



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 |
|-----------------------|------|

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 |
| Public contact | Patrick Chinnery, Newcastle University, +44 01912418611, patrick.chinnery@ncl.ac.uk |
| Scientific contact | Patrick Chinnery, Newcastle University, +44 01912418611, patrick.chinnery@ncl.ac.uk |

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

| | |
|--|--------------|
| 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 2 | 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

| | |
|--|--------------|
| 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 3 | Group 1 |
|---------------------------------------|---------|
| Started | 6 |
| Completed | 6 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Baseline |
|-----------------------|----------|

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 ⁻¹ x g tissue ⁻¹ | | | |
| 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 | | |

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|---|--------|---|--|
| 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 | | | |

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

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

| | | | |
|---|------------------------|--|--|
| 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 ⁻¹ x g tissue ⁻¹ 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) | | | |

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 ^[1] |
| 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

| | |
|---|---|
| Statistical analysis title | 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 ^[2] |
| 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

| | |
|---|--|
| Statistical analysis title | 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 ^[3] |
| 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 |
|-----------------|---|

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: CIVCS | | | | |
| arithmetic mean (standard error) | 1.406 (\pm 0.096) | 1.399 (\pm 0.1189) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | 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 ^[4] |
| P-value | = 0.96 |
| Method | paired t test |

Notes:

[4] - exploratory

Secondary: Change in Citrate Synthase

| | |
|-----------------|----------------------------|
| End point title | Change in Citrate Synthase |
|-----------------|----------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|----------------------------|--|

| | |
|-------------------|-------------------|
| Comparison groups | Group 1 v Group 1 |
|-------------------|-------------------|

| | |
|---|----|
| Number of subjects included in analysis | 12 |
|---|----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|----------------------|
| Analysis type | other ^[5] |
|---------------|----------------------|

| | |
|---------|--------|
| P-value | = 0.72 |
|---------|--------|

| | |
|--------|---------------|
| Method | paired t test |
|--------|---------------|

Notes:

[5] - exploratory

Secondary: Change in mitochondrial DNA copy number

| | |
|-----------------|---|
| End point title | Change in mitochondrial DNA copy number |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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

| Statistical analysis title | 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 ^[6] |
| 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

| Statistical analysis title | 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 ^[7] |
| P-value | = 0.021 ^[8] |
| 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 |
|-----------------|------------------------|

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) | 1973 (± 110.2) | 2432 (± 171.8) | 2795 (± 160.3) | |

Statistical analyses

| | |
|---|-----------------------------|
| Statistical analysis title | 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 ^[9] |
| P-value | = 0.007 ^[10] |
| 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 |
|-----------------|-----------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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

| | |
|---|---------------------------|
| Statistical analysis title | 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 ^[11] |
| P-value | = 0.63 |
| Method | paired t test |

Notes:

[11] - exploratory

Secondary: Change in τ 1/2 PCr between 0 and 12 weeks

| | |
|-----------------|---|
| End point title | Change in τ 1/2 PCr between 0 and 12 weeks |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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

| | |
|-----------------------------------|---|
| Statistical analysis title | Change in τ 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 ^[12] |
| P-value | = 0.345 ^[13] |
| 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 |
|-----------------|------------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 ^[14] | 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

| | |
|---|------------------------------------|
| Statistical analysis title | 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 ^[15] |
| 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 |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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

| | |
|---|---|
| Statistical analysis title | 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 ^[16] |
| P-value | = 0.8 ^[17] |
| 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 |
|-----------------|-------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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

| | |
|----------------------------|--------------------|
| Statistical analysis title | 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 ^[18] |
| 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 |
|-----------------|----------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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

| | |
|---|-------------------------------|
| Statistical analysis title | 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 ^[19] |
| P-value | = 0.87 ^[20] |
| 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 |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 ₂ /dl | | | | |
| arithmetic mean (standard deviation) | 11.4 (± 0.7) | 10.4 (± 2.0) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Change in mean peak a-VO ₂ 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 ^[21] |
| 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

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | 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 ^[22] |
| 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 |
|-----------------|--------------------------|

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) | 60 (± 14.7) | 72 (± 25.3) | 69 (± 12.5) | |

Statistical analyses

| | |
|---|-----------------------------|
| Statistical analysis title | 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 ^[23] |
| P-value | = 0.127 |
| Method | Repeated measures ANOVA |

Notes:

[23] - exploratory

Secondary: Change in NMQ - ADLs

| | |
|-----------------|----------------------|
| End point title | Change in NMQ - ADLs |
|-----------------|----------------------|

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) | 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 ^[24] |
| 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 ^[25] |
| P-value | = 0.127 |
| Method | Repeated measures ANOVA |

Notes:

[25] - exploratory

Secondary: Change in NMQ - Vision

| | |
|-----------------|------------------------|
| End point title | Change in NMQ - Vision |
|-----------------|------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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

| | |
|---|-----------------------------|
| Statistical analysis title | 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 ^[26] |
| P-value | = 0.425 |
| Method | Repeated measures ANOVA |

Notes:

[26] - exploratory

Secondary: Change in NMQ - Communication

| | |
|-----------------|-------------------------------|
| End point title | Change in NMQ - Communication |
|-----------------|-------------------------------|

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) | 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 ^[27] |
| 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 ^[28] |
| P-value | = 0.08 |
| Method | Repeated measures ANOVA |

Notes:

[28] - exploratory

Secondary: Change in NMQ - Food

| | |
|-----------------|----------------------|
| End point title | Change in NMQ - Food |
|-----------------|----------------------|

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) | 77 (\pm 17.6) | 85.4 (\pm 13.8) | 75 (\pm 20.4) | |

Statistical analyses

| | |
|-----------------------------------|---------------------|
| Statistical analysis title | change in NMQ _food |
|-----------------------------------|---------------------|

| | |
|-------------------|-----------------------------|
| Comparison groups | Group 1 v Group 1 v Group 1 |
|-------------------|-----------------------------|

| | |
|---|----|
| Number of subjects included in analysis | 18 |
|---|----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-----------------------|
| Analysis type | other ^[29] |
|---------------|-----------------------|

| | |
|---------|---------|
| P-value | = 0.094 |
|---------|---------|

| | |
|--------|-------------------------|
| Method | Repeated measures ANOVA |
|--------|-------------------------|

Notes:

[29] - exploratory

Secondary: Change in NMQ - Pain

| | |
|-----------------|----------------------|
| End point title | Change in NMQ - Pain |
|-----------------|----------------------|

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) | 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 ^[30] |
| 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 ^[31] |
| P-value | = 0.235 |
| Method | Repeated measures ANOVA |

Notes:

[31] - exploratory

Secondary: Change in NMQ - Migraine

| | |
|-----------------|--------------------------|
| End point title | Change in NMQ - Migraine |
|-----------------|--------------------------|

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) | 79 (\pm 25.0) | 77 (\pm 36.0) | 83 (\pm 23.6) | |

Statistical analyses

| | |
|---|-----------------------------|
| Statistical analysis title | 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 ^[32] |
| P-value | = 0.471 |
| Method | Repeated measures ANOVA |

Notes:

[32] - exploratory

Secondary: Change in NMQ - Emotions

| | |
|-----------------|--------------------------|
| End point title | Change in NMQ - Emotions |
|-----------------|--------------------------|

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) | 56 (\pm 21.9) | 66.5 (\pm 32.6) | 66 (\pm 32.6) | |

Statistical analyses

| Statistical analysis title | 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 ^[33] |
| 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

| Statistical analysis title | 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 ^[34] |
| P-value | = 0.47 |
| Method | Repeated measures ANOVA |

Notes:

[34] - exploratory

Secondary: Change in NMQ - Family Role

| | |
|-----------------|-----------------------------|
| End point title | Change in NMQ - Family Role |
|-----------------|-----------------------------|

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) | 58 (\pm 19.4) | 62.5 (\pm 27.0) | 56 (\pm 15.5) | |

Statistical analyses

| | |
|----------------------------|-----------------------------|
| Statistical analysis title | 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 ^[35] |
|---------------|-----------------------|

| | |
|---------|---------|
| P-value | = 0.546 |
|---------|---------|

| | |
|--------|-------------------------|
| Method | Repeated measures ANOVA |
|--------|-------------------------|

Notes:

[35] - exploratory

Secondary: Change in NMQ - Personal Relations

| | |
|-----------------|------------------------------------|
| End point title | Change in NMQ - Personal Relations |
|-----------------|------------------------------------|

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) | 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 ^[36] |
| 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 |
|-----------------|-----------------------------|

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) | 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 ^[37] |
| P-value | = 0.258 |
| Method | Repeated measures ANOVA |

Notes:

[37] - exploratory

Secondary: Change in Physical Component Score

| | |
|-----------------|------------------------------------|
| End point title | Change in Physical Component Score |
|-----------------|------------------------------------|

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) | 37.5 (± 13.2) | 34 (± 9.9) | 34 (± 8.6) | |

Statistical analyses

| | |
|----------------------------|------------------------------------|
| Statistical analysis title | Change in Physical 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 ^[38] |
|---------------|-----------------------|

| | |
|---------|---------|
| P-value | = 0.663 |
|---------|---------|

| | |
|--------|-------------------------|
| Method | Repeated measures ANOVA |
|--------|-------------------------|

Notes:

[38] - exploratory

Secondary: Change in Mental Component Score

| | |
|-----------------|----------------------------------|
| End point title | Change in Mental Component Score |
|-----------------|----------------------------------|

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) | 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 ^[39] |
| 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 ^[40] |
| P-value | = 0.252 |
| Method | Repeated measures ANOVA |

Notes:

[40] - exploratory

Secondary: Change in Fatigue Impact Score_Physical

| | |
|-----------------|---|
| End point title | Change in Fatigue Impact Score_Physical |
|-----------------|---|

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) | 31 (± 5.0) | 25 (± 4.8) | 26 (± 3.0) | |

Statistical analyses

| | |
|---|-----------------------------|
| Statistical analysis title | 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 ^[41] |
| P-value | = 0.127 |
| Method | Repeated measures ANOVA |

Notes:

[41] - exploratory

Secondary: Change in Fatigue Impact Score_Cognitive

| | |
|-----------------|--|
| End point title | Change in Fatigue Impact Score_Cognitive |
|-----------------|--|

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) | 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 ^[42] |
| 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 |
|-----------------|---------------------------------------|

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 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 ^[43] |
| P-value | = 0.602 |
| Method | Repeated measures ANOVA |

Notes:

[43] - exploratory

Secondary: Change in IPAQ Score

| | |
|-----------------|----------------------|
| End point title | Change in IPAQ Score |
|-----------------|----------------------|

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: MET/mins/week | | | | |
| median (standard error) | 1303 (± 531.8) | 787.5 (± 575.3) | 132.0 (± 324.4) | |

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Change in IPAQ 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 ^[44] |
|---------------|-----------------------|

| | |
|---------|-------------------------|
| P-value | = 0.084 ^[45] |
|---------|-------------------------|

| | |
|--------|-------------------------|
| Method | Repeated measures ANOVA |
|--------|-------------------------|

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 |
|-----------------|--------------------------------|

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 | 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

| Statistical analysis title | 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 ^[46] |
| P-value | = 0.074 ^[47] |
| 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 |
|-----------------|-----------------------------|

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 | 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

| Statistical analysis title | 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 ^[48] |
| P-value | = 0.021 ^[49] |
| 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 |
|-----------------|-----------------------------|

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 | 5 | 6 | |
| Units: seconds | | | | |
| arithmetic mean (standard error) | 70.49 (± 19.35) | 60.51 (± 25.41) | 54.98 (± 20.45) | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | 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 ^[50] |
| P-value | = 0.165 |
| Method | Repeated measures ANOVA |

Notes:

[50] - exploratory

Secondary: Change in Light Activity

| | |
|-----------------|--------------------------|
| End point title | Change in Light Activity |
|-----------------|--------------------------|

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 | 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 ^[51] |
| P-value | = 0.041 |
| Method | Repeated measures ANOVA |

Notes:

[51] - exploratory

Secondary: Change in Muscle heteroplasmy

| | |
|-----------------|-------------------------------|
| End point title | Change in Muscle heteroplasmy |
|-----------------|-------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|--------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 20 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Group 1 |
|-----------------------|---------|

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 | | | |

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

| | | | |
|------------------------------------|----------------|--|--|
| 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:

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: