Clinical trial results:
Effect on fasting plasma glucose (FPG) of once daily oral administration during 28 days of O304 suspension in subjects with Type 2 Diabetes (T2D). A single-centre, randomised, parallel-group, double-blinded, placebo controlled Phase IIa study (TELLUS).

Summary

EudraCT number	2016-002183-13
Trial protocol	SE
Global end of trial date	09 August 2017

Results information

Result version number	v1 (current)
This version publication date	04 June 2021
First version publication date	04 June 2021

Trial information

Trial identification

Sponsor protocol code	O304-2016-02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Betagenon AB
Sponsor organisation address	Tvistevägen 48C, Umeå, Sweden, 907 36
Public contact	CEO, Betagenon AB, 0046 070277 89 97, thomas.edlund@betagenon.com
Scientific contact	CEO, Betagenon AB, 0046 070277 89 97, thomas.edlund@betagenon.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	09 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 August 2017
Global end of trial reached?	Yes
Global end of trial date	09 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the effect of O304 on FPG levels after 28 days of treatment in subjects with T2D, as compared to placebo.

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference of Harmonization (ICH)/Good Clinical Practice (GCP), European Union (EU) Clinical Trials Directive, and applicable local regulatory requirements.
It was the responsibility of the Investigator to give each potential study patient adequate verbal and written information before any study specific assessments were performed.
The information included the objectives and procedures of the study as well as any risks or inconvenience involved. It was emphasised that participation in the study was voluntary and that the patient could withdraw from participation at any time and for any reason, without any prejudice. All patients were given the opportunity to ask questions about the study and was given sufficient time to consider participation before signing the ICF.
Before performing any study-related procedures the ICF was signed and personally dated by the patient and by the Investigator. A copy of the patient information including the signed ICF was provided to the patient.
Documentation of the patient information and the date of informed consent were recorded in the medical records and in the CRF. The patient information sheet and the signed ICF were filed by the Investigator.

Background therapy:

All patients used their prescribed product and dose of metformin. This was not supplied by the Sponsor.

Evidence for comparator:

Main inclusion criteria: Male and female patients, 18-80 years of age, with uncomplicated T2D, on stable T2D treatment with metformin monotherapy for ≥ 3 months.
Study patients were on stable (i.e. no dose adjustment) metformin treatment for at least 3 months prior to inclusion in the study. No other diabetes medications than metformin was allowed.

Actual start date of recruitment	20 September 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: 65
Worldwide total number of subjects	65
EEA total number of subjects	65

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)	24
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Main inclusion criteria: Male and female patients, 18-80 years of age, with uncomplicated T2D, on stable T2D treatment with metformin monotherapy for ≥ 3 months.

Pre-assignment

Screening details:

A screening visit was performed within 3 weeks before randomisation and the start of IMP administration.

Period 1

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

Blinding implementation details:

This was a double-blind study and the allocation of treatments was not disclosed until clean file had been declared and the database has been locked on 14 September 2017.
Placebo and O304 suspension were of identical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	O304

Arm description:

Patients were treated with O304 for a period of 28 days. During the treatment period, there were weekly visits to the clinic, where blood sampling for FPG, safety, and exploratory parameters were collected. During the visits to the clinic, IMP for the next period was dispensed and the patients received the IMP dose for that day.

Arm type	Experimental
Investigational medicinal product name	O304
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Test product: O304 oral suspension, 20 mg/ml. Dose: 1000 mg (50 ml) once daily in the morning.

Arm title	Placebo

Arm description:

Patients were treated with Placebo for a period of 28 days. During the treatment period, there were weekly visits to the clinic, where blood sampling for FPG, safety, and exploratory parameters were collected. During the visits to the clinic, IMP for the next period was dispensed and the patients received the IMP dose for that day.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Reference product: Placebo oral suspension. Dose: 50 ml once daily in the morning.

Number of subjects in period 1	O304	Placebo
Started	33	32
Completed	31	28
Not completed	2	4
Physician decision	1	1
Consent withdrawn by subject	1	1
Adverse event, non-fatal	-	2

Baseline characteristics

Reporting groups	
Reporting group title	O304
Reporting group description:	
Patients were treated with O304 for a period of 28 days. During the treatment period, there were weekly visits to the clinic, where blood sampling for FPG, safety, and exploratory parameters were collected. During the visits to the clinic, IMP for the next period was dispensed and the patients received the IMP dose for that day.	
Reporting group title	Placebo
Reporting group description:	
Patients were treated with Placebo for a period of 28 days. During the treatment period, there were weekly visits to the clinic, where blood sampling for FPG, safety, and exploratory parameters were collected. During the visits to the clinic, IMP for the next period was dispensed and the patients received the IMP dose for that day.	

Reporting group values	O304	Placebo	Total
Number of subjects	33	32	65
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	66.15	64.59	
standard deviation	± 9.65	± 8.12	-
Gender categorical			
Units: Subjects			
Female	9	8	17
Male	24	24	48

End points

End points reporting groups

Reporting group title	O304

Reporting group description:

Patients were treated with O304 for a period of 28 days. During the treatment period, there were weekly visits to the clinic, where blood sampling for FPG, safety, and exploratory parameters were collected. During the visits to the clinic, IMP for the next period was dispensed and the patients received the IMP dose for that day.

Reporting group title	Placebo

Reporting group description:

Patients were treated with Placebo for a period of 28 days. During the treatment period, there were weekly visits to the clinic, where blood sampling for FPG, safety, and exploratory parameters were collected. During the visits to the clinic, IMP for the next period was dispensed and the patients received the IMP dose for that day.

Primary: Difference in FPG (Fasting Plasma Glucose)

End point title	Difference in FPG (Fasting Plasma Glucose)

End point description:

Primary objective: To assess the effect of O304 on FPG levels after 28 days of treatment in subjects with T2D, as compared to placebo.
Primary endpoint: The primary endpoint is the mean difference in FPG (mmol/L) after 28 days of treatment. However, due to that compliance with magnetic resonance imaging (MRI) analysis of calf muscle at screen was used as an inclusion criteria, FPG at baseline could not be used as inclusion criteria.
The study did not show a statistically significant effect on the primary endpoint -change in FPG during 28 days of treatment with O304 as compared to placebo. However, within- treatment comparisons showed a statistically significant reduction of FPG, insulin and HOMA-IR from baseline to Day 28 in the O304 group but not in the placebo group.
The table presents descriptive statistics of actual FPG values over time, by treatment (FAS).

End point type	Primary

End point timeframe:

FPG levels were collected from the screening visit to study day 40.

End point values	O304	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	32		
Units: mmol/L				
arithmetic mean (standard deviation)				
Screening	9.35 (± 1.85)	8.62 (± 1.24)		
Day 1	8.82 (± 1.95)	8.15 (± 1.13)		
Day 7	9.11 (± 2.08)	8.41 (± 1.39)		
Day 14	9.17 (± 1.85)	8.40 (± 1.29)		
Day 21	9.03 (± 2.17)	8.25 (± 1.74)		
Day 28	8.64 (± 2.41)	8.01 (± 1.16)		
Day 40	9.29 (± 2.12)	8.22 (± 1.21)		

Statistical analyses

Statistical analysis title	Absolute change from baseline to Day 28

Statistical analysis description:

Sample size was calculated with a two-sample T-test, assuming a standard deviation of 0.8 and a mean fasting glucose value of 8.0 mmol/l in the placebo group. This would give a possibility to detect a difference of 0.7 mmol/l in mean blood glucose with 92% power.
Mean difference in change in FPG was compared between the treatment groups by means of analysis of covariance with treatment, age, gender, and weight at baseline as covariates. Other parameters are presented with descriptive statistics

Comparison groups	O304 v Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.356
Method	t-test, 2-sided
Confidence interval	
level	95 %
Variability estimate	Standard deviation

Secondary: Occurrence and frequency of Adverse Events (AEs)

End point title	Occurrence and frequency of Adverse Events (AEs)

End point description:

Secondary objective: To assess safety and tolerability [of O304] after 28 days treatment in subjects with T2D, as compared to placebo.
Secondary endpoint: Safety and tolerability will be assessed by occurrence and frequency of Adverse Events (AEs).
A total of 87 AEs were reported for 42 patients (64.6%), with a slightly higher frequency in the placebo group. There was one reported SAE in this study. Two (2) patients, including the one with the SAE, were withdrawn from the placebo group due to AEs.

End point type	Secondary

End point timeframe:

AEs were collected from first administration of IMP to study day 40.

End point values	O304	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	32		
Units: Number of AEs				
No. of patients with at least one AE	19	23		
No. of AEs	38	49		
No. of patients with at least one SAE	0	1		
No. of SAEs	0	1		
No. of patients with at least one related AE	15	10		
No. of related AEs	18	20		
No of patients with AEs leading to discontinuation	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in laboratory parameters

End point title	Changes in laboratory parameters

End point description:

Secondary objective: To assess safety and tolerability [of O304] after 28 days treatment in subjects with T2D, as compared to placebo.
Secondary endpoint: Safety and tolerability will be assessed by changes in laboratory parameters.
No effects were seen on laboratory safety parameters.

End point type	Secondary

End point timeframe:

Safety blood samples were collected from screening to study day 28.

End point values	O304	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	32		
Units: No. of clinically significant changes				
Clinically significant changes	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in vital signs

End point title	Changes in vital signs

End point description:

Secondary objective: To assess safety and tolerability [of O304] after 28 days treatment in subjects with T2D, as compared to placebo.
Secondary endpoint: Safety and tolerability will be assessed by changes in vital signs.
No effects were seen on vital signs.

End point type	Secondary

End point timeframe:

Vital signs (systolic/diastolic blood pressure and heart rate) were collected from screening to study day 40.

End point values	O304	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	32		
Units: No. of clinically significant changes				
Clinically significant changes	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in physical examination

End point title	Changes in physical examination

End point description:

Secondary objective: To assess safety and tolerability [of O304] after 28 days treatment in subjects with T2D, as compared to placebo.
Secondary endpoint: Safety and tolerability will be assessed by changes in physical examination.
No effects were seen on physical examination findings.

End point type	Secondary

End point timeframe:

Physical examination (head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen, lymph nodes, extremities) including weight were checked at screening and study day 40.

End point values	O304	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	32		
Units: No. of clinically significant changes				
Clinically significant changes	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax

End point title	Cmax[1]

End point description:

Secondary objective: To assess the exposure of O304 in subjects with T2D and potential relationship to secondary and explorative PD variables.
Secondary endpoint: The following exposure parameter will be assessed after the last multiple dose: Cmax.
There was little difference between maximum and minimum concentrations during the dosage interval; mean Cmax was 55.5 µg/ml and mean Cmin 45.4 µg/ml. On the other hand, the serum levels varied greatly between patients.

End point type	Secondary

End point timeframe:

PK samples were collected from study day 7 to study day 40.

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: This endpoint reports PK parameters for patients who received the test product O304, not for the placebo group.

End point values	O304			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: µg/ml				
median (full range (min-max))				
Cmax	55.70 (28.10 to 89.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin

End point title	Cmin[2]

End point description:

Secondary objective: To assess the exposure of O304 in subjects with T2D and potential relationship to secondary and explorative PD variables.
Secondary endpoint: The following exposure parameter will be assessed after the last multiple dose: Cmin.
There was little difference between maximum and minimum concentrations during the dosage interval; mean Cmax was 55.5 µg/ml and mean Cmin 45.4 µg/ml. On the other hand, the serum levels varied greatly between patients.

End point type	Secondary

End point timeframe:

PK samples were collected from study day 7 to study day 40.

Notes:

[2] - 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: This endpoint reports PK parameters for patients who received the test product O304, not for the placebo group.

End point values	O304			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: µg/ml				
median (full range (min-max))				
Cmin	46.60 (22.20 to 74.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Css

End point title	Css[3]

End point description:

Secondary objective: To assess the exposure of O304 in subjects with T2D and potential relationship to secondary and explorative PD variables.
Secondary endpoint: The following exposure parameter will be assessed after the last multiple dose: Css.
Css was calculated as AUCtau/24. Average concentrations during the dosage interval; (Css) ranged from 24.6 to 82.9 µg/ml.

End point type	Secondary

End point timeframe:

PK samples were collected from study day 7 to study day 40.

Notes:

[3] - 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: This endpoint reports PK parameters for patients who received the test product O304, not for the placebo group.

End point values	O304			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: µg/ml				
median (full range (min-max))				
Css	52.74 (24.56 to 82.88)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau

End point title	AUCtau[4]

End point description:

Secondary objective: To assess the exposure of O304 in subjects with T2D and potential relationship to secondary and explorative PD variables.
Secondary endpoint: The following exposure parameters will be assessed after the last multiple dose: AUCtau.
The actual sampling times were used in the calculations. The linear trapezoidal rule was used for calculation of AUC, and the estimated concentration at 24 hours was used in the calculation of AUCtau.

End point type	Secondary

End point timeframe:

PK samples were collected from study day 7 to study day 40.

Notes:

[4] - 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: This endpoint reports PK parameters for patients who received the test product O304, not for the placebo group.

End point values	O304			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: µg/ml·h				
median (full range (min-max))				

AUCtau	1265.7 (589.38 to 1989.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from first IMP treatment to study day 40 (end of study).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	O304

Reporting group description:

Patients were treated with O304 for a period of 28 days. During the treatment period, there were weekly visits to the clinic, where blood sampling for FPG, safety, and exploratory parameters were collected. During the visits to the clinic, IMP for the next period was dispensed and the patients received the IMP dose for that day.

Reporting group title	Placebo

Reporting group description:

Patients were treated with Placebo for a period of 28 days. During the treatment period, there were weekly visits to the clinic, where blood sampling for FPG, safety, and exploratory parameters were collected. During the visits to the clinic, IMP for the next period was dispensed and the patients received the IMP dose for that day.

Serious adverse events	O304	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	O304	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 33 (57.58%)	23 / 32 (71.88%)	
Injury, poisoning and procedural complications			

Arthropod bite			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Joint injury			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	2	
Chest discomfort			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	3 / 33 (9.09%)	7 / 32 (21.88%)	
occurrences (all)	4	11	
Tension headache			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 33 (6.06%)	1 / 32 (3.13%)	
occurrences (all)	2	1	

Oedema mucosal			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Social circumstances			
Dental prosthesis user			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 33 (3.03%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 33 (3.03%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	3 / 33 (9.09%)	1 / 32 (3.13%)	
occurrences (all)	4	1	
Dyspepsia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Faeces hard			
subjects affected / exposed	2 / 33 (6.06%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Nausea			

subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	0 / 33 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	5 / 33 (15.15%)	11 / 32 (34.38%)	
occurrences (all)	6	13	
Psychiatric disorders			
Nightmare			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 33 (3.03%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Muscle spasms			
subjects affected / exposed	2 / 33 (6.06%)	2 / 32 (6.25%)	
occurrences (all)	2	2	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Myalgia			

subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Infections and infestations			
Folliculitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2016	Amendment No. 1 was approved and implemented before inclusion of the first patient in the study. The following changes were made to the Final CSP version 1.0, as a response to requests from the Swedish Medical Product Agency (MPA) following the initial CTA: • The benefit/risk section was expanded. A discussion of exposure margins (to Cmax and AUC) at the anticipated exposure from the clinical dose to the NOAEL in the non-clinical safety studies was added. • A full PK profile following the last dose of IMP on Day 28 was added, resulting in some modified wording of secondary objectives and endpoints. The original protocol only included pre-dose sampling at several occasions during the study. As a result of this change, Visit 6 (Day 28) became a full-day visit to the clinic and an additional visit was added on Day 29 for the 24-hour PK sampling. • Revised restrictions for concomitant medications to avoid potential interactions both from the perspective of O304 as a victim and as a perpetrator were added.
10 November 2016	Amendment No. 2 was approved and implemented before inclusion of the first patient in the study. The following changes were made to the Revised Final CSP version 2.0: • To facilitate recruitment, a second study site was added (CTC Linköping). • The screening period was prolonged from 14 to 21 days. • The time window of ± 1 day for study Day 27 was deleted since the 28-day treatment period was not to be exceeded. • A section for definition of re-screening procedures and criteria was added. • Changes were made in exclusion criterion no. 5: Creatinine clearance determined according to the Cockroft-Gault method was replaced by an estimated glomerular filtration rate (eGFR) (cystatin-C), and the limit for total bilirubin was changed from2.0 mg/dL to >2xULN. • To achieve consistent image quality, a restriction regarding food intake prior to the MRI assessments was added. • A change was made in the section concerning concomitant medication: Substitution therapy with vitamin B12, folic acid and thyroxin were allowed if the dose has been stable for four weeks prior to first dose of IMP. • Text was added to state that only 1 sample PK sample would be analysed for patients in the placebo group. • Measurement of B lactate was removed from the tests performed at screening.
13 December 2016	Amendment No. 3 applied to patients Nos. 1015 –1066. The text in this report reflects the last version of the CSP, version 4.0. The following changes were made to the Revised Final CSP version 3.0: • Changes to the MRI protocol (exploratory analyses) protocol were introduced. Novel results, obtained after the initiation of the clinical study, demonstrate that O304 protects mice on a high-fat induced diet against body weight gain and body fat gain, without affecting muscle mass, indicating that O304 increases energy expenditure. An additional examination to assess the volume of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) depots in the remaining patients was therefore added. • A new procedure for reading the MRI images was also introduced to assure that any incidental findings, possibly meeting exclusion criterion No. 9 ("Any clinically significant incidental finding at the MRI scan performed before randomisation") were discovered before randomisation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported