Clinical trial results:
A, single center, controlled, multiple dose, randomized study during two weeks, investigating the effect of the test formulation on efficacy, safety and markers for appetite regulation, glucose and lipid absorption and metabolism and body composition, in comparision with Xenical®.

Summary

EudraCT number	2016-001055-50
Trial protocol	SE
Global end of trial date	19 December 2016

Results information

Result version number	v1 (current)
This version publication date	21 March 2019
First version publication date	21 March 2019

Trial information

Trial identification

Sponsor protocol code	EP-001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Empros Pharma AB
Sponsor organisation address	Fogdevreten 2, Solna, Sweden, 17165
Public contact	Arvid Söderhäll, PhD, CEO, Empros Pharma AB, +46 (0)707233363, arvid.soderhall@emprospharma.com
Scientific contact	Arvid Söderhäll, PhD, CEO, Empros Pharma AB, +46 (0)707233363, arvid.soderhall@emprospharma.com

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	19 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2016
Global end of trial reached?	Yes
Global end of trial date	19 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the appetite/tolerability score of the test formulation (EMP16-01 90/30) with the reference product (Xenical®).

Protection of trial subjects:

The ICF included information that data would be recorded, collected and processed and could be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the EU Data Protection Directive (95/46/EC), the data would not identify any persons taking part in the study.
The potential study subject was informed that by signing the ICF he approved that authorized representatives from Sponsor and CTC, the concerned IEC and Competent Authority had direct access to his medical records for verification of clinical study procedures. This agreement was substantiated in a separate document as per local requirements.
The subject had the right to request access to his personal data and the right to request rectification of any data that was not correct and/or complete.
The Investigator filed a Subject Identification List which included sufficient information to link records, i.e. the e-CRF and clinical records. This list will be preserved for possible future inspections/audits but has not been made available to the Sponsor except for monitoring or auditing purposes.

Background therapy:

NA

Evidence for comparator:

The study used a randomised, comparator-controlled design with four parallel treatment arms evaluating three different dose combinations of EMP16-01 (60/20, 90/30 or 120/40) in comparison to Xenical®. Xenical® was chosen as comparator since it is one of the most common weight-reducing agents on the market and has shown to be safe and to give clinical benefit [27]. Xenical® contains orlistat (120 mg) in a conventional oral dosage form, one of the two active pharmaceutical ingredients in EMP16-01.

Actual start date of recruitment	16 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 67
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	67
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with overweight or obese, but otherwise healthy, were recruited from a database of healthy subjects at CTC and from advertising in newspapers, social media, flyers and TV- screens for commercial use.
Date of first subject screened: 2016-08-16
The subjects were recruited at CTC Clinical Trial Consultants clinic in Uppsala, Sweden.

Pre-assignment

Screening details:

The planned sample size was 60 male subjects aged 24-60 years, inclusive, with a BMI of 32- 40 kg/m2 or a BMI of 30-32 kg/m2 combined with a waist circumference above 102 cm.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study was not blinded thus no attempt was made to alter the appearance of the Xenical® capsule.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment arm 1

Arm description:

EMP16-01 60/20; 60 mg orlistat and 20 mg acarbose

Arm type	Experimental
Investigational medicinal product name	EMP16-01 60/20
Investigational medicinal product code	EMP16-01 60/20
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

EMP16-01 60/20; 60 mg orlistat and 20 mg acarbose, capsules.
The IMP was administered orally TID together with all three main meals for 14 consecutive days. On study days 1 and 14 (Visits 2 and 4) the IMP was administered at the clinic. For the remaining days, the IMP was self-administered by the subject at home.

Arm title	Treatment arm 2

Arm description:

EMP16-01 90/30; 90 mg orlistat and 30 mg acarbose

Arm type	Experimental
Investigational medicinal product name	EMP16-01 90/30
Investigational medicinal product code	EMP16-01 90/30
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

EMP16-01 90/30; 90 mg orlistat and 30 mg acarbose, capsules.
The IMP was administered orally TID together with all three main meals for 14 consecutive days. On study days 1 and 14 (Visits 2 and 4) the IMP was administered at the clinic. For the remaining days, the IMP was self-administered by the subject at home.

Arm title	Treatment arm 3

Arm description:

EMP16-01 120/40; 120 mg orlistat and 40 mg acarbose

Arm type	Experimental
Investigational medicinal product name	EMP16-01 120/40
Investigational medicinal product code	EMP16-01 120/40
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

EMP16-01 120/40; 120 mg orlistat and 40 mg acarbose, capsules.
The IMP was administered orally TID together with all three main meals for 14 consecutive days. On study days 1 and 14 (Visits 2 and 4) the IMP was administered at the clinic. For the remaining days, the IMP was self-administered by the subject at home.

Arm title	Treatment arm 4

Arm description:

Xenical®; 120 mg orlistat

Arm type	Active comparator
Investigational medicinal product name	Xenical® 120 mg
Investigational medicinal product code	Xenical® 120 mg
Other name	orlistat
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Xenical®; 120 mg orlistat, capsules.
The IMP was administered orally TID together with all three main meals for 14 consecutive days. On study days 1 and 14 (Visits 2 and 4) the IMP was administered at the clinic. For the remaining days, the IMP was self-administered by the subject at home.

