



Clinical trial results:

Synergy effect of the appetite hormone GLP-1 (LiragluTide) and Exercise on maintenance of weight loss and health after a low calorie diet - the S-LiTE randomized trial

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-005585-32 |
| Trial protocol | DK |
| Global end of trial date | 17 December 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 18 June 2022 |
| First version publication date | 18 June 2022 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | 111111733104 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | U1111-1173-3104 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University of Copenhagen |
| Sponsor organisation address | Blegdamsvej 3B, Copenhagen, Denmark, |
| Public contact | Signe Torekov, Department of Biomedical Sciences, Faculty of Health Sciences, University of Copenhagen, torekov@sund.ku.dk |
| Scientific contact | Signe Torekov, Department of Biomedical Sciences, Faculty of Health Sciences, University of Copenhagen, torekov@sund.ku.dk |

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 June 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 November 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 December 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To investigate the maintenance of weight loss and health outcomes over 1 year with GLP-1 treatment (liraglutide), exercise treatment and the combination in persons with obesity who hav obtained at least 5 % body weight loss by low calorie diet during 8 weeks.

Protection of trial subjects:

Regular consultations to control medication uptitration and assess adverse events

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 29 August 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Denmark: 215 |
| Worldwide total number of subjects | 215 |
| EEA total number of subjects | 215 |

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) | 215 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment was be done via local newspapers, online media and flyers from Department of Endocrinology, Hvidovre University Hospital, and Department of Biomedical Sciences, University of Copenhagen.

Pre-assignment

Screening details:

Inclusion criteria: BMI: 32–43kg/m²; Age: 18–65 years; Safe contraceptive method or menopause for women.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | Low-calorie diet |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|---|--------------------------|
| Arm title | Low-calorie diet |
| Arm description: 800 cal/day for 8 weeks | |
| Arm type | Pre-randomization run-in |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Low-calorie diet |
|--------------------------------|------------------|
| Started | 215 |
| Completed | 195 |
| Not completed | 20 |
| Consent withdrawn by subject | 1 |
| inclusion/exclusion criteria | 5 |
| Lost to follow-up | 4 |
| non-compliance | 4 |
| Personal life condition | 3 |
| not specified | 3 |

Period 2

| | |
|------------------------------|---|
| Period 2 title | Randomization period |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst, Assessor |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo treatment

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Volume-matched to liraglutide.

| | |
|------------------|----------|
| Arm title | Exercise |
|------------------|----------|

Arm description:

Exercise program + placebo

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Volume-matched to liraglutide.

| | |
|------------------|-------------|
| Arm title | Liraglutide |
|------------------|-------------|

Arm description:

Liraglutide 3.0 mg

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | |
| Other name | Saxenda |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Starting dose was 0.6 mg/day with weekly increments of 0.6 mg until 3.0 mg/day (or highest tolerable dose) was reached.

| | |
|------------------|------------------------|
| Arm title | Exercise + Liraglutide |
|------------------|------------------------|

Arm description:

Exercise program plus liraglutide 3.0 mg

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--|
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | |
| Other name | Saxenda |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Starting dose was 0.6 mg/day with weekly increments of 0.6 mg until 3.0 mg/day (or highest tolerable dose) was reached.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: This was an initial low-calorie diet phase that preceded the randomization period. Therefore, baseline was after completion of the first study period.

| Number of subjects in period 2^[2] | Placebo | Exercise | Liraglutide |
|---|---------|----------|-------------|
| Started | 49 | 48 | 49 |
| Completed | 40 | 40 | 41 |
| Not completed | 9 | 8 | 8 |
| Consent withdrawn by subject | 2 | - | - |
| Adverse event, non-fatal | - | - | 1 |
| Lost to follow-up | 1 | 2 | 2 |
| Personal life condition | 4 | 3 | 4 |
| non-compliance | - | 1 | - |
| Lack of efficacy | 1 | - | - |
| not specified | 1 | 2 | 1 |

| Number of subjects in period 2^[2] | Exercise + Liraglutide |
|---|------------------------|
| Started | 49 |
| Completed | 45 |
| Not completed | 4 |
| Consent withdrawn by subject | - |
| Adverse event, non-fatal | 1 |
| Lost to follow-up | - |
| Personal life condition | 1 |
| non-compliance | - |
| Lack of efficacy | - |
| not specified | 2 |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Only participants who completed the initial low-calorie diet were randomized.

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Randomization period |
|-----------------------|----------------------|

Reporting group description: -

| Reporting group values | Randomization period | Total | |
|--|----------------------|-------|--|
| Number of subjects | 195 | 195 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 43 | | |
| standard deviation | ± 12 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 124 | 124 | |
| Male | 71 | 71 | |
| Body mass index | | | |
| Units: kg/m ² | | | |
| arithmetic mean | 32.6 | | |
| standard deviation | ± 2.9 | - | |

End points

End points reporting groups

| | |
|--|------------------------|
| Reporting group title | Low-calorie diet |
| Reporting group description: 800 cal/day for 8 weeks | |
| Reporting group title | Placebo |
| Reporting group description: Placebo treatment | |
| Reporting group title | Exercise |
| Reporting group description: Exercise program + placebo | |
| Reporting group title | Liraglutide |
| Reporting group description: Liraglutide 3.0 mg | |
| Reporting group title | Exercise + Liraglutide |
| Reporting group description: Exercise program plus liraglutide 3.0 mg | |

Primary: Change in body weight

| | |
|--|-----------------------|
| End point title | Change in body weight |
| End point description: | |
| End point type | Primary |
| End point timeframe: From week 0 (randomization) to week 52 | |

| End point values | Low-calorie diet | Placebo | Exercise | Liraglutide |
|--|------------------------|------------------|-------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 195 | 49 | 48 | 49 |
| Units: kg | | | | |
| least squares mean (confidence interval 95%) | -13.1 (-13.7 to -12.4) | 6.1 (3.5 to 8.7) | 2.0 (-0.7 to 4.6) | -0.7 (-3.2 to 1.8) |

| End point values | Exercise + Liraglutide | | | |
|--|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: kg | | | | |
| least squares mean (confidence interval 95%) | -3.4 (-5.9 to -0.9) | | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Linear mixed model analysis |
| Comparison groups | Placebo v Exercise + Liraglutide |
| Number of subjects included in analysis | 98 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -9.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.1 |
| upper limit | -5.9 |

| | |
|---|--------------------------------|
| Statistical analysis title | Linear mixed model analysis |
| Comparison groups | Placebo v Liraglutide |
| Number of subjects included in analysis | 98 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -6.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.4 |
| upper limit | -3.1 |

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | Linear mixed model analysis |
| Comparison groups | Liraglutide v Exercise + Liraglutide |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 98 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.3 |
| upper limit | 0.8 |

| | |
|---|--------------------------------|
| Statistical analysis title | Linear mixed model analysis |
| Comparison groups | Placebo v Exercise |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -4.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.8 |
| upper limit | -0.4 |

| | |
|---|-----------------------------------|
| Statistical analysis title | Linear mixed model analysis |
| Comparison groups | Exercise v Exercise + Liraglutide |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (final values) |
| Point estimate | -5.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9 |
| upper limit | -1.7 |

Secondary: Change in body fat percentage

| | |
|-----------------|-------------------------------|
| End point title | Change in body fat percentage |
|-----------------|-------------------------------|

End point description:

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

End point timeframe:

From week 0 (randomization) to week 52

| End point values | Low-calorie diet | Placebo | Exercise | Liraglutide |
|--|---------------------|-------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 195 | 49 | 48 | 49 |
| Units: percentage points | | | | |
| least squares mean (confidence interval 95%) | -2.3 (-2.6 to -2.1) | 0.4 (-0.6 to 1.5) | -1.8 (-2.9 to -0.7) | -1.6 (-2.6 to -0.6) |

| End point values | Exercise + Liraglutide | | | |
|--|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: percentage points | | | | |
| least squares mean (confidence interval 95%) | -3.5 (-4.5 to -2.5) | | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Linear mixed model analysis |
| Comparison groups | Exercise + Liraglutide v Liraglutide |
| Number of subjects included in analysis | 98 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.3 |
| upper limit | -0.5 |

| | |
|----------------------------|-----------------------------|
| Statistical analysis title | Linear mixed model analysis |
| Comparison groups | Exercise v Placebo |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.8 |
| upper limit | -0.7 |

| | |
|---|-----------------------------------|
| Statistical analysis title | Linear mixed model analysis |
| Comparison groups | Exercise v Exercise + Liraglutide |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.2 |
| upper limit | -0.2 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

week 0 (randomization) to week 52

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | Exercise |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|-------------|
| Reporting group title | Liraglutide |
|-----------------------|-------------|

Reporting group description: -

| | |
|-----------------------|------------------------|
| Reporting group title | Exercise + Liraglutide |
|-----------------------|------------------------|

Reporting group description: -

| Serious adverse events | Placebo | Exercise | Liraglutide |
|---|----------------|----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 4 / 48 (8.33%) | 6 / 49 (12.24%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 48 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 48 (0.00%) | 2 / 49 (4.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 48 (2.08%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 48 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 48 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 48 (0.00%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 2 / 48 (4.17%) | 1 / 49 (2.04%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 48 (2.08%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 48 (0.00%) | 0 / 49 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------------------|--|--|
| Serious adverse events | Exercise + Liraglutide | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Road traffic accident | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |

| | | | |
|---|----------------|--|--|
| Urosepsis | | | |
| subjects affected / exposed | 0 / 49 (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 | Placebo | Exercise | Liraglutide |
|---|------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 49 (85.71%) | 39 / 48 (81.25%) | 49 / 49 (100.00%) |
| Injury, poisoning and procedural complications | | | |
| Accident/injury | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 6 / 48 (12.50%) | 3 / 49 (6.12%) |
| occurrences (all) | 3 | 6 | 3 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 48 (0.00%) | 6 / 49 (12.24%) |
| occurrences (all) | 1 | 0 | 6 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 9 / 49 (18.37%) | 10 / 48 (20.83%) | 10 / 49 (20.41%) |
| occurrences (all) | 9 | 10 | 10 |
| Dizziness | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 4 / 48 (8.33%) | 15 / 49 (30.61%) |
| occurrences (all) | 3 | 4 | 15 |
| Other | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 4 / 48 (8.33%) | 0 / 49 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| General disorders and administration site conditions | | | |
| Injection site reaction | | | |
| subjects affected / exposed | 8 / 49 (16.33%) | 10 / 48 (20.83%) | 11 / 49 (22.45%) |
| occurrences (all) | 8 | 10 | 11 |
| Fatigue | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | 6 / 48 (12.50%) | 15 / 49 (30.61%) |
| occurrences (all) | 4 | 6 | 15 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------|------------------|------------------|
| Constipation | | | |
| subjects affected / exposed | 6 / 49 (12.24%) | 7 / 48 (14.58%) | 9 / 49 (18.37%) |
| occurrences (all) | 6 | 7 | 9 |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | 7 / 48 (14.58%) | 13 / 49 (26.53%) |
| occurrences (all) | 4 | 7 | 13 |
| Nausea | | | |
| subjects affected / exposed | 8 / 49 (16.33%) | 15 / 48 (31.25%) | 32 / 49 (65.31%) |
| occurrences (all) | 8 | 15 | 32 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 6 / 48 (12.50%) | 11 / 49 (22.45%) |
| occurrences (all) | 2 | 6 | 11 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 48 (2.08%) | 9 / 49 (18.37%) |
| occurrences (all) | 0 | 1 | 9 |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 13 / 48 (27.08%) | 18 / 49 (36.73%) |
| occurrences (all) | 3 | 13 | 18 |
| Flatulence or abdominal distension | | | |
| subjects affected / exposed | 5 / 49 (10.20%) | 4 / 48 (8.33%) | 5 / 49 (10.20%) |
| occurrences (all) | 5 | 4 | 5 |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 48 (0.00%) | 3 / 49 (6.12%) |
| occurrences (all) | 2 | 0 | 3 |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | 9 / 48 (18.75%) | 7 / 49 (14.29%) |
| occurrences (all) | 4 | 9 | 7 |
| Other | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | 5 / 48 (10.42%) | 6 / 49 (12.24%) |
| occurrences (all) | 4 | 5 | 6 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Other | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 4 / 48 (8.33%) | 3 / 49 (6.12%) |
| occurrences (all) | 3 | 4 | 3 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| Hair loss subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 0 / 48 (0.00%) 0 | 3 / 49 (6.12%) 3 |
| Other subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 4 / 48 (8.33%) 4 | 5 / 49 (10.20%) 5 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 2 / 48 (4.17%) 2 | 4 / 49 (8.16%) 4 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 4 / 48 (8.33%) 4 | 3 / 49 (6.12%) 3 |
| Other subjects affected / exposed occurrences (all) | 9 / 49 (18.37%) 9 | 12 / 48 (25.00%) 12 | 5 / 49 (10.20%) 5 |
| Infections and infestations Influenza or influenza-like symptoms subjects affected / exposed occurrences (all) | 8 / 49 (16.33%) 8 | 8 / 48 (16.67%) 8 | 11 / 49 (22.45%) 11 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 13 / 49 (26.53%) 13 | 17 / 48 (35.42%) 17 | 12 / 49 (24.49%) 12 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 5 / 48 (10.42%) 5 | 6 / 49 (12.24%) 6 |
| Other subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 8 / 48 (16.67%) 8 | 7 / 49 (14.29%) 7 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 4 / 48 (8.33%) 4 | 18 / 49 (36.73%) 18 |
| Hunger | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 48 (0.00%) | 2 / 49 (4.08%) |
| occurrences (all) | 1 | 0 | 2 |
| Taste disorder | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 48 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---------------------------|--|--|
| Non-serious adverse events | Exercise + Liraglutide | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 49 (91.84%) | | |
| Injury, poisoning and procedural complications | | | |
| Accident/injury | | | |
| subjects affected / exposed | 13 / 49 (26.53%) | | |
| occurrences (all) | 13 | | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | | |
| occurrences (all) | 2 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 11 / 49 (22.45%) | | |
| occurrences (all) | 11 | | |
| Dizziness | | | |
| subjects affected / exposed | 11 / 49 (22.45%) | | |
| occurrences (all) | 11 | | |
| Other | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | | |
| occurrences (all) | 3 | | |
| General disorders and administration site conditions | | | |
| Injection site reaction | | | |
| subjects affected / exposed | 7 / 49 (14.29%) | | |
| occurrences (all) | 7 | | |
| Fatigue | | | |
| subjects affected / exposed | 8 / 49 (16.33%) | | |
| occurrences (all) | 8 | | |
| Gastrointestinal disorders | | | |

| | | | |
|---|------------------|--|--|
| Constipation | | | |
| subjects affected / exposed | 12 / 49 (24.49%) | | |
| occurrences (all) | 12 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 14 / 49 (28.57%) | | |
| occurrences (all) | 14 | | |
| Nausea | | | |
| subjects affected / exposed | 26 / 49 (53.06%) | | |
| occurrences (all) | 26 | | |
| Vomiting | | | |
| subjects affected / exposed | 15 / 49 (30.61%) | | |
| occurrences (all) | 15 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 9 / 49 (18.37%) | | |
| occurrences (all) | 9 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 12 / 49 (24.49%) | | |
| occurrences (all) | 12 | | |
| Flatulence or abdominal distension | | | |
| subjects affected / exposed | 8 / 49 (16.33%) | | |
| occurrences (all) | 8 | | |
| Dry mouth | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | | |
| occurrences (all) | 4 | | |
| Pyrexia | | | |
| subjects affected / exposed | 14 / 49 (28.57%) | | |
| occurrences (all) | 14 | | |
| Other | | | |
| subjects affected / exposed | 5 / 49 (10.20%) | | |
| occurrences (all) | 5 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Other | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | | |
| occurrences (all) | 3 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|--|---|--|--|
| Hair loss subjects affected / exposed occurrences (all) | 6 / 49 (12.24%) 6 | | |
| Other subjects affected / exposed occurrences (all) | 7 / 49 (14.29%) 7 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Other subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 10 / 49 (20.41%) 10 | | |
| Infections and infestations Influenza or influenza-like symptoms subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Other subjects affected / exposed occurrences (all) | 13 / 49 (26.53%) 13 13 / 49 (26.53%) 13 3 / 49 (6.12%) 3 5 / 49 (10.20%) 5 | | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hunger | 16 / 49 (32.65%) 16 | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences (all) | 1 | | |
| Taste disorder | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 08 December 2016 | <ul style="list-style-type: none">• Increasing the upper body mass index limit (inclusion criteria) from 40 kg/m² to 43 kg/m² to increase the possibility that the aimed number of study participants will be reached within the planned trial period.• Adding an exclusion criteria (upper limit of max 2 hours of regular exercise training at vigorous intensity) to ensure that the physical activity levels of the study participants are comparable.• Specifying methodological details on the exercise intervention (e.g. target intensity)• Specifying methodological details and add ethical considerations of the genomic examinations from blood and semen samples (cf. new Danish regulations on this area from 2016), including which genomic tests are performed and why. |
| 08 October 2018 | <ul style="list-style-type: none">• Adding a post-treatment follow-up visit to investigate anthropometric and metabolic outcomes one year after completion of the trial.• Prolonging the trial period from August 2016-August 2021 to August 2016-August 2023 due to addition of the post-treatment follow-up visit.• Increasing the number of included study participants from 180 to 200 to increase the possibility that the aimed number of study participants of minimum 30 persons in each treatment arm complete the trial within the planned trial period.• Removing statement of two planned exploratory examinations (MR scan for hepatic fat content and activation of brown fat tissue) as these were not performed. |
| 20 November 2019 | <ul style="list-style-type: none">• Increasing the total number of included study participants from 200 to 222 because some of the individuals who had been given a study ID number at pre-screening never attended the first day of the run-in phase and thus did never initiate the trial (e.g. due to waiting time from prescreening to the first day of run-in).• Specifying details of the definition of the intention-to-treat analysis set to include all randomized participants• Specifying details on the statistical method and refer to the statistical analysis plan |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33951361>