# Clinical trial results:
# Perindopril and Leucine to improve muscle function in older people

## Summary

| | |
|---|---|
| EudraCT number | 2014-003455-61 |
| Trial protocol | GB |
| Global end of trial date | 15 January 2020 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 29 May 2021 |
| First version publication date | 29 May 2021 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 2013GR06 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | ISRCTN90094835 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | University of Dundee |
| Sponsor organisation address | Ninewells Hospital, Dundee, United Kingdom, DD1 9SY |
| Public contact | Professor Miles Witham<br>0191 208 1317, Tayside Academic Health Sciences Centre Level 10, Ninewells Hospital, Dundee DD1 9SY<br>01382 383140, +44 01912081317, Miles.Witham@newcastle.ac.uk |
| Scientific contact | Professor Miles Witham<br>0191 208 1317, Tayside Academic Health Sciences Centre Level 10, Ninewells Hospital, Dundee DD1 9SY<br>01382 383140, +44 01382 383140, tctu@dundee.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 | 18 February 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 January 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 January 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To determine the efficacy of leucine and ACEi in improving physical function in older people with sarcopenia

Protection of trial subjects:

Monitoring of serum potassium, creatinine, and orthostatic blood pressure (safety for perindopril)
Selection of outcomes and study length to minimise burden on participants

Background therapy:

Usual care. Participants undertaking exercise training were excluded as the trial aimed to test the efficacy of perindopril and leucine in participants who were not already exercising. Previous work had already examined the effect of perindopril and leucine as adjuncts to exercise training.

Evidence for comparator:

Placebo selected as this was an efficacy trial and there are no other pharmacological interventions with proven efficacy for sarcopenia.

| | |
|---|---|
| Actual start date of recruitment | 01 May 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: 145 |
| Worldwide total number of subjects | 145 |
| EEA total number of subjects | 0 |

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) | 0 |

| | |
|---|---|
| From 65 to 84 years | 112 |
| 85 years and over | 33 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment in UK (14 centres) from June 2018 to December 2020

### Pre-assignment

Screening details:

320 attended screening visit. Screen fail reasons:
- Not met sarcopenia criteria: 129
- Symptomatic orthostatic hypotension: 13
- High potassium: 6
- Excluded medication: 4
- Excluded medical condition: 10
- Other: 16

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer |

Blinding implementation details:

Matching placebo for perindopril and for leucine

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Perindopril + Leucine |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Perindopril |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral powder |
| Routes of administration | Oral use |

Dosage and administration details:

2mg once daily, rising to 4mg once daily after 2 weeks if tolerated

| | |
|---|---|
| Investigational medicinal product name | Leucine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral powder |
| Routes of administration | Oral use |

Dosage and administration details:

2.5g three times a day with meals

| | |
|---|---|
| **Arm title** | Perindopril placebo + Leucine |

Arm description: -

| | |
|---|---|
| Arm type | Mixed placebo/active arm |
| Investigational medicinal product name | Placebo for perindopril |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral powder |
| Routes of administration | Oral use |

| | |
|---|---|
| Dosage and administration details: | |
| placebo for 2mg perindopril once daily, changing to placebo for 4mg perindopril once daily after 2 weeks if tolerated | |
| Investigational medicinal product name | Leucine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral powder |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 2.5g three times a day with meals | |
| **Arm title** | Perindopril + Leucine placebo |
| Arm description: - | |
| Arm type | Mixed placebo/active arm |
| No investigational medicinal product assigned in this arm | |
| **Arm title** | Placebo/Placebo |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo for perindopril and placebo for leucine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral powder |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Placebo for 4mg perindopril once daily and placebo for leucine 2.5g three times a day with food | |

| **Number of subjects in period 1** | Perindopril + Leucine | Perindopril placebo + Leucine | Perindopril + Leucine placebo |
|---|---|---|---|
| Started | 39 | 33 | 34 |
| Completed | 28 | 24 | 24 |
| Not completed | 11 | 9 | 10 |
| Adverse event, serious fatal | - | - | 1 |
| Physician decision | 3 | 1 | 1 |
| Adverse event, non-fatal | 1 | 1 | - |
| Other | 2 | 1 | - |
| Patient choice | 5 | 6 | 8 |

| **Number of subjects in period 1** | Placebo/Placebo |
|---|---|
| Started | 39 |
| Completed | 33 |
| Not completed | 6 |
| Adverse event, serious fatal | - |
| Physician decision | - |
| Adverse event, non-fatal | - |
| Other | - |
| Patient choice | 6 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Perindopril + Leucine |
| Reporting group description: - | |
| Reporting group title | Perindopril placebo + Leucine |
| Reporting group description: - | |
| Reporting group title | Perindopril + Leucine placebo |
| Reporting group description: - | |
| Reporting group title | Placebo/Placebo |
| Reporting group description: - | |

| Reporting group values | Perindopril + Leucine | Perindopril placebo + Leucine | Perindopril + Leucine placebo |
|---|---|---|---|
| Number of subjects | 39 | 33 | 34 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 32 | 29 | 31 |
| 85 years and over | 7 | 4 | 3 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 78.1 | 78.6 | 79.5 |
| standard deviation | ± 5.5 | ± 6.5 | ± 6.6 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 22 | 16 | 17 |
| Male | 17 | 17 | 17 |
| Short Physical Performance Battery<br>Units: Points | | | |
| arithmetic mean | 7.3 | 6.7 | 6.8 |
| standard deviation | ± 2.1 | ± 2.2 | ± 2.5 |
| Number of medications<br>Units: count | | | |
| median | 4 | 5 | 5 |
| inter-quartile range (Q1-Q3) | 2 to 6 | 2.5 to 7 | 4 to 7 |

| Reporting group values | Placebo/Placebo | Total | |
|---|---|---|---|
| Number of subjects | 39 | 145 | |
| Age categorical<br>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) | 0 | 0 | |
| From 65-84 years | 33 | 125 | |
| 85 years and over | 6 | 20 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 79.0 | | |
| standard deviation | ± 5.7 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 23 | 78 | |
| Male | 16 | 67 | |
| Short Physical Performance Battery | | | |
| Units: Points | | | |
| arithmetic mean | 7.1 | | |
| standard deviation | ± 2.6 | - | |
| Number of medications | | | |
| Units: count | | | |
| median | 5 | | |
| inter-quartile range (Q1-Q3) | 3 to 7 | - | |

| **Subject analysis sets** | |
|---|---|
| Subject analysis set title | Perindopril vs placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All randomised participants; comparison of all those receiving perindopril vs all those receiving the placebo for perindopril | |
| Subject analysis set title | Leucine vs placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All randomised participants. Analysis of all those receiving leucine vs all those receiving leucine placebo | |

| **Reporting group values** | Perindopril vs placebo | Leucine vs placebo | |
|---|---|---|---|
| Number of subjects | 145 | 145 | |
| 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) | 0 | 0 | |
| From 65-84 years | 125 | 125 | |

| | | | |
|---|---|---|---|
| 85 years and over | 20 | 20 | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| arithmetic mean | 78.8 | 78.8 | |
| standard deviation | ± 6.0 | ± 6.0 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 78 | 78 | |
| Male | 67 | 67 | |
| Short Physical Performance Battery<br>Units: Points | | | |
| arithmetic mean | 7.0 | 7.0 | |
| standard deviation | ± 2.3 | ± 2.3 | |
| Number of medications<br>Units: count | | | |
| median | 5 | 5 | |
| inter-quartile range (Q1-Q3) | 3 to 7 | 3 to 7 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Perindopril + Leucine |
| Reporting group description: - | |
| Reporting group title | Perindopril placebo + Leucine |
| Reporting group description: - | |
| Reporting group title | Perindopril + Leucine placebo |
| Reporting group description: - | |
| Reporting group title | Placebo/Placebo |
| Reporting group description: - | |
| Subject analysis set title | Perindopril vs placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All randomised participants; comparison of all those receiving perindopril vs all those receiving the placebo for perindopril | |
| Subject analysis set title | Leucine vs placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All randomised participants. Analysis of all those receiving leucine vs all those receiving leucine placebo | |

### Primary: Short physical performance battery

| | |
|---|---|
| End point title | Short physical performance battery |
| End point description: | |
| Repeated measures mixed model adjusted for baseline age, sex, Charlson score, handgrip | |
| End point type | Primary |
| End point timeframe: | |
| 12 months | |

| End point values | Perindopril vs placebo | Leucine vs placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 145 | 145 | | |
| Units: points | | | | |
| arithmetic mean (confidence interval 95%) | -0.1 (-1.2 to 1.0) | 0.1 (-1.0 to 1.1) | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Repeated measures mixed model |
| Comparison groups | Perindopril vs placebo v Leucine vs placebo |

| | |
|---|---|
| Number of subjects included in analysis | 290 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | = 0.89 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference, repeated measures |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 1 |

Notes:

[1] - Unable to enter results for both comparisons in this 2x2 trial, and the software has incorrectly added the two analysis sets together. The comparison involving perindopril has been reported here, and the number in the analysis is 145 participants.

## Secondary: Six minute walk distance

| | |
|---|---|
| End point title | Six minute walk distance |

End point description:

Repeated measures mixed model adjusted for baseline age, sex, Charlson score, handgrip

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

End point timeframe:

12 months

| End point values | Perindopril vs placebo | Leucine vs placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 145 | 145 | | |
| Units: metres | | | | |
| arithmetic mean (confidence interval 95%) | -32 (-75 to 12) | 17 (-25 to 59) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Appendicular muscle mass

| | |
|---|---|
| End point title | Appendicular muscle mass |

End point description:

Repeated measures mixed model adjusted for baseline age, sex, Charlson score, handgrip

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

End point timeframe:

12 months

| End point values | Perindopril vs placebo | Leucine vs placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 145 | 145 | | |
| Units: kg/m2 | | | | |
| arithmetic mean (confidence interval 95%) | -0.4 (-1.1 to 0.3) | -0.25 (-0.95 to 0.44) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From consent to 30 days after completion of participation for each individual | |
| Adverse event reporting additional description: | |
| AEs collected at each study visit and by medical records review | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21 |

| Reporting groups | |
|---|---|
| Reporting group title | Perindopril + Leucine |
| Reporting group description: - | |
| Reporting group title | Perindopril placebo + Leucine |
| Reporting group description: - | |
| Reporting group title | Perindopril + Leucine placebo |
| Reporting group description: - | |
| Reporting group title | Placebo/Placebo |
| Reporting group description: - | |

| Serious adverse events | Perindopril + Leucine | Perindopril placebo + Leucine | Perindopril + Leucine placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 33 (0.00%) | 1 / 34 (2.94%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| leukaemia | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 33 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| Serious adverse events | Placebo/Placebo | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Blood and lymphatic system disorders | | | |
| leukaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Perindopril + Leucine | Perindopril placebo + Leucine | Perindopril + Leucine placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 38 / 39 (97.44%) | 29 / 33 (87.88%) | 31 / 34 (91.18%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin cancer | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 33 (0.00%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 0 | 2 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | 2 / 33 (6.06%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | 0 / 33 (0.00%) | 2 / 34 (5.88%) |
| occurrences (all) | 1 | 0 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 6 / 39 (15.38%) | 3 / 33 (9.09%) | 3 / 34 (8.82%) |
| occurrences (all) | 6 | 3 | 3 |
| Psychiatric disorders | | | |
| Anxiety disorder | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 33 (0.00%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 0 | 2 |
| Depression | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | 0 / 33 (0.00%) | 2 / 34 (5.88%) |
| occurrences (all) | 1 | 0 | 2 |
| Injury, poisoning and procedural complications | | | |
| Joint injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 33 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle strain | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | 0 / 33 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 33 (0.00%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 0 | 2 |
| Soft tissue injury | | | |
| subjects affected / exposed | 8 / 39 (20.51%) | 3 / 33 (9.09%) | 4 / 34 (11.76%) |
| occurrences (all) | 8 | 3 | 4 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | 1 / 33 (3.03%) | 0 / 34 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | 0 / 33 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 39 (12.82%) | 2 / 33 (6.06%) | 5 / 34 (14.71%) |
| occurrences (all) | 5 | 2 | 5 |
| Headache | | | |
| subjects affected / exposed | 5 / 39 (12.82%) | 0 / 33 (0.00%) | 1 / 34 (2.94%) |
| occurrences (all) | 5 | 0 | 1 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 2 / 33 (6.06%) | 0 / 34 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | 0 / 33 (0.00%) | 2 / 34 (5.88%) |
| occurrences (all) | 1 | 0 | 2 |
| Migraine | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | 2 / 33 (6.06%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Cataract | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | 0 / 33 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 39 (7.69%) | 0 / 33 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | 2 / 33 (6.06%) | 5 / 34 (14.71%) |
| occurrences (all) | 1 | 2 | 5 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | 2 / 33 (6.06%) | 3 / 34 (8.82%) |
| occurrences (all) | 2 | 2 | 3 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 33 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | 0 / 33 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 3 / 39 (7.69%) | 1 / 33 (3.03%) | 2 / 34 (5.88%) |
| occurrences (all) | 3 | 1 | 2 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 33 (0.00%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 0 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 39 (10.26%) | 0 / 33 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | 1 / 33 (3.03%) | 0 / 34 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 33 (0.00%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 0 | 2 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|---|---|---|
| Arthralgia | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | 2 / 33 (6.06%) | 1 / 34 (2.94%) |
| occurrences (all) | 1 | 2 | 1 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 33 (0.00%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 0 | 2 |
| Back pain | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | 2 / 33 (6.06%) | 1 / 34 (2.94%) |
| occurrences (all) | 2 | 2 | 1 |
| Muscle spasms | | | |
| subjects affected / exposed | 3 / 39 (7.69%) | 0 / 33 (0.00%) | 1 / 34 (2.94%) |
| occurrences (all) | 3 | 0 | 1 |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | 1 / 33 (3.03%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Infections and infestations | | | |
| Ear infection | | | |
| subjects affected / exposed | 3 / 39 (7.69%) | 0 / 33 (0.00%) | 1 / 34 (2.94%) |
| occurrences (all) | 3 | 0 | 1 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 33 (0.00%) | 1 / 34 (2.94%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | 0 / 33 (0.00%) | 2 / 34 (5.88%) |
| occurrences (all) | 1 | 0 | 2 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | 0 / 33 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 3 / 39 (7.69%) | 0 / 33 (0.00%) | 1 / 34 (2.94%) |
| occurrences (all) | 3 | 0 | 1 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 4 / 39 (10.26%) | 0 / 33 (0.00%) | 3 / 34 (8.82%) |
| occurrences (all) | 4 | 0 | 3 |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 39 (2.56%) | 3 / 33 (9.09%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 39 (7.69%) | 1 / 33 (3.03%) | 1 / 34 (2.94%) |
| occurrences (all) | 3 | 1 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 39 (7.69%) | 7 / 33 (21.21%) | 4 / 34 (11.76%) |
| occurrences (all) | 3 | 7 | 4 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 39 (7.69%) | 0 / 33 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |

| **Non-serious adverse events** | Placebo/Placebo | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 33 / 39 (84.62%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin cancer | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 4 / 39 (10.26%) | | |
| occurrences (all) | 4 | | |
| Psychiatric disorders | | | |
| Anxiety disorder | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Depression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Joint injury | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | | |
| occurrences (all) | 2 | | |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Soft tissue injury | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | | |
| occurrences (all) | 2 | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 39 (7.69%) | | |
| occurrences (all) | 3 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Migraine | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | | |
| occurrences (all) | 2 | | |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | | |
| occurrences (all) | 2 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |
| Skin ulcer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | | |
| occurrences (all) | 2 | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | | |
| occurrences (all) | 2 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 39 (0.00%) | | |
| occurrences (all) | 0 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | | |
| occurrences (all) | 2 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |
| Lower respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 39 (10.26%) | | |
| occurrences (all) | 4 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 39 (7.69%) | | |
| occurrences (all) | 3 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 39 (5.13%) | | |
| occurrences (all) | 2 | | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 19 March 2019 | Changes made over course of trial:<br>- Recruitment extended from 18 months to 30 months<br>- Screening criteria for muscle mass changed (to use Sergi equation and to use cutoffs stratified by BMI)<br>- Removal of pedometer step count as a secondary outcome<br>- Lowering of SARC-F screening threshold from 4 points to 3 points |

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.

Number of participants recruited (145) is lower than planned recruitment (440) due to slow recruitment. Confidence intervals around outcomes are therefore wider than anticipated and may not exclude minimum clinically important changes

Notes:

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/29301558