ANOVA

Notes:

[51] - exploratory

### Secondary: Change in Muscle heteroplasmy

End point title	Change in Muscle heteroplasmy
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 and 12.

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: percentage				
arithmetic mean (full range (min-max))	72 (53 to 84)	71 (56 to 87)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Urine Heteroplasmy

End point title	Change in Urine Heteroplasmy
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 and 12.

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: percentage				
arithmetic mean (full range (min-max))	65 (33 to 89)	61 (38 to 83)	72 (46 to 92)	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Blood Heteroplasmy

End point title	Change in Blood Heteroplasmy
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 and 12.

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: percentage				
arithmetic mean (full range (min-max))	19 (11 to 27)	19 (13 to 30)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in COX deficient Fibres

End point title	Change in COX deficient Fibres
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End point description:

End point type	Secondary
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End point timeframe:

Measured at weeks 0 and 12.

End point values	Group 1	Group 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: percentage				
arithmetic mean (full range (min-max))	5.0 (2.0 to 10.0)	6.0 (3.0 to 12.0)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Timed Up and Go

End point title Change in Timed Up and Go

End point description:

End point type Secondary

End point timeframe:

Measured at 0, 6 and 12 weeks.

End point values	Group 1	Group 1	Group 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: seconds				
arithmetic mean (full range (min-max))	8.9 (7.13 to 11.47)	8.71 (6.22 to 11.7)	8.46 (6.46 to 10.6)	

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Enrolment in study up to 2 weeks after taking final dose of IMP.

Adverse event reporting additional description:

Given the multi-systemic feature of mitochondrial disorders, and the low numbers of participants, all adverse events were captured during the study period.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20
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### Reporting groups

Reporting group title	Group 1
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Reporting group description:

All participants recruited to study, who it was anticipated at onset would take 6 weeks bezafibrate at 200mg TDS; followed by 400mg TDS for 6 weeks.

Serious adverse events	Group 1		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Constipation	Additional description: Participant attended hospital on morning of planned week 12 muscle biopsy with acute onset abdominal pain. Admitted under surgeons for assessment. Abdominal X-Ray confirmed faecal loading. Pain improved following passing stool.		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Group 1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Vascular disorders			
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Increased appetite			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Improved sleep			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Muscle tingling			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Energy increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Improved myalgia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Post-menopausal haemorrhage			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Investigations			
Glomerular filtration rate decreased			

subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	3		
Blood creatine increased			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Elevated creatine phosphokinase			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Eosinophil count increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	5 / 6 (83.33%)		
occurrences (all)	40		
Headache			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Eye disorders			
Refraction disorder			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Flatulence			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Oral dryness and saliva altered			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Abdominal Pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rosaceas			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pruritis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Skin odour abnormal			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dermatitis contact			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Incision site dermatitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 6 (16.67%)</p> <p>1</p> <p>1 / 6 (16.67%)</p> <p>1</p>		
<p>Endocrine disorders</p> <p>Hypoglycaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Decreased insulin requirement</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Increased insulin requirement</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 6 (83.33%)</p> <p>44</p> <p>1 / 6 (16.67%)</p> <p>1</p> <p>1 / 6 (16.67%)</p> <p>2</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Myalgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Spondylitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Muscle spasms</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Metatarsalgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 6 (83.33%)</p> <p>9</p> <p>1 / 6 (16.67%)</p> <p>7</p> <p>2 / 6 (33.33%)</p> <p>5</p> <p>1 / 6 (16.67%)</p> <p>1</p> <p>1 / 6 (16.67%)</p> <p>1</p>		
<p>Infections and infestations</p> <p>Viral upper respiratory tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Viral sinusitis</p>	<p>4 / 6 (66.67%)</p> <p>12</p>		

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Respiratory tract infection viral			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	4		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2015	MHRA approval for use of protocol V2.0 obtained 11 June 2015. REC Approval for protocol V2.0 24 July 2015.  Protocol updated from V1.0 to reflect changes in eligibility criteria to make sure the study was relevant to the patient population. MHRA only approved V2.0 protocol. Amendment submitted to ensure REC approval in place for V2.0 protocol also.
09 December 2015	REC approval for addition of Prof Horvath as PI; increased time between screen and baseline; change in accelerometry equipment; addition of statin washout; removal of site specific muscle biopsy details; clarification that potential biomarkers will be analysed in muscle tissue and serum; streamlining information within the protocol.
19 April 2016	Updated following Trial Oversight Committee meeting, to improve blood glucose monitoring for participants in light of hypoglycaemic episodes.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Adverse event profile in the first six participants, and in particular hypoglycaemic episodes, led to discontinuation of study after 6 individuals. It was not thought that persons would tolerate a higher dose.

Notes: