Clinical trial results:
A multicentre double blind placebo controlled clinical trial to assess efficacy and safety of Alvalin® (cathine hydrochloride) vs. placebo in 265 obese patients/group with a body mass index (BMI) between 30 and 45 kg/m2

Summary

EudraCT number	2012-003426-24
Trial protocol	DE
Global end of trial date	05 November 2015

Results information

Result version number	v1 (current)
This version publication date	01 July 2022
First version publication date	01 July 2022

Trial information

Trial identification

Sponsor protocol code	CTU079G

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Riemser Pharma GmbH
Sponsor organisation address	An der Wiek 7, Greifswald - Insel Riems, Germany, 17493
Public contact	Medical Science & Operations, RIEMSER Pharma GmbH, +49 38351760, info.germany@esteve.com
Scientific contact	Medical Science & Operations, RIEMSER Pharma GmbH, +49 38351760, info.germany@esteve.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	13 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2014
Global end of trial reached?	Yes
Global end of trial date	05 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the efficacy and safety of 32 mg of Alvalin® compared to placebo given intermittently over 52 weeks (three treatment periods interrupted by two periods with basal therapy only) in the treatment of diet-related obesity in patients with a BMI of 30 to 45 kg/m².
Primary endpoint is the weight reduction of at least 10% overall in the treatment group with at least 5% greater weight reduction than in the placebo group) after 52 weeks of treatment.

Protection of trial subjects:

This study will be conducted in accordance with the following:
• Federal Ministry of Health (2005). ""Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), das zuletzt durch Artikel 1 der Verordnung vom 19. Juli 2011 (BGBl. I S. 1398) geändert worden ist"
• 6. Bekanntmachung zur Anzeige von Nebenwirkungen und Arzneimittelmissbrauch nach §63b Abs. 1 bis 8 des Arzneimittelgesetzes (AMG) vom 19.1.2010 ; . [6. Announcement Concerning the Reporting of
Side Effects and Drug Abuse in Accordance with § 63b Abs. 1 to 8 AMG)].
• WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI. Revidierte Deklaration von Helsinki (Somerset West 2004) [Revised Declaration Somerset West (South Africa, 1996)]
• ICH Topic E 6 (R1) Guideline for Good Clinical Practice (2002)
• General insurance conditions for the clinical trials of medicinal products (subject insurance).
• GCP-Verordnung [GCP-Regulation] – GCP-V: Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen vom 9. August 2004
• 3. Bekanntmachung zur klinischen Prüfung von Arzneimitteln am Menschen. Gemeinsame Bekanntmachung des Bundesinstituts für Arzneimittel und Medizinprodukte und des Paul-Ehrlich-Instituts vom 10. August 2006
• RIEMSER Arzneimittel AG: Standard Operating Procedures (SOP)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 529
Worldwide total number of subjects	529
EEA total number of subjects	529

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)	529
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Multi-center study: 18 centers
Planned sample size was 265 patients / group, including an expected drop-out rate of 40%. Patients who drop out will not be replaced. At least 56.700 applications of Alvalin® will have to be observed, to reach a sufficient accuracy for the detection of very rare adverse drug reactions.

Pre-assignment

Screening details:

In case of AE, investigator can interrupt or reduce medication. If the same AE occurs again after rechallenging, the medical therapy is reduced or stopped. Individuals who want to discontinue due to lack of efficiency should be encouraged to remain in the study and to attend their study visits.

Period 1

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

Blinding implementation details:

The investigator obtained sealed emergency envelopes containing a letter with the individual treatment (test or reference drug) of the patient. The patient specific envelope was only opened if the medical condition of the patient and the adverse event required this. Reason, signature and date for opening had to be noted on the letter and the project manager at the sponsor had to be informed immediately. Normally, decoding only could have been performed after database closure.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test Preparation

Arm description:

The study medication has to be applied every morning after breakfast.
32 mg cathine hydrochloride per day, i.e. 12 drops of Alvalin® intermittent for thrice 12 weeks separated by 2 periods of eight weeks with basal therapy only.
Patients receive basal therapy throughout the study and in addition during 52 weeks an active treatment / placebo therapy which is
separated in:
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
The basal therapy in this trial was standardised according to the programme established in the study of Hauner et al. (2004): Basal therapy comprised education, a moderately hypocaloric diet, and an increase in physical activity.

Arm type	Experimental
Investigational medicinal product name	cathine hydrochloride (Alvalin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, liquid
Routes of administration	Oral use

Dosage and administration details:

32 mg cathine hydrochloride per day, i.e. 12 drops of Alvalin® intermittent for thrice 12 weeks separated by 2 periods of eight weeks with basal therapy only.

Arm title	Placebo Preparation

Arm description:

The study medication / placebo has to be applied every morning after breakfast.

0 mg cathine hydrochloride per day 12 drops of Alvalin® placebo for 52 weeks.

Patients receive basal therapy throughout the study and in addition during 52 weeks an active treatment / placebo therapy which is
separated in:
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
The basal therapy in this trial was standardised according to the programme established in the study of Hauner et al. (2004): Basal therapy comprised education, a moderately hypocaloric diet, and an increase in physical activity.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, liquid
Routes of administration	Local use

Dosage and administration details:

0 mg cathine hydrochloride per day 12 drops of Alvalin® placebo for 52 weeks.

Number of subjects in period 1	Test Preparation	Placebo Preparation
Started	264	265
Completed	251	245
Not completed	13	20
Lost to follow-up	6	9
No visit 2	7	11

Period 2

Period 2 title	Period 2 - eITT
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Test Preparation

Arm description:

The study medication has to be applied every morning after breakfast.
32 mg cathine hydrochloride per day, i.e. 12 drops of Alvalin® intermittent for thrice 12 weeks separated by 2 periods of eight weeks with basal therapy only.
Patients receive basal therapy throughout the study and in addition during 52 weeks an active treatment / placebo therapy which is
separated in:
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy

• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
The basal therapy in this trial was standardised according to the programme established in the study of Hauner et al. (2004): Basal therapy comprised education, a moderately hypocaloric diet, and an increase in physical activity.

Arm type	Experimental
Investigational medicinal product name	cathine hydrochloride (Alvalin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, liquid
Routes of administration	Oral use

Dosage and administration details:

32 mg cathine hydrochloride per day, i.e. 12 drops of Alvalin® intermittent for thrice 12 weeks separated by 2 periods of eight weeks with basal therapy only.

Arm title	Placebo Preparation

Arm description:

The study medication / placebo has to be applied every morning after breakfast.
0 mg cathine hydrochloride per day 12 drops of Alvalin® placebo for 52 weeks.

Patients receive basal therapy throughout the study and in addition during 52 weeks an active treatment / placebo therapy which is
separated in:
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
The basal therapy in this trial was standardised according to the programme established in the study of Hauner et al. (2004): Basal therapy comprised education, a moderately hypocaloric diet, and an increase in physical activity.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, liquid
Routes of administration	Local use

Dosage and administration details:

0 mg cathine hydrochloride per day 12 drops of Alvalin® placebo for 52 weeks.

Number of subjects in period 2	Test Preparation	Placebo Preparation
Started	251	245
Completed	101	83
Not completed	150	162
Consent withdrawn by subject	39	55
Adverse event, non-fatal	6	7
Other	66	45
Lost to follow-up	20	28
Protocol deviation	13	7
Lack of efficacy	6	20

Baseline characteristics

Reporting groups	
Reporting group title	Test Preparation

Reporting group description:

The study medication has to be applied every morning after breakfast.
32 mg cathine hydrochloride per day, i.e. 12 drops of Alvalin® intermittent for thrice 12 weeks separated by 2 periods of eight weeks with basal therapy only.
Patients receive basal therapy throughout the study and in addition during 52 weeks an active treatment / placebo therapy which is
separated in:
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
The basal therapy in this trial was standardised according to the programme established in the study of Hauner et al. (2004): Basal therapy comprised education, a moderately hypocaloric diet, and an increase in physical activity.

Reporting group title	Placebo Preparation

Reporting group description:

The study medication / placebo has to be applied every morning after breakfast.
0 mg cathine hydrochloride per day 12 drops of Alvalin® placebo for 52 weeks.

Patients receive basal therapy throughout the study and in addition during 52 weeks an active treatment / placebo therapy which is
separated in:
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
The basal therapy in this trial was standardised according to the programme established in the study of Hauner et al. (2004): Basal therapy comprised education, a moderately hypocaloric diet, and an increase in physical activity.

Reporting group values	Test Preparation	Placebo Preparation	Total
Number of subjects	264	265	529
Age categorical 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)	264	265	529
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Calculated for Safety Population (n=514)			
Units: years			
arithmetic mean	46.44	45.82	
standard deviation	± 11.78	± 12.02	-

Gender categorical			
Gender of Safety population (n=514)			
Units: Subjects			
Female	218	209	427
Male	46	56	102

End points

End points reporting groups

Reporting group title	Test Preparation

Reporting group description:

The study medication has to be applied every morning after breakfast.
32 mg cathine hydrochloride per day, i.e. 12 drops of Alvalin® intermittent for thrice 12 weeks separated by 2 periods of eight weeks with basal therapy only.
Patients receive basal therapy throughout the study and in addition during 52 weeks an active treatment / placebo therapy which is
separated in:
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
The basal therapy in this trial was standardised according to the programme established in the study of Hauner et al. (2004): Basal therapy comprised education, a moderately hypocaloric diet, and an increase in physical activity.

Reporting group title	Placebo Preparation

Reporting group description:

The study medication / placebo has to be applied every morning after breakfast.
0 mg cathine hydrochloride per day 12 drops of Alvalin® placebo for 52 weeks.

Patients receive basal therapy throughout the study and in addition during 52 weeks an active treatment / placebo therapy which is
separated in:
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
The basal therapy in this trial was standardised according to the programme established in the study of Hauner et al. (2004): Basal therapy comprised education, a moderately hypocaloric diet, and an increase in physical activity.

Reporting group title	Test Preparation

Reporting group description:

The study medication has to be applied every morning after breakfast.
32 mg cathine hydrochloride per day, i.e. 12 drops of Alvalin® intermittent for thrice 12 weeks separated by 2 periods of eight weeks with basal therapy only.
Patients receive basal therapy throughout the study and in addition during 52 weeks an active treatment / placebo therapy which is
separated in:
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
The basal therapy in this trial was standardised according to the programme established in the study of Hauner et al. (2004): Basal therapy comprised education, a moderately hypocaloric diet, and an increase in physical activity.

Reporting group title	Placebo Preparation

Reporting group description:

The study medication / placebo has to be applied every morning after breakfast.
0 mg cathine hydrochloride per day 12 drops of Alvalin® placebo for 52 weeks.

Patients receive basal therapy throughout the study and in addition during 52 weeks an active treatment / placebo therapy which is
separated in:
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy
• 08 weeks of basal therapy only
• 12 weeks of active treatment or placebo therapy

The basal therapy in this trial was standardised according to the programme established in the study of Hauner et al. (2004): Basal therapy comprised education, a moderately hypocaloric diet, and an increase in physical activity.

Primary: Change of weight in total

End point title	Change of weight in total

End point description:

Primary endpoint is the weight reduction of at least 10% overall in the treatment group with at least 5% greater weight reduction than in the placebo group) after 52 weeks of treatment.
Following the EMA Guideline on Clinical Evaluation of Medicinal Products used in Weight Control [Guideline on Weight Control (2007)], administering Alvalin®, a weight reduction of at least 10% compared to baseline and a superiority in weight reduction of at least 5% compared to placebo after a period of 12 months of therapy are necessary to fulfil the primary criterion.

End point type	Primary

End point timeframe:

52 weeks

End point values	Test Preparation	Placebo Preparation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	245		
Units: percentage of weight				
arithmetic mean (standard deviation)	6.29 (± 6.74)	2.72 (± 5.63)		

Statistical analyses

Statistical analysis title	Hypothesis 1 (eITT)

Statistical analysis description:

A two sided t-test was used for analysis of the reduction of body weight with a global α level of 0.05. Because there were two hypotheses, the α level for H1 is 0.025 (one sample t-test) and for H2 α is also 0.025 (two sample t-test)

Comparison groups	Placebo Preparation v Test Preparation
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided

Secondary: Percentage of patients with weight loss >10%

End point title	Percentage of patients with weight loss >10%

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Test Preparation	Placebo Preparation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	245		
Units: patients	60	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with weight loss > 5 %

End point title	Percentage of patients with weight loss > 5 %

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Test Preparation	Placebo Preparation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	245		
Units: patients	127	58		

Statistical analyses

No statistical analyses for this end point

Secondary: Weight loss during the trial(V1-V13)

End point title	Weight loss during the trial(V1-V13)

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Test Preparation	Placebo Preparation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	245		
Units: kg				
arithmetic mean (standard deviation)	6.41 (± 6.99)	2.86 (± 5.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in waist circumference (WC)

End point title	Change in waist circumference (WC)

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Test Preparation	Placebo Preparation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	245		
Units: cm				
arithmetic mean (standard deviation)	6.26 (± 7.93)	3.09 (± 6.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in waist-hip ratio (WHR)

End point title	Change in waist-hip ratio (WHR)

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Test Preparation	Placebo Preparation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	245		
Units: ratio				
arithmetic mean (standard deviation)	0.0108 (± 0.0670)	-0.0012 (± 0.0630)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in BMI

End point title	Change in BMI

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Test Preparation	Placebo Preparation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	245		
Units: kg/m^2				
arithmetic mean (standard deviation)	2.28 (± 2.48)	1.01 (± 2.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phisicians assessment of efficacy

End point title	Phisicians assessment of efficacy

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Test Preparation	Placebo Preparation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	245		
Units: patients				
Very good	51	26		
Good	54	29		
Moderate	25	22		
Poor	15	11		
Very poor	37	60		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient's assessment of efficacy

End point title	Patient's assessment of efficacy

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Test Preparation	Placebo Preparation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	245		
Units: patients				
Very good	49	21		
Good	56	37		
Moderate	31	22		
Poor	12	8		
Very poor	34	60		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed during the 52 weeks of study, additionally at follow-up visit 1 (3 months after end of treatment) and follow-up visit 2 (12 months after end of treatment).

Adverse event reporting additional description:

15 randomised patients (2.3 %) had no intake of study medication and therefore 514 patients (79.9 %) were valid for the safety analysis.
In 349/514 patients (67.9%) 959 AEs occurred: in 182 patients (52.1%) treated with Alvalin®, and in 167 patients (47.9%) receiving placebo.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Safety Placebo Preparation

Reporting group description:

All persons with documented intake of trial medication in the course of the clinical trial were valid for the safety analysis.

Reporting group title	Safety Test preparation

Reporting group description:

All persons with documented intake of trial medication in the course of the clinical trial were valid for the safety analysis.

Serious adverse events	Safety Placebo Preparation	Safety Test preparation	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 256 (8.20%)	19 / 258 (7.36%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer tumor			
subjects affected / exposed	0 / 256 (0.00%)	4 / 258 (1.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medicinal procedures			
subjects affected / exposed	9 / 256 (3.52%)	4 / 258 (1.55%)	
occurrences causally related to treatment / all	0 / 11	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Prothesis dislocation			
subjects affected / exposed	0 / 256 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Reproductive system and breast			
subjects affected / exposed	2 / 256 (0.78%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			
subjects affected / exposed	1 / 256 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Crystal urine present			
subjects affected / exposed	1 / 256 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	3 / 256 (1.17%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Chest pain			
subjects affected / exposed	0 / 256 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorders	Additional description: Sciatica, Dizziness, Restlessness, VIIth nerve paralysis		
subjects affected / exposed	2 / 256 (0.78%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Inner ear disorder			
subjects affected / exposed	1 / 256 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gatrointestinal			
subjects affected / exposed	1 / 256 (0.39%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	1 / 256 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal calculus			
subjects affected / exposed	1 / 256 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goiter			
subjects affected / exposed	1 / 256 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muskuloskeletal and connective tissue			
subjects affected / exposed	1 / 256 (0.39%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Infections and infestations			
subjects affected / exposed	1 / 256 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolism	Additional description: hypercalcaemia, periarthritis calcarea		
subjects affected / exposed	1 / 256 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	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	Safety Placebo Preparation	Safety Test preparation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 256 (65.23%)	182 / 258 (70.54%)	
Vascular disorders			
Cardiovascular disorder, Flushing, Hypertension			
subjects affected / exposed	9 / 256 (3.52%)	10 / 258 (3.88%)	
occurrences (all)	9	11	
General disorders and administration site conditions			
General disorders and administration site conditions	Additional description: withdrawal syndrome, fatigue, malaise, irritability, thirst		
subjects affected / exposed	5 / 256 (1.95%)	27 / 258 (10.47%)	
occurrences (all)	5	37	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 256 (0.00%)	1 / 258 (0.39%)	
occurrences (all)	0	1	
Psychiatric disorders			
Psychiatric disorders	Additional description: sleep disorder, middle insomnia, depression, nervousness, emotional distress, burnout syndrome, stress, depressed mood, anxiety, mood swings, anxiety disorder		
subjects affected / exposed	16 / 256 (6.25%)	23 / 258 (8.91%)	
occurrences (all)	17	32	
Investigations			

Investigations	Additional description: Blood preassure increased, Blood preassure decreased, skin test positive, EKG abnormal		
subjects affected / exposed	6 / 256 (2.34%)	2 / 258 (0.78%)	
occurrences (all)	6	2	
Cardiac disorders			
Tachycardia, Heart valve incompetence, Extrasystoles, Bundle branch block right			
subjects affected / exposed	2 / 256 (0.78%)	8 / 258 (3.10%)	
occurrences (all)	2	10	
Nervous system disorders			
Nervous system disorders	Additional description: Headache, restlessness, restless legs syndrome, dizziness, migraine, vertigo, agitation, somnolence, abnormal dreams		
subjects affected / exposed	31 / 256 (12.11%)	46 / 258 (17.83%)	
occurrences (all)	39	54	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 256 (0.00%)	1 / 258 (0.39%)	
occurrences (all)	0	1	
Eye disorders			
Blepharospasm			
subjects affected / exposed	1 / 256 (0.39%)	0 / 258 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	0 / 256 (0.00%)	17 / 258 (6.59%)	
occurrences (all)	0	21	
Nausea, Tongue disorder			
subjects affected / exposed	1 / 256 (0.39%)	3 / 258 (1.16%)	
occurrences (all)	1	3	
Diarrhoea, Pulpitis dental, Toothache, Abdominal discomfort			
subjects affected / exposed	26 / 256 (10.16%)	16 / 258 (6.20%)	
occurrences (all)	26	16	
Skin and subcutaneous tissue disorders			
Urticaria, Hyperhidrosis, Alopecia			
subjects affected / exposed	2 / 256 (0.78%)	2 / 258 (0.78%)	
occurrences (all)	2	2	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	51 / 256 (19.92%)	67 / 258 (25.97%)	
occurrences (all)	51	67	
Bronchitis			
subjects affected / exposed	6 / 256 (2.34%)	4 / 258 (1.55%)	
occurrences (all)	6	4	
Urinary tract infection			
subjects affected / exposed	5 / 256 (1.95%)	5 / 258 (1.94%)	
occurrences (all)	5	5	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	9 / 256 (3.52%)	22 / 258 (8.53%)	
occurrences (all)	11	28	
Glucose tolerance impaired, Hyperuricaemia			
subjects affected / exposed	1 / 256 (0.39%)	1 / 258 (0.39%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported