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	2 / 49 (4.08%)	0 / 48 (0.00%)	3 / 49 (6.12%)
occurrences (all)	2	0	3
Other			
subjects affected / exposed	4 / 49 (8.16%)	4 / 48 (8.33%)	5 / 49 (10.20%)
occurrences (all)	4	4	5
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 49 (8.16%)	2 / 48 (4.17%)	4 / 49 (8.16%)
occurrences (all)	4	2	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 49 (4.08%)	4 / 48 (8.33%)	3 / 49 (6.12%)
occurrences (all)	2	4	3
Other			
subjects affected / exposed	9 / 49 (18.37%)	12 / 48 (25.00%)	5 / 49 (10.20%)
occurrences (all)	9	12	5
Infections and infestations			
Influenza or influenza-like symptoms			
subjects affected / exposed	8 / 49 (16.33%)	8 / 48 (16.67%)	11 / 49 (22.45%)
occurrences (all)	8	8	11
Upper respiratory tract infection			
subjects affected / exposed	13 / 49 (26.53%)	17 / 48 (35.42%)	12 / 49 (24.49%)
occurrences (all)	13	17	12
Urinary tract infection			
subjects affected / exposed	3 / 49 (6.12%)	5 / 48 (10.42%)	6 / 49 (12.24%)
occurrences (all)	3	5	6
Other			
subjects affected / exposed	2 / 49 (4.08%)	8 / 48 (16.67%)	7 / 49 (14.29%)
occurrences (all)	2	8	7
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 49 (4.08%)	4 / 48 (8.33%)	18 / 49 (36.73%)
occurrences (all)	2	4	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 occurrences (all)	12 / 49 (24.49%) 12		
Diarrhoea subjects affected / exposed occurrences (all)	14 / 49 (28.57%) 14		
Nausea subjects affected / exposed occurrences (all)	26 / 49 (53.06%) 26		
Vomiting subjects affected / exposed occurrences (all)	15 / 49 (30.61%) 15		
Dyspepsia subjects affected / exposed occurrences (all)	9 / 49 (18.37%) 9		
Abdominal pain subjects affected / exposed occurrences (all)	12 / 49 (24.49%) 12		
Flatulence or abdominal distension subjects affected / exposed occurrences (all)	8 / 49 (16.33%) 8		
Dry mouth subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 4		
Pyrexia subjects affected / exposed occurrences (all)	14 / 49 (28.57%) 14		
Other subjects affected / exposed occurrences (all)	5 / 49 (10.20%) 5		
Respiratory, thoracic and mediastinal disorders Other subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3		
Skin and subcutaneous tissue disorders			

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

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	• 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	• 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	• 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