Number of subjects in period 1	Treatment arm 1	Treatment arm 2	Treatment arm 3
Started	17	17	16
Completed	16	17	16
Not completed	1	0	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
Protocol deviation	1	-	-

Number of subjects in period 1	Treatment arm 4
Started	17
Completed	15
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Treatment arm 1
Reporting group description:	
EMP16-01 60/20; 60 mg orlistat and 20 mg acarbose	

Reporting group title	Treatment arm 2
Reporting group description:	
EMP16-01 90/30; 90 mg orlistat and 30 mg acarbose	
Reporting group title	Treatment arm 3
Reporting group description:	
EMP16-01 120/40; 120 mg orlistat and 40 mg acarbose	
Reporting group title	Treatment arm 4
Reporting group description:	
Xenical®; 120 mg orlistat	

Reporting group values	Treatment arm 1	Treatment arm 2	Treatment arm 3
Number of subjects	17	17	16
Age categorical			
All included subjects were male adults 24-60 years.			
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)	17	17	16
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
The mean age was 42.9 (9.1) years (median 44.0) among subjects in the FAS population. No major differences across treatment groups were seen.			
Units: years			
arithmetic mean	40.47	43.35	42.25
standard deviation	± 8.65	± 8.5	± 9.6
Gender categorical			
Only male subjects participated in the study.			
Units: Subjects			
Female	0	0	0
Male	17	17	16
BMI			
Weight and height were measured at screening and BMI (Body Mass Index) was calculated.			
Units: kg/m2			
arithmetic mean	34.47	34.12	34.75
standard deviation	± 2.98	± 2.83	± 2.32

Reporting group values	Treatment arm 4	Total	
Number of subjects	17	67	
Age categorical			
All included subjects were male adults 24-60 years.			
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)	17	67	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
The mean age was 42.9 (9.1) years (median 44.0) among subjects in the FAS population. No major differences across treatment groups were seen.			
Units: years			
arithmetic mean	45.35		
standard deviation	± 9.77	-	
Gender categorical			
Only male subjects participated in the study.			
Units: Subjects			
Female	0	0	
Male	17	67	
BMI			
Weight and height were measured at screening and BMI (Body Mass Index) was calculated.			
Units: kg/m2			
arithmetic mean	35.41		
standard deviation	± 2.83	-	

End points

End points reporting groups

Reporting group title	Treatment arm 1
Reporting group description:	
EMP16-01 60/20; 60 mg orlistat and 20 mg acarbose	

Reporting group title	Treatment arm 2
Reporting group description:	
EMP16-01 90/30; 90 mg orlistat and 30 mg acarbose	

Reporting group title	Treatment arm 3
Reporting group description:	
EMP16-01 120/40; 120 mg orlistat and 40 mg acarbose	

Reporting group title	Treatment arm 4
Reporting group description:	
Xenical®; 120 mg orlistat	

Primary: Appetite/tolerability score EMP16-01 90/30 versus Xenical

End point title	Appetite/tolerability score EMP16-01 90/30 versus Xenical[1]
End point description:	
The primary objective of the study was to compare the appetite/tolerability score of the test formulation (EMP16-01 90/30) with the reference product (Xenical®). The appetite/tolerability score, i.e. ratio between subjective appetite score (sum of appetite questions, measured with questionnaire) and GI symptoms score (sum of GI symptoms such as diarrhoea, flatulence, oily spotting, gastric distention and frequency and intensity of nausea and pain, measured with questionnaire). Daily scores were tabulated to form a 14 days' composite appetite/tolerability score. t-test for pairwise comparison using total score (FAS)	

End point type	Primary
End point timeframe:	
From baseline to last dose.	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective was to compare the appetite/tolerability score of the test formulation (EMP 16-01 90/30, treatment arm 2) with the reference product (Xenical, treatment arm 4)

End point values	Treatment arm 2	Treatment arm 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	14.57 (± 20.26)	16.32 (± 21.14)		
During study	3.60 (± 3.41)	2.90 (± 1.92)		
Difference in ratio	-11.0 (± 21.29)	-14.0 (± 22.27)		
Rel. difference in ratio	-62.8 (± 46.55)	-72.4 (± 28.13)		

Statistical analyses

Statistical analysis title	Appetite/tolerability score

Statistical analysis description:

Descriptive statistics of the appetite/tolerability score ratio at baseline and at last visit together with the absolute and relative changes using the total score are presented for the FAS population. The absolute and relative changes have been analysed using an un-paired Student's t-test.

Comparison groups	Treatment arm 2 v Treatment arm 4
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	Student´s t-test

Secondary: Appetite/tolerability (GSS) score, pairwise comparisons

End point title	Appetite/tolerability (GSS) score, pairwise comparisons

End point description:

Pairwise comparisons for all combinations other than the primary outcome have been made.
t-test for pairwise comparison using total score (FAS)

End point type	Secondary

End point timeframe:

From baseline to day 14

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	16	16[2]
Units: Score				
arithmetic mean (standard deviation)				
Baseline	15.62 (± 25.47)	14.57 (± 20.26)	25.49 (± 23.20)	16.32 (± 21.14)
During study	4.07 (± 2.54)	3.60 (± 3.41)	2.66 (± 2.23)	2.90 (± 1.92)

Notes:

[2] - At baseline: 17 subjects
During study: 16 subjects

Statistical analyses

Statistical analysis title	Appetite/tolerability score, pairwise comparisons

Statistical analysis description:

Descriptive statistics for the score ratio at baseline and at last visit together with the absolute and relative changes using the total score and the mean score, respectively, are presented for the FAS population. The absolute and relative changes have been analysed using an un-paired Student's t-test.

The absolute and relative changes have also been analysed using analysis of covariance with treatment, age, BMI, fasting glucose at baseline and baseline ratio as covariates.

Comparison groups	Treatment arm 1 v Treatment arm 2 v Treatment arm 3 v Treatment arm 4
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [3]
Method	ANCOVA

Notes:

[3] - Some statistically significant differences were detected.

Secondary: Global assessment of satisfaction

End point title	Global assessment of satisfaction

End point description:

At completion of the last questionnaire (at lunch Day 14), the subject was asked to answer the question: "How probable is it that you would take this drug for an extended time?" The question was answered based on a scale from 0 to 9 where 0 represented Unlikely and 9 represented Very likely.

End point type	Secondary

End point timeframe:

Day 14

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	15
Units: Mean score				
arithmetic mean (standard deviation)	6.00 (± 2.58)	6.47 (± 2.37)	5.75 (± 3.15)	5.87 (± 2.39)

Statistical analyses

Statistical analysis title	Global assessment of satisfaction

Statistical analysis description:

Descriptive statistics are presented by treatment group for the FAS population. Pairwise comparisons have been made across treatment groups using Student's t-test.

Comparison groups	Treatment arm 1 v Treatment arm 2 v Treatment arm 3 v Treatment arm 4
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [4]
Method	t-test, 2-sided

Notes:

[4] - The mean score on a scale from 0-9 was similar across treatment groups. No statistically significant differences were detected.

Secondary: Plasma pharmacokinetics of orlistat - AUClast

End point title	Plasma pharmacokinetics of orlistat - AUClast

End point description:

Blood samples for determination of concentration of orlistat in plasma were drawn from a peripheral vein at time-points at Visit 2 and Visit 4.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 4

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[5]	17	16	14[6]
Units: nmol/h * h				
arithmetic mean (standard deviation)				
Visit 2	0.61 (± 0.48)	1.27 (± 1.19)	1.13 (± 1.05)	3.94 (± 3.48)
Visit 4	0.99 (± 0.51)	1.53 (± 1.10)	1.51 (± 1.36)	3.90 (± 3.31)

Notes:

[5] - Visit 2: 17 subjects were analysed
Visit 4: 15 subjects were analysed
[6] - Visit 2: 17 subjects were analysed
Visit 4: 14 subjects were analysed

Statistical analyses

Statistical analysis title	Plasma pharmacokinetics of orlistat - AUClast

Statistical analysis description:

There were minor differences in the mean plasma concentrations of orlistat after administration of any of the EMP16-01 doses compared with Xenical®. The GI absorption of orlistat from both test and reference dosage forms was higher after lunch than after breakfast.

Comparison groups	Treatment arm 2 v Treatment arm 3 v Treatment arm 1 v Treatment arm 4
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - No statistically significant differences were detected.

Secondary: Plasma pharmacokinetics of orlistat - Tmax

End point title	Plasma pharmacokinetics of orlistat - Tmax

End point description:

Blood samples for determination of concentration of orlistat in plasma were drawn from a peripheral vein at time-points at Visit 2 and Visit 4.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 4

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[8]	17	16	15[9]
Units: hour				
arithmetic mean (standard deviation)				
Visit 2	5.78 (± 0.56)	5.95 (± 0.17)	5.74 (± 0.66)	5.47 (± 1.32)
Visit 4	4.98 (± 1.85)	5.63 (± 1.03)	6.00 (± 0.00)	5.90 (± 0.21)

Notes:

[8] - Visit 2: 17 subjects were analysed
Visit 4: 15 subjects were analysed
[9] - Visit 2: 17 subjects were analysed
Visit 4: 15 subjects were analysed

Statistical analyses

Statistical analysis title	Plasma pharmacokinetics of orlistat - Tmax
Comparison groups	Treatment arm 1 v Treatment arm 2 v Treatment arm 3 v Treatment arm 4
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - No statistically significant differences were detected.

Secondary: Plasma pharmacokinetics of orlistat - Cmax

End point title	Plasma pharmacokinetics of orlistat - Cmax

End point description:

Blood samples for determination of concentration of orlistat in plasma were drawn from a peripheral vein at time-points at Visit 2 and Visit 4.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 4

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[11]	17	16	15[12]
Units: nmol/L				
arithmetic mean (standard deviation)				
Visit 2	0.68 (± 0.57)	1.26 (± 1.42)	1.05 (± 0.87)	3.32 (± 1.93)
Visit 4	0.93 (± 9.70)	1.55 (± 1.13)	1.24 (± 1.10)	2.90 (± 2.12)

Notes:

[11] - Visit 2: 17 subjects were analysed
Visit 4: 15 subjects were analysed
[12] - Visit 2: 17 subjects were analysed
Visit 4: 15 subjects were analysed

Statistical analyses

Statistical analysis title	Plasma pharmacokinetics of orlistat - Cmax
Comparison groups	Treatment arm 1 v Treatment arm 2 v Treatment arm 3 v Treatment arm 4
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [13]
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - No statistically significant differences were detected.

Secondary: Biomarkers in plasma - AUClast

End point title	Biomarkers in plasma - AUClast

End point description:

Samples for analyses of plasma/serum kinetics for the biomarkers glucose, insulin, C-peptide, glucagon, TG, GLP-1, GIP and CCK were drawn from a peripheral vein at time-points at Visit 2 and Visit 4.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 4

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[14]	17	16	15[15]
Units: nmol/h * h				
arithmetic mean (standard deviation)				
C-Peptid Visit 2	12.29 (± 2.25)	11.75 (± 3.11)	11.84 (± 13.33)	14.44 (± 4.58)
C-Peptid Visit 4	11.88 (± 2.30)	11.49 (± 2.78)	11.12 (± 3.02)	12.03 (± 3.15)
GIP Visit 2	859.1 (± 351.1)	876.5 (± 368.8)	721.7 (± 237.0)	903.7 (± 248.5)
GIP Visit 4	891.9 (± 351.6)	1087 (± 609.8)	850.6 (± 251.7)	1071 (± 380.1)
GLP1 Visit 2	84.37 (± 22.25)	76.24 (± 16.75)	86.54 (± 28.8)	83.34 (± 24.40)
GLP1 Visit 4	94.62 (± 24.03)	81.88 (± 14.53)	89.57 (± 21.90)	84.79 (± 24.85)
Glucagon Visit 2	34.60 (± 18.06)	27.92 (± 9.87)	35.45 (± 15.54)	31.64 (± 12.52)
Glucagon Visit 4	37.38 (± 17.05)	26.67 (± 9.35)	34.37 (± 10.57)	27.55 (± 12.84)
P-Glucose Visit 2	33.75 (± 3.61)	34.03 (± 3.43)	33.28 (± 3.06)	37.37 (± 3.79)
P-Glucose Visit 4	33.11 (± 3.02)	34.61 (± 3.87)	33.89 (± 3.51)	35.41 (± 5.01)
P-Triglycerides Visit 2	14.02 (± 3.99)	13.28 (± 4.17)	18.94 (± 9.52)	15.33 (± 6.57)
P-Triglycerides Visit 4	15.63 (± 5.32)	12.80 (± 3.22)	16.38 (± 7.30)	13.53 (± 5.01)
S-Insulin Visit 2	281.9 (± 102.0)	256.4 (± 137.8)	274.9 (± 119.2)	409.9 (± 293.6)
S-Insulin Visit 4	272.7 (± 93.71)	244.1 (± 109.3)	236.1 (± 110.0)	270.9 (± 112.2)

Notes:

[14] - Visit 2: 17 subjects were analysed
Visit 4: 16 subjects were analysed
[15] - Visit 2: 17 subjects were analysed
Visit 4: 15 subjects were analysed

Statistical analyses

Statistical analysis title	Biomarkers in plasma - AUClast
Comparison groups	Treatment arm 1 v Treatment arm 2 v Treatment arm 3 v Treatment arm 4
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [16]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - Some statistically significant differences were detected.

Secondary: Biomarkers in plasma - Tmax

End point title	Biomarkers in plasma - Tmax

End point description:

Samples for analyses of plasma/serum kinetics for the biomarkers glucose, insulin, C-peptide, glucagon, TG, GLP-1, GIP and CCK were drawn from a peripheral vein at time-points at Visit 2 and Visit 4.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 4

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17[17]	17	16	15[18]
Units: hour				
arithmetic mean (standard deviation)				
C-Peptid Visit 2	5.03 (± 1.26)	3.89 (± 1.94)	4.16 (± 1.86)	5.15 (± 0.63)
C-Peptid Visit 4	4.42 (± 1.82)	4.21 (± 1.88)	4.59 (± 1.49)	4.75 (± 1.22)
GIP Visit 2	0.71 (± 0.40)	0.85 (± 0.39)	0.94 (± 0.40)	0.76 (± 0.36)
GIP Visit 4	0.85 (± 0.34)	0.91 (± 0.32)	0.91 (± 0.42)	0.82 (± 0.52)
GLP1 Visit 2	4.83 (± 0.61)	4.47 (± 1.35)	4.31 (± 1.26)	4.24 (± 1.51)
GLP1 Visit 4	4.55 (± 0.14)	4.28 (± 1.29)	4.46 (± 1.12)	4.05 (± 1.94)
Glucagon Visit 2	1.02 (± 0.48)	1.19 (± 0.54)	1.08 (± 0.53)	0.93 (± 0.50)
Glucagon Visit 4	1.26 (± 0.34)	1.12 (± 0.42)	1.20 (± 0.36)	1.05 (± 0.57)
P-Glucose Visit 2	3.06 (± 2.19)	3.71 (± 2.03)	2.78 (± 1.98)	4.06 (± 1.67)
P-Glucose Visit 4	3.73 (± 2.22)	3.47 (± 2.13)	3.27 (± 2.10)	4.52 (± 1.38)
P-Triglycerides Visit 2	5.65 (± 0.98)	5.80 (± 0.44)	5.91 (± 0.27)	5.83 (± 0.42)
P-Triglycerides Visit 4	5.95 (± 0.18)	5.63 (± 1.22)	5.85 (± 0.35)	5.58 (± 1.61)
S-Insulin Visit 2	3.35 (± 2.22)	3.26 (± 2.05)	2.56 (± 1.92)	4.65 (± 1.60)
S-Insulin Visit 4	3.20 (± 2.33)	2.62 (± 2.24)	2.70 (± 2.15)	4.22 (± 1.89)

Notes:

[17] - Visit 2: 17 subjects were analysed
Visit 4: 16 subjects were analysed
[18] - Visit 2: 17 subjects were analysed
Visit 4: 15 subjects were analysed

Statistical analyses

Statistical analysis title	Biomarkers in plasma - Tmax
Comparison groups	Treatment arm 1 v Treatment arm 2 v Treatment arm 3 v Treatment arm 4
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - No statistically significant differences were detected.

Secondary: Biomarkers in plasma - Cmax

End point title	Biomarkers in plasma - Cmax

End point description:

Samples for analyses of plasma/serum kinetics for the biomarkers glucose, insulin, C-peptide, glucagon, TG, GLP-1, GIP and CCK were drawn from a peripheral vein at time-points at Visit 2 and Visit 4.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 4

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[20]	17	16	15[21]
Units: nmol/L				
arithmetic mean (standard deviation)				
C-Peptid Visit 2	2.87 (± 0.53)	2.79 (± 0.72)	2.62 (± 0.73)	3.84 (± 1.31)
C-Peptid Visit 4	2.96 (± 0.70)	2.69 (± 0.70)	2.68 (± 0.81)	3.33 (± 1.01)
GIP Visit 2	693.8 (± 272.1)	732.8 (± 281.6)	583.9 (± 170.3)	711.0 (± 185.1)
GIP Visit 4	776.9 (± 308.9)	904.8 (± 545.4)	700.9 (± 213.8)	872.9 (± 324.4)
GLP1 Visit 2	20.60 (± 5.80)	19.98 (± 5.92)	22.53 (± 8.41)	20.56 (± 5.97)
GLP1 Visit 4	24.00 (± 6.98)	20.44 (± 4.17)	21.79 (± 6.22)	20.23 (± 6.04)
Glucagon Visit 2	24.36 (± 12.56)	20.96 (± 8.07)	25.79 (± 11.51)	22.11 (± 9.55)
Glucagon Visit 4	26.62 (± 10.72)	18.98 (± 6.74)	24.58 (± 7.66)	20.75 (± 9.04)
P-Glucose Visit 2	6.24 (± 0.66)	6.45 (± 0.78)	6.09 (± 0.68)	7.59 (± 1.19)
P-Glucose Visit 4	6.26 (± 0.50)	6.48 (± 0.87)	6.16 (± 0.90)	7.38 (± 1.66)
P-Triglycerides Visit 2	3.18 (± 0.71)	2.97 (± 0.95)	3.89 (± 1.85)	3.37 (± 1.13)
P-Triglycerides Visit 4	3.64 (± 1.14)	3.01 (± 0.77)	3.33 (± 1.38)	2.87 (± 0.97)

S-Insulin Visit 2	77.76 (± 25.44)	79.18 (± 37.93)	76.55 (± 37.22)	144.1 (± 105.3)
S-Insulin Visit 4	85.81 (± 25.11)	73.24 (± 30.24)	73.94 (± 34.26)	98.60 (± 54.06)

Notes:

[20] - Visit 2: 17 subjects were analysed
Visit 4: 16 subjects were analysed
[21] - Visit 2: 17 subjects were analysed
Visit 4: 15 subjects were analysed

Statistical analyses

Statistical analysis title	Biomarkers in plasma - Cmax
Comparison groups	Treatment arm 1 v Treatment arm 2 v Treatment arm 3 v Treatment arm 4
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [22]
Method	Wilcoxon (Mann-Whitney)

Notes:

[22] - Some statistically significant differences were detected.

Secondary: Body composition - fat

End point title	Body composition - fat

End point description:

Body composition (% total body fat, % total water) was assessed by bio-impedance (Tanita BC-545N).

End point type	Secondary

End point timeframe:

From Visit 2 (baseline) to Visit 4

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[23]	17	16	15[24]
Units: percent				
arithmetic mean (standard deviation)				
Visit 2	32.67 (± 2.66)	31.82 (± 4.72)	32.19 (± 4.55)	32.82 (± 4.89)
Visit 4	32.38 (± 2.83)	31.76 (± 4.66)	32.06 (± 3.92)	33.07 (± 4.20)

Notes:

[23] - Visit 2: 15 subjects
Visit 4: 16 subjects
[24] - Visit 2: 17 subjects
Visit 4: 15 subjects

Statistical analyses

Statistical analysis title	Body composition - fat

Statistical analysis description:

Descriptive statistics for body weight, body composition and waist circumference at Visit 2 (baseline) and Visit 4 together with absolute and relative changes from Visit 2 to Visit 4. Differences between treatment groups have been analysed using the Wilcoxon rank-sum test.

Comparison groups	Treatment arm 1 v Treatment arm 2 v Treatment arm 3 v Treatment arm 4
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [25]
Method	Wilcoxon (Mann-Whitney)

Notes:

[25] - No statistically significant differences were detected.

Secondary: Body composition - total water

End point title	Body composition - total water

End point description:

Body composition (% total body fat, % total water) was assessed by bio-impedance (Tanita BC-545N).

End point type	Secondary

End point timeframe:

From Visit 2 (baseline) to Visit 4

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[26]	17	16	15[27]
Units: percent				
arithmetic mean (standard deviation)				
Visit 2	47.53 (± 2.59)	48.24 (± 3.67)	48.13 (± 3.54)	47.71 (± 3.57)
Visit 4	47.75 (± 2.74)	48.18 (± 3.57)	48.13 (± 3.07)	47.33 (± 3.13)

Notes:

[26] - Visit 2: 15 subjects
Visit 4: 16 subjects
[27] - Visit 2: 17 subjects
Visit 4: 15 subjects

Statistical analyses

Statistical analysis title	Body composition - total water

Statistical analysis description:

Descriptive statistics for body weight, body composition and waist circumference at Visit 2 (baseline) and Visit 4 together with absolute and relative changes from Visit 2 to Visit 4 are presented. Differences between treatment groups have been analysed using the Wilcoxon rank-sum test.

Comparison groups	Treatment arm 1 v Treatment arm 2 v Treatment arm 3 v Treatment arm 4
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [28]
Method	Wilcoxon (Mann-Whitney)

Notes:

[28] - No statistically significant differences were detected.

Secondary: Body composition - weight

End point title	Body composition - weight

End point description:

The body weight was assessed wearing light clothing and no shoes and was read in kilogram (kg), to one decimal.

End point type	Secondary

End point timeframe:

From Visit 2 (baseline) to Visit 4

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[29]	17	16	15[30]
Units: kilogram				
arithmetic mean (standard deviation)				
Visit 2	115.0 (± 15.68)	110.2 (± 13.18)	112.8 (± 10.59)	112.6 (± 13.48)
Visit 4	113.3 (± 16.66)	109.6 (± 12.91)	111.5 (± 10.20)	110.9 (± 14.52)

Notes:

[29] - Visit 2: 15 subjects
Visit 4: 16 subjects
[30] - Visit 2: 17 subjects
Visit 4: 15 subjects

Statistical analyses

Statistical analysis title	Body composition - weight

Statistical analysis description:

Descriptive statistics for body weight, body composition and waist circumference at Visit 2 (baseline) and Visit 4 together with absolute and relative changes from Visit 2 to Visit 4 are presented. Differences between treatment groups have been analysed using the Wilcoxon rank-sum test.

Comparison groups	Treatment arm 1 v Treatment arm 2 v Treatment arm 3 v Treatment arm 4
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Notes:

[31] - The only statistically significant difference between treatment groups was seen in the PPS population when comparing EMP16-01 90/30 with Xenical®. The mean weight change from baseline to end of treatment was -0.56 kg in the EMP16-01 90/30 treatment group as compared to -1.57 kg after treatment with Xenical®. The p-value for the absolute and relative differences was 0.05.

Secondary: Body composition - waist

End point title	Body composition - waist

End point description:

The waist circumference was measured midway between the lowest rib and the iliac crest. Measurements were done at the end of a normal exhalation and in a standing position.

End point type	Secondary

End point timeframe:

From Visit 2 (baseline) to Visit 4

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[32]	17	16	15[33]
Units: centimeter				
arithmetic mean (standard deviation)				
Visit 2	119.2 (± 9.38)	118.6 (± 8.35)	120.6 (± 10.21)	118.8 (± 9.05)
Visit 4	119.3 (± 9.69)	116.8 (± 8.71)	118.6 (± 9.12)	117.5 (± 9.46)

Notes:

[32] - Visit 2: 17 subjects
Visit 4: 16 subjects
[33] - Visit 2: 17 subjects
Visit 4: 15 subjects

Statistical analyses

Statistical analysis title	Body composition - waist
Comparison groups	Treatment arm 1 v Treatment arm 2 v Treatment arm 3 v Treatment arm 4
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [34]
Method	Wilcoxon (Mann-Whitney)

Notes:

[34] - No statistically significant differences were detected.

Secondary: Activity pattern

End point title	Activity pattern

End point description:

Daily activity (amount and intensity) was subjectively assessed using the question "Have you performed any heavy exercise of longer duration (more than 20 min)?", included in the questionnaire completed by the subject three times per day.

End point type	Secondary

End point timeframe:

Day -3 to day 14

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[35]	16[36]	16	15[37]
Units: Number of subjects answering "yes"				
Day -3	2	5	5	1
Day -2	1	2	3	4
Day -1	2	1	5	5
Day 1	0	0	0	1

Day 2	4	1	5	3
Day 3	6	3	4	3
Day 4	4	1	4	2
Day 5	7	4	4	5
Day 6	4	3	7	2
Day 7	3	4	4	3
Day 8	2	4	4	6
Day 9	3	5	9	4
Day 10	4	4	7	2
Day 11	3	2	4	3
Day 12	5	7	1	4
Day 13	2	5	3	3
Day 14	0	0	0	0

Notes:

[35] - Day -3 to day 3: 17 subjects
Day 4 to day 13: 16 subjects
Day 14: 15 subjects
[36] - Day -3 to -1: 17 subjects
Day 1: 16 subjects
Day 2: 18 subjects
Day 3-14: 17 subjects
[37] - Day -3 to -1: 17 subjects
Day 1 to 4: 16 subjects
Day 5 to 14: 15 subjects

Statistical analyses

Statistical analysis title	Activity pattern

Statistical analysis description:

Pairwise comparisons across treatment groups have been made using Student’s t-test.
Overall, no clinically relevant difference between treatment arms in self-reported sleep and physically activity was found. Statistically significant differences between treatment groups were found for individual days.

Comparison groups	Treatment arm 1 v Treatment arm 2 v Treatment arm 3 v Treatment arm 4
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	> 0.05
Method	Chi-squared

Notes:

[38] - The proportion of subjects answering Yes to the question “Have you performed any heavy exercise of longer duration (more than 20 min)?” was significantly higher on Day 10 after treatment with EMP16-01 120/4, as compared to Xenical®, in both populations (p- value=0.030 [FAS] and 0.008 [PPS]).
On Day 9, EMP16-01 120/4 had a significantly better effect on the activity pattern than both EMP16-01 90/30 (p-value=0.026) and Xenical® p-value=0.028.

Secondary: Sleep pattern

End point title	Sleep pattern

End point description:

Daily sleep (duration and quality) was subjectively assessed using the question "Did you have a normal night´s sleep (about as long and as deep as usual?", included in the questionnaire completed by the subject three times per day.

End point type	Secondary

End point timeframe:

Day -3 to Day 14

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[39]	16[40]	16	14[41]
Units: Number of subjects answering "yes"				
Day -3	16	16	16	14
Day -2	15	15	16	16
Day -1	16	16	14	15
Day 1	14	14	16	11
Day 2	16	16	16	15
Day 3	16	16	15	15
Day 4	15	15	15	13
Day 5	16	14	14	14
Day 6	15	17	16	14
Day 7	14	16	15	12
Day 8	15	17	16	12
Day 9	13	16	13	14
Day 10	13	16	14	14
Day 11	14	13	14	14
Day 12	13	15	13	14
Day 13	14	16	14	12
Day 14	11	14	15	9

Notes:

[39] - Day -3 to 3: 17 subjects
Day 4 to 13: 16 subjects
Day 14: 15 subjects
[40] - Day -3, -1 and 3-14: 17 subjects
Day -2 and 1: 16 subjects
Day 2: 18 subjects

[41] - Day -3 to -1: 17 subjects
Day 1-4: 16 subjects
Day 5-6, 9-12, 14: 15 subjects
Day 7-8, 13: 14 sub

Statistical analyses

Statistical analysis title	Sleep pattern

Statistical analysis description:

Pairwise comparisons across treatment groups have been made using Student’s t-test. Overall, no clinically relevant difference between treatment arms in self-reported sleep and physically activity was found. Statistically significant differences between treatment groups were found for individual days.

Comparison groups	Treatment arm 2 v Treatment arm 3 v Treatment arm 4 v Treatment arm 1
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	> 0.05
Method	Chi-squared

Notes:

[42] - A significantly higher proportion of subjects treated with Xenical® answered Yes to the question "Did you have a normal night's sleep (about as long and as deep as usual)?" on Day 11, as compared to EMP16-01 90/30, when analysing the PPS population (p- value=0.046).

Secondary: Meal pattern- main courses

End point title	Meal pattern- main courses

End point description:

Meal pattern was assessed using a short diet diary developed by Berteaus-Forslund et al. The questionnaire was completed by the subject three times per day.

End point type	Secondary

End point timeframe:

At baseline and at the end of treatment

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[43]	17	16	14[44]
Units: Number of subjects				
Predose, bad meal pattern	1	0	2	3
Predose, OK meal pattern	3	5	4	6
Predose, good meal pattern	13	12	10	7
Last day, bad meal pattern	0	0	0	0
Last day, OK meal pattern	2	2	5	2
Last day, good meal pattern	13	15	11	12

Notes:

[43] - Pre dose: 17 subjects
Last day: 15 subjects
[44] - Pre dose: 16 subjects
Last day: 14 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Meal pattern- light courses

End point title	Meal pattern- light courses

End point description:

Meal pattern was assessed using a short diet diary developed by Berteaus-Forslund et al. The questionnaire was completed by the subject three times per day.

End point type	Secondary

End point timeframe:

At baseline and at the end of treatment

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14[45]	15[46]	13[47]	13[48]
Units: Number of subjects				
Pre dose, bad meal pattern	4	1	0	1
Pre dose, OK meal pattern	2	1	1	2
Pre dose, good meal pattern	11	13	15	13
Last day, bad meal pattern	0	0	0	0
Last day, OK meal pattern	0	0	0	0
Last day, good meal pattern	14	16	13	13

Notes:

[45] - Pre dose: 17 subjects
Last day: 14 subjects
[46] - Pre dose: 15 subjects
Last day: 16 subjects
[47] - Pre dose: 16 subjects
Last day: 13 subjects
[48] - Pre dose: 16 subjects
Last day: 13 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Meal pattern- snacks

End point title	Meal pattern- snacks

End point description:

Meal pattern was assessed using a short diet diary developed by Berteaus-Forslund et al. The questionnaire was completed by the subject three times per day.

End point type	Secondary

End point timeframe:

At baseline and at the end of treatment

End point values	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[49]	11[50]	10[51]	7[52]
Units: Number of subjects				
Pre dose, bad meal pattern	13	10	12	8
Pre dose, OK meal pattern	1	4	0	2
Pre dose, good meal pattern	1	2	2	3
Last day, bad meal pattern	0	0	0	0
Last day, OK meal pattern	6	7	5	5
Last day, good meal pattern	2	4	5	2

Notes:

[49] - Pre dose: 15 subjects
Last day: 8 subjects
[50] - Pre dose: 16 subjects
Last day: 11 subjects
[51] - Pre dose: 14 subjects
Last day: 10 subjects

[52] - Pre dose: 13 subjects
Last day: 7 subjects

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from signing the ICF until the follow-up assessment. Events occurring before first administration of IMP were defined as baseline events. Adverse Events occurring after first administration of IMP were defined as TEAEs.

Adverse event reporting additional description:

AEs were spontaneously reported by the subjects and observed or elicited based on non-leading questions by the Investigator or medical personnel.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Treatment arm 1

Reporting group description:

EMP16-01 60/20; 60 mg orlistat and 20 mg acarbose

Reporting group title	Treatment arm 2

Reporting group description:

EMP16-01 90/30; 90 mg orlistat and 30 mg acarbose

Reporting group title	Treatment arm 3

Reporting group description:

EMP16-01 120/40; 120 mg orlistat and 40 mg acarbose

Reporting group title	Treatment arm 4

Reporting group description:

Xenical®; 120 mg orlistat

Serious adverse events	Treatment arm 1	Treatment arm 2	Treatment arm 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Treatment arm 4		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Treatment arm 1	Treatment arm 2	Treatment arm 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 17 (17.65%)	7 / 17 (41.18%)	11 / 16 (68.75%)
Cardiac disorders			
Presyncope			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 17 (0.00%)	3 / 17 (17.65%)	3 / 16 (18.75%)
occurrences (all)	0	3	3
Insomnia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			

subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Faecal incontinence			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Gingival pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis			
subjects affected / exposed	2 / 17 (11.76%)	4 / 17 (23.53%)	6 / 16 (37.50%)
occurrences (all)	2	4	6
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Stress			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Depressed mood			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Insomnia			

subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Treatment arm 4		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 17 (64.71%)		
Cardiac disorders			
Presyncope			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Faecal incontinence			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Gingival pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Stress			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Depressed mood			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2016	Subject replacement: To ensure the 12 evaluable subjects in each treatment arm required for the primary comparison, it was decided that subjects who prematurely discontinued participation and subjects for whom baseline PD samples on Day 14 were missing could be replaced. Randomization: A new randomization list was created for the extra subjects included based on the decision described in Section 9.8.1.1. The PD-related endpoints have been analysed both with and without the seven extra subjects included. Analysis of meal pattern: The following analyses were described in the Study Protocol: A mean value per day will be calculated using the total amount prior and after first dose. The actual values will be analysed using the Wilcoxon rank-sum test. The meal pattern variables will be presented using tables including summary statistics, actual and corrected p-value. During analysis, it was agreed between Sponsor and the statistician that the pre-planned analysis was not possible to perform. Instead, the total number of main courses, light courses and snacks at baseline (Day -1 to Day -3) and at the end of treatment (Day 13) should be categorised and presented as number and proportion of subjects in each category for each meal type.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